Catalytic Epoxidation of Alkenes with Molecular Dioxygen activated by CuX_n–Ascorbic Acid Systems (X = F, Cl, Br or I; n = 1 or 2)

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Copper-(I) or -(II) salt–ascorbic acid systems have been found to catalyse facile epoxidation of *trans*-stilbene without concomitant formation of benzaldehyde, by utilizing molecular dioxygen under mild conditions.

Much attention has been drawn to the functional modelling of copper-containing monooxygenases.[1] In many attempts, however, not molecular dioxygen but iodosylbenzene and hydrogen peroxide have been employed as an oxygen source,[2] except for a few recent studies.[3] Dopamine β-monooxygenase, which contains copper, catalyses the hydroxylation of dopamine [4-(2-aminoethyl)benzene-1,2-diol] with molecular dioxygen in the presence of ascorbic acid.[1a] This enzymatic reaction motivated us to apply a CuX_n–ascorbic acid system to model the monooxygenase reaction. We present the first report of the catalytic epoxidation of alkenes using the CuX_n–ascorbic acid system and molecular dioxygen.

In the presence of the copper-(I) or -(II) salt–ascorbic acid system, epoxidation of *trans*-stilbene by molecular dioxygen proceeded smoothly in pyridine under mild conditions [30 °C, 1 atm (*ca.* 10^5 Pa) O_2] after a long induction period of *ca.* 24 h.† The amount of *trans*-stilbene oxide obtained was almost the same as the amount of *trans*-stilbene consumed, indicating that no side reaction occurred. Although benzaldehyde is a by-product in many biomimetic oxygenations,[2b] it was not formed in our system. The turnover number reached 12–17 after 48 h,‡ when CuCl, CuBr, CuI, $CuCl_2$ or $CuBr_2$ was employed in the reaction (Table 1). However, the CuF_2–ascorbic acid system exhibited very low activity, about half those of the other systems. No reaction occurred in the absence of either copper salt or ascorbic acid.§ Even when a copper(I) salt was used there was no reaction in the absence of ascorbic acid. When hydroquinone was employed as a reductant instead of ascorbic acid the epoxidation was much suppressed, whereas hydroquinone can reduce copper(II) to copper(I). This result indicates that ascorbic acid is indispensable for the epoxidation, not only as a reductant but also in some other way, probably as a ligand. Ascorbate anion has been reported to co-ordinate to transition metals,[4] in particular to the copper(II) ion in ascorbate oxidase.[1a]

Table 1 Epoxidation of *trans*-stilbene with molecular dioxygen catalysed by the CuX_n–ascorbic acid system[a]

Run	Copper salt	Solvent[b]	Turnover number[c] 24 h	48 h
1	CuCl	py	5.41 (16.4)	15.1 (45.8)
2	CuCl[d]	py	Trace	Trace
3	CuBr	py	8.27 (25.1)	17.1 (51.8)
4	CuI	py	8.02 (24.3)	12.4 (37.6)
5	CuF_2	py	1.85 (5.61)	6.04 (18.3)
6	$CuCl_2$	py	10.2 (30.9)	15.3 (46.4)
7	$CuCl_2$[e]	py	Trace	0.02
8	$CuCl_2$	4Me-py	10.3 (31.2)	16.3 (49.4)
9	$CuCl_2$	2Me-py	0.30 (0.91)	0.91 (2.76)
10	$CuCl_2$	dmf	1.47 (4.45)	—
11	$CuCl_2$	dmso	0.69 (2.09)	—
12	$CuBr_2$	py	7.76 (23.5)	15.1 (45.8)

[a] [Cu] = 1.5 × 10^{-3} mol dm^{-3}, Cu:*trans*-stilbene:ascorbic acid = 1:33:333 at 30 °C, under O_2. [b] py = Pyridine, 4Me-py = 4-methylpyridine, 2Me-py = 2-methylpyridine. [c] Mol of *trans*-stilbene oxide per mol of catalyst. The yield (%) of the epoxide based on the starting material is given in parentheses. [d] In the absence of ascorbic acid. [e] Hydroquinone was employed instead of ascorbic acid.

The catalytic activity significantly depends on the solvent. Pyridine derivatives, dimethylformamide (dmf) and dimethyl sulfoxide (dmso) were used as solvents, since these dissolve *trans*-stilbene, ascorbic acid and copper salts. The epoxidation proceeded efficiently in 4-methylpyridine as in pyridine (run 8), whereas the reaction was suppressed in 2-methylpyridine (run 9), dmf (run 10) and dmso (run 11). Co-ordination of 2-methylpyridine is difficult because of the presence of the methyl group at a neighbouring site to the N atom. These results suggest that co-ordination of pyridine is necessary for the active species.

The catalytic activity also depends on the substrate. Epoxidation of *trans*-β-methylstyrene proceeded more slowly than that of *trans*-stilbene, accompanied with some side reaction (by-product is unknown); the consumption of *trans*-β-methylstyrene and yield of *trans*-β-methylstyrene oxide after 24 h were 7.95 and 4.28 mol per mol catalyst, respectively, when

† In a typical run, $CuCl_2$ (4.5 × 10^{-5} mol), *trans*-stilbene (1.5 × 10^{-3} mol), ascorbic acid (1.5 × 10^{-2} mol), molecular sieves 5A (0.02 g) and pyridine (30 cm^3) were mixed under O_2 at 30 °C. The product and reactant were analysed by HPLC, using durene (1,2,4,5-tetramethylbenzene) as an internal standard.

‡ The reaction became much slower after 48 h but did not stop. In the epoxidation of *trans*-stilbene catalysed by $CuCl_2$ the turnover numbers were 15.3 after 48 h, 18.1 after 72 h and 19.0 after 96 h.

§ Lower concentrations of ascorbic acid result in lower yields of product. When the molar ratio of $CuCl_2$:*trans*-stilbene:ascorbic acid = 1:33:33 was adopted the turnover number after 48 h was merely 0.47. Ascorbic acid might be wastefully consumed by oxidation under these reaction conditions.

$CuCl_2$ and pyridine were employed. In the oxygenation of α-methylstyrene catalysed by $CuCl_2$, a small amount of epoxide was obtained (1.77 mol per mol catalyst) but acetophenone was the main product (2.99 mol per mol catalyst). Cyclohexene was not oxygenated by the present system. These facts indicate that the present system is effective for such electron-poor alkenes as *trans*-stilbene, but less effective for such electron-rich alkenes as methylstyrene and cyclohexene.

To shed some light on the induction period of the epoxidation a spectroscopic study was performed. Copper(II) chloride in pyridine exhibits a characteristic d–d absorption at 776 nm, which disappeared immediately after mixing *trans*-stilbene and ascorbic acid (33 and 333 mol to 1 mol copper, respectively) under either O_2 or N_2. This means that $CuCl_2$ is immediately reduced to copper(I) by ascorbic acid. Corresponding to this change, the ESR signals of $CuCl_2$ in pyridine (at 77 K $g_{\|} = 2.22$, $A_{\|} = 139 \times 10^{-4}$ cm^{-1}, $g_{\perp} = 2.02$, $A_{\perp} = 14.9 \times 10^{-4}$ cm^{-1}) disappeared after mixing with ascorbic acid and *trans*-stilbene. Although copper(II) was immediately reduced to copper(I) by ascorbic acid, the epoxidation hardly proceeded until 24 h after mixing with ascorbic acid and *trans*-stilbene, indicating that the copper(I) species, formed by reduction of $CuCl_2$, was not the active species. This induction period was little shortened by using CuCl instead of $CuCl_2$. After 24 h the ESR signal of a copper(II) species had appeared ($g_{\|} = 2.29$, $A_{\|} = 186 \times 10^{-4}$ cm^{-1}, $g_{\perp} = 2.07$), and efficient epoxidation started. This signal could be related to the formation of the active species, the induction period being necessary for the formation of this species. When $CuCl_2$ was pretreated with ascorbic acid for 24 h under O_2 in pyridine the same ESR signal was observed. This system catalysed the epoxidation of *trans*-stilbene without an induction period (turnover number after 12 h was 9.2). When $CuCl_2$ was pretreated with ascorbic acid for 24 h under N_2 in pyridine the induction period did not disappear. These results indicate that the active species is formed from CuX_2 (or CuX), ascorbic acid, pyridine and O_2.

References

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