*Journal of Organometallic Chemistry*, 246 (1983) 53–56
Elsevier Sequoia S.A., Lausanne – Printed in The Netherlands

# ENANTIOSELECTIVE EPOXIDATION OF AN ALLYLIC ALCOHOL CATALYZED BY (ACETYLACETONATO)-(L-*N*-METHYLPROLINOL)DIOXOMOLYBDENUM. THE DECREASE OF ENANTIOSELECTIVITY WITH CHEMICAL CONVERSION

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(Received November 16th, 1982)

## Summary

Epoxidation of 3-methyl-2-buten-1-ol with cumene hydroperoxide catalyzed by $MoO_2(acac)_2$ in the presence of L-*N*-methylprolinol yields epoxy alcohol of 50% optical purity at relatively low conversions. This enantioselectivity decreases with increase in conversion, which is due to the destruction of the chirality of the catalyst via oxidation of the chiral ligand or its replacement. It is possible to maintain the initial chiral selectivity of 50% AT over 80% conversion by periodically adding more chiral ligand.

## Introduction

Enantioselective epoxidation of allylic alcohols using hydroperoxide and chiral catalysts was first reported for molybdenum [1] and vanadium [2] complexes. Since the initiation of the present work Sharpless [3] reported a titanium system that achieves almost total stereoselection in this reaction. Since Yamada's original publication of the $MoO_2(acac)_2$/*N*-methylephedrine catalyst system for the chiral epoxidation of allylic alcohols, no further studies of this reaction have been reported.

During the investigation of the molybdenum-catalyzed epoxidation of an allylic alcohol mediated by a chiral amino alcohol, we observed that the chiral selectivity decreased with increasing conversion. We discuss this observation below and the measures required to overcome the problem and so maintain the initial chiral selectivity to high conversions.

## Results and discussion

The reaction under study is shown in eq. 1. The ligand *N*-methylprolinol was used in a 2/1 molar ratio to the $MoO_2(acac)_2$ catalyst (1 mol% on allylic alcohol) in the

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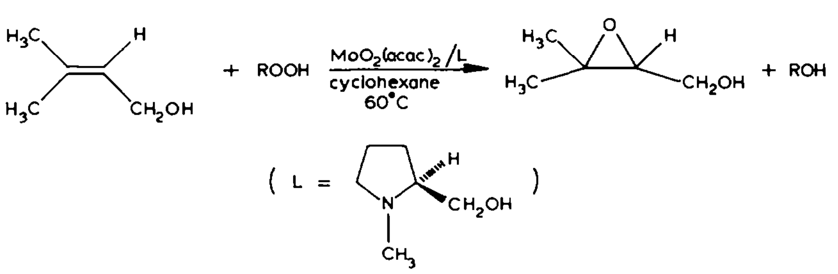


(1)

epoxidation of 3-methyl-2-buten-1-ol with cumene hydroperoxide in cyclohexane solvent. The reaction was performed at 60°C. From aliquots taken from the reaction mixture at regular intervals, the epoxy alcohol was isolated and converted into the diastereomeric esters of Mosher's acid [4]. Figure 1 shows a plot of diastereomeric ratios (as determined by $^{19}$F NMR), together with the degree of conversion as a function of time. As shown in the figure, at low conversion the epoxy alcohol produced was 50% optically pure, but this high enantioselectivity decreased to 20% at 70% conversion. In fact, when these experimental values for optical purity are calculated as instantaneous values at each time, it is found that the epoxide formed after the first 3 h (45% conversion) is practically racemic.

When the epoxidation mixture was allowed to continue refluxing for another 16 h at 60°C beyond 85% conversion, the optical purity of the product did not change from the value obtained at 85% conversion. Thus the product does not racemize under these conditions. The addition of the free-radical scavenger 2,6-di-t-butyl-4-methylphenol to the reaction mixture had no effect on the optical purity of the epoxy alcohol, thus no concurrent chirally aselective, free-radical epoxidation takes place. Thus it seems likely that changes in the chiral catalyst, such as dechiralization, is responsible for the observed decrease in chiral selectivity.

In the present system the metal catalyst is rendered chiral by the complexation of the chiral amino alcohol ligand via the substitution of one of the acetylacetonate ligands (eq. 2). Such a complex has been characterized by NMR and IR spectroscopy [1]. This complexation renders the metal itself chiral, resulting in diastereomeric complexes.

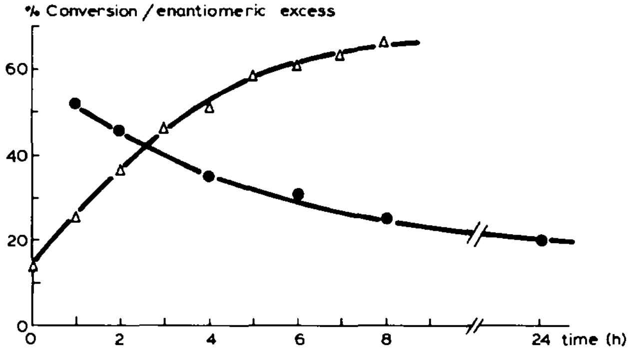
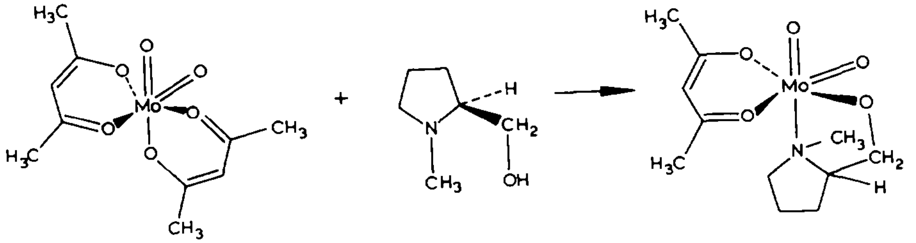


Fig. 1. Conversion and optical purity vs. time in the enantioselective epoxidation of 3-methyl-2-buten-1-ol with cumene hydroperoxide catalyzed by MoO$_2$(acac)$_2$/L-*N*-methylprolinol.

$\Delta = \dfrac{\text{epoxy alcohol}}{\text{epoxy alcohol} + \text{allyl alcohol}} \times 100$, ● = % optical purity.



(2)

At the beginning of the reaction all the epoxide is formed by this chiral catalyst, which yields a product of 50% optical purity. However, as the reaction proceeds, dechiralization of the catalyst could occur by means of a number of reactions, e.g. reversible replacement of the chiral ligand by product alcohols or reaction with epoxide to form diol complexes, as observed by Sheldon et al. [5].

Another, possibly more important, reaction that would destroy the chirality of the metal catalyst is oxidation of the chiral $\alpha$-amino alcohol ligand. Sheng and Zajacek [6] found that oxidation of tertiary amines to amine oxides by hydroperoxides is catalyzed by soluble molybdenum complexes. This ligand oxidation could change the catalyst sufficiently to affect its abilities towards enantioselection.

That the chirality of the catalyst is destroyed in this system during the reaction is confirmed by the effect of measures taken to keep the concentration of chiral ligand high at any given moment. When more chiral ligand was periodically added to the reaction mixture such that the Mo/ligand ratio changed from 1/2 to 1/5, the epoxy alcohol formed over 80% conversion was 50% optically pure, the same as observed in the initial 20% conversion. Similar chiral selectivity at high conversion was achieved when a high initial ligand concentration (Mo/ligand 1/5) was used.

In conclusion, our observation that chiral selectivity decreases with increase in conversion has obvious consequences for the evaluation of work done in this area. In both of the published cases of chiral molybdenum [1] and vanadium catalyzed [2] epoxidations of allylic alcohols, the highest chiral inductions were observed at lower conversions. This could be due to a related process of dechiralization as described here. Thus, in the light of our work an evaluation of the effect of various reaction parameters such as ligand structure, temperature and solvent polarity on chiral metal-catalyzed reactions can only be valid if any change in the chiral selectivity with time or conversion is properly taken into account.

## Experimental

3-Methyl-2-buten-1-ol, cumene hydroperoxide and $MoO_2(acac)_2$ were commercial products. *N*-Methyl-prolinol, synthesized from commercial L-prolinol (Aldrich) via the route described below, yielded a product of 92% optical purity. (Synthesis of this ligand via methylation of proline with formic acid/formaldehyde followed by esterification and reduction yielded a product of only 60% optical purity.) Proton NMR spectra were measured on a Bruker 90 MHz spectrometer, and polarimetric data on a Perkin–Elmer 241 polarimeter with a thermostatted 10 cm cell at the Na D line.

*L-N-Methylprolinol: via the methylation of S-prolinol*

To 100 ml of ice-cold acetic acid in a hydrogenation apparatus 12.2 g of (*S*)-prolinol (Aldrich; $\alpha_D = +3.4°$ ($c = 2$, $CH_3OH$) dissolved in 50 ml of water, 12.2 g of 37% formaldehyde and catalytic amounts of $PtO_2$ were successively added. The total volume was brought up to 500 ml, the solution was degassed by repeated evacuations and exposed to $H_2$ pressure. After approx. 24 h slightly more than the theoretical amount of $H_2$ was absorbed. The catalyst was removed by filtration through Hyflo and washed with warm water. The filtrate was concentrated at room temperature under vacuum to yield a syrupy residue which contained the product contaminated with acetic acid. Stirring the ether solution of this residue with solid potassium carbonate removed most of the acetic acid. Further purification by distillation yielded 2.4 g of pure product. $[\alpha_D]^{20}$ 46.1° ($c = 1$, EtOH). (Literature [7], $[\alpha_D]_{max} = 49.5°$).

*Epoxidation procedure*

To a mixture of 326.5 mg (1.0 mmol) of $MoO_2(acac)_2$, 8.6 g (0.1 mol) of 3-methyl-2-buten-1-ol, and 0.23 g (2 mmol) of *N*-methylprolinol was added 300 ml of cyclohexane. The mixture was stirred for 15 minutes at 60°C then 24.75 g (0.13 mol) of 80% cumene hydroperoxide was added dropwise with vigorous stirring the degree of conversion was measured by GLC (6 ft, 10% Carbowax 20M; temp.: 100–250°C, 10°C/min). Aliquots of the reaction mixture were taken every hour, chilled in ice and immediately worked up by passing them through 10 cm of dry Florisil (⌀ 1 cm) which removed the catalyst. When the allylic alcohol was replaced by ethanol in order to prevent epoxidation occurring and the reaction was conducted in the same manner, no optically active material could be detected after the Florisil treatment, which shows that this method is a safe way of separating the chiral epoxide from other optically active material. After this treatment the solvent was removed in vacuo and the residual oil was chromatographed on a second Florisil (50 cm, ⌀ 1.5 cm) column using ether. This procedure yielded chemically pure epoxy alcohol and did not cause any racemization even after two repetitions. The optical purity was determined by polarimetery at 20°C, at the Na D line and in chloroform solvent. $[\alpha_D]^{20}$ 18.7° ($c = 7$, $CHCl_3$) [1]. The enantiomeric excess was also measured by derivatizing the product with (*R*)-α-methoxy-α-trifluoromethylphenylacetyl chloride and determining the diastereomeric excess by $^{19}F$ NMR. The two values agreed within the experimental error.

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