

Enhancement of the enantioselectivity in the epoxidation of sterically hindered substrates by decreasing the contribution of the blank reaction

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Abstract: In the case of asymmetric epoxidation reactions catalysed by Jacobsen's catalyst, the substrate/catalyst ratios used are low. Often additives, such as N-oxides, are employed to enhance the enantioselectivity of the reaction. We have found that for reactions of sterically hindered, less reactive substrates, a non-selective blank reaction competes with the catalysed reaction. When low substrate/catalyst ratios or additives are used, an acceleration of the epoxidation reaction is observed. As a result a larger difference in rate with the blank reaction occurs, resulting in an increase in the enantioselectivity.
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The development of Jacobsen's catalyst represented great progress in the enantioselective oxidation reaction of olefins. This catalyst has been demonstrated to catalyse the epoxidation of cis-disubstituted and trisubstituted olefins with rather good chemical yield and high enantiomeric excess.^{1,2} Yet the used molar substrate/catalyst ratios are low, about between 25 and 50.³ Often additives, such as N-oxides, are added to the reaction to increase the enantioselectivity and the product yield.^{2,4,5} This effect is more pronounced in the case of relatively unreactive substrates.⁵ There are several explanations for the effect of the N-oxide on the enantiomeric excess and the reaction rate in the literature. The enantioselective enhancement induced by N-oxide can be due to the suppression of non-selective Lewis acid-catalysed oxidation reactions of the substrate or the epoxide product.^{4a,5} Another explanation is that the co-ordination of the N-oxide as an axial ligand decreases the reactivity of the oxo species and thus enhances the enantioselectivity, because reaction with a less reactive oxo species proceeds via a more product-like transition state, resulting in more specific non-bonded interactions.^{6a} Katsuki *et al.*⁶ are the only ones who have claimed that the N-oxide decreases the reaction rate. On the contrary, Jacobsen *et al.* observed an acceleration in the epoxidation rate which they explained by the equilibrium shift of the inactive μ -oxo dimer, formed by reaction between the active (salen) $Mn^V=O$ complex with a Mn^{III} complex, toward the active Mn^V -oxo intermediate in the presence of N-oxide derivatives.⁵ We show here that the increase of the enantioselectivity is caused, at least in some cases, by an acceleration of the reaction rate due to co-ordination of the nitrogen and/or oxygen bases. Enhancement of the enantioselective epoxidation rate causes higher enantiomeric excess due to a larger difference in rate with the non-selective blank epoxidation reaction. This is especially true for reactions with sterically hindered, less reactive substrates, such as 1-phenyl-1-cyclohexene.

The asymmetric epoxidation of 1-phenyl-1-cyclohexene was investigated at different substrate/catalyst ratios (S/C) using dichloromethane as a solvent (Figure 1). The relation between S/C and the olefin conversion is obvious: the lower the S/C, the higher the conversion of the olefin. The increasing enantiomeric excess (ee) of the epoxide with decreasing S/C suggests that an achiral blank reaction is competing with the catalysed reaction. Therefore, a blank reaction was performed under the same conditions. As seen in Table 1, a racemic mixture of epoxides was formed. This idea

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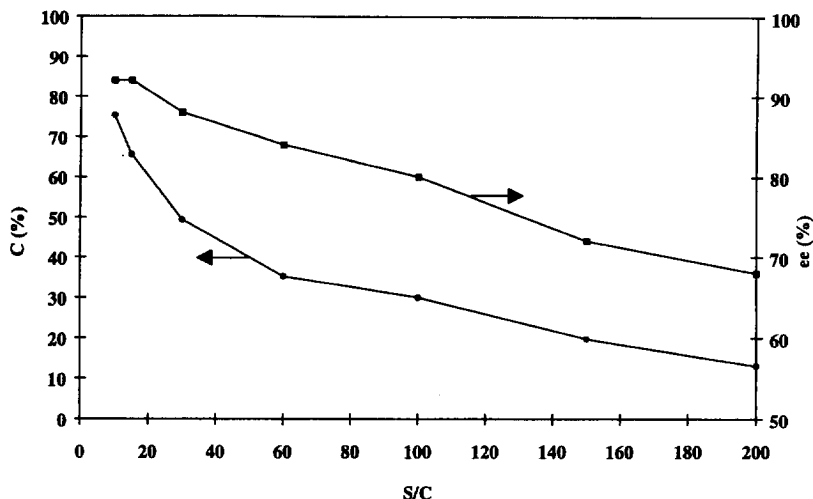


Figure 1. Conversion (C) of 1-phenyl-1-cyclohexene and enantiomeric excess (ee) of the epoxide against the substrate over catalyst ratio (S/C).⁷

Table 1. Asymmetric epoxidation^a of 1-phenyl-1-cyclohexene at different solvents and different substrate/catalyst (S/C) ratios

S / C (mol / mol)	Conversion (%)	TON ^b	ee ^c (%)	Calculated ee ^d (%)	k ^e (min ⁻¹)	r ² (f)	Theoretical blank reaction ^g (%)
solvent = dichloromethane							
10	75.3	7.1	92				-
15	65.6	9.4	92	91	1.3 10 ⁻²	0.99	-
30	49.3	13.9	88	88	4.8 10 ⁻³	0.99	1.02
60	35.2	20.3	84	86	2.9 10 ⁻³	0.98	1.46
100	30.0	26.6	80	82	1.4 10 ⁻³	0.99	1.87
150	19.7	28.2	72	77	9.4 10 ⁻⁴	0.98	2.05
200	13.1	23.8	68	69	5.1 10 ⁻⁴	0.97	1.64
blank	2.20	-	0		1.7 10 ⁻⁴	0.95	
solvent = diethylether							
15	17.0	2.4	83				-
60	13.4	8.0	83				-
100	4.6	4.4	70				0.33
200	2.7	5.2	40				0.63
blank	0.40	-	0				

(a) Reaction conditions see note 7. (b) Turnover number (c) The ee is measured by GC analysis over a chiral G-TA column. (d) Calculated ee based on the k-values⁹. (e) Rate constant. (f) R-square value. (g) % blank reaction necessary to decrease the ee from 92% (or 83% in diethylether) to the experimental observed value.

was confirmed by calculating the kinetic rate equations⁸ (Eq. 1). At high S/C values the difference between the rate constants of the catalysed reaction k_{catal} and the blank reaction k_{blank} is only a factor of 3. As S/C decreases, the difference between k_{catal} and k_{blank} exceeds a factor of 70. Based on the experimentally obtained rate constants, an ee value can be calculated for each S/C ratio.⁹ A good match can be found between the calculated and the experimental ee. It indicates that for 1-phenyl-1-cyclohexene the catalysed reaction is too slow to neglect the rate of the blank reaction at high S/C. So in order to obtain a high ee, it is better to work under conditions that maximise the difference in reaction rate between catalysed and blank reaction, i.e. low S/C ratios and low reaction temperatures.

$$-\frac{d[S]}{dt} = k_{\text{catal}}[S] + k_{\text{blank}}[S] \quad (1)$$

Table 2. Asymmetric epoxidation^a of 1-phenyl-1-cyclohexene with S/C=200

pyridine-N-oxide (mmol)	Conversion (%)	TON ^b	ee ^c (%)	Calculated ee ^d (%)	k ^e (min ⁻¹)	r ² (f)
0	13.1	23.8	68	69	5.5 10 ⁻⁴	0.97
0.149	37.1	69.8	84	81	1.3 10 ⁻³	0.99

(a) Reaction conditions see note 7. (b) Turnover number (c) The ee is measured by GC analysis over a chiraldex G-TA column. (d) Calculated ee based on the k-values⁹. (e) Rate constant. (f) R-square value.

As seen in the second part of Table 1, in a solvent such as ether, the blank reaction is less pronounced than in dichloromethane, but the epoxidation reaction does not go as fast as in dichloromethane. Upon calculating the amount of blank reaction needed to decrease the ee from 83% (S/C=15) to the observed ee at a given S/C ratio, a good match is found between the calculated (theoretical blank reaction) and the real value (Table 1).

These findings can also give an alternative explanation for the increase in enantioselectivity in the presence of N-oxides.² The hypothesis of Jacobsen *et al.* describes a shift from the inactive μ -oxo dimer to the active oxo intermediate upon co-ordination with N-oxide. This increases the total catalytic activity and so the difference with the blank reaction. The enantiomeric excess will be higher in that case than in conditions without N-oxides. To prove this, the epoxidation of 1-phenyl-1-cyclohexene was done again in dichloromethane with a S/C of 200 and in the presence of pyridine-N-oxide. As seen in Table 2 the enantioselectivity and reaction rate are indeed higher in the presence of N-oxide.

The occurrence of a significant blank reaction gives an explanation for the necessary low substrate/catalyst ratios and for the frequent use of additives to improve the activity and enantioselectivity. Both methods enhance the rate of the epoxidation reaction and consequently the rate difference with the blank reaction. This is especially the case with sterically hindered substrates like trisubstituted olefins, e.g. 1-phenyl-1-cyclohexene, because they show a slow catalytic conversion in comparison with other substrates. In conclusion, every factor that can change the rate of the blank reaction and/or the rate of the epoxidation reaction, also influences the enantioselectivity of the reaction in addition to an obvious change in yield or conversion. Until now, this aspect has been neglected in enantioselective catalysis. Research efforts will be directed in the future towards conditions in which the contribution of a blank reaction is decreased or, if possible, inhibited completely. The use of a counter current membrane reactor using a Jacobsen-PDMS catalytic membrane might offer interesting prospects in this respect.¹⁰ Also, the ee of a reaction can be increased upon decreasing the reaction temperature^{6b} as blank reactions inherently possess higher activation energies than catalysed reactions.

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7. The epoxidation reactions in CH₂Cl₂ were carried out at 4°C in 22.5 ml solvent, with 2.235 mmol substrate and 3.351 mmol NaOCl (13% solution in water). The reactions in ether were carried out in 7.5 ml solvent with 0.745 mmol substrate and 1.117 mmol NaOCl. S/C is varied by changing the amount of catalyst at a constant quantity of 1-phenyl-1-cyclohexene. The results are obtained after 4 hours of reaction.
8. [NaOCl] solved in the organic phase can be held constant, because it is used in excess, and is combined in the rate constant.
9. $E_{e\text{calculated}} = 92 * \frac{k_{\text{catal}}}{k_{\text{catal}} + k_{\text{blank}}}$ with 92 the the highest ee obtained (S/C=15).
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