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The influence of solvent choice, acid activation and surfactant addition on the hydrolytic kinetic resolution (HKR) of terminal epoxides

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Abstract—The recently developed hydrolytic kinetic resolution (HKR) of epoxides catalysed by the Co-Jacobsen catalyst, is one of the most useful methods to obtain enantiomerically pure epoxides and/or diols. Several parameters can significantly influence the homogeneous reaction. Several factors including the used solvent, the activation of the catalyst and the use of surfactants, are investigated.
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1. Introduction

The recently developed hydrolytic kinetic resolution (HKR) of epoxides, catalysed by the Co(III)-Jacobsen catalyst, is one of the most elegant methods for the synthesis of both enantiomerically pure epoxides and diols.[1] Water is an extremely appealing reagent for the resolution of epoxides, since it does not generate any waste, it is cost effective, safe and environmentally benign.

The HKR is typically carried out using diethylether (Et_2O)[2] or tetrahydrofuran (THF)[3] as a solvent or under solvent-free conditions.[1] Prior to the reaction, the Co(II)-Jacobsen complex, which is catalytically inactive, has to be activated through a one-electron oxidation to produce the active Co(III)-Jacobsen catalyst. Originally, the Co(II)-complex was activated ex situ through oxidation of the complex with acetic acid dissolved in toluene.[1] Lately however, it has been reported that in situ activation of the Co(II)-Jacobsen complex in the presence of epoxide is possible. The use of acetic acid[4] is an option, but it was shown recently that the use of electron-deficient aromatic acids afforded better results.[5]

During the reaction, the immiscibility of certain epoxides with the water used in the HKR can pose problems with regard to mass transfer. However, it is stated in literature that the addition of (±)-1,2-epoxyhexane rendered the reaction mixture homogeneous.[1]

These factors, which influence the activity and selectivity of the HKR reaction, are investigated using 1,2-epoxyhexane and styrene oxide as test substrates. Different solvents are used in the HKR of 1,2-epoxyhexane to select the optimal solvent. The method of catalyst activation and the influence of the addition of a surfactant to the reaction mixture is investigated for the HKR of styrene oxide under solvent-free conditions.

2. Results and discussion

The possibility to use Et_2O[2] or THF[3] as a solvent in the HKR of epoxides has been suggested. Nevertheless, use of other solvents for the HKR could be very interesting. The results for 1,2-epoxyhexane are shown in Figure 1. Figure 1 clearly shows that besides Et_2O the use of IPA also resulted in good reactivity and selectivity. All other tested solvents exhibit a significantly lower reactivity and besides THF, toluene and hexane, they also exhibit a significantly lower ee for the formed diol. The enantioselectivities of the remaining epoxides cannot

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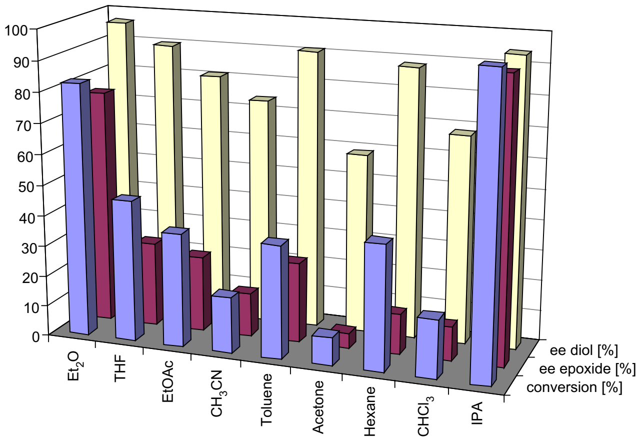

Figure 1. Conversions and selectivities for the HKR of 1,2-epoxyhexane in different solvents (S/C = 100, $H_2O/S = 0.56$ at rt after 24 h).

be compared because of the conversion dependency of the ee of the epoxide.

Use of IPA in the HKR of epoxides offers the advantage that the reaction mixture becomes one-phase since the water dissolves completely in the IPA solution, whereas use of Et_2O results in a two-phase system. This is one of the reasons why the reaction in IPA proceeds faster than the reaction in Et_2O. A disadvantage of the use of IPA as solvent is the faster deactivation of the Co(III)-Jacobsen catalyst compared to Et_2O, but the deactivated Co(II)-Jacobsen catalyst can be easily reactivated by acid treatment in the presence of air.

Besides IPA several other alcohols were screened, namely methanol (MeOH), ethanol (EtOH) and *n*-propanol (PrOH). Use of these primary alcohols as solvents resulted in the formation of the corresponding β-hydroxyethers instead of the desired diol (Fig. 2). Primary alcohols are used as the nucleophile in this case. Use of IPA as solvent on the other hand resulted in the formation of the desired alcohol and formation of the corresponding β-hydroxyether was not observed. The formation of the hydroxyethers proved to be regioselective, since only the formation of the 1-alkoxy-2-hydroxy products was observed. The reactions with the different alcohols furthermore revealed that the reaction rate decreased with increasing chain length of the primary alcohol (Fig. 3).

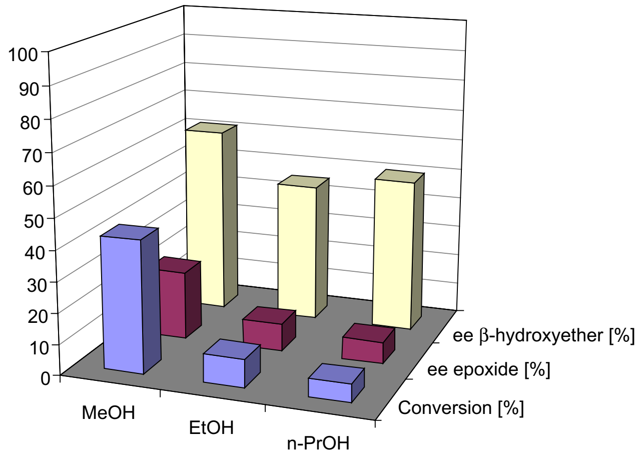

Figure 3. Conversion, ee of the epoxide and of the β-hydroxyether for 1,2-epoxyhexane in different primary alcohols after 24 h.

As mentioned earlier, the inactive Co(II)-Jacobsen catalyst has to be activated via acid treatment in the presence of air to the active Co(III)-complex. Four aromatic acids, namely benzoic acid (BA), 4-toluic acid (4-TA), 4-fluorobenzoic acid (4-FBA) and 4-nitrobenzoic acid (4-NBA), were tested in the in situ activation of the Co(II)-Jacobsen catalyst for the HKR of styrene oxide and the obtained results are shown in Figure 4 (conversion) and Table 1 (enantioselectivities).

Figure 4 confirms the results obtained by Liu et al.[5] The in situ activation by 4-TA clearly affords the slowest reaction, while the activation by the two aromatic acids with an electron withdrawing group in the *para*-position shows the highest reaction rate, with 4-NBA the most

Table 1. Obtained ee for styrene oxide and 1-phenyl-1,2-ethanediol for different aromatic acids after 4 h

Acid	$Ee_{epoxide}$ (%)	Ee_{diol} (%)
BA	53	96
4-TA	45	97
4-FBA	71	96
4-NBA	84	95

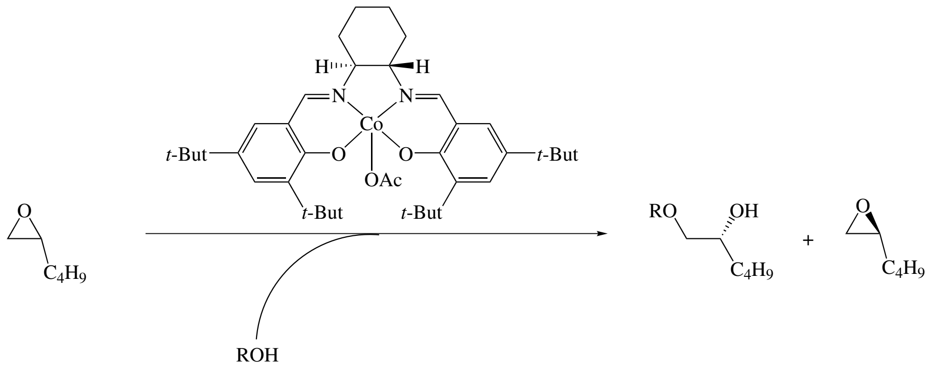

Figure 2. Formation of β-hydroxyethers through ARO with primary alcohols.

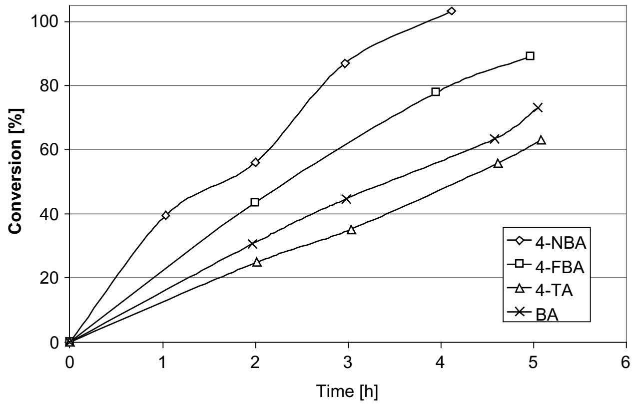

Figure 4. Conversion as a function of time for the HKR of styrene oxide with the catalyst activated by means of four different aromatic acids.

reactive. The rate enhancing effect of electron deficient acids can be ascribed to the fact that the activation of the nucleophile by the Co-Jacobsen complex occurs more rapidly in the presence of these acids. Indeed, they draw electrons away from the Co centre, making it more susceptible to nucleophilic attack.

The immiscibility of certain epoxides with the water used in the HKR can pose problems with regard to mass transfer. Tokunaga et al. stated that the addition of (±)-1,2-epoxyhexane rendered the reaction mixture homogeneous.[1] Several surfactants (Fig. 5) were screened in the HKR of styrene oxide to determine whether they had a beneficial effect on the reaction rate. Figure 6 shows the conversions as a function of time for the different surfactants. None of the tested surfactants increased the reaction rate of the HKR of styrene oxide. In fact, Brij 30 was the only surfactant, which did not result in a decreased reaction rate. All other surfactants had an unfavourable effect on the reaction rate, possibly attributable to the drastic increase in viscosity of the reaction mixture. The ionic bis-(2-ethylhexyl)-sulfosuccinate sodium salt afforded the worst results in combining the lowest conversion after 4 h and the lowest enantioselectivity (Table 2). The lower enantioselectivity can possibly be explained by an interaction between the ionic surfactant and the Co-Jacobsen catalyst.

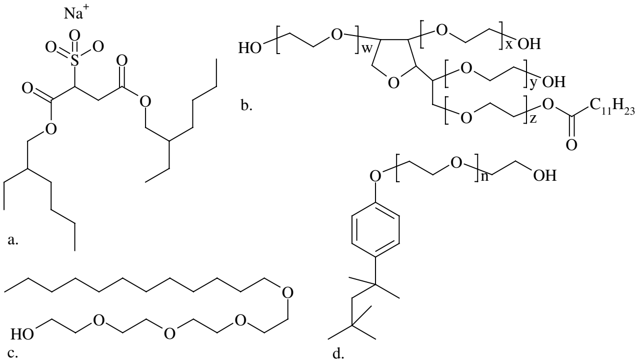

Figure 5. Different surfactants [(a) bis-(2-ethylhexyl)-sulfosuccinate sodium salt, (b) Tween 20 ($w + x + y + z = 20$), (c) Brij 30, (d) Igepal CA 630 ($n = 8$)] used in the HKR of styrene oxide.

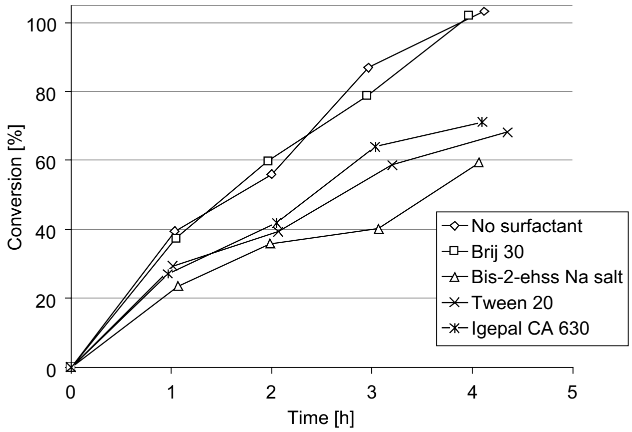

Figure 6. Comparison of the conversion obtained in the HKR of styrene oxide after the addition of different surfactants.

Table 2. Obtained ee for styrene oxide and 1-phenyl-1,2-ethanediol for the different surfactants after 4 h

Surfactant	$Ee_{epoxide}$ (%)	Ee_{diol} (%)
—	84	95
Brij 30	81	95
Bis-(2-ethylhexyl)-sulfosuccinate sodium salt	24	77
Tween 20	48	93
Igepal CA 630	53	93

3. Conclusion

Solvent screening revealed that besides Et_2O, IPA was also a suitable solvent for the HKR of epoxides. The use of IPA as a solvent increased the reaction rate compared to Et_2O. In contrast to the other alcohols tested, no formation of the corresponding β-hydroxyether was observed. Use of IPA did result in a faster deactivation of the catalyst, but re-activation of the catalyst by acid treatment is possible. The best results for the in situ activation of the catalyst were obtained using electron deficient aromatic acids. In an attempt to solve the problems with the immiscibility of water and the epoxide under solvent-free conditions, several surfactants were tested, but none of these afforded good results.

4. Experimental

4.1. Materials

The commercially available reagents (1,2-epoxyhexane (Acros Organics, 97%) and styrene oxide (Acros Organics 98%) were used without further purification. The different solvents were bought from Merck, except tetrahydrofuran, ethyl acetate (Acros Organics) and toluene (Aldrich); all solvents were used without further purification. The Co-Jacobsen catalyst was bought from Strem Chemicals.

4.2. General method

Reactions were carried out in stainless steel reactors (Premex) with a volume of 100 mL and equipped with a mechanical stirrer (1100 rpm). Experiments were performed on a 20 mL scale and samples were analysed[6] via GC. The efficiency of the catalyst is described through the conversion and the enantiomeric excess (ee). A kinetic resolution reaction has a maximum conversion of 50%, since only one enantiomer reacts. All conversions are therefore rescaled to a 100% scale.

4.3. HKR of 1,2-epoxyhexane

A mixture of (*S*,*S*)-Co(II)-Jacobsen (0.1 g, 0.17 mmol) and acetic acid (20.4 mg, 0.34 mmol) in toluene (3 mL) was stirred under air for 2 h at room temperature. The solvent was removed under reduced pressure. Afterwards, 0.1 g (0.17 mmol) of the activated catalyst was added to the reactor and subsequently 1,2-epoxyhexane (1.6 g, 16 mmol), water (0.16 g, 8.9 mmol) and 20 mL solvent were added. The reactions were carried out at room temperature. The conversion and the enantiomeric excess (ee) were determined via GC analysis.

4.4. HKR of styrene oxide

The (*S*,*S*)-Co(II)-Jacobsen (0.5 g, 0.8 mmol) catalyst was put directly into the reactor. Subsequently, the acid (1.6 mmol), styrene oxide (21 g, 175 mmol) and water (6 g, 333 mmol) were added. For the surfactant experiments 20 mol % (to styrene oxide) of the surfactant was added. The reactor was pressurised with compressed air to 6 bar and conversions and ee were determined via GC analysis.

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