Changes of enantioselectivity with the substrate ratio for the addition of diethylzinc to aldehydes using a catalyst coupled to a soluble polymer

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α,α-Diphenyl-L-prolinol, when coupled to a polymer soluble in organic solvents, gives surprising results for the addition of diethylzinc to aldehydes. For benzaldehyde, the enantiomeric excess strongly depends on the initial substrate ratio: an excess of diethylzinc yields (S)-1-phenylpropanol with up to 80% ee, while an excess of benzaldehyde leads to the (R)-1-phenylpropanol with up to 50% ee. The kinetic properties of the catalyst and the results with other aldehydes are also described. The polymer 1 is a copolymer of octadecyl methacrylate and 2-hydroxyethyl methacrylate.
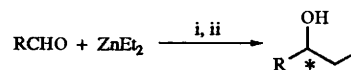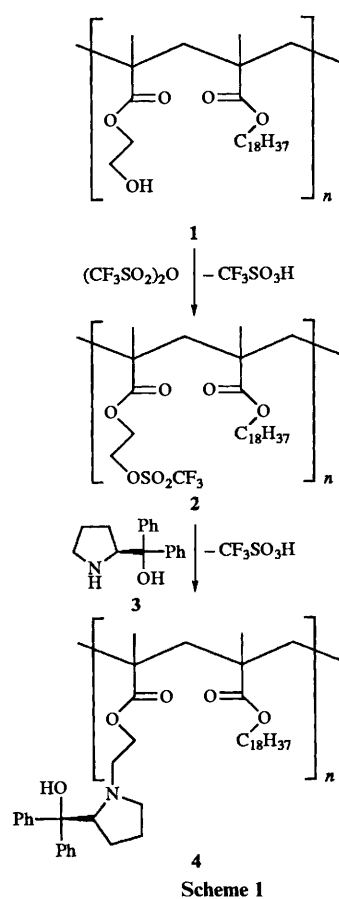
The enantioselective addition of organozinc compounds to aldehydes is one of the best known reactions in catalytic asymmetric synthesis.[1] The great number of catalysts described in the literature makes it possible to perform this reaction under a wide range of reaction conditions. Since the reaction mechanism using chiral amino alcohols such as (−)-3-*exo*-(dimethylamino)isoborneol[2] or *N*-methyl-α,α-diphenyl-L-prolinol[3] as catalysts is well known, we chose the addition of diethylzinc to aldehydes as a model system to perform an enantioselective reaction in a continuously operated membrane reactor.[4] As demonstrated for enzymatic co-factors like NADH[5] and ferrocene[6] along with catalysts for the co-factor regeneration,[7] the coupling of these molecules to a soluble polymer offers a way to increase the total turnover number by retaining them using an ultrafiltration membrane within a reactor. In this paper, we present some surprising results, found during the kinetic characterization of the polymer-enlarged catalyst 4 synthesized for this application.

Results and discussion

α,α-Diphenyl-L-prolinol 3 and a methacrylate copolymer 1 were used to synthesize our desired catalyst 4. The co-polymer 1 was made from 2-hydroxyethyl methacrylate and octadecyl methacrylate and had a molecular weight of about 96 000 u. It showed an OH-number of 42 mg $KOH/g_{polymer}$, which is equivalent to 0.75 mmol of hydroxy groups per g of polymer.[8] The octadecyl moiety is responsible for the solubility of the polymer in organic solvents such as hexane, toluene, dichloromethane, diethyl ether etc. and its insolubility in both acetone and water. The 2-hydroxyethyl methacrylate moiety is used to immobilize the α,α-diphenyl-L-prolinol, after activation of the hydroxy function with trifluoromethanesulfonic anhydride, to give the desired catalyst 4 (Scheme 1).

To investigate the catalytic properties of the polymer 4 we varied the quantities of $ZnEt_2$ and benzaldehyde (R = Ph, Scheme 2) from 1 to 10 mmol in 2.5 mmol increments. In all experiments, we used the polymer 4 (200 mg), which corresponded to 0.1 mmol α,α-diphenyl-L-prolinol, calculated from elemental analysis. During the reaction which was allowed to proceed for 19.5 h, aliquots were removed to measure the rate of conversion and the value of the enantiomeric excess (ee).

We found that the ee was highly dependent upon the starting ratio of the substrates (Fig. 1). Thus, for reactions with an excess of $ZnEt_2$ in relation to benzaldehyde, (S)-1-phenylpropanol was formed with an ee of up to 80% (Fig. 1). Soai and co-workers reported a compound of similar configuration in their

work with *N*-methyl-α,α-diphenyl-L-prolinol as the catalyst.[3] With an excess of benzaldehyde, however, (R)-1-phenylpropanol was formed with an ee of up to 50% (Fig. 1). With equimolar proportions of the substrates, we found that the enantiomeric excess was unpredictable. The different values found for one ratio of substrates are related to different absolute amounts of reagents, *e.g.* 1 mmol:1 mmol or 5 mmol:5 mmol, respectively.

As indicated in Fig. 1, the ee changes with time (conversion). Fig. 2 shows some selected examples, marked by the arrows in
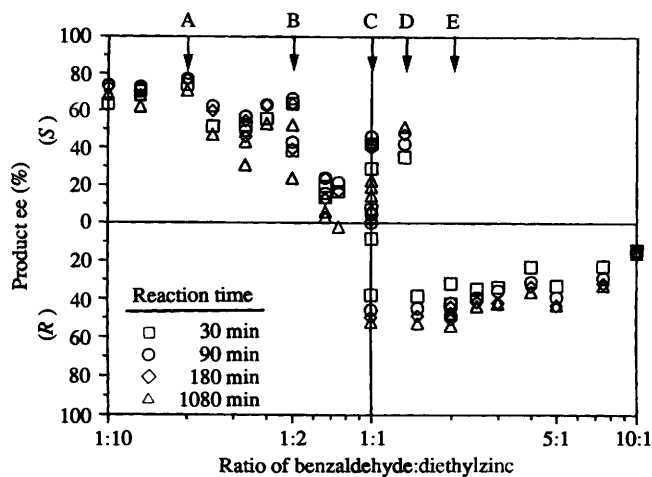
Scheme 1

Scheme 2 *Reagents:* i, Polymer 4; ii, H^+-H_2O

Fig. 1 Dependence of the ee of the product alcohol on the ratio of the starting substrates
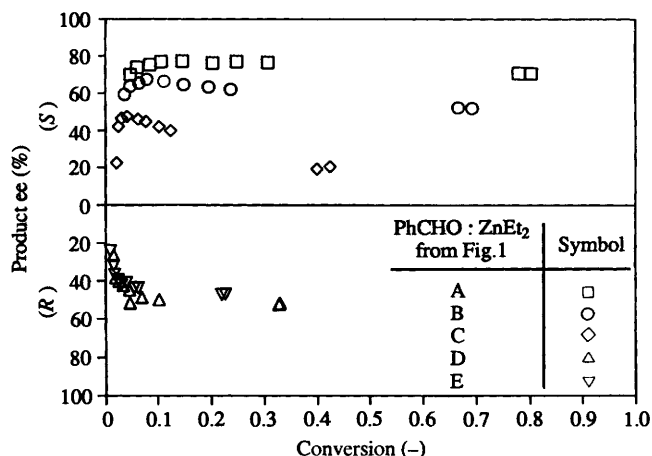
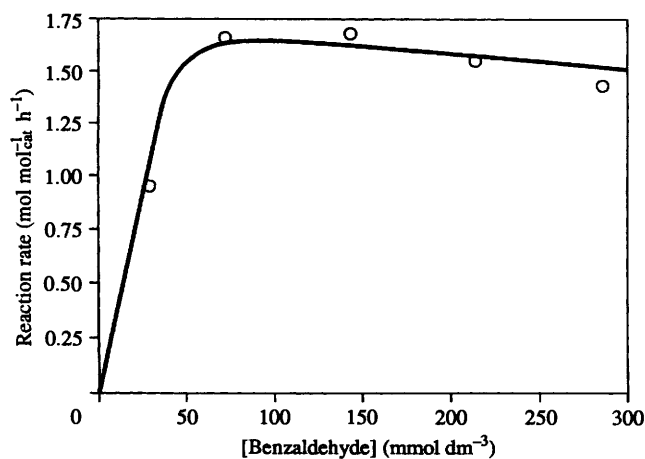**Fig. 2** Dependence of the ee of the product alcohol on conversion at various initial substrate ratios

Fig. 3 Dependence of the rate of reaction as a function of [PhCHO], for a constant value of [ZnEt$_2$] (143 mmol dm^{-3})
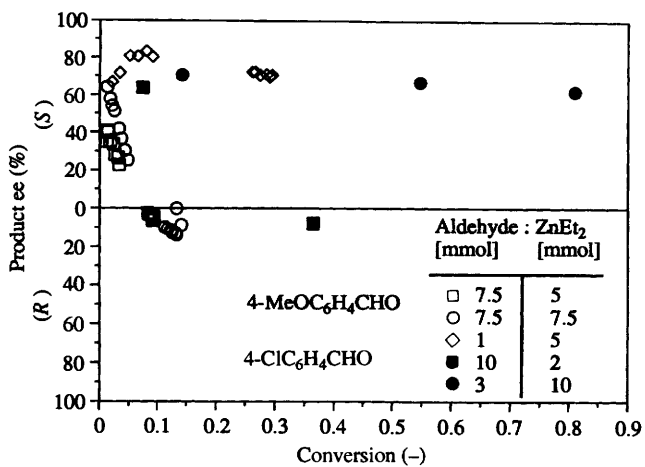

Fig. 4 Dependence of ee on conversion of the aldehydes 4-ClC$_6$H$_4$CHO and 4-MeOC$_6$H$_4$CHO

Fig. 1 (A–E). The conversion rates shown in Fig. 2 were calculated for benzaldehyde, although an excess of benzaldehyde was partly used. This was done in order to enable a better comparison of the results, as shown in Figs. 2 and 4. In these cases, the conversion seems to be very low since a quantitative conversion of the aldehyde was impossible due to the stoichiometry of the reaction. The highest conversion achieved was about 0.95 using a 10-fold excess of ZnEt$_2$ (data not included in Fig. 2). At conversions up to 0.1 the ees were lower than for higher conversions *i.e.* the ees were seen to increase throughout the reaction, except where an equimolar ratio of reagents was used (*e.g.* 5 mmol : 5 mmol, Fig. 1, C). In this case, the ees show a maximum at low conversion.

The chemoselectivity also showed a dependence upon conversion. The side product, benzyl alcohol, is formed from the known reduction of benzaldehyde with diethylzinc.[2] We found that the reaction proceeds with low chemoselectivity between 0.5 and 0.9 and this increases as the reaction proceeds. At conversion rates between 0.05 and 0.1 the selectivity was > 0.9, a value maintained during the rest of the reaction. In general, an excess of ZnEt$_2$ gave a greater chemoselectivity.

In contrast to the results of Noyori and co-workers,[2] we found a very strong dependence of the initial reaction rate on the starting concentration of ZnEt$_2$ as calculated from the amount of 1-phenylpropanol formed. For the pseudo first order rate constant at a fixed benzaldehyde concentration of 143 mmol dm^{-3}, we found the rate to be 11.0 ± 0.7 µmol h^{-1} dm^{-3}. For benzaldehyde as substrate we found that the initial reaction

rate was independent of the starting concentration over a wide range (Fig. 3). This type of saturation kinetics is similar to a Michaelis–Menten kinetics found for enzymes or Hougon–Watson kinetics for heterogeneous reactions.[9]

Addition of ZnEt$_2$ to other aldehydes was then investigated, the results for which are summarized in Table 1. Three types of behaviour were noted, depending upon the aldehydes employed. (1) The addition product of 4-methylbenzaldehyde, cinnamaldehyde and 2-chlorobenzaldehyde showed no significant dependence on the ratio of aldehyde : ZnEt$_2$. (2) 4-Chlorobenzaldehyde and 4-methoxybenzaldehyde gave the expected (*S*)-alcohols with up to 45 to 70% ee when an excess of ZnEt$_2$ was employed, whilst with an excess of the aldehyde, (*R*)-alcohols with very poor ees (1–14% ee) were obtained. Results for the dependence of the ee on the amount of the substrate converted are much more interesting. The most interesting and descriptive results are depicted in Fig. 4. At the start of the reaction, the product alcohols were predominately of the (*S*)-configuration and this was found to be independent of the ratio of the aldehyde : ZnEt$_2$. However, when the aldehyde was used in either an equimolar ratio or in excess, the starting ee was seen to decrease throughout the reaction as more of the (*R*)-alcohol was synthesized. By the end of the reaction, the (*R*)-alcohols predominated (Fig. 4). (3) One aldehyde, 2-methoxybenzaldehyde, gave only (*R*)-1-(2-methoxyphenyl)propanol (ee 52%); its formation was independent of the starting substrate ratio (Table 1). To determine the influence of the 2-methoxy group, we used *N*-methyl-α,α-diphenyl-L-prolinol as a catalyst and obtained, as reported for a number of aldehydes,

Table 1 Results for the addition of $ZnEt_2$ to various aldehydes using the polymer 4

Aldehyde	Aldehyde (mmol)	$ZnEt_2$ (mmol)	t/h	Ee	Yield	Conf.
4-ClC$_6$H$_4$CHO	20	5	48	1	0.24	R
	10	3	48	8	0.22	R
	10	2	48	29	0.12	S
	5	20	48	45	0.95	S
	2	10	48	62	0.80	S
	1	8	48	63	0.85	S
4-MeC$_6$H$_4$CHO	5	2	48	68	0.16	S
	3	1	48	67	0.04	S
	12	2	96	40	0.08	S
	1	3	48	73	0.34	S
	1	5	48	76	0.50	S
	2	12	48	57	0.77	S
4-MeOC$_6$H$_4$CHO	7.5	5	27	7	0.08	R
	7.5	7.5	27	14	0.13	R
	1	5	27	70	0.29	S
2-ClC$_6$H$_4$CHO	15	3	48	13	0.15	S
	5	2	24	76	0.34	S
	3	15	48	59	0.90	S
	2	10	24	80	0.90	S
2-MeOC$_6$H$_4$CHO	15	10	48	53	0.18	R
	15	3	48	19	0.01	R
	10	15	48	52	0.48	R
	3	15	48	32	0.66	R
	1	5	5	88	0.75	S[a]
PhCH=CHCHO	15	3	72	17	0.03	S
	5	2	24	70	0.09	S
	3	15	72	67	0.89	S
	2	10	24	75	0.61	S

[a] N-Methyl-α,α-diphenyl-L-prolinol was used instead of the polymer 4.

the expected (S)-alcohol (Table 1). This result indicates, that the 2-methoxy group exerts no influence. On checking whether N-methyl-α,α-diphenyl-L-prolinol produced the (R)-alcohol with an excess of benzaldehyde, we obtained only the customary (S)-product. Both results indicate that coupling the catalyst to the soluble polymer is the main reason for the observed effects.

As far as we know, this is the first time that a reversal of enantioselectivity has occurred as a result of a change in the initial substrate ratio, although an increase of ee from 80 to 95% with an increasing excess of $ZnEt_2$ using (1R,2S)-N-isopropylephedrine as the catalyst has been described.[10] Obviously, these effects strongly depend on the structure of the catalyst used since for (−)-3-exo-(dimethylamino)isoborneol, no such effect has been observed.[2] Although the polymer-enlarged catalyst 4 and (1R,2S)-N-isopropylephedrine have in common three different substituents at the nitrogen, whereas (−)-3-exo-(dimethylamino)isoborneol has only two, the relevance of this feature is not known. These findings suggest that the substitution pattern of the nitrogen atoms heavily influences the enantioselectivity when using this type of ligand for the addition of diethylzinc to aldehydes. Attempts to explore the use of less-bulky analogues of the present polymer-enlarged catalyst failed because of their insolubility in hexane.[11] However, the differences in the behaviour of the various aldehydes used indicated, that their structure also plays an important role. These results, especially the dependence of the ee on the substrate ratio and the dependence of the initial reaction rates on the $ZnEt_2$ concentration, show that the well known reaction mechanism stated by Noyori[2] has to be modified for the polymer-enlarged catalyst 4. The dependence of the ee on the conversion of 4-chloro- and

4-methoxy-benzaldehyde, makes it likely that the generated sec-alcohols are responsible for the change of the enantioselectivity; this occurs as a result of their co-complexation to the catalytic active species which changes its catalytic properties. This may also occur with the ester groups of the polymer. For benzaldehyde, the co-complexation is strong enough to change the enantioselectivity almost immediately, while in the case of the two other aldehydes, this only occurs at higher concentrations. In the presence of an excess of $ZnEt_2$ the co-complexation is inhibited. With aldehydes which do not exhibit a dependence on the initial substrate ratio, no co-complexation occurs. Using 2-methoxybenzaldehyde the co-complexation is able to change to enantioselectivity immediately.

In spite of the above arguments, it is still possible that the change of enantioselectivity may arise as a result of kinetic effects, thus with only small amounts of $ZnEt_2$ it may be that the regeneration of the reactive species in the Noyori cycle is only partial, so that other complexes similar to those already present are able to transfer the ethyl groups and give rise to the change of enantioselectivity.

Experimental

General

α,α-Diphenyl-L-prolinol [(S)-(−)-diphenylpyrrolidin-2-yl-methanol] was obtained from Fluka, Buchs, Switzerland. The co-polymer was a gift from Bayer AG, Germany. Hexane was dried over P_4O_{10}, distilled and then dried over sodium and then redistilled. All other chemicals were of the highest purity commercially available.

Conversion, chemoselectivity and ee were determined by means of gas chromatography (GC) using a commercially

available permethylated β-cyclodextrin column from CS-Chromatographic Service, Langerwehe, Germany.[12] The column (50 m × 0.32 mm diam.) used hydrogen as the carrier gas (0.9 bar) with a split ratio of 1 : 75. The configuration of the synthesized alcohols was determined by the sign of the optical rotation.

Poly(1-{[2-(hydroxydiphenylmethyl)pyrrolidin-1-yl]ethoxycarbonyl}-1,3-dimethyl-3-(octadecyloxycarbonyl)tetramethylene) 4

Because triflates are moisture-sensitive, the reaction was carried out under an atmosphere of argon. Polymer 1 (1 g, 0.75 mmol of OH-groups) was dissolved in dried hexane (100 cm^3) and then the hexane was reduced by 50 cm^3 (by distillation) to remove all traces of water. After addition of dried NEt$_3$ (0.44 cm^3, 3.1 mmol) the solution was cooled to 0 °C. Trifluoromethanesulfonic anhydride (0.5 cm^3, 3 mmol) was then added and the resultant solution was stirred for 16 h at 0 °C, followed by the addition of α,α-diphenyl-L-prolinol (760 mg, 3 mmol). The mixture was refluxed for 24 h, after which it was washed twice with a HCl solution (1 mol dm^{-3}), then twice with dilute aqueous NaHCO$_3$, and finally dried (Na$_2$SO$_4$). The polymer was precipitated with acetone, recrystallized twice from hot acetone and dried in vacuo (18 h, 10^{-3} mbar); 827 mg (70%) (Found: C, 73.6; H, 11.0; N, 0.8).

Addition of ZnEt$_2$ to the aldehydes using the polymer 4

This reaction was carried out under an argon atmosphere. The polymer 4 (200 mg, approx. 0.1 mmol α,α-diphenyl-L-prolinol) was dissolved in hexane (30 cm^3) of which 10 cm^3 was distilled off to remove all traces of water. ZnEt$_2$ (1 mol dm^{-3}; hexane) and the aldehyde were added in appropriate quantities (see Fig. 1 and Table 1). If necessary, aliquots of 1 cm^3 were removed and hydrolysed with concentrated aqueous NH$_4$Cl for GC analysis.

N-Methyl-α,α-diphenyl-L-prolinol

To a boiling solution of α,α-diphenyl-L-prolinol (2 g, 7.4 mmol), water (0.5 cm^3) and formic acid (98%, 2.35 cm^3), formaldehyde (37%, 1.69 cm^3, 20.8 mmol) was added over a period of 5 min followed by additional heating for 4 h. The mixture was adjusted to pH 11, after which it was extracted with dichloromethane (3 × 50 cm^3). The combined organic phases were dried (Na$_2$SO$_4$) and evaporated and the resultant residue was recrystallized from hexane and fully dried in vacuo (18 h, 10^{-3} mmbar) to give the title compound; 1.12 g (57%); mp 68 °C; δ$_H$(200 MHz; CDCl$_3$) 1.6–2.0 (4 H), 1.85 (3 H, s), 2.4–2.5 (1 H,

m), 3.05–3.15 (1 H, m), 3.6–3.7 (1 H, dd, J 9.0 and 9.1), 4.8 (1 H, b) and 7.1–7.7 (10 H, m); δ$_C$(50 MHz; CDCl$_3$) 24.09 (1 C), 29.94 (1 C), 43.03 (1 C), 59.19 (1 C), 71.98 (1 C), 77.49 (1 C), 125.47 (2 C), 125.51 (2 C), 126.16 (2 C), 128.06 (4 C), 146.76 (1 C) and 148.31 (1 C).

Addition of ZnEt$_2$ to 2-methoxybenzaldehyde using N-methyl-α,α-diphenyl-L-prolinol

Following the same procedure as stated above N-methyl-α,α-diphenyl-L-prolinol (27 mg, 0.1 mmol) and 2-methoxybenzaldehyde (0.13 cm^3, 0.1 mmol) and a solution of ZnEt$_2$ (1 mol dm^{-3} in hexane; 5 cm^3) were used. After 5 h, the reaction mixture was hydrolysed with concentrated aqueous NH$_4$Cl and analysed by GC.

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