Pergamon

Tetrahedron: Asymmetry, Vol. 8, No. 20, pp. 3481–3487, 1997

Printed in Great Britain
PII: S0957-4166(97)00465-5
0957-4166/97 $17.00 + 0.00

A dimeric form of Jacobsen's catalyst for improved retention in a polydimethylsiloxane membrane

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Abstract: A dimeric form **1** of Jacobsen's catalyst was synthesized for better steric occlusion in a polydimethylsiloxane membrane. In homogeneous conditions, the dimer is about as active and enantioselective as Jacobsen's catalyst itself. The relationship between leaching of the complex out of the membrane on one hand and the solubility of the complex and the swelling of the membrane in the solvent used on the other, showed that leaching could be avoided only if low solubility was combined with low swelling or in the case of complete insolubility. As the dimer is less soluble and larger than the monomeric form, this form leaches less. The yields and enantioselectivities of the heterogenised system are comparable to those of the homogeneous monomer. © 1997 Published by Elsevier Science Ltd

Heterogenisation of enantioselective catalysts is advantageous as it allows easy removal of the catalyst from the reaction mixture, as well as operation in a continuous mode. Moreover, a larger number of solvents becomes available as only reactants and products need to be solubilised. When heterogenised as a catalytic membrane, a membrane reactor makes the use of solvents redundant and even allows reactive separation of substrate and products.

Reported attempts to heterogenise Jacobsen's catalyst [(N,N′)-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediamine]Mn(III)chloride, a chiral (salen)Mn(III) complex for the epoxidation of alkenes,[1] consist in the chemical linking of the complex to a polymer chain,[2,3] the steric occlusion in the nano-sized cages of cubic[4] and hexagonal[5] Y-type zeolites and by "Van der Waals wrapping" in the elastomer network of a polydimethylsiloxane (PDMS) membrane.[6,7] Chemical binding in a polymer invariably shows low enantioselectivity, possibly resulting from structural or conformational changes of the complex when linked to the support.[8] *In situ* synthesis of chiral (salen)Mn(III) complexes in zeolitic cages proves the validity of the "ship-in-a-bottle" concept, but fails to enhance the enantioselectivity and resistance to self-degradation above the homogeneous level.[4,5] Physical entrapment in the PDMS membrane shows mostly unaltered enantioselectivity and good stability. Depending on the nature of the solvent, complex leaching from the membrane seems to be possible.[6,7]

As only a limited number of substrate–solvent couples qualify, an attempt is reported to improve steric retention of Mn(III)(salen)-type complexes in PDMS membranes. We therefore synthesised a dimeric complex, **1**, which we expect to show improved retention in a PDMS membrane.

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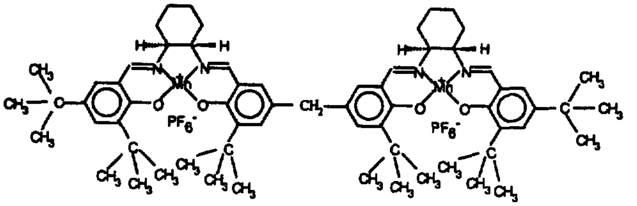
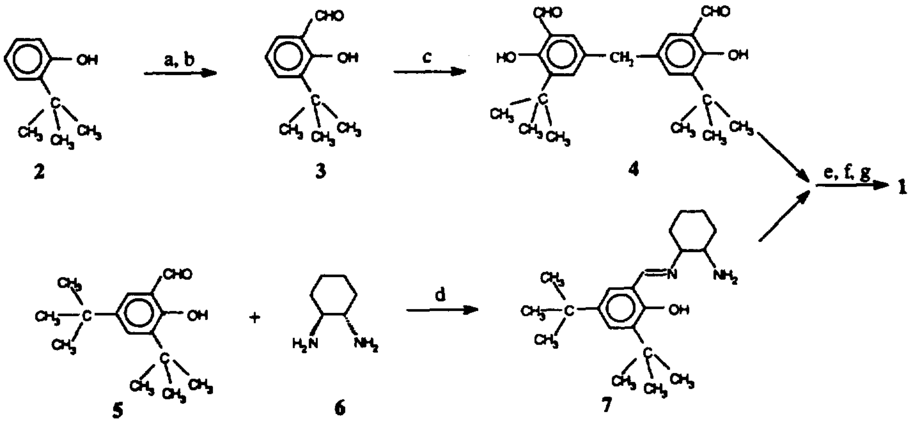


1

Conceptual synthesis of 1

The synthesis sequence of the dimer is shown in Scheme 1. 2-*tert*-Butylphenol **2** was converted through a Grignard reaction with paraformaldehyde to 3-*tert*-butyl-2-hydroxybenzaldehyde **3**[9] which in a successive step was converted to a dialdehyde **4** by treating it with trioxane and sulfuric acid in an acetic acid solution.[10] The dialdehyde was purified by column chromatography on silica gel. A chiral Schiff base **7**[11] was formed between 3,5-di-*tert*-butylsalicylaldehyde **5** and an excess of (1S,2S)-(+)-1,2-diaminocyclohexane **6**. The dimer **1** was finally formed out of **4** and **7** in three steps: first a Schiff base was formed between **4** and **7**, then metallated with Mn(II) and finally oxidized to Mn(III) by ferrocenium hexafluorophosphate. The side product, ferrocene, was removed by washing with hexane.[12]



(a) C_2H_2Br, **Mg in ether, RT; (b) paraformaldehyde, HMPA in toluene, 80°C; (c) trioxane in glacial acetic acid, conc.** H_2SO_4, **90–95°C under** N_2; **(d) in EtOH, RT; (e) in deaerated** CH_3CN, **RT; (f)** $Mn(OAc)_2.H_2O$ **in deaerated** CH_3CN, **RT; (g) + ferrocenium hexafluorophosphate in deaerated** CH_3CN, **washed with hexane.**

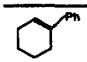
Scheme 1.

Homogeneous asymmetric epoxidation of olefins catalyzed by the dimeric Jacobsen complex 1

The activity and the enantioselectivity of the synthesized dimer were examined with 1-phenyl-1-cyclohexene, 1,3-cyclo-octadiene and *trans*-β-methylstyrene as substrates and NaOCl as oxidant in dichloromethane. These reactions were also carried out with Jacobsen's catalyst using the same amount of active metal centres. The results are shown in Table 1. The activity and enantioselectivity of the two catalysts seem to be comparable.

The activity of a salen complex can decrease rapidly by formation of a non-active μ-oxo-dimer, formed between the active (salen)Mn^{IV}=O complex and an Mn^{III} complex.[13] In the case of an Mn–salen complex with methyl groups at the 5- and 5′-positions, the catalyst is often inactive already after 35–40 turnovers.[1b] To study a possible extended activity of the dimeric form of Jacobsen's catalyst,

Table 1. Asymmetric epoxidation[a] of different substrates with the dimer and Jacobsen's catalyst

	dimer			Jacobsen's catalyst		
	Y[b] (%)	ee[c] (%)	TON[d]	Y[b] (%)	ee[c] (%)	TON[d]
	6.6	74.9	13.4	10.1	69.1	23.9
	10.5	28.5	19.0	17.0	24.5	30.2
	5.9	27.0	12.6	5.7	28.8	10.3

(a) Substrate / Mn = 200; other reaction conditions: see experimental. (b) Yield = conversion to oxidation products * selectivity of the epoxide (c) Measured after 7 hours of reaction by GC analysis over a chiraldex G-TA column. (d) Turnover number: total moles of oxidised olefin per mole of active metal centre.

Table 2. Swelling of the membrane, leaching from the membrane and solubility for Jacobsen's catalyst and the dimer in different solvents

	leaching (%)		solubility (mg/ml)		swelling (%)	
	Jacobsen	dimer	Jacobsen	dimer	Jacobsen	dimer
chlorobenzene	100	56	21	10	173	189
diethylether	90	44	7	6	240	261
dichloromethane	84	58	156	95	150	196
acetone	62	33	90	31	15	11
acetonitrile	54	16	154	57	11	11
methanol	54	30	162	68	2	2
heptane	12	19	0.3	0.5	235	224

the epoxidation cycle was repeated several times by adding new substrate and new oxidant. Complete conversion was reached each time. The reaction was performed at room temperature in dichloromethane with 1-phenyl-1-cyclohexene as substrate. After 10 cycles, both the dimer and the Jacobsen's catalyst had equal activity and more than 300 turnovers already. This agrees with Skarzewski *et al.*,[14] who also observed a rather high resistance to degradation when NaOCl is used as oxidant for salen complexes with *tert*-butyl groups at the 5- and 5′-positions.

Inclusion of the dimer in a polydimethylsiloxane (PDMS) membrane

A PDMS membrane was formed in a Pt catalysed hydrosilylation reaction between a prepolymer and a crosslinker. To include the dimer in a PDMS membrane, the complex was added to the synthesis mixture of the membrane. After evaporation of the solvent, the complex is retained in the crosslinked membrane partially sterically, partially by physical interactions.

To gain better insight into the factors that play a role in the leaching of the complex, some comparative experiments were done between the dimer and the Jacobsen complex (Table 2). The swelling of the membrane, in which the complex is included, and the solubility of the complexes were investigated in several solvents at 25°C. These results are then compared with the leaching of the complexes from the membrane in those solvents. The degree of leaching expressed as the percentage of the complex in solution after stirring in the solvent or during a reaction, was determined by UV absorption at 325 nm.

As can be seen in Table 2, leaching of the complexes depends on a combined effect of the swelling of the PDMS membrane and the solubility of the complex in the solvent used. For example, the Jacobsen complex significantly leaches (>80%) in solvents that cause a high degree of membrane swelling (>15%), such as chlorobenzene, diethylether and dichloromethane. When the complex hardly dissolves in the solvent, e.g. in heptane, even in swollen membranes leaching is absent. If the swelling is low, but the solubility of the complex is good such as for acetone, acetonitrile and methanol, a moderate degree of leaching is found (50–60%). To prevent leaching, insolubility of the complex in

Table 3. Leaching (%) of the complex in reaction conditions[a]

	trans-β-methylstyrene		1,3-cyclo-octadiene		1-phenyl-1-cyclohexene	
	dimer	Jacobsen	dimer	Jacobsen	dimer	Jacobsen
heptane	0.9	12.4	1.0	8.4	7.8	18.0
acetonitrile	8.7	19.5	7.4	14.3	38.1	51.9
chloorbenzene	22.1	78.3	17.8	75.7	-	-

(a) 0.6 vol% solution of the substrate in the solvent. Substrate / Mn = 25.

Table 4. Epoxidation of *trans*-β-methylstyrene with the dimer and Jacobsen's catalyst in heterogeneous (PDMS included) conditions with acetonitrile as solvent

	Dimer			Jacobsen's catalyst		
substrate	Y[b] (%)	ee (%)	TON[c]	Y[b] (%)	ee (%)	TON[c]
trans-β-methylstyrene	23.0	14.4	6.3	64.0	20.5	17.4
regeneration	17.0	15.8	4.8	27.6	10.6	7.5
blank[d]	3.0	15.0		4.0	16.0	

(a) Substrate / Mn = 25; other reaction conditions: see experimental. Measured after 24 hours of reaction by GC analysis over a chiraldex G-TA column. (b) Yield = conversion to oxidation products * selectivity of the epoxide. (c) Turnover number: total moles of reacted olefin per mole of active metal centre. (d) with a substrate/Mn ratio of 100.

the applied solvent or a combination of a low degree of swelling of the membrane and low solubility of the complex is necessary.

In general, the same relationship between leaching and solubility and swelling is found with the dimeric form of the Jacobsen complex. The dimer clearly leaches less than the corresponding monomeric Jacobsen complex as a result of a lower solubility and a better steric retention of the larger dimer. This correlation between leaching and solubility indicates the important role of the solubility of the complexes in the determination of the reaction conditions for catalysis with membrane-included complexes.

The next step was the study of the leaching under reaction conditions. Through the formation of an Mn–oxo species, the complex becomes more polar and therefore less soluble in apolar solvents such as heptane. Also the fact that the oxo-species takes a folded structure,[8] possibly giving a better retention, indicates that this leaching under reaction conditions can be different from the one determined in pure solvents. The results are shown in Table 3.

Both complexes obviously show a decreased degree of leaching under real reaction conditions. In the case of *trans*-β-methylstyrene and 1,3-cyclo-octadiene in heptane, less than 1% leaching is detected for both catalysts, which makes them good heterogeneous systems. In acetonitrile or chlorobenzene as a solvent or in the case of 1-phenyl-1-cyclohexene as a substrate, the dimer shows a much lower degree of leaching compared to Jacobsen's catalyst.

Heterogeneous epoxidation of olefins

Finally, the catalytic activity of the dimer included in the membrane was investigated. The rapid screening was done in a batch reactor with the catalytic membrane cut into 3–4 mm pieces. *trans*-β-Methylstyrene was taken as substrate and the reactions were performed in acetonitrile because higher conversions were realized in this solvent compared to heptane. The results are shown in Table 4.

In acetonitrile, some leaching occurs as seen in Table 3. The blank results give an estimation of the catalytic activity that can be attributed to leaching. Therefore, a complete regeneration of the PDMS-included complex will not be possible. As Jacobsen's catalyst leaches more than the dimer (19.5% compared to 8.7%), the higher yield obtained with the former catalyst in the first reaction is related to the substantial leaching of the complex (Table 3) during the first reaction. After the first regeneration reaction, the PDMS-included Jacobsen's catalyst has lost more of its activity compared to the heterogenised dimer.

Conclusions

The synthesis of a dimeric form of Jacobsen's catalyst resulted in a catalyst that in homogeneous conditions is about as active and enantioselective as Jacobsen's catalyst. In heterogeneous conditions, by inclusion in a PDMS membrane, the dimer leaches less than the original complex. It is still necessary to work in solvents in which the complex shows low solubility and to select conditions that limit membrane swelling.

Experimental

General

The ^{1}H NMR spectra were obtained on a 90 MHz Varian EM390 spectrometer. All signals were expressed as ppm downfield from tetramethylsilane, used as an internal standard (δ-value in $CDCl_3$). IR spectral measurements were carried out with a Nicolet 730 FT-IR spectrometer. UV-absorption measurements were performed on a UV/Vis spectrometer lambda 12. Gas chromatographic (GC) analyses were carried out on a Hewlett Packard 5890 instrument equipped with a FID detector, an HP 7673A control unit, an automatic sampler and injector, an HP 3392A integrator and a 30 m×0.32 mm Astec Chiraldex G-TA (G: γ-cyclodextrine; TA: trifluoroacetyl) column. Chromatographiegel C-560 (Chemie Uetikon) was used as an adsorbent for column chromatography.

*3-*tert*-Butyl-2-hydroxybenzaldehyde 3*

The literature procedure[9] was followed with some modifications. To a solution of Mg (4.9 g; 202 mmol) in 200 ml diethylether (dried with zeolite A), small amounts of ethylbromide (29.18 g; 268 mmol) dissolved in 40 ml diethylether were added. A small amount of I_2 was added to initiate the reaction. 2-*tert*-Butylphenol **2** (26.7 g; 178 mmol) in 50 ml diethylether was added dropwise at RT with stirring. After removal of the ether by distillation, toluene (1 l, dried with zeolite A), hexamethylphosphoramide (35.8 g; 200 mmol) and paraformaldehyde (15 g; 501 mmol) were added and the mixture was stirred at 80°C for 15 h. After cooling, the mixture was acidified with 10 vol% HCl and extracted with diethylether (3×300 ml). The combined extracts were washed with a saturated NaCl solution (100 ml) and dried over $MgSO_4$. After evaporation of the volatile products, the residue was purified on a silica column with a 1:1 dichloromethane:petroleum ether solvent mixture to give the pure aldehyde (7.6 g, 24%) as a yellow–white solid. ^{1}H NMR: 1.4 (s, 9 H), 6.9–7.9 (m, 3 H), 9.9 (s, 1 H), 11.9 (s, 1 H).

*5,5′-Methylene-di-3-*tert*-butylsalicylaldehyde 4*

A solution of **3** (5 g; 28.1 mmol) and trioxane (0.8 g; 8.85 mmol) in 20 ml of glacial acetic acid was heated to a temperature of 90–95°C under nitrogen atmosphere. 1 ml of a mixture of concentrated sulfuric acid and glacial acetic acid (1:45) was added dropwise. The temperature was maintained for 22 h while stirring was continued during the entire period. Subsequently, the reaction mixture was poured into 200 ml of ice–water and allowed to stand overnight. The precipitated solid was filtered and extracted twice with n-hexane (2×5 ml). The remaining solid was pulverised three times with diethylether (3×5 ml) and the ether solutions, with the tarry material, were decanted. Recrystallization from 7.5 ml acetone gave the pure dialdehyde. IR (KBr): 3445 (br), 2958 (s), 2916 (m), 2869 (m), 2745 (w), 1650 (s), 1438 (s), 1384 (m), 1363 (m), 1331 (m), 1268 (m), 1230 (m), 1205 (m), 1161 (m), 1028 (w), 980 (w), 933 (w), 890 (w), 773 (m), 752 (w), 709 (w), 523 (m) cm^{-1}; ^{1}H NMR: 1.4 (s, 18 H), 3.9 (m, 2 H), 7.1–7.4 (m, 4 H), 9.8 (m, 2H), 11.8 (m, 2 H).

Schiff base 7

A solution of (1S,2S)-(+)-1,2-diaminocyclohexane (0.57 g; 5 mmol) in ethanol (3 ml) was added to a solution of 3,5-di-*tert*-butylsalicylaldehyde (0.12 g; 0.5 mmol) in ethanol (7 ml) and stirred for 8 h at room temperature. The mixture was concentrated to dryness *in vacuo* and washed with water to remove the excess diaminocyclohexane. A yellow solid was obtained. IR (KBr): 3430 (br), 2950 (s), 2860 (s), 1630 (s), 1585 (m), 1475 (s), 1440 (w), 1361 (m), 1270 (m), 1170 (m), 1130 (w), 1085 (w), 1038 (w), 878 (w), 828 (w), 772 (w), 713 (w), 644 (w), 559 (w), 492 (w) cm^{-1}.

Dimer 1

To a solution of the Schiff base **7** (0.11 g; 0.32 mmol) and 5,5′-methylene-di-3-*tert*-butylsalicylaldehyde **4** (0.06 g; 0.16 mmol) in deoxygenated acetonitrile (5 ml), $Mn(OAc)_2.4H_2O$ (0.04 g; 0.16 mmol) was added. This was stirred at RT for 17 h. A solution of ferrocenium hexafluorophosphate (0.05 g; 0.16 mmol) in deoxygenated acetonitrile (3 ml) was then added at RT. After stirring for 12 h, the mixture was concentrated *in vacuo*. The crystalline residue was washed with hexane to remove the produced ferrocene and recrystallized from a mixture of dichloromethane and hexane to give **1** as very dark brown crystals. IR (KBr): 3420 (br), 2950 (s), 2870 (m), 1613 (s), 1539 (s), 1438 (m), 1390 (m), 1342 (m), 1310 (m), 1205 (w), 1172 (w), 1103 (w), 848 (s), 784 (w), 560 (m) cm^{-1}.

General procedure for the homogeneous asymmetric epoxidation

Substrate/Mn=200. Jacobsen's catalyst (2.37 mg; 3.725 μmol) or dimer (2.59 mg; 1.86 μmol) was added to a solution of the substrate (0.745 mmol) in 7.5 ml dichloromethane. This solution was stirred at 25°C for 5 minutes and aqueous NaOCl (1.117 mmol, 13% in water) was added. The reaction was stirred for 7 h before a sample was analysed by GC over a chiraldex G-TA column.

Inclusion in a PDMS membrane

The complex (2 w%) was added to a 20 vol% solution in chloroform of a 10/1 weight ratio of prepolymer (RTV-615A, linear polydimethylsiloxane chains with terminal vinyl groups) and crosslinker (RTV-615B, linear polydimethylsiloxane chains carrying several hydride groups) from General Electric. After stirring for 1 h at RT, the solvent was allowed to evaporate under air for 12 h and finally 1 h under vacuum. The membrane was then cured under vacuum at 150°C for 1 h. The average thickness of the catalytic membrane was 0.4 mm. The leaching is determined by UV-adsorption at 325 nm.

General procedure for the heterogeneous asymmetric epoxidation

Substrate/Mn=25. To a solution of the substrate (0.3 mmol) in 6 ml solvent, an amount of PDMS-membrane, containing 6 μmol dimer or 12 μmol Jacobsen complex, cut into small pieces, and aqueous NaOCl (3 mmol, 13% in water) were added. This mixture was put on a Heidolph unimax 1010 shaking instrument at a frequency of 450 min^{-1} for 24 h at 25°C. The membrane pieces were then removed and the organic phase was analysed by GC. For the regeneration experiments, the membranes were washed with acetone and dried at RT.

Acknowledgements

This research is done in the frame of an IUAP-PAI grant from the Federal Government. IWT and FWO are acknowledged for PhD and postdoctoral grants to K.B.M.J. and I.F.J.V., respectively.

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(Received in UK 3 September 1997)