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Intramolecular Acceleration of Asymmetric Epoxide Ring-Opening by Dendritic Polyglycerol Salen–Cr^{III} Complexes

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Dedicated to Professor Dr. Armin de Meijere on the occasion of his 70th birthday

Keywords: Supported catalysts / Ring opening / Dendrimers / Epoxides / Enantioselectivity / Chromium

We present the synthesis of symmetrical (pyrrolidine-salen)-Cr^{III} complexes immobilized on hyperbranched polyglycerol **1** through linkers of different lengths and their application in the asymmetric ring-opening of *meso*-epoxides. This reaction proceeded through a cooperative bimetallic mechanism and for the polymeric catalysts a positive dendritic effect with regard to the reaction rate was found. In addition, the introduction of long linkers (C6, C10, and C18) forced the favored head-to-tail orientation of two catalyst molecules and led to greater enantioselectivity with *ee* values of 48 % (cyclohexene oxide) and 64 % (cyclopentene oxide) for the ring-opening of *meso*-epoxides with $TMSN_3$ catalyzed by hPG-C10-CrCl (**13**). The soluble polyglycerol-supported catalyst was recovered five times by dialysis to afford similar activities and a 10 % increase in the enantioselectivity.

Introduction

Enantioselective catalysis plays an important role in the synthesis of chiral organic compounds in research, as well as in the pharmaceutical and fine chemical industries. Metalated chiral salen ligands, for example, Jacobsen's Mn catalyst, are among the most successful asymmetric catalysts today.[1,2] They were first introduced in the 1990s by Jacobsen and Katsuki and their co-workers as highly enantioselective catalysts for the asymmetric epoxidation of unfunctionalized olefins.[3,4] Until today, their easy preparation and versatile catalytic performance, depending on the nature of the chelated metal, made them "privileged" ligands.[5] Metalated salens have been prepared with a variety of transition metals, including Mn, Cr, Co, V, Cu, Ti, Ru, Pd, Au, Zn, and Al, and have been used for a multitude of asymmetric organic transformations, for example, the epoxidation of olefins,[4,6,7] the ring-opening of epoxides,[8–11] hydrolytic kinetic resolution of epoxides,[12–15] conjugate addition reactions to α,β-unsaturated imides,[16] (hetero)-Diels–Alder reactions,[17–19] and many others.[1]

Owing to the cost of the catalysts, which usually exceeds the value of the products, and the challenge to simplify product purification from metal residues, it is desirable to immobilize salen ligands and several attempts have been made in this field.[1,20,21] In contrast to insoluble supports,[21] soluble ones are able to combine the best features of heterogeneous supports (simplified separation from small molecules and potential for recycling) with the advantages of homogeneous synthesis (more normal reaction kinetics, higher reactivity and selectivity, lack of diffusion phenomena, simple characterization) and allow the application of continuous flow membrane techniques.[22]

Salen ligands have been immobilized on various soluble polymeric supports, for example, non-crosslinked poly(styrene),[23,24] poly(norbornene),[7,25] and monomethylated poly(ethylene glycol).[23] Dendritic structures are a special kind of solid support. Their properties, compared with linear polymeric supports, such as good solubility, low viscosity, and high density of the functional groups in their periphery, make them very suitable as supports for catalysis.[26] In particular, the high density of functional groups on the surface can have a high impact on catalytic reactions, for example, if they follow a cooperative bimetallic mechanism,[27] which has been proven for the asymmetric ring-opening (ARO) of epoxides with nucleophiles catalyzed by chiral (salen)Cr complexes[10] and the hydrolytic kinetic resolution (HKR) of epoxides catalyzed by (salen)Co complexes.[28]

The two reactions follow the same mechanism, with two different catalytic moieties activating the epoxide and nucleophile simultaneously.[10] Because of this mechanism, a close proximity of the (salen)metal complexes, which can be achieved by a covalent connection of two salen units or by

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attachment of catalyst molecules to a dendritic support, should lead to a rate enhancement of these reactions (Figure 1). This has already been shown for the ARO of epoxides with dimers of (salen)Cr complexes[8] as well as for the HKR of epoxides with oligomeric[14] or macrocyclic (salen)-Co complexes[13] or (salen)Co complexes immobilized on PAMAM[28] or gold nanoparticles.[15] If dendritic structures are involved, this effect on the catalytic reaction is called a positive dendritic effect.

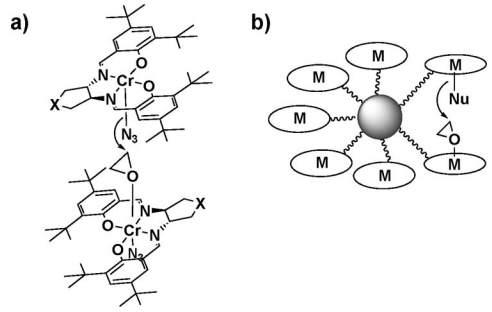


Figure 1. Representation of the simultaneous activation of epoxide and nucleophile by a) monomeric (intermolecular) and b) dendritic systems[28] (intramolecular).

Because perfect dendrimers are expensive and very tedious to synthesize, we recently developed the hyperbranched polyglycerol **1** (hPG; Figure 2) as a soluble dendritic support for organic synthesis[29,30] and catalysis.[19,31] This polyether polyol can be synthesized on a kilogram-scale by ring-opening polymerization of glycidol[32] and contains linear monohydroxy and terminal dihydroxy functional groups, which can be easily converted by standard synthetic methods. Its versatile properties, such as high-loading capacity (13.5 mmol g^{-1}), good solubility in a wide range of solvents (depending on the functional groups in the periphery), chemical stability, and noncoordinating properties, make it a promising support for reagents and catalysts, especially metal complexes.

Herein we present the synthesis of hPG-supported complexes of salen analogues with a pyrrolidine backbone, their application to the ARO of *meso*-epoxides with trimethylsilyl azide ($TMSN_3$), and their recycling by membrane filtration.

Results and Discussion

There are two possible approaches to the covalent immobilization of salen ligands on hPG (**1**); the symmetrical and the unsymmetrical method. The unsymmetrical approach

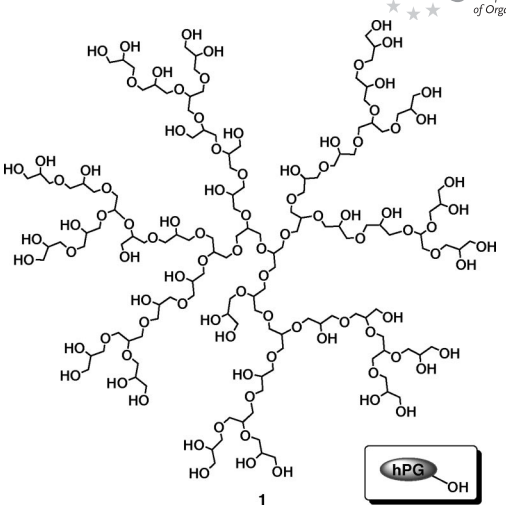


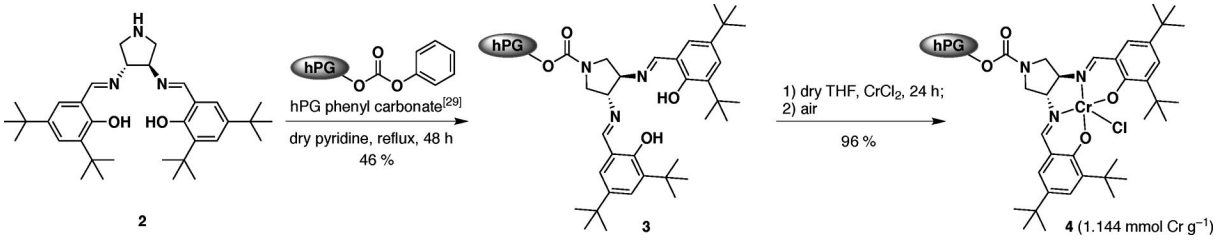
Figure 2. Part of the structure of hyperbranched polyglycerol (**1**, hPG).

has been used before in our group,[19] but because the salen ligand builds up on the support this approach suffers from ill-defined catalyst species on the polymer, because full conversion of all functional groups on the polymer cannot be guaranteed. Owing to the labile nature of the imine bond, synthesis of the unsymmetrical salen ligand leads to mixtures of symmetrical and unsymmetrical ligands and low yields are obtained.

The symmetrical approach utilizes the symmetrical pyrrolidine-salen ligand **2**, which is easily synthesized starting from (*R*,*R*)-(+)-tartaric acid[8,33] and can be coupled to **1** through the N atom in the backbone of the ligand.

For the synthesis of immobilized pyrrolidine-salen derivatives, **1** with M_n = 6000 g mol^{-1} was used and either activated with phenyl chloroformate to form the mixed carbonate (30% functionalization) or the OH groups of **1** were transformed into amines (hPG-amine, 55% functionalization).[29]

Pyrrolidine-salen (**2**) can be coupled directly to hPG-phenyl carbonate (Scheme 1) and chromium was inserted as described before.[19] Purification by preparative gel permeation chromatography (GPC) and full characterization by ^{1}H and ^{13}C NMR and IR spectroscopy was performed on the hPG-C1-pyrrolidine-salen ligand **3**. For the final metal complex **4** only IR spectroscopy and ICP-MS (inductively coupled plasma mass spectrometry) were used for characterization because, due to the paramagnetic nature of chromium, NMR methods cannot be applied.



Scheme 1. Synthesis of hPG-C1-CrCl (**4**).

To construct a comparable monomeric catalyst we decided to synthesize the Boc-protected (pyrrolidine-salen)-chromium complex **5** because the protecting group mimics the linker used to attach pyrrolidine-salen **2** to hPG **1**. The monomeric catalyst **5** (Figure 3) was synthesized from the known Boc-protected pyrrolidine-salen[34] by chromium insertion.[19]

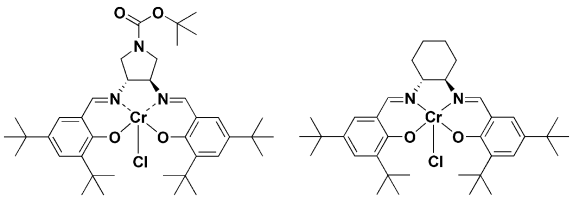


Figure 3. Structures of the monomeric Boc(pyrrolidine-salen)CrCl **5** and Jacobsen's catalyst **6**.

The catalyst hPG-C1-CrCl (**4**), its monomeric counterpart **5**, and the commercially available Jacobsen's chromium catalyst (**6**, see Figure 3) were used in the ARO of cyclohexene oxide with $TMSN_3$ (method A; reaction conditions as in ref.[9]). First we wanted to prove that immobilization of salen analogues on a dendritic support leads to a significant rate enhancement for this reaction in comparison with the monomeric catalysts. This positive dendritic effect can be clearly observed from the conversion vs. time plots shown in Figure 4.

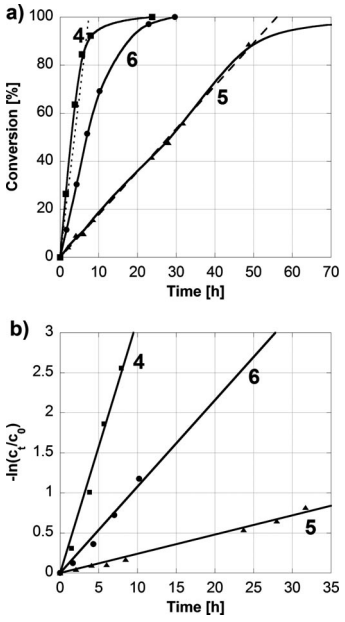
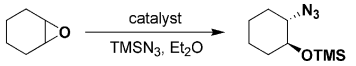


Figure 4. Conversion vs. time (a) and rate plots (b) for the ARO of cyclohexene oxide with $TMSN_3$ with hPG-C1-CrCl (**4**) (■), Boc-(pyrrolidine-salen)CrCl (**5**) (▲), and Jacobsen's catalyst (**6**) (●) (method A; for catalyst **5** the next measuring point was 120 h with 100% conversion).

Whereas the Boc(pyrrolidine-salen)CrCl complex needs approximately 55 h to reach full conversion, the reaction with hPG-supported analogue **4** was completed after only 9 h. The reaction time for Jacobsen's catalyst of 24 h lies between the two (pyrrolidine-salen)Cr catalysts. This becomes even clearer when the rate plots (Figure 4) are taken into consideration. The highest rate constant is obtained for the polymer-supported ligand **4** (Table 1, Entry 1), and is one order of magnitude higher than that of Boc(pyrrolidine-salen)CrCl (**5**) (Entry 2) and approximately three times higher than that of Jacobsen's CrCl complex (Entry 3).

Table 1. Results for the ARO of cyclohexene oxide with $TMSN_3$ with catalysts **4**–**6**.[a]



	Catalyst (*R*,*R*)-configuration	Rate constant [s^{-1}][b]	Time [h][c]
1	hPG-C1-CrCl (**4**)	8.772×10^{-5}	8.6
2	Boc(pyrr.-salen)CrCl (**5**)	6.664×10^{-6}	54.9
3	Jacobsen's catalyst (**6**)	2.995×10^{-5}	23.6

[a] Reaction conditions: method A, 2 mol-% of chromium catalyst. [b] Rate constants calculated from the slope of the rate plots in Figure 4 (b). [c] Time extrapolated from the last measuring point before 100% conversion.

Because it is known that the active species is not the chloride but the azide complex **7**[9,10] (Figure 5), we developed a new method (method B) in which the azide complex is formed in situ before addition of the substrate to avoid an initial activation time.

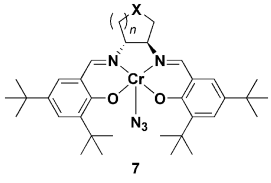


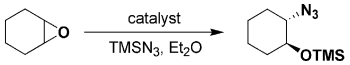
Figure 5. Catalytically active species of (salen) analogues in the ARO of *meso*-epoxides.

For this purpose the "precatalyst" **4** was stirred with $TMSN_3$ for 16 h for the counterion exchange to occur. In the ARO of cyclohexene oxide this resulted in an additional rate enhancement for all three catalysts and under the same conditions the reaction catalyzed by **4** was finished after 6 h [rate constants, **4**: 1.875×10^{-4} s^{-1}, **5**: 3.931×10^{-5} s^{-1}, and **6**: 7.992×10^{-5} s^{-1}].

Concerning the enantioselectivities, it is quite clear that the hPG-supported catalyst **4** performs much worse than the monomeric catalysts **5** and **6** (Table 2, Entries 1–3). By method A, at a catalyst loading of 2 mol-%, the two monomers **5** and **6** catalyze the ARO of cyclohexene oxide with similar *ee* values of around 65%, whereas **4** achieves an *ee* of only 12%. Lowering the catalyst loading to 0.5 mol-% results in an increase of *ee* to 21% (Entry 3) for the reaction catalyzed by **4**. The *ee* values obtained with Boc(pyrrolidine-salen)CrCl remain more or less the same (Entries 4–6), but for Jacobsen's catalyst **6** they drop dramatically to 30%

for a catalyst loading of 0.5 mol-% (Entry 9). Application of method B results in slightly higher enantioselectivities of around 70% for **5** (Table 2, Entries 4–6), whereas with Jacobsen's catalyst *ee* values of 41–51% were obtained (Entries 7–9). In contrast, the *ee* values achieved with the supported catalyst **4** are at all catalyst loadings around 30% higher than with method A (Entries 1–3) with a 28% *ee* for a loading of 0.5 mol-% (Entry 3). It has already been reported by Jacobsen and co-workers[35] that the azide complex in some cases catalyzes with higher enantioselectivity, but the increase they observed was not as high as the rise we observed.

Table 2. Enantioselectivities for the ARO of cyclohexene oxide with $TMSN_3$; comparison of methods A and B for different catalyst loadings.



	Catalyst *R,R* configuration	Loading [mol-%]	*ee* [%][a] Method A	Method B
1	hPG-C1-CrCl (**4**)	2	12	18
2	hPG-C1-CrCl (**4**)	1	16	22
3	hPG-C1-CrCl (**4**)	0.5	21	28
4	Boc(pyrr.-salen)CrCl (**5**)	2	68	70
5	Boc(pyrr.-salen)CrCl (**5**)	1	67	72
6	Boc(pyrr.-salen)CrCl (**5**)	0.5	74	73
7	Jacobsen's catalyst (**6**)	2	65	51
8	Jacobsen's catalyst (**6**)	1	64	44
9	Jacobsen's catalyst (**6**)	0.5	30[b]	41

[a] Determined by chiral GC. The *S,S* enantiomer is in excess. [b] A second experiment gave 27% *ee*.

The enantioselectivities obtained with the hPG-supported system **4** are still very low and can be explained by a "negative dendritic effect", which results from the orientation of the immobilized catalytic units with respect to one another. It has been reported in the literature that there are two possible orientations of the catalyst molecules, one is the so-called "head-to-head" arrangement and the second the "head-to-tail" orientation in which one catalyst unit is turned around by 180°.[8] Through the construction of salen dimers, it was shown that the head-to-tail arrangement is necessary to achieve high enantioselectivities, whereas the head-to-head arrangement led to an *ee* of only 8%.[8]

For hPG-C1-CrCl (**4**) we expect a head-to-head arrangement because the linker is very short and the hyperbranched polymer can be assumed to have a globular structure. Therefore most of the interactions that take place on the polymer surface should match the head-to-head arrangement, as indicated in Figure 6.

To achieve higher enantioselectivities we decided to introduce linkers of different lengths between the pyrrolidine-salen ligand **3** and the polymeric support. With a long enough linker we hoped to enable back-folding of the catalytic unit, which should lead to the favored head-to-tail orientation and therefore to higher enantioselectivities. For this purpose α,ω-diols of different lengths (C6, C10, and

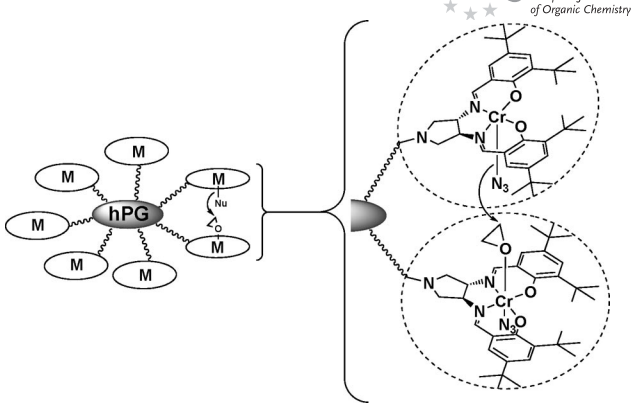


Figure 6. Azide complex of hPG-C1-CrCl (**4**) and the expected head-to-head orientation of the catalytic units during the cooperative catalysis.

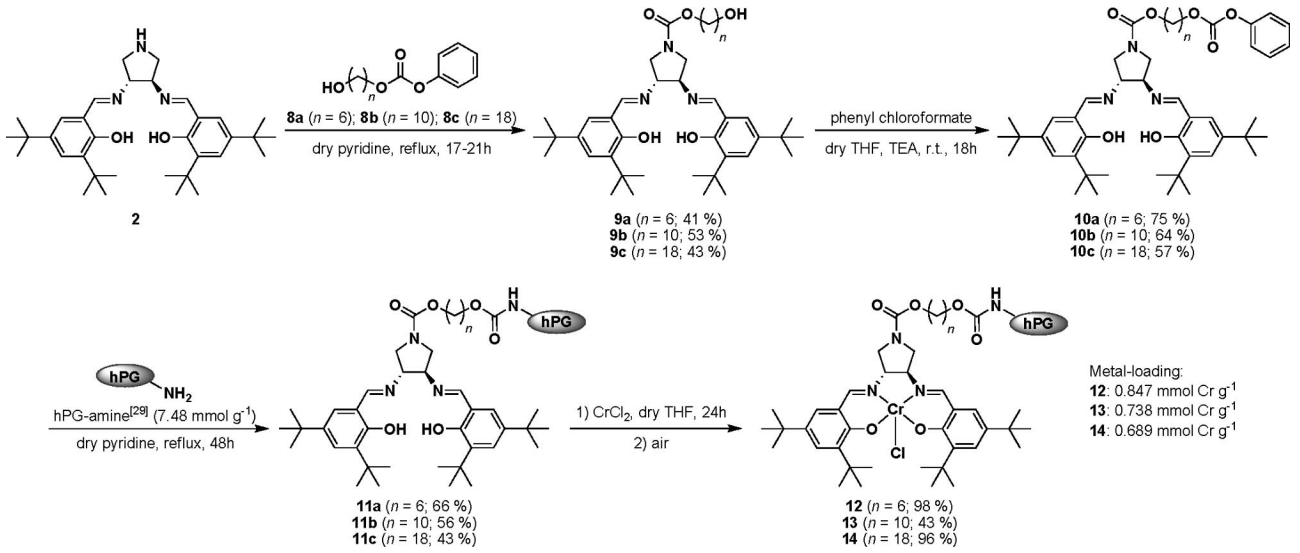
C18) were mono-activated with phenyl chloroformate and coupled to the secondary amine of the pyrrolidine-salen ligand **2**. Subsequently, activation of the second hydroxy group of the linker was achieved with phenyl chloroformate and the resulting modified pyrrolidine-salen ligands **10a**–**c** were coupled to hPG-amine (Scheme 2) and purified by preparative GPC.

All nonpolymeric compounds were fully characterized by ^1H and ^{13}C NMR spectroscopy, ESI-MS, elemental analysis, and IR spectroscopy. The hPG-supported ligands were characterized by ^1H and ^{13}C NMR, and IR spectroscopy. After chromium insertion the metal complexes **12**–**14** were characterized by IR spectroscopy and ICP-MS (see Scheme 2).

When catalysts **12**–**14** were applied to the ARO of cyclohexene oxide with $TMSN_3$ the rate enhancement of the polymeric systems was retained and it was observed that the introduction of linkers of different lengths leads to higher enantioselectivities (Table 3).

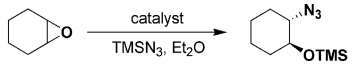
The best catalyst is hPG-C10-CrCl (**13**) with the linker derived from 1,10-decanediol. At a catalyst loading of 1 mol-% it achieved the highest *ee* of 48% (Table 3, Entry 3). This was also supported by the results of the ARO of cyclopentene oxide with $TMSN_3$ (Table 4). With the exception of hPG-C1-CrCl (**7**), all polymeric catalysts produced higher enantioselectivities, but it is known from the literature that epoxides fused to five-membered rings afford higher enantioselectivities than their six-membered ring analogues.[9] In Table 4 (Entry 3) it can be seen that **13** again presents the best performance, affording an *ee* of 64%. From these results we can conclude that C10 is the correct length for the expected back-folding (Figure 7).

To prove the recyclability, **4** was reused in five consecutive cycles and the product was separated from the polymeric catalyst **4** successfully by dialysis. For the last two cycles the conversion slightly decreased to 97%, which indicates that the catalyst is slowly losing activity, but at the same time the enantioselectivity increased from 20 (Table 5, 1st run) to 30% (5th run). The chemical yields after work-



Scheme 2. Synthesis of hPG-supported pyrrolidine-salen ligands **11a**–**c** and their corresponding chromium complexes **12**, **13**, and **14**.

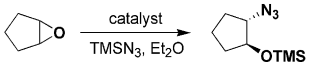
Table 3. Results of the ARO of cyclohexene oxide with $TMSN_3$.[a]



	Catalyst *R*,*R* configuration	*ee* [%][b] 2 mol-%	1 mol-%	0.5 mol-%
1	hPG-C1-CrCl (**4**)	18	22	28
2	hPG-C6-CrCl (**12**)	31	36	36
3	hPG-C10-CrCl (**13**)	39	48	44
4	hPG-C18-CrCl (**14**)	35	43	44
5	Boc(pyrr.-salen)CrCl (**5**)	70	72	73
6	Jacobsen's catalyst (**6**)	51	44	41

[a] Performed by method B. [b] Determined at three levels of catalyst loading by chiral GC. The *S*,*S* enantiomer is in excess.

Table 4. Results of the ARO of cyclopentene oxide with $TMSN_3$.[a]



	Catalyst *R*,*R* configuration	*ee* [%][b]
1	hPG-C1-CrCl (**4**)	16
2	hPG-C6-CrCl (**12**)	47
3	hPG-C10-CrCl (**13**)	64
4	hPG-C18-CrCl (**14**)	56
5	Boc(pyrr.-salen)CrCl (**5**)	81
6	Jacobsen's catalyst (**6**)	85

[a] Performed by method B with a catalyst loading of 1 mol-%. [b] Determined by chiral GC. The *S*,*S* enantiomer is in excess.

up decrease after the 3rd run, which indicates that separation by dialysis is becoming less effective. Here the application of continuously operating systems can improve the performance of the process and has promise because of the low metal leaching of the catalyst into the product.

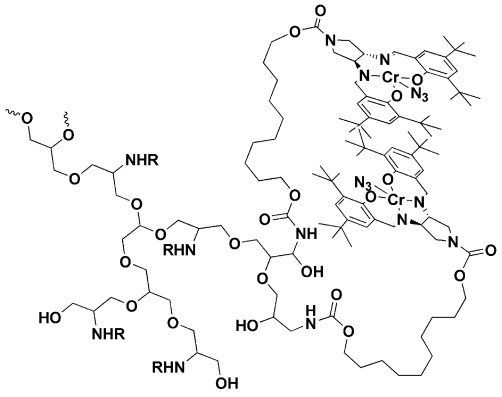


Figure 7. Possible back-folding mechanism for the favored head-to-tail orientation with a C10 linker.

Table 5. Recycling of hPG-C1-CrCl (**4**) in the ARO of cyclohexene oxide with $TMSN_3$.[a]

	1st run	2nd run	3rd run	4th run	5th run
Conversion [%][b]	>99	>99	>99	99	97
ee [%][c]	20	27	22	28	30
Yield [%][d]	97	95	89	77	75
Metal leaching [ppm][e]	8.4	7.6	3.9	3.8	2.4

[a] 1 mol-% catalyst; 1st run method B, 2nd–5th run method A. [b] Determined by GC. The *S*,*S* enantiomer is in excess. [c] Determined by chiral GC. [d] After column chromatography. [e] Determined by ICP-MS.

Conclusions

We have shown that dendritic polymers are suitable for the immobilization of catalysts that interact by a cooperative bimetallic mechanism. The close proximity of pyrrolidine-salen **2** at the periphery of a hyperbranched polyglycerol was used to force the cooperative catalysis in the asymmetric ring-opening of *meso*-epoxides with $TMSN_3$, which led to an increase in the rate constant by one order

of magnitude compared with the monomeric analogue **5**. By introducing different length linkers (C6, C10, and C18) between hPG and the (pyrrolidine-salen)CrCl complex we improved the enantioselectivity by a factor of two, with a maximum for the catalyst with the C10 linker. This was ascribed to a partial back-folding of the catalytic units, which leads to the favored head-to-tail orientation and therefore to higher *ee* values of up to 48% for cyclohexene oxide and 64% for cyclopentene oxide by catalysis with hPG-C10-CrCl. Recycling of the catalyst was successfully achieved five times by dialysis with very low metal leaching of the catalyst into the product, revealing a slight loss of activity, and an increase in the *ee* by 10% from the 1st to the 5th run. Investigations into the application of the polymeric catalyst in a continuously operating membrane reactor are in progress.

Experimental Section

General Procedure (GP) A. Mono-Activation of α,ω-Diol with Phenyl Chloroformate: α,ω-Diol (1.0 equiv.) and TEA (5.0 equiv.) were dissolved in THF (p.a.). Phenyl chloroformate (1.0 equiv.) in THF was added dropwise over 30 min and the mixture was stirred for 18 h. The precipitated TEA·HCl salt was removed by filtration, the solvent was removed under vacuum, and the residue was purified by column chromatography.

General Procedure B. Coupling of ω-Hydroxyalkyl Phenyl Carbonate to Pyrrolidine-Salen 3: This reaction was performed under dry conditions. Pyrrolidine-salen ligand **2** (1.0 equiv.) and ω-hydroxyalkyl phenyl carbonate **8a**–**c** (2.0 equiv.) were dissolved in dry pyridine and the mixture was heated at reflux for 17–21 h (conversion was monitored by TLC). The solvent was removed in vacuo and the crude product was purified by HPLC. When only a small excess of the ω-hydroxyalkyl phenyl carbonate was used, the product could be purified by column chromatography.

General Procedure C. Activation of ω-Hydroxyalkyl-1-(pyrrolidine-salen): This reaction was performed under dry conditions. ω-Hydroxyalkyl-1-(pyrrolidine-salen) **9a**–**c** and TEA (5.0 equiv.) were dissolved in dry THF and phenyl chloroformate (2.0 equiv.) was added dropwise over 15 min. The mixture was stirred at room temp. for 18 h, the solvent was removed in vacuo, and the crude product was purified by flash column chromatography.

General Procedure D. Coupling of ω-Phenyl Carbonate-alkyl-1-(pyrrolidine-salen) to hPG-amine: This reaction was performed under dry conditions. ω-Phenyl carbonate-alkyl-1-(pyrrolidine-salen) **10a**–**c** and hPG-amine[29] (7.48 mmol g^{-1} NH_2, 1.0 equiv.) in dry pyridine were heated at reflux for 2 d. Subsequently the solvent was removed in vacuo and the crude product was purified by preparative GPC (eluent: THF).

General Procedure E. Insertion of Chromium:[17] This reaction was performed under dry conditions. The ligand (1.0 equiv.) was dissolved in dry THF and $CrCl_2$ (1.1 equiv.) was added immediately. The mixture was stirred at room temp. for 24 h. Subsequently THF was removed in an air stream to afford the oxidation of Cr^{II} to Cr^{III}. TBME was added and the mixture was stirred at room temp. for 1–2 h. After filtration, the organic layer was washed with sat. aq. NH_4Cl and brine, and dried with anhydrous Na_2SO_4.

hPG-C1-(pyrrolidine-salen) Ligand 4: This reaction was performed under dry conditions. Pyrrolidine-salen ligand **2** (1.72 g, 3.23 mmol) and hPG-phenyl carbonate[29] (2.79 mmol g^{-1} carbonate groups, 1.16 g, 3.23 mmol, 1.0 equiv.) were heated at reflux in dry pyridine (10 mL) for 2 d. The solvent was removed in vacuo and the crude product was purified by preparative GPC to yield 921 mg (46%) of a glassy orange foam.

Supporting Information (see also the footnote on the first page of this article): Complete experimental details and characterization data for compounds **3**–**5** and **8**–**14**.

Acknowledgments

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