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Polyglycerol-Supported Chromium-Salen as a High-Loading Dendritic Catalyst for Stereoselective Diels–Alder Reactions

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Abstract: In this paper we demonstrate the application of hyperbranched polyglycerol (PG) **3** as a polymeric support for asymmetric catalysis. A new polyglycerol-supported unsymmetrical salen ligand **4** is described, which was successfully purified by gel permeation chromatography (GPC) or by ultrafiltration. After the insertion of the metal, e.g., chromium, the corresponding polymeric chromium complex was used as catalyst for asymmetric Diels–Alder reactions between Danishefsky's diene and benzaldehyde. The catalytic activities (up to 98% conversion) and enantioselectivities (up to 78% *ee*) were comparable to the original catalyst reported by Jacobsen. The soluble polyglycerol-supported catalysts were recovered by dialysis after the catalytic reactions and were recycled two times to afford identical reactivities as in the first run, with slightly reduced enantioselectivities. Moreover, this polymeric support catalyst showed a high retention (99.02%) in a continuously operated membrane reactor.

Keywords: dendritic architecture; Diels–Alder reaction; hyperbranched polymer; polyglycerol; polymeric support; salen ligand

Introduction

Dendritic architectures have attracted increasing interest for their ability to act as soluble supports for catalysis.[1,2]

Investigations on polymer-supported catalysts have been ongoing for many decades, and rapidly increasing numbers of new polymeric supports, cross-linked (insoluble)[3] and non-cross-linked (soluble) polymers,[4,5] have recently been reported.

Since one of the major benefits of polymer-supported catalysis is the recovery and reuse of immobilized species, especially when dealing with chiral catalysts, which can be extremely expensive,[4a] effective separation methods are required.[6] Soluble polymers can be separated from low molecular weight compounds in solution either by physicochemical properties, e.g., extraction, precipitation, filtration over silica gel, or by size (ultrafiltration, dialysis, GPC).[4–7]

Tetradentate Schiff bases known as salen [*N,N'*-bis-(salicylidene)ethylenediamine], are powerful ligands for asymmetric catalysis.[8] The best known and most widely used is the so-called Jacobsen's catalyst **1** (Figure 1),[9] whereas the most selective are those developed by Katsuki and co-workers.[10] Salen metal complexes and their immobilized analogues have been used for a wide range of catalytic asymmetric reactions,[11] mainly enantioselective epoxidations,[8a,k,9,10,12] asymmetric ring openings of *meso*-epoxides,[13] kinetic resolutions of terminal epoxides,[13f,14] cyanations of aryl aldehydes (CACHyTM),[13b,15] α-oxidations of ketone silyl enol ethers,[16] reductions of aromatic ketones,[13b] cyclopropanations,[17] sulfide oxidations,[18] kinetic resolutions of sulfoxides,[18] as well as (hetero)-Diels–Alder reactions.[14f,19]

The immobilization of these salen ligands onto performed polymer supports **2** (Figure 1) has attracted a number of research groups. Over the past decades, the metalated salens immobilized on polystyre-

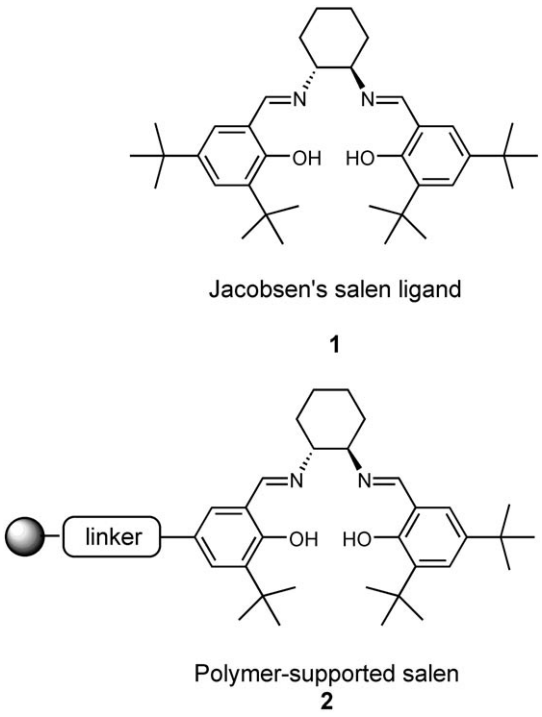


Figure 1. Jacobsen's salen ligand and polymer supported salen.

ne,[14g,20] polyamidoamine (PAMAM),[14a] poly(ethylene glycol) (PEG),[21] Merriefield resin,[21] *J*anda*J*el resin,[21] or poly(norbornene),[22] have been successfully employed as catalysts in a variety of asymmetric transformations like asymmetric epoxidation reactions[21,22] and kinetic resolution of epoxides.[14a,g,20,22]

Another class of high loading supports for organic synthesis are hyperbranched polymers such as polyglycerol (PG) **3** (Figure 2).[23] This soluble polymer is easily accessible *via* anionic ring-opening polymerization of glycidol in kilogram quantities[24] and has recently become commercially available.[24e] These aliphatic polyether polyols possess a chemically stable backbone.

Due to the breadth of applications for salen catalysts it was an aim of this work to synthesize hyperbranched polyglycerol-supported salen analogues **4** (Figure 2) and to investigate their use in asymmetric catalysis. These catalysts should be retained in a continuously operated membrane reactor and their recycling should be investigated.

Results and Discussion

For the preparation of the polymer-supported salen ligand, we used hyperbranched polyglycerol **3** (M_n = 8000 g mol^{-1}). We have recently demonstrated that the polyether backbone of the PG **3** is advantageous due to its high chemical stability and weak complexing ability compared to dendritic polyamine scaffolds.[5d,22,23]

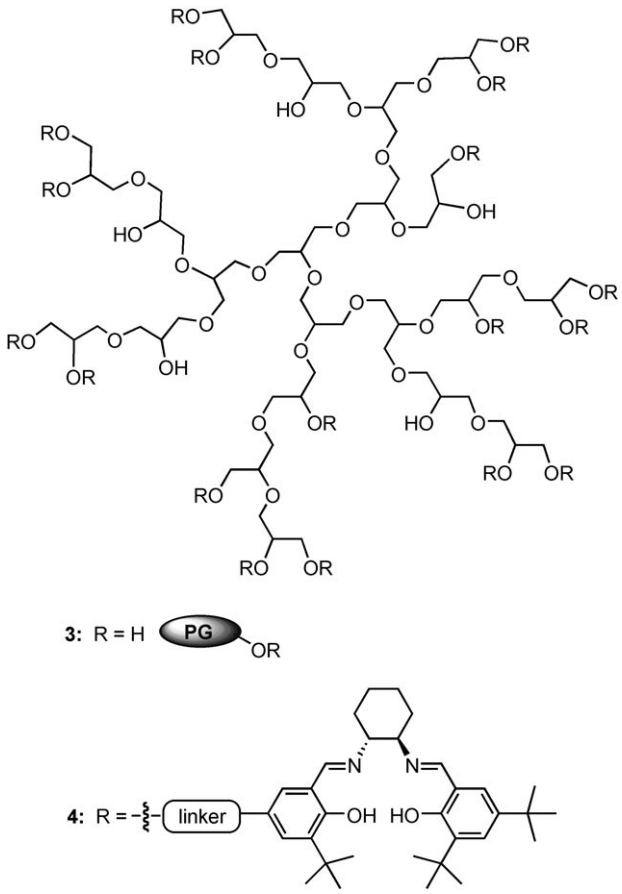
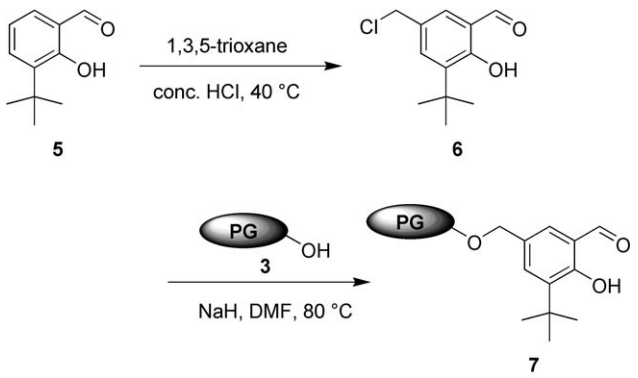


Figure 2. Hyperbranched polyglycerol **3** and polyglycerol supported salen **4**.

The first arene moiety of the salen ligand was generated by attachment of 3-*tert*-butyl-5-(chloromethyl)-2-hydroxybenzaldehyde **6**[25] to the PG **3**.[11] Product **7** was obtained in good conversion (68%) and yield (81%) after 2 dialyses in toluene and dichloromethane. The 3-*tert*-butyl-5-(chloromethyl)-2-hydroxybenzaldehyde **6** was obtained quantitatively by chloromethylation using metaformaldehyde as a formaldehyde source of 3-*tert*-butylsalicylaldehyde **5** (Scheme 1).[26]

Salen systems with two different salicylaldimine moieties (designated as unsymmetrical salens) are not very common in literature. This may be ascribed to equilibrium between the unsymmetrical salen ligand and the corresponding two symmetrical salen ligands. This related equilibrium makes their synthesis more difficult.[10c]

Since a soluble support is used here, the problem of how to synthesize unsymmetrical salen ligands in solution arose. It is therefore not surprising that there is only one publication dealing with salen systems immobilized in the shell of a dendritic polymer[15a] and



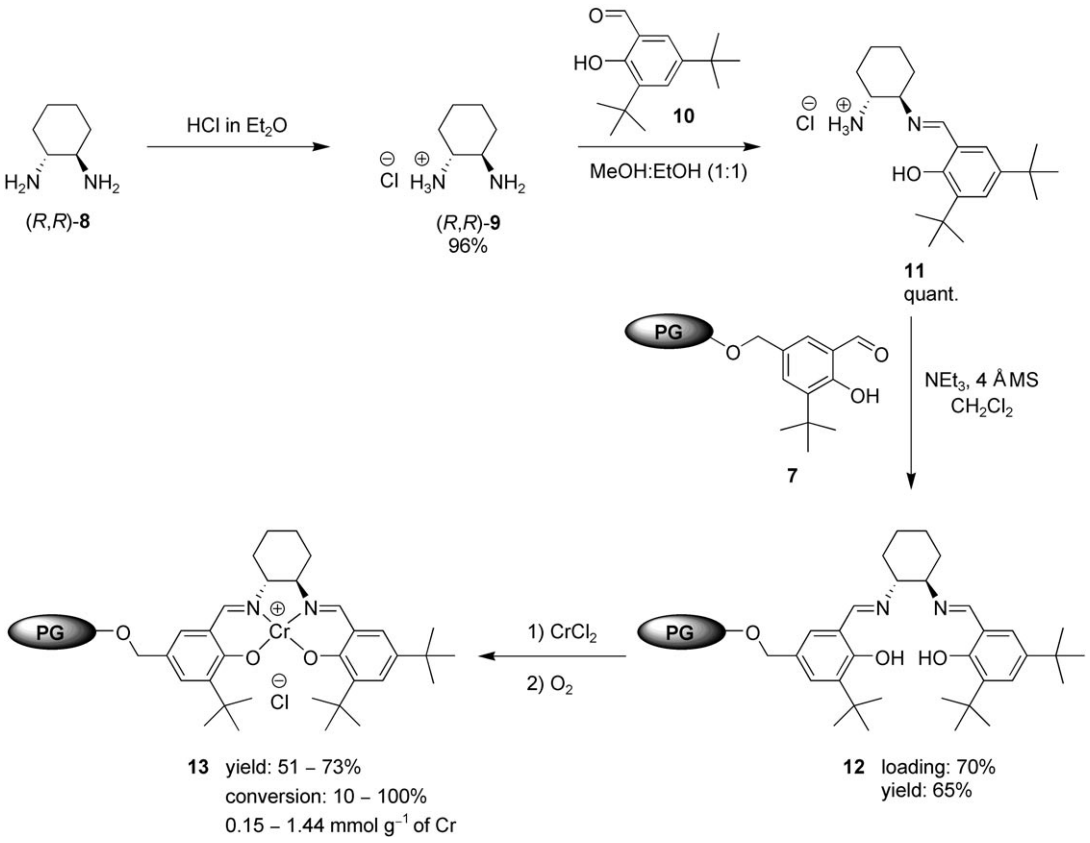
Scheme 1. Synthesis of the first arene moiety on the PG-support.

only a further one on the immobilization of salen ligands on polysiloxane polymers yielding homogeneously soluble chemzymes.[16b] This is due to the enormous problems that occur when one tries to build up salen ligands on such supports in a step-wise manner.

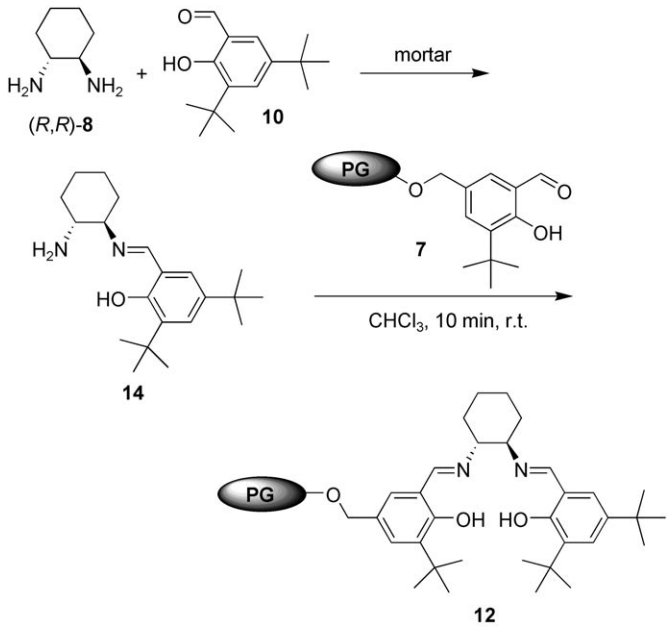
The selective mono-reaction of symmetrical diamines is the next step of the procedure.[27] For the synthesis of these unsymmetrical salen ligands, the (*R,R*)-1,2-diaminocyclohexane **8** was mono-protected with ethereal hydrochloric acid, yielding the mono-hydrochloride **9** as a white precipitate in almost quantitative yield.[28] The second step consisted of a condensation of the free amino group with the first salicylaldehyde derivative **10** and good conversion (83%) was observed. In the last step, compound **11** was used without further purification and condensed with the polyglycerol-supported salicylaldehyde **7** under *in situ* deprotection by means of an excess of triethylamine in dichloromethane (Scheme 2).[11]

An alternative route was used to obtain the polyglycerol-supported salen ligand **12** *via* a solid-phase reaction (Scheme 3). The monoimine **14** was formed from a 1:1-mixture of (*R,R*)-1,2-diaminocyclohexane **8** and 3,5-di-*tert*-butylsalicylaldehyde **10** in a mortar and subsequent trituration. The resulting material was dissolved in $CHCl_3$ and quickly reacted with the polymer-supported counterpart **7** in order to obtain a mixture of polyglycerol-supported salen ligand **12**. With this approach a full conversion was also observed according to the disappearance of the polymeric benzaldehyde signals.[11]

As described above, two ways to generate the salen from the polyglycerol benzaldehyde derivative have been developed. Unfortunately, the resulting material contained significant amounts of free salen with both approaches. Separation of low molecular weight salen from its polyglycerol supported analogue was achieved by preparative GPC, where two bands can be



Scheme 2. Synthesis of unsymmetrical salen ligand **13** *via* a monoprotected *trans*-1,2-diaminocyclohexane.



Scheme 3. Synthesis of polyglycerol-supported salen ligand **12** *via* a solid-phase reaction.

seen. The first one resulted from the desired polyglycerol supported salen **12**, and the second from free salen **1**. The elugramm is shown in Figure 3.[11]

It was also possible to purify the polymeric ligand and free salen using ultrafiltration as a separation method.[7] We used commercially available Millipore® cells with Koch MPF-50 membranes and chloroform or dichloromethane as solvents. In this case, it was necessary to flash the cell seven to ten times (for approx. 500 mg of the mixture) to not detect free salen in the corresponding filtrate as well as in the retentate.[11]

The resulting polymeric ligand **12** was fully characterized by means of ^{1}H NMR, ^{13}C NMR, H-C-COSY, H-C-long-range-COSY, and IR spectroscopy.[11]

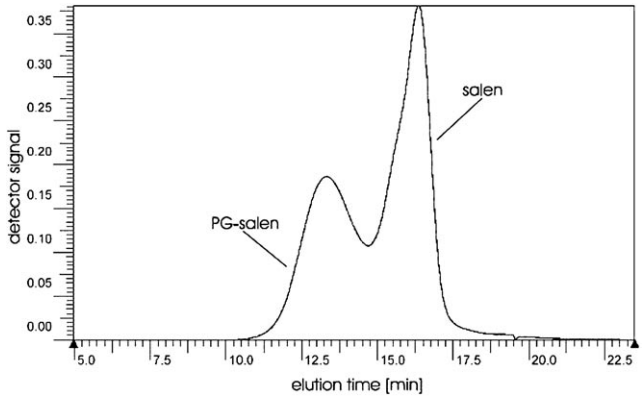


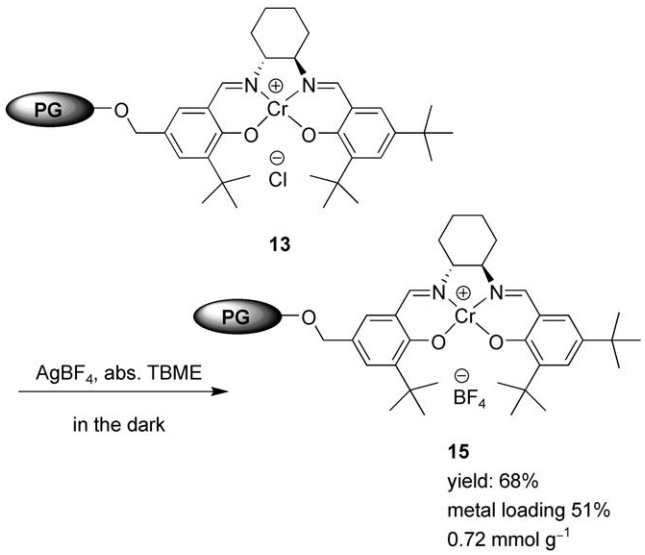
Figure 3. GPC elugrams after injection of a mixture of polymeric and free salen onto a PSS GRAL 100 Å column with chloroform as an eluent.

After purification of polyglycerol-supported salen **12**, metal insertion took place employing water-free chromium(II) chloride and the neutral complex was formed *in situ*. Subsequent air oxidation of the latter furnished the respective chromium(III) species. Following this route it was possible to obtain polyglycerol-supported chromium salen complexes **13** (Scheme 2).[13d]

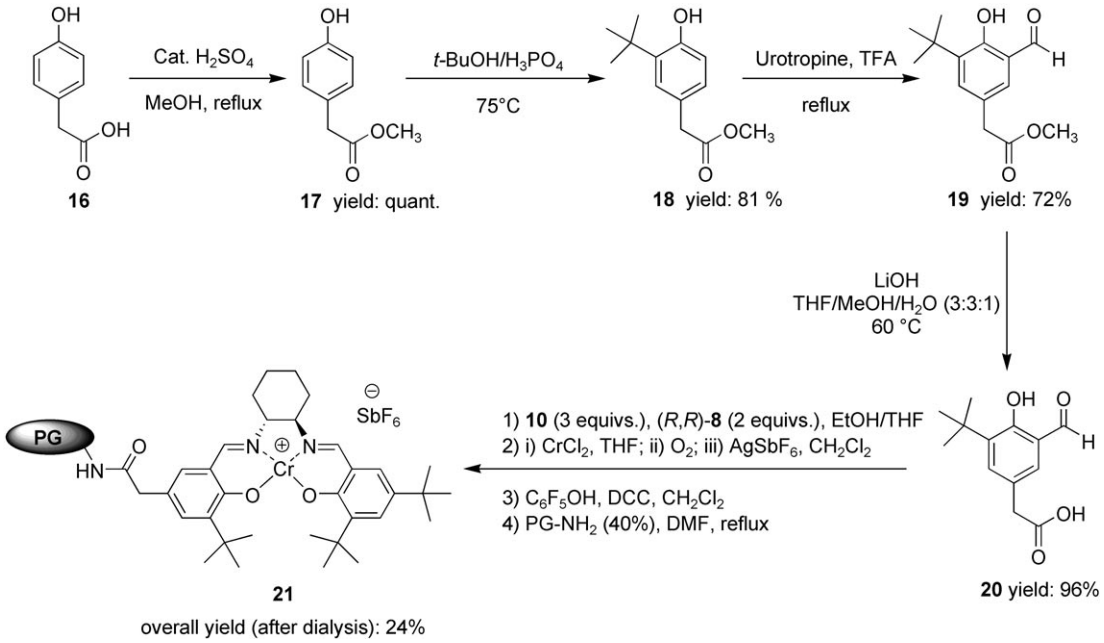
To determine the metal content (Cr) into the salen, we used IR characterization, and inductive coupled plasma atomic emission spectroscopy (ICP-AES).[11]

It was reported that the identity of the catalyst counterion is also a critical parameter for attaining high enantioselectivity in hetero-Diels–Alder reactions between Danishefsky's diene and aldehydes. It was shown that the salen complex containing a tetrafluoroborate counteranion is the best catalyst combining both high enantioselectivity and yield.[29] For this reason, anion exchange was also performed with the polymeric salen complexes **13** (Scheme 4). Again, the route reported for low molecular weight species[29] was followed commencing from the polyglycerol-supported chromium(III) salen chloride **13** using $AgBF_4$ in absolute TBME in the dark, afforded **15** in 68% yield.[11] Since the metal loading should not change during this reaction, it was not examined once more and it was assumed to be the same as in the substrate **13**.

Furthermore, we prepared another polymeric support where we used a different linker. 2-(3-*tert*-Butyl-5-formyl-4-hydroxyphenyl)acetic acid **20** was obtained from 4-hydroxyphenylacetic acid **16** by esterification of the latter to yield the corresponding methyl ester **17**. After the reaction of **17** with *tert*-butanol where



Scheme 4. Anion exchange affording a polyglycerol-supported chromium(III) salen complex with tetrafluoroborate counteranions.



Scheme 5. Synthesis of unsymmetrical salen ligand **21**.

we obtained **18**, reaction with urotropine and subsequent hydroxylation with LiOH, the corresponding carboxylic acid **20** was obtained (Scheme 5). The reaction between 3,5-di-*tert*-butylsalicylaldehyde **10**, 2-(3-*tert*-buthyl-5-formyl-4-hydroxyphenyl)acetic acid **20**, and (*R*,*R*)-1,2-diaminocyclohexane **8** in a ratio of 3:1:2,[14a] was followed *in situ* by insertion of chromium using $CrCl_2$. Oxidation of Cr(II) to Cr(III) was achieved with air and substitution of the counteranion Cl to SbF_6 using $AgSbF_6$. The resulting mixture was reacted with pentafluorophenol and the product coupled *in situ* with polyglycerol amine[30] (PG-NH_2). The resulting mixture was dialyzed in chloroform yielding a polyglycerol-supported chromium salen ligand **21**.

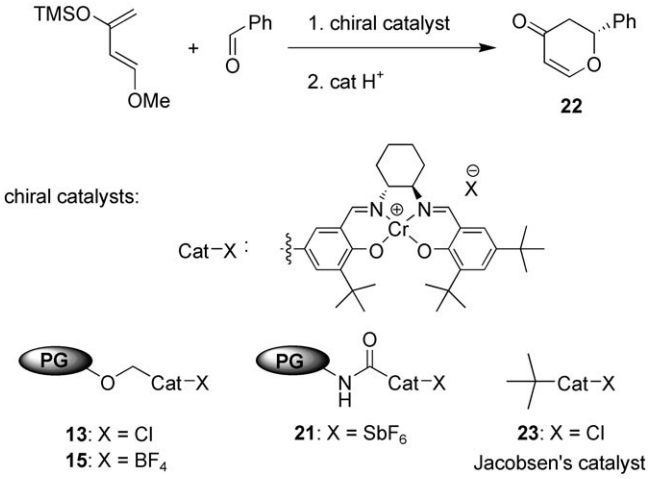
Transition metal complexes with salen ligands can serve as catalysts for a multitude of stereogenic reactions including Diels–Alder reactions. In our case we decided to use the reaction between Danishefsky's diene and benzaldehyde as a model process for the new polyglycerol-supported transition metal complexes. We selected as catalysts the polyglycerol-supported chromium salen ligands **13**, **15** and **21**. The first reaction with the polyglycerol-supported chromium chloride complex **13** (0.5 mol%) was carried out in TBME starting at −21 °C (Table 1, entry 2). The following procedure was followed: After 12 h stirring at a certain temperature, reaction control was performed by means of TLC. If no product had formed, the temperature was increased and the mixture stirred for another 12 h. As a blank test, the same reaction was carried out without catalyst at analogous temperatures (Table 1, entry 1). At temperatures above 1 °C the catalyzed reaction showed significant progress, whereas the blank reaction still showed no conversion. Consequently, the catalyzed reaction was kept at 4 °C. To find out at which temperature the background reaction starts, the temperature at the corresponding flask was further increased. A small conversion (< 5 %) was observed above 10 °C.[11]

After increasing the amount of catalyst **13**, the reaction showed an increase in the conversion up to 96 % in the case of 5 mol % of catalyst. Nevertheless, the enantiomeric excess of **22** remained constant (Table 1, entries 3 and 4). Since the complexes are bound to a hyperbranched polymer, the local catalyst concentration should not be dependent on the polymer concentration. Because the catalytic centers are fixed to the polymer shell they should always face a similar environment. It is therefore assumed that regardless of the polymer concentration, the same catalytic species always exist with the same chiral induction.[11]

Our results with catalyst **13** were compared with those obtained with Jacobsen's complex (**23**, M = Cr, X = Cl). Employing the high amount of catalyst **23** (5 mol%), a full conversion was obtained even at −21 °C (60 h) with an *ee* of 75 % (Table 1, Entry 10). Jacobsen and co-workers found 70 % conversion and 64 % *ee* after 24 h at −30 °C.[29] The reaction with Jacobsen's catalyst **23** was also performed with 1.9 mol % at the temperature of 4 °C as in the polymeric version (Table 1, entry 2). A lower conversion (23 %) but a higher *ee* (86 %) were obtained (Table 1, entry 9).[11]

Several reasons, like conversion dependency of the enantiomeric excess, "thermodynamically controlled" enantioselectivity, and the isoinversion principle,[31]

Table 1. Results of the reaction between Danishefsky's diene and benzaldehyde and subsequent hydrolysis to afford (*R*)-2-phenyl-2,3-dihydro-4*H*-pyran-4-one **22**.



Entry	Catalyst	Cat. amount [mol%]	Temp. [°C]	Conversion[b] [%]	*ee* [%]
1	-	-	10[a]	<5	n.d.
2	PG-Cr/Cl **13**	0.5	4 (1)[a]	55	64[c]
3	PG-Cr/Cl **13**	1.9	4	64	64[c]
4	PG-Cr/Cl **13**	5	4	96	65[d]
5	PG-Cr/BF_4 **15**	2.5	4 (−10)[a]	13	78[c]
6	PG-Cr/SbF_6 **21**	1.9	4	72	62[d]
7	PG-Cr/SbF_6 **21**	5	4	85	69[d]
8	PG-Cr/SbF_6 **21**	10	4	98	63[d]
9	Cat-Cr/Cl **23**	1.9	4	23	86[c]
10	Cat-Cr/Cl **23**	5	−21	quant.	75[c]

[a] Temperature corresponding to the start of activity.
[b] According to ^{1}H NMR of the crude product after catalyst removal.
[c] Determined on a chiral HPLC column.
[d] Calculated from $[\alpha]_D$; $[\alpha]_{lit}$: −100.8° (*c* 1, $CHCl_3$).

might be responsible for this observation. This means that at high (local) concentrations alternative catalytic species and/or catalytic cycles can exist by increasing or decreasing the activity and/or selectivity. Also without a dendritic support different species may be present. At higher concentrations there might even be a higher tendency to bridged or even π-π-stacking or coordination oligomers and polymers with a different activity and/or selectivity than the unimolecular salen complexes. Such coordination polymers have also been postulated by Jacobsen et al.[13c] Changes in enantioselectivity (and yields) with changing catalyst concentration have been observed with other catalytic systems,[32] so it can be assumed that an optimum catalyst concentration exists. However, as mentioned above, with the supported ligands the same chiral induction was observed at different polymer concentrations. The constant local catalyst concentration in the polymer shell, which should not be dependent on the polymer concentration, is assumed to be a reason for this finding.[11]

Besides the influence of solvent, substrate concentration, and temperature, Jacobsen and co-workers reported that the identity of the catalyst counterion is a critical parameter for reaching high enantioselectivity. The authors examined chromium(III) salen complexes bearing chloride, azide, hexafluoroantimonate, and tetrafluoroborate anions. In combination with powdered 4 Å molecular sieves the latter provided the best results.[29] Therefore the polymer supported tetrafluoroborate complex **15** was synthesized. Indeed a higher enantioselectivity (78% *ee*) was observed in a comparative experiment (Table 1, entry 5). However, due to the low conversion (13%), this may rather be ascribed to a conversion-selectivity dependence.[11]

In the case of the catalyst **21**, hexafluoroantimonate was used as anion. Increasing the amount of the catalyst used from 1.9 to 5 to 10 mol% (Table 1, Entries 6 to 8), the conversion increased up to 98% and is significantly the same as for catalyst **13**. The enantiomeric excess is approximately constant; this result confirms again the independence of the polymer concentration from the chiral induction.

Table 2. Recycling of catalysts **13** and **21** in the Diels–Alder reaction.[a]

	Cycle 1 Conv.[b]	*ee*[c]	Cycle 2 Conv.[b]	*ee*[c]	Cycle 3 Conv.[b]	*ee*[c]
PG-Cr/Cl **13**	96 %	65 %	98 %	59 %	98 %	62 %
PG-Cr/SbF_6 **21**	99 %	63 %	89 %	53 %	96 %	39 %

[a] Using 5 mol % of catalyst at 4 °C.
[b] According to ^{1}H NMR of the crude product after catalyst removal.
[c] Calculated from $[\alpha]_D$; $[\alpha]_{lit}$: −100.8° (*c* 1, $CHCl_3$).

The recycling of the polymer supported Cr-salen complex was studied in regard to using the catalysts **13** and **21**. The recycling of the catalysts was studied by dialysis of the mixture after the Diels–Alder reaction between Danishefsky's diene and benzaldehyde and subsequent hydrolysis. The catalysts were dried and reused under the same conditions as the first run. The catalytic reactivity of both reused catalysts remained almost unchanged after two cycles, and the enantioselectivity fell gradually (Table 2).

One of the main advantages of dendrimeric catalysts is the retainability in continuously operated systems by applying membrane technology.[33] Application of this technology is especially attractive in those cases where a high catalyst loading is required to reach acceptable reaction times.[1d] Extremely high retention of molecular-weight enlarged catalysts (chemzymes) is a prerequisite for their practical application in a continuous reactor to reach long operation times. The importance of retention (R) is shown in Figure 4 which indicates that small changes in retention make a considerable difference in the time in which a polymer is flushed out from the reactor.

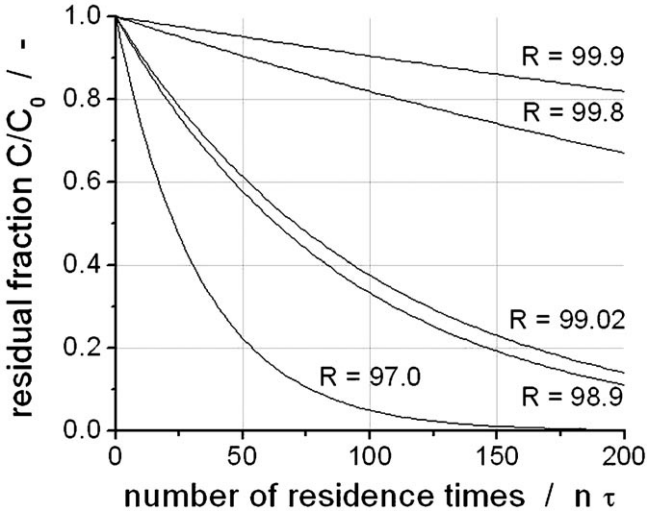


Figure 4. Theoretical scheme for residual concentration of the molecular weight-enlarged catalyst as a function of the number of residence times (residence time: $\tau = v$[reactor volume]/f [flow rate]).

For estimating the retention in the case of PG supported catalyst, the gravimetric method was applied. The experimental set is described in Laue et al.[16b]

The solvent was pumped through the reactor using a piston pump (Pharmacia 200). The stirred ultrafiltration cell made of PEEK (polyether ether ketone) with a reaction volume of 3 mL was applied. The membranes were preconditioned in the solvent overnight before being installed in the reactor. Prior to addition of the molecular weight enlarged catalyst the membrane was thoroughly washed with solvent until a constant pressure of 2.5 MPa was reached. Then a specific amount of polymer (*ca.* 200 mg) was injected to the CMR and was washed with solvent until a certain number of residence times were collected ($\Sigma\tau =$ 200).

The retained and permeated polymers were collected separately and retention was determined using Eq. (1). The results are shown in Table 3.

$$\frac{c}{c_0} = e^{-(1-R).\sum\tau} \Rightarrow R = 1 - \frac{\ln\left(\frac{c_0}{c}\right)}{\sum\tau} \quad (1)$$

Conclusions

In this paper, it has been shown that hyperbranched polyglycerol is suitable as a high loading support for asymmetric catalysis. The polyglycerol-supported unsymmetrical chromium salen ligand was synthesized and successfully used as supported catalyst for hetero-Diels–Alder reactions between Danishefsky's diene and benzaldehyde. This polymeric catalyst showed outstanding catalytic activities (up to 98 % conver-

Table 3. Retention measurements of PG-support.

Polymer	Molecular weight [g mol^{-1}]	Membrane[a]	Solvent	Retention (vol %)
PG-OH **3**	~8000	Starmem 120	Toluene	98.9
PG-Cr/Cl **13**	~4800	Starmem 120	Toluene	99.02

[a] Membrane extraction technology.[34]

sion) and selectivities (up to 78% *ee*) that are comparable to the original catalysts reported by Jacobsen, thus proving the effectiveness of our design criteria. The polymeric catalyst can be easily recycled two times from the reaction mixture, and showed a high retention in the membrane reactor ($\geq$ 99%). Currently, we are investigating the applications of this interesting polymeric catalyst in asymmetric synthesis.

Experimental Section

The characterization data of the compounds are available in the Supporting Information.

3-*tert*-Butyl-5-(chloromethyl)-2-hydroxybenzaldehyde 6

In a one-necked flask with a magnetic stirring bar 1,3,5-trioxane (4.79 g, 52.2 mmol, 2 equivs.), 3-*tert*-butyl-hydroxybenzaldehyde **5** (4.55 mL, 4.74 g, 26.6 mmol), and concentrated aqueous HCl (100 mL) were mixed. The mixture was stirred for 3 days at 40 °C. Full conversion was ascertained *via* TLC [isohexane/EtOAc, 30:1, R_f(product) = 0, R_f(substrate) = 0.43] and diethyl ether was added. After phase separation, the organic layer was washed three times with both saturated aqueous $NaHCO_3$ and brine. Drying with $MgSO_4$ and evaporation of the solvent afforded **6** as yellow crystals; yield: 99%.

3-*tert*-Butyl-5-polyglyceryloxymethylsalicylaldehyde 7

This reaction was performed under an inert gas atmosphere and with exclusion of water. In a 250-mL Schlenk flask with a magnetic stirrer, polyglycerol **3** (2.58 g, 13.5 mmol g^{-1}, 34.9 mmol OH groups) was dried for 2 h in high vacuum at 60 °C. Subsequently, the polymer was dissolved in absolute DMF (30 mL) and NaH (95%) (2.11 g, 83.7 mmol, 2 equivs.) was added. While stirring, a solution of 3-*tert*-butyl-5-chloromethylsalicylaldehyde **6** (9.45 g, 41.8 mmol, 1.2 equivs.) in absolute DMF (20 mL) was dropped into the mixture. After this, the color of the solution changed from bright yellow to green and then to dark brown, and the development of gas was observed. It was heated to 80 °C for 2 h, after which, 2 N HCl was added drop by drop till neutralization. Then when the drop reached the mixture, a yellow precipitate formed. Chloroform was added and the phases were separated. Following this, the aqueous phase was extracted three times with chloroform. The combined brown organic layers were washed with saturated aqueous $NaHCO_3$ and H_2O each three times, upon which considerable phase separation problems occurred. After drying over $MgSO_4$ and concentration, the crude product was dialyzed in toluene followed by a second dialysis in CH_2Cl_2; conversion: 68%; yield: 81%.

(*R,R*)-1,2-Diaminocyclohexane Monohydrochloride 9

This reaction was performed under an inert gas atmosphere and with exclusion of water. In a 50-mL Schlenk flask with a magnetic stirrer, (*R,R*)-(−)-diaminocyclohexane **8** (0.78 g, 6.85 mmol) was dissolved in dry diethyl ether. Under intensive stirring 2 N HCl in diethyl ether (3.4 mL, 6.9 mmol, 1 equiv.) was added, upon which a white solid precipitated. After stirring overnight at room temperature, the mixture was filtered and the residue was washed with diethyl ether and dried under high vacuum; yield: 96%.

N-(3′,5′-Di-*tert*-butylsalicylidene)-(*R,R*)-1,2-diaminocyclohexane Monohydrochloride 11

This reaction was performed under an inert gas atmosphere and with exclusion of water. In a 100-mL Schlenk flask with a magnetic stirrer and septum, (*R,R*)-1,2-diaminocyclohexane monohydrochloride **9** (0.63 g, 4.2 mmol) was dissolved in a mixture of absolute MeOH and absolute EtOH (1:1) (30 mL). Under stirring, 3,5-di-*tert*-butylsalicylaldehyde **10** (0.98 g, 4.2 mmol, 1 equiv) was added in one go, upon which a yellow hue arose. The mixture was stirred at room temperature for 24 h. Evaporation of the solvents under vacuum and drying at high vacuum furnished a yellow solid which was then used without further purification; conversion: 83%; yield: quantitative.

N-(3′,5′-Di-*tert*-butylsalicylidene)-*N*′-(3″-*tert*-butyl-5″-polyglyceryloxymethylsalicylidene)-(*R,R*)-1,2-diaminocyclohexane using *N*-(3′,5′-Di-*tert*-butylsalicylidene)-(*R,R*)-1,2-diaminocyclohexane Monohydrochloride 12

This reaction was performed under an inert gas atmosphere and with exclusion of water. In a 100-mL Schlenk flask with a magnetic stirrer and septum *N*-(3′,5′-di-*tert*-butylsalicylidene-(*R,R*)-1,2-diaminocyclohexane monohydrochloride **11** (1.65 g of the crude product containing 17% starting material, 3.74 mmol, 1 equiv.) was dissolved in absolute CH_2Cl_2 (20 mL) and freshly activated 4 Å molecular sieves were added. In a separate 100-mL Schlenk flask 3-*tert*-butyl-5-polyglyceryloxymethylsalicylaldehyde **7** (1.12 g, 3.34 mmol g^{-1}, 3.74 mmol aldehyde groups) was dissolved in absolute CH_2Cl_2 (20 mL) and mixed with absolute NEt_3 (1.1 mL, 0.77 g, 7.5 mmol, 2 equivs.). Under stirring, the resulting solution was dropped rapidly to the solution of **11**. After stirring for 18 h at room temperature, a sample was taken, which showed full conversion of the aldehyde groups of **7** *via* ^{1}H NMR ($CDCl_3$). The mixture was filtered over a frit and the filtrate was transferred into a separation funnel. The organic phase was washed three times with brine and H_2O, respectively, and was dried over Na_2SO_4. Evaporation of the solvent under vacuum furnished the crude product, which contained low molecular weight salen as a by-product (symmetrical salen). The pure polyglycerol-supported salen ligand **12** was obtained after preparative GPC (eluent: $CHCl_3$, flow: 25 mL min^{-1}, detector wavelength: 300 nm) or ultrafiltration in CH_2Cl_2 (8 × 30 mL); yield: 58%; conversion: quantitative.

N-(3′,5′-Di-*tert*-butylsalicylidene)-(*R,R*)-1,2-diaminocyclohexane 14

In a mortar, (*R,R*)-1,2-diaminocyclohexane **8** (0.050 g, 0.44 mmol) was mixed thoroughly with 3,5-di-*tert*-butylsalicylaldehyde **10** (0.103 g, 0.440 mmol), and the mixture was triturated, upon which the color immediately turned inten-

sively yellow and the consistency became slippery. The resulting mixture was dissolved in $CDCl_3$ and analyzed *via* ^{1}H NMR, ^{13}C NMR, H/H-COSY, H/C-COSY, and H/C-long-range-COSY. According to this, it contains diimine (symmetrical salen) (11%) and substrate **8** (15%).

N-(3′-*tert*-Butyl-5′-polyglyceryloxymethylsalicylidene)-*N*′-(3″,5″-di-*tert*-butylsalicylidene)-(*R,R*)-1,2-diaminocyclohexane 12 *via in situ* Formation of *N*-(3′,5′-Di-*tert*-butylsalicylidene)-(*R,R*)-1,2-diaminocyclohexane 14

In a mortar, (*R,R*)-1,2-diaminocyclohexane **8** (0.050 g, 0.44 mmol, 1 equiv.) was mixed thoroughly with 3,5-di-*tert*-butylsalicylaldehyde **10** (0.103 g, 0.440 mmol, 1 equiv.), and the mixture was triturated, upon which the color at once turned intensively yellow and the consistency became slippery. The resulting mixture was taken up in $CHCl_3$ and filtered over a frit to remove remaining undissolved (*R,R*)-1,2-diaminocyclohexane **8**. Under intensive stirring, a solution of 3-*tert*-butyl-5-polyglyceryloxymethylsalicylaldehyde **7** (1.00 g, 3.34 mmol g^{-1}, 3.34 mmol aldehyde groups, 1 equiv.) in *p.a.* $CHCl_3$ (20 mL) was slowly dropped to the filtrate *via* a dropping funnel. After stirring for 0.5 h, the reaction mixture was dried over Na_2SO_4, concentrated under vacuum, and dried at high vacuum. ^{1}H NMR of the crude product indicated full conversion of the polymer-bound aldehyde groups. Subsequent preparative GPC chromatography (eluent: $CHCl_3$, flow: 25 mL min^{-1}, detector wavelength: 300 nm) afforded pure **12**. Alternatively, pure **12** could be obtained *via* ultrafiltration in CH_2Cl_2; yield: 61%; conversion: quantitative.

N-(3′-*tert*-Butyl-5-polyglyceryloxymethylsalicylidene)-*N*′-(3″,5″-di-*tert*-butylsalicylidene)-(*R,R*)-cyclohexane-(1,2)-diaminochromium(III) Chloride 13

This reaction was performed under an inert gas atmosphere and with exclusion of water. In a 50-mL Schlenk flask with a magnetic stirrer, to water free $CrCl_2$ (0.009 g, 0.07 mmol, 2 equivs.) was added a solution of *N*-(3′-*tert*-butyl-5′-polyglyceryloxymethylsalicylidene)-*N*′-(3″,5″-di-*tert*-butylsalicylidene)-(*R,R*)-(1,2)-diaminocyclohexane **12** (0.021 g, 1.6 mmol g^{-1}, 0.035 mmol ligand) in absolute THF (10 mL) in one portion. In doing so, the color of the mixture shifted from yellowish green over orange-brown to brown. The mixture was stirred at room temperature for 24 h and was then concentrated in an air-stream to accomplish the complete oxidation of chromium. TBME was added, and a green brown precipitate formed which was soluble in MeOH. The TBME phase was washed with saturated aqueous NH_4Cl and with brine, each three times. The organic layer was dried over Na_2SO_4, concentrated under vacuum, and dried at high vacuum; yields: 51–73%; conversion according to ICP-AES: 10–100%.

N-(3′-*tert*-Butyl-5-polyglyceryloxymethylsalicylidene)-*N*′-(3″,5″-di-*tert*-butylsalicylidene)-(*R,R*)-cyclohexane-(1,2)-diaminochromium(III) Tetrafluoroborate 15

This reaction was performed under an inert gas atmosphere and with exclusion of water. In a 50-mL Schlenk flask with a magnetic stirrer, to $AgBF_4$ (0.003 g, 0.01 mmol, 1.25 equivs.) was added a solution of *N*-(3′-*tert*-butyl-5-polyglyceryloxymethylsalicylidene)-*N*′-3″,5″-di-*tert*-butylsalicylidene)-(*R,R*)-cyclohexane-(1,2)-diaminochromium(III) chloride **13** (0.01 g, 0.8 mmol g^{-1}, 0.008 mmol chromium complex) in absolute TBME (10 mL). The flask was wrapped with aluminium foil, and the mixture was stirred in the dark at room temperature for 24 h, after which a black precipitate formed. Filtration over Celite® resulted in a yellow brown filtrate and a black residue. The former was concentrated under vacuum and dried at high vacuum; yield: 68%.

Methyl 2-(4-Hydroxyphenyl)acetate 17

To a solution of 4-hydroxyphenylacetic acid **16** (3.014 g, 19.09 mmol) in methanol (100 mL), was added a catalytic amount of H_2SO_4 and the mixture was refluxed overnight. The solvent was removed under vacuum affording **17**; yield: quantitative.

Methyl 2-(3-*tert*-Butyl-4-hydroxyphenyl)acetate 18

A mixture of methyl 2-(4-hydroxyphenyl)acetate **17** (2.99 g, 18.0 mmol), *tert*-butyl alcohol (4.01 g, 54.0 mmol) and phosphoric acid (5.30 g, 54.0 mmol) was stirred at 75–80 °C for 8 h. After cooling to room temperature, the reaction mixture was concentrated under vacuum. The mixture was dissolved in CH_2Cl_2 (40 mL), washed with water (40 mL), saturated $NaHCO_3$ (3 × 40 mL) and brine (40 mL). The organic phase was dried over Na_2SO_4 and the solvent removed; yield: 81%.

Methyl 2-(3-*tert*-Butyl-5-formyl-4-hydroxyphenyl)-acetate 19

A mixture of methyl 2-(3-*tert*-butyl-4-hydroxyphenyl)acetate **18** (2.93 g, 13.20 mmol), hexamethylenetetramine (1.892 g, 13.5 mmol), and trifluoroacetic acid (27 mL) was heated at reflux during 9 h. The reaction mixture was cooled at room temperature and 2 N HCl (100 mL) was added. The mixture was extracted with CH_2Cl_2, the extract was washed with brine and dried over Na_2SO_4. The solvent was removed under vacuum. Purification by column chromatography on silica gel, using *n*-hexane/EtOAc, afforded pure **19**; yield: 72%.

2-(3-*tert*-Butyl-5-formyl-4-hydroxyphenyl)acetic Acid 20

To a solution of methyl 2-(3-*tert*-butyl-5-formyl-4-hydroxyphenyl)acetate **19** (2.0 g, 8.0 mmol) in a (1:1) mixture of MeOH and THF (240 mL) was added a solution of LiOH (1.15 g, 48.0 mmol) in H_2O (40 mL). The reaction mixture was stirred at 60 °C for 2 h and the solvent was evaporated under vacuum. Then the residue was diluted with CH_2Cl_2, poured into 1 N HCl, and the aqueous layer was extracted 2 times with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, and the solvent was removed under vacuum; yield: 96%.

N-(3′-*tert*-Butyl-5-(*N*-polyglyceryl)methylamidesalicylidene)-*N*′-(3″,5″-di-*tert*-butylsalicylidene)-(*R,R*)-cyclohexane-(1,2)-diaminochromium(III) Hexafluoroantimonate 21

To a solution of 2-(3-*tert*-butyl-5-formyl-4-hydroxyphenyl)-acetic acid **20** (0.236 g, 1.0 mmol) and 3,5-di-*tert*-butyl-2-hydroxybenzaldehyde **10** (0.703 g, 3.0 mmol, 3 equivs.) in a mixture of absolute THF (6 mL) and absolute ethanol (6 mL) was added (*R*,*R*)-1,2-diaminocyclohexane **8** (0.228 g, 2.0 mmol, 2 equivs.). The reaction mixture was stirred at room temperature for 24 h. The solvent was removed under vacuum. In a flask under an inert atmosphere, the reaction mixture was charged with a solution of in dry THF. Anhydrous $CrCl_2$ (1 equiv) was added and the resulting solution was stirred during 20 h. After this time, the reaction mixture was exposed to air overnight. It was diluted with TBME (30 mL), washed with brine (3×10 mL), and a saturated aqueous solution of NH_4Cl. The organic layer was dried over Na_2SO_4 and the solvent was removed under vacuum.

In a flask under an N_2 atmosphere, the reaction mixture was dissolved in dry CH_2Cl_2 (60 mL) and $AgSbF_6$ (1.2 equivs.) was added. The reaction mixture was stirred at room temperature in the dark for 24 h, filtered over Celite® and the filtrate was concentrated under vacuum.

The resulting product was dissolved in CH_2Cl_2 (30 mL) and pentaflurophenol (1 equiv.) and DCC (1 equiv.) were added. The reaction mixture was stirred at room temperature for 48 h and the solvent was removed under vacuum.

The mixture was dissolved in DMF (10 mL) and added to a solution of PG-NH_2 (40 %) (96 mg, 5.4 mmol of NH_2 g^{-1}, 0.52 mmol) in DMF (10 mL). The reaction mixture was stirred under reflux for 2 h. The solvent was removed under vacuum and purification by dialysis for 50 h in $CHCl_3$ afforded **21** as a brown solid; yield: 24 %.

General Procedure for the Hetero-Diels–Alder reaction between *trans*-1-Methoxy-3-trimethylsiloxy-1,3-butadiene (Danishefsky's Diene) and Benzaldehyde: Synthesis of 2-phenyl-2,3-dihydro-4*H*-pyran-4-one 22

This reaction was performed under an inert gas atmosphere and with exclusion of water. In a 50-mL Schlenk tube with magnetic stirrer and septum, the catalyst (0.005–0.05 equivs.) was dissolved in an appropriate solvent (TBME for the Cr catalysts **13**, **15** and **23** or CH_2Cl_2 for the Cr catalyst **21**). After addition of freshly activated powdered molecular sieves (4 Å) and freshly distilled benzaldehyde, the mixture was cooled down to the desired temperature. *trans*-1-Methoxy-3-trimethylsiloxy-1,3-butadiene (Danishefsky's diene) (1 equiv.) was added and the mixture was stirred at reduced temperature. For reaction control, a small sample was taken from the reaction mixture, diluted with TBME, mixed with one drop of TFA and, after 5 min, shaken with H_2O, and the reaction progress was followed by TLC. When the reaction had finished, three drops of TFA were added to the reaction mixture, which was stirred for another 5 min at the reduced temperature and subsequently while warming up to room temperature. It was filtered over Celite®, the filtrate was concentrated under vacuum, and the catalyst was recycled by dialysis in $CHCl_3$ for 48 h. The filtrate was concentrated under vacuum, taken up in isohexane/EtOAc (1:1), and filtered over silica gel. The conversion was determined from this silica filtrate by means of ^{1}H NMR. To isolate the pure product, the crude mixture was purified *via* flash chromatography using as eluent: isohexane/EtOAc (3:1). To establish a method for the determination of the optical purity of **22**, the racemate was synthesized following the same procedure as described above but with Ti(O-*i*-Pr)$_4$ as catalyst. The optical purity was determined on a chiral HPLC column [Chiralcel OD, eluent: heptane/2-propanol, 9:1, flow: 1 mL min^{-1}, injection volume: 5 μL, $t_R(S) = 11.3$ min, $t_R(R) = 13.1$ min].

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