

# Coordination of Cr<sup>III</sup>(salen) on functionalised silica for asymmetric ring opening reactions of epoxides

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The heterogeneous asymmetric ring opening (ARO) of *meso*-epoxides with trimethylsilylazide (TMSN<sub>3</sub>) catalysed by a Cr(salen) catalyst coordinated on an aminopropyl functionalised silica material combines good enantioselectivities with high conversions and suffers low leaching (<1%).

**KEY WORDS:** asymmetric ring opening; epoxides; coordinative anchoring; chiral Cr(salen) complex.

## 1. Introduction

The enantioselective addition of nucleophiles to epoxides is an attractive strategy for asymmetric synthesis. Particularly the desymmetrisation of *meso*-epoxides is of interest since it simultaneously establishes two adjacent stereogenic centres [1]. In this context, the asymmetric ring opening (ARO) of *meso*-epoxides catalysed by chiral metal complexes has emerged as an important synthetic approach for the preparation of valuable chiral building blocks. A variety of nucleophiles have been employed successfully in ARO reactions, with the majority of these being heteroatom-based [2]; of which the Cr<sup>III</sup>(salen) catalysed addition of TMSN<sub>3</sub> developed by Jacobsen and co-workers [3] is the best procedure to date (figure 1).

Whereas several heterogenisation strategies have been described for this Cr<sup>III</sup>(salen) catalyst, none could combine low leaching rates with high enantioselectivities and conversions for the ARO of *meso*-epoxides. Catalysts chemically bonded via ligand tethering resulted in catalytic systems with little or no leaching but the reduced activity and selectivity were major drawbacks [3]. The changes in the steric environment of the transition metal reduce the enantioselective discrimination power of the catalyst [4,5]. The encapsulation of the complex in the large pores of zeolites experienced a lowering of the asymmetric induction ability of the supported complex and the loss of the cooperative catalytic effect [6]. The complexes immobilised by coordination suffered from significant leaching [4]. The Cr(salen) complex impregnated on silica offers only moderate enantioselectivities for the ARO of *meso*-epoxides [7].

## 2. Experimental

Nevertheless, the option to immobilise the Cr(salen) complex by coordination was further investigated since the coordination procedure [8] as such is straightforward and fast. Moreover, today one can rely on the availability of the commercial catalyst [9], the issue of redesigning the ligand can thus be avoided.

### 2.1. Preparation of silica

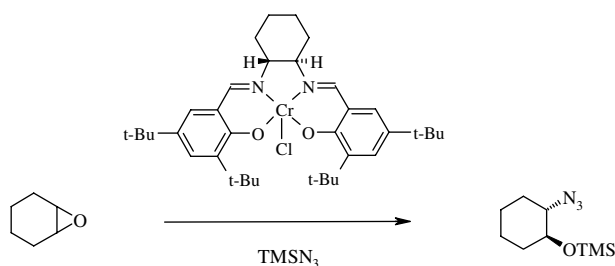
In a first step, the inorganic support material in case silica, was functionalised with amino-groups. The silica material [10] was dried in a vacuum oven for 12 h at 60 °C and suspended in dry toluene. 3-Aminopropyl trimethoxysilane (~2.5 mmol silane per gram of silica) was added and the resulting suspension was refluxed under nitrogen atmosphere for 24 h. The silica material was filtered and washed overnight with a Soxhlet extractor using dichloromethane as solvent (figure 2). The aminopropyl loading was determined by thermogravimetric analysis (TGA) and was found to be 0.85 mmol/g.

### 2.2. Preparation of catalyst

The second step in the synthesis comprises of the coordination of the Cr(salen) catalyst with the aminogroups on the support surface. The Cr(salen) catalyst was dissolved in acetonitrile and 1.25 eq. of AgClO<sub>4</sub> was added. Thus the chloride could be removed from the coordination sphere of the complex. After filtration through celite and solvent removal, dichloromethane and the functionalised silica material were added. The resulting suspension was stirred at room temperature for 24 h (figure 3). After a Soxhlet extraction with dichloromethane and drying, the catalyst was ready to use. The catalyst loading on the silica surface was determined with TGA to be 0.185 mmol/g of silica.

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Figure 1. ARO of cyclohexene oxide catalysed by (*R,R*)-Cr<sup>III</sup>(salen).

### 2.3. Asymmetric ring opening reactions

The catalyst (50 mg of loaded silica material) was loaded in a small glass vial equipped with a stirring bar. The solvent (3 mL), internal standard (75  $\mu$ L) and the epoxide substrate (in a 3 mol% catalyst/substrate ratio) are added. After 10 minutes of stirring, TMSN<sub>3</sub> is added (0.6, 0.7 or 1.1 equivalent, for the terminal epoxides, limonene epoxides and *meso*-epoxides respectively) and the vial is adequately stirred at room temperature to keep the silica material in suspension. The reaction is followed by chiral GC analysis [11]. After reaction, the catalyst can easily be recovered by means of sedimentation/filtration.

## 3. Results and discussion

Although the anchoring of Cr(salen) complexes by coordination has been described previously, the results were disappointing: 20–45% leaching in a single catalytic run in the ARO of cyclohexene oxide [4], and rapidly decreasing reactivity and selectivity upon recycling for asymmetric epoxidation [12].

The main issue in the application of coordinative anchoring is leaching. In this context, the choice of solvent is crucial. In homogeneous reaction conditions, the Cr(salen) catalysed ARO reactions are typically performed in ethereal solvents. These coordinating solvents are preferred because they easily dissolve the catalyst and allow very high reactivity and optimal selectivity [13]. In contrast to the superiority of ethereal solvents in homogeneous conditions, these solvents should be avoided for heterogeneous reactions since they greatly enhance leaching due to ligand exchange processes

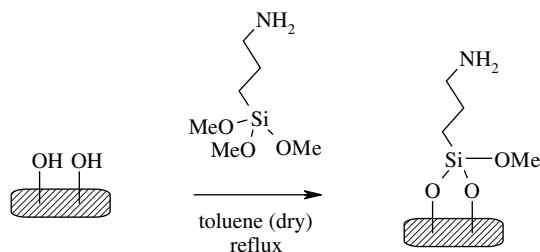
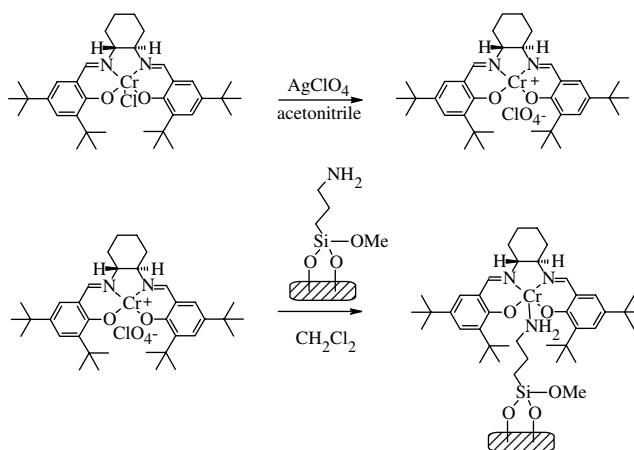


Figure 2. Modification of the silica surface.

Figure 3. Preparation of a heterogeneous (*R,R*)-Cr<sup>III</sup>(salen) catalyst.

occurring during the reaction. To assess the influence of the solvent on leaching, a range of solvents was screened. Apolar, noncoordinating solvents such as hexane, octane and toluene proved to be an acceptable alternative (figure 4). Hexane was preferred since it offered somewhat higher selectivities for the ARO reactions.

Since the catalyst loading on the support material also influences the leaching rates, a silica material with a lower catalyst loading (0.185 mmol/g) than those described in literature [4] (1.0 mmol/g) was tested.

### 3.1. Catalytic performance

These two elements were combined and the catalyst was tested for a range of substrates using hexane as solvent. In this screening it became obvious that the system performed the ARO of *meso*-epoxides with high selectivity (up to 77% e.e.). The ring opening of aliphatic terminal epoxides occurred with very good selectivity (over 94% e.e.) and the resolution of the (+) limonene epoxide diastereomers [14] displays high selectivity as well. The leaching proved to be substrate dependant, a leaching of 2.7% was found for epoxyhexane, for all other substrates it was less than 1.1% as determined by UV–VIS absorption spectroscopy at 430 nm [15]. An overview of the catalytic results is given in figure 5.

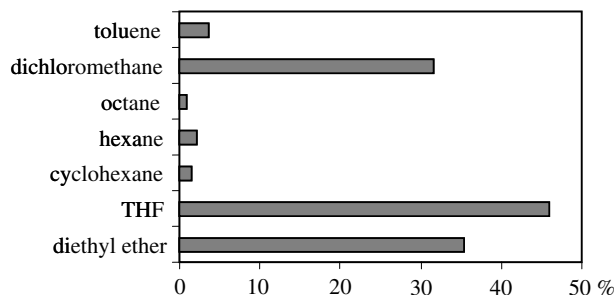


Figure 4. Leaching rates for different solvents after 24 h stirring.

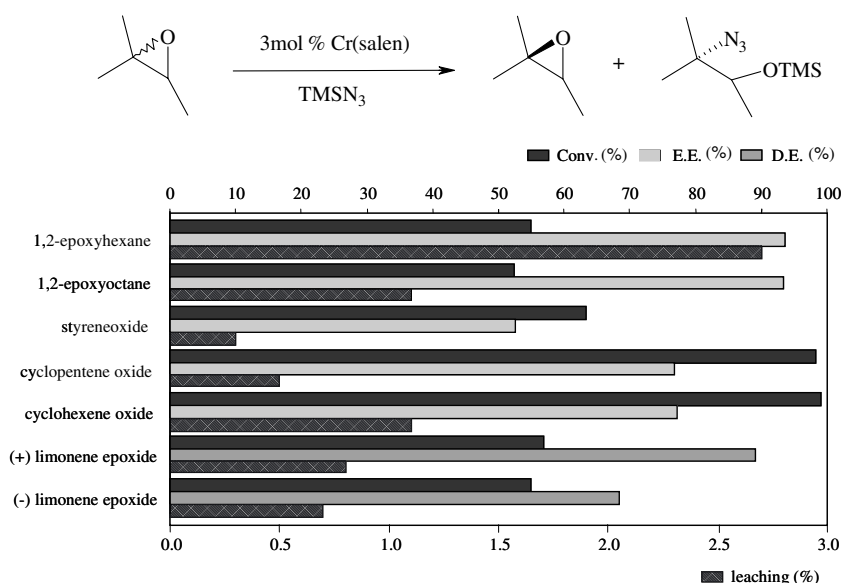


Figure 5. Substrate screening for an ARO reaction at 295 K using a 3 mol% catalyst/substrate ratio, hexane as solvent and toluene as internal standard. The equivalents of TMSN<sub>3</sub> used depend on substrate class: 0.6 eq. for the terminal epoxides, 0.7 eq. for the limonene epoxides and 1.1 eq. for the *meso*-epoxides. The optimal conversion is 100% for the *meso*-epoxides (cyclopentene and cyclohexene oxide); for the other substrates it is 50%.

### 3.2. Heterogeneity test

To confirm that the ARO reactions are catalysed heterogeneously and that the small amounts of leached catalyst do not contribute to the conversion, a split test for heterogeneity was performed. Of all tested substrates, epoxyhexane suffered from the largest leaching degree (2.7%), hence it was selected as substrate for this test.

Two samples have been taken during the reaction: the reaction mixture was subjected to centrifugation and 1 mL of supernatant was sampled in small vials. These samples were analysed in time and the change of the conversion was investigated. As the conversion levels do not increase, this test undoubtedly corroborates the heterogeneous character of the ARO catalysis (figure 6).

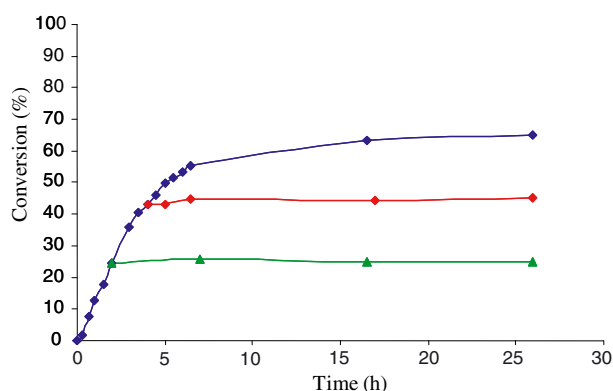
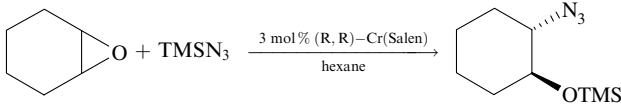


Figure 6. Heterogeneity test.

### 3.3. Catalyst recycling

A recycling experiment in which the same heterogeneous catalyst is used for 10 consecutive runs in the ARO of cyclohexene oxide demonstrates that the supported catalyst continues to offer excellent reactivity and good enantioselectivity. The catalytic properties of the catalyst during the recycling experiment are summarised in table 1. The overall leaching over ten runs

Table 1  
Catalytic results of the recycling experiment



Run	Reaction time (h)	Conversion (%)	E.E. (%)	Leaching (%)
1	12	99.5	65.4	0.9
2	18	100.0	67.9	0.8
3	18	100.0	68.7	0.5
4	18	100.0	73.3	1.0
5	19	99.3	73.1	1.0
6	21	99.5	75.0	0.7
7	21	99.5	75.5	0.6
8	23	99.0	76.6	0.6
9	24	99.1	77.2	0.8
10	24	99.2	76.9	0.9

50 mg catalyst; 3 mL hexane; toluene (75  $\mu$ L) = internal standard; catalyst/substrate ratio = 3 mol%; 1.1 eq. TMSN<sub>3</sub>, stirred batch reactor at RT.

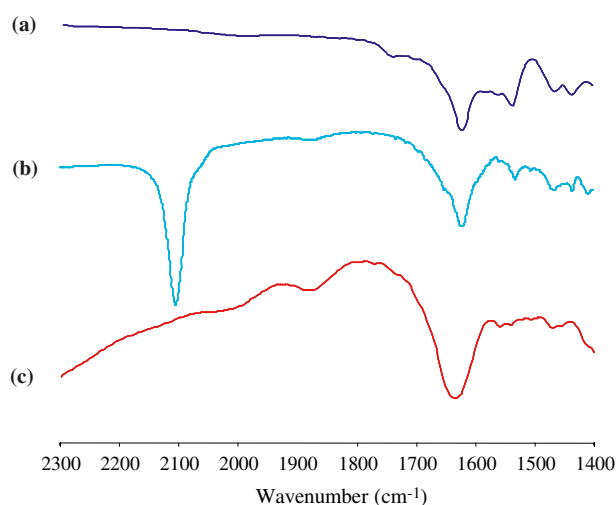


Figure 7. Infrared spectrum of (a) fresh catalyst, (b) used catalyst (10 runs) and (c) functionalised silica material.

amounts to ~8%. Note that the ARO of cyclohexene oxide in homogeneous conditions offers e.e. values of 85% [2]. With e.e.'s up to 77%, this heterogeneous system offers a possible alternative for the homogeneous ARO. The slightly lower selectivity is possibly due to the free aminopropyl groups on the silica surface. They may be responsible for a blanco reaction in which the epoxides are derivatised in a random fashion. Also during the first run, the transformation of the pre-catalyst Cr(salen)Cl to the actually active species Cr(salen)N<sub>3</sub> causes the formation of ring opened products with reduced selectivity [3].

For the terminal epoxides an increase in leaching can be observed upon recycling [16]. This can be due to the surfactant character of these epoxides, making the complex more soluble in hexane upon coordination.

The remarkable increase in reaction time for the second run compared to the first, can possibly be due to the formation of six-coordinate Cr<sup>III</sup> species which are relatively inert [17]. The steady increase of the reaction time (after run 2) is due to the fragmentation of the silica support caused by the vigorous stirring in the batch reactor. The application of this heterogeneous catalyst in a continuous flow process can avoid this problem. Preliminary experiments indicate good results for this type of reactor: good conversions and high selectivities can be obtained combined with a considerably longer process time than in a batch reactor.

Evidence for the Cr–NH<sub>2</sub> interaction was found in IR spectra [18] (figure 7). The NH<sub>2</sub> bending signal of both the fresh and the recycled catalyst can be found at ~1615 cm<sup>-1</sup> and differs from the NH<sub>2</sub> bending signal of the aminopropyl functionalised silica material (~1630 cm<sup>-1</sup>) [19]. Moreover an intense azide stretch vibration (~2100 cm<sup>-1</sup>) could be observed, corresponding with the ring opened product still bound to the catalyst [20]. Upon addition of TMSN<sub>3</sub>, this

species is converted into the active Cr(salen)N<sub>3</sub> catalyst and the ring opened product is released [13]. Therefore this demonstrates the presence of active catalyst after 10 runs.

#### 4. Conclusion

The ARO of cyclohexene oxide in homogeneous conditions offers e.e. values of 85%. With e.e.'s up to 77% this heterogeneous system offers a good alternative for the homogeneous ARO. This is the first easily recyclable heterogeneous catalyst for the ARO of *meso*-epoxides that combines high selectivity with optimal conversion levels.

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- [8] The procedure used for the preparation of the catalyst is based on references [4] and [12] with some small modifications.
- [9] (R,R)-Cr<sup>III</sup>(salen) catalyst was bought from Aldrich.
- [10] Silica gel 60 for preparative column chromatography was bought from Fluka.
- [11] All enantiomeric/diastereomeric excesses were determined by chiral GC on a Chrompack-CHIRASIL-DEX CB column (0.32 mm × 0.25 μm × 25 m) using FID detection.
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- [15] Cr<sup>3+</sup> ions have two absorption bands at about 430 and 614 nm due to d-d transitions.
- [16] In a recycling experiment for the ARO of epoxyhexane over three consecutive runs, leaching increased from 2% in the first run to 5 and 8% in the second and third run respectively. An analogous increase in leaching is found for epoxyoctane.
- [17] Depending on ligand type, hexacoordinate Cr<sup>3+</sup> species are relatively inert.
- [18] The IR analyses were performed on KBr samples of the silica material used for 10 runs.
- [19] The imine stretch signal is found at 1620 cm<sup>-1</sup> as well, but its intensity is small in comparison with the NH<sub>2</sub> bending signal. Therefore the resulting IR absorption in this region is mainly due to the NH<sub>2</sub> bending.
- [20] The IR absorption signal at 2100 cm<sup>-1</sup> corresponds with an organic azide stretch. This can be due to ring opened product still bound to the catalyst or ring opened product adsorbed on the silica material. Nevertheless, because of the small excess of TMSN<sub>3</sub> present in the reaction mixture, a small shoulder can be observed at 2050 cm<sup>-1</sup>, typically for the active Cr(salen)N<sub>3</sub> species [13].