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ARTICLE TYPE

Molecularly enlarged *S,S*-BnTsDPEN ligands for iron-catalyzed asymmetric olefin epoxidation reactions using hydrogen peroxide

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A convenient approach for the anchoring of *S,S*-BnTsDPEN ligands (*S,S*-*N*-tosyl-1,2-diphenylethylenediamine)to branched carbosilane scaffolds was investigated. It is based on a high-yielding reductive amination reaction between commercially available *S,S*-TsDPEN and readily accessible carbosilanes furnished with benzaldehyde terminal fragments. These molecularly enlarged ligands, bearing four *S,S*-BnTsDPEN units, and their simplified monomeric and "dimeric" analogues were evaluated in iron(III)-catalyzed asymmetric *trans*-stilbene epoxidation reactions using hydrogen peroxide as an environmentally benign oxidant. The catalytic investigations showed a large degree of variation in the activity and stereoselectivity of the series of DPEN catalysts. In combination with ESI-MS investigations, these data revealed an important role for the ligand orientation in determining the overall activity of the catalyst system. Accordingly, a proper deign of the molecularly enlarged ligands resulted in a fully retained activity and selectivity in catalysis. Finally, a number of strategies for the recovery and reuse of the best performing carbosilane-tethered DPEN ligands were explored.

Introduction

Enantiopure epoxides have found a wide application in organic synthesis.[1] For instance, they are key precursors and intermediates in the preparation of vicinal diols, aminoalcohols, and diamines, each of which are found abundantly in chiral auxiliaries, ligands, and organocatalysts.[2] Among the general strategies[1-5] for the assembly of an oxirane ring, a direct olefin oxidation[5] is economically appealing and it might have the least negative ecological impact, utilizing air or hydrogen peroxide as the terminal oxidant.

Recently, Beller et al. reported on the application of the *S,S*-BnTsDPEN ligand (*S,S*-**1**), a benzylated derivative of *S,S*-TsDPEN, in the high yielding and enantioselective iron(III)-catalyzed epoxidation of aromatic alkenes with hydrogen peroxide.[6] The overall catalytic protocol is easy to apply at ambient conditions, but requires column chromatography to separate the epoxide product from substantial sacrificial amounts of catalyst residue (ca. 10-20 mol%). More importantly, the most expensive part of the catalytic system is the optically pure ligand, whereas the total value of the other components, i.e. hydrated ferric chloride, 2,6-pyridinedicarboxylic acid (H_2PDC) and *tert*-amyl alcohol as the reaction solvent, does not exceed €2 per mmol of substrate.

We envisioned that the ability to recycle the *S,S*-**1** ligand would significantly improve the overall practical use of the catalytic protocol. Most common methodologies aimed at the recycling and reuse of a homogeneous catalyst are associated with the immobilization of the catalyst on a solid support.[7] The separation of such insoluble, heterogenized catalysts from reaction media is straightforward, e.g. by filtration, yet most often such catalysts show a decreased activity and selectivity.[8] Soluble polymeric supports have been shown to be a viable alternative to solid supports, allowing for the immobilized catalysts to maintain their single-site characteristics.[9,10,11a-d] Such molecularly enlarged catalysts are recoverable from reaction solutions by means of precipitation using an anti-solvent or *via* any size discriminative method (e.g. membrane nanofiltration).[12]

Information on the parent catalyst composition, structure, reaction and deactivation pathways are key hints aiding to choose a proper immobilization strategy. For epoxidations using *S,S*-**1**, the reported ratio of catalyst components Fe/*S,S*-**1**/H_2PDC 1:2.4:1 (i.e. over-stoichiometric ligand loading) and the available spectral data suggest that the formation of $[Fe^{III}Cl_2(S,S\text{-}\mathbf{1})_2(H_2PDPC)]^+$ ions is of importance.[6] Accordingly, it was decided to explore soluble symmetric molecules bearing multiple *S,S*-TsDPEN units. The application of such structures in catalysis could be beneficial, because of ligand pre-orientation and pre-concentration phenomena in oligomeric entities, which can facilitate the formation of active species with a 2:1 Fe/L ratio.

A number of molecularly-enlarged DPEN-based catalysts have been reported to date.[11e-h] All of them were developed

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exclusively for hydrogenation or hydrogen transfer processes and, unfortunately, contain fragments that are vulnerable to oxidation or hydrolysis, or that can potentially coordinate to a metal center. Examples include Fréchet-type benzylic dendrons, PEG-moieties, and Newcome-type polyamides. Herein, we report on a detailed study on the design and preparation of molecularly enlarged carbosilane analogues of *S,S*-**1** and on their use in asymmetric alkene epoxidation reactions. In addition, we provide a prospective on the recovery and reuse of these ligands in catalysis.

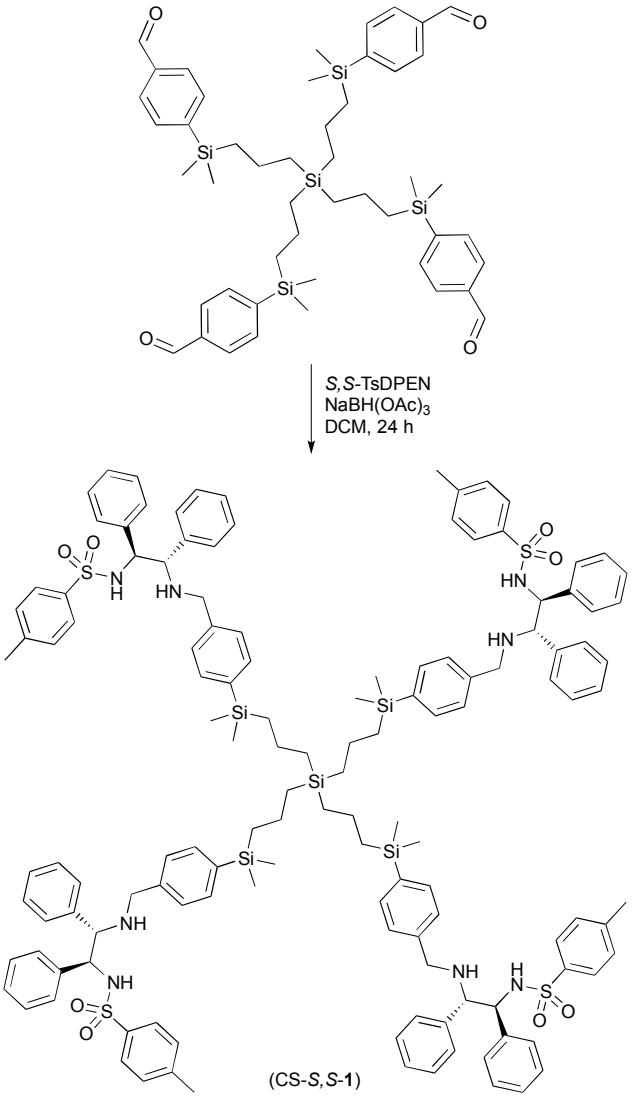
Results and Discussion

The carbosilane-linked chiral ligand CS-*S,S*-**1** bearing four *S,S*-BnTsDPEN units was prepared *via* a quantitative one-pot reductive amination reaction[13] between the branched aldehyde reported by Van Koten et al.[14] and commercially available *S,S*-TsDPEN (Scheme 1). Characteristic signals of the carboxaldehyde support in IR (ν(C=O) 1701 cm^{-1}), ^{1}H-(δ(C(O)H) 10.00 ppm) and ^{13}C-NMR (δ(CO) 192.5 ppm) disappeared within 24 h, indicating the completion of the reaction. The isolated material was efficiently purified using passive membrane dialysis.[15] Size exclusion chromatography (SEC) confirmed the monodispersity (PDI 1.02) of the obtained polymeric material (Page 43 in Supporting Info). In ESI-MS, CS-*S,S*-**1** predominantly appeared as a doubly charged ion with *m/z* 1126.4945 (calcd. for $[M+2H]^{2+}$ 1126.4985).

CS-*S,S*-**1** was investigated in the epoxidation of several *trans*-stilbenes (**2a-d**) under conditions previously developed and optimized for the parent *S,S*-**1** ligand by Beller et al. (Scheme 2).[6] The loading of CS-*S,S*-**1** was adjusted taking into account the total number of DPEN units (see Supporting Information).

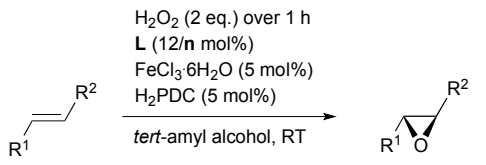
The results of independently reproduced oxidation experiments with *S,S*-**1** were consistent with previously reported data (Table 1). However, in some cases the isolated epoxide yields were higher than the ones previously estimated using GC analysis. This can be attributed to a moderate stability of certain epoxides under flame ionisation detection conditions. For that reason the main epoxide products were also carefully isolated and their composition monitored by NMR. Moreover, no alkene cleavage or epoxide isomerization products were observed by ^{1}H-NMR analysis of crude product mixtures in reactions with *trans*-stilbenes **2a-c**. In contrast, while no essential by-products were detected by GC in the case of **2d** oxidation with *S,S*-**1**, the same crude sample subjected to ^{1}H-NMR analysis appeared to be a complex mixture of products. In addition, the corresponding epoxide **3d** was found to be prone towards degradation upon its purification on silica gel.

Surprisingly, a very low catalytic activity within the normal reaction time of 1 h was observed using CS-*S,S*-**1** for the oxidation **of 2a-d**. Only upon extending the reaction time to 24 h, a substrate conversion of 67% was achieved without extra oxidant addition for *trans*-stilbene (**2a**). The corresponding epoxide (**3a**) was isolated in 23% yield only. CS-*S,S*-**1** demonstrated a moderate chemoselectivity in the epoxidation of substituted stilbenes over a longer reaction time. For instance, the epoxides **3b** and **3c** derived from 4,4'-disubstituted *trans*-stilbenes **2b** and **2c** were isolated in satisfactory 53 and 34% yields, respectively, which corresponds to a reasonable reaction chemoselectivity around 80%.



Scheme 1. Synthesis of optically pure ligand CS-*S,S*-1.

In contrast, epoxide **3d** was only isolated in a modest yield of 8.7%, whereas 59% of the substrate **2d** was consumed. Such a low chemoselectivity (15%) most likely relates to product stability issues, which have been encountered as well when oxidizing **2d** with the parent *S,S*-**1** ligand.



2 **3**

	n:	**L**:
2a, **3a**: $R^1 = R^2$ = -Ph	4	CS-*S,S*-**1**
2b, **3b**: $R^1 = R^2$ = -*p*-tol	1	*S,S*-**1**
2c, **3c**: $R^1 = R^2$ = -*p*-*t*BuPh	1	*S,S*-**4a-c**
2d, **3d**: R^1 = -*p*-*t*BuPh, R^2 = -2-naphtyl	2	*S,S*-**4d**
	4	CS-*S,S*-**5**
	1	CS-*S,S*-**6**

Scheme 2. *trans*-Stilbene epoxidation with DPEN ligands.

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The enantioselectivities of epoxidations carried out with CS-*S,S*-**1** were essentially lower than with the parent monomeric ligand *S,S*-**1**. *Trans*-stilbene oxide (**3a**) was obtained with only 7.7% *ee*. The highest enantiomeric enrichment of the epoxide product obtained with CS-*S,S*-**1** was found for the epoxidation of **2c** and **2d** (36% in both cases), which is roughly two times lower than the values obtained with the original ligand (71 and 73%, respectively). Hence, tetramer CS-*S,S*-**1** can in general be considered as a poor ligand for the epoxidation of the selected substrates, showing neither good activity nor good enantioselectivity.

Table 1. Stilbenes epoxidation with *S,S*-**1** and CS-*S,S*-**1**.[a)]

Entry	Substrate	Ligand	Yield [%][b)] / Conv. [%][c)]	*ee* [%][d,e)]
1[f)]	**2a**	*S,S*-**1**	87[c)]/99	42
2	**2a**	*S,S*-**1**	95/99	41
3[g)]	**2a**	CS-*S,S*-**1**	23/67	7.7
4[f)]	**2b**	*S,S*-**1**	92[c)]/99	64
5	**2b**	*S,S*-**1**	86/99	61
6[g)]	**2b**	CS-*S,S*-**1**	53/63	12
7[f)]	**2c**	*S,S*-**1**	82[c)]/99	81
8	**2c**	*S,S*-**1**	85/99	71
9[g)]	**2c**	CS-*S,S*-**1**	34/43	36
10[f,h)]	**2d**	*S,S*-**1**	46[c)]/99	91
11	**2d**	*S,S*-**1**	46/99	73
12[g)]	**2d**	CS-*S,S*-**1**	8.7/59	36

[a)] *Reaction conditions:* stilbene (0.5 mmol), H_2O_2 (1.0 mmol), $FeCl_3{\cdot}6H_2O$ (5.0 mol%), H_2PDC (5.0 mol%), *S,S*-ligand (12 mol%), *tert*-amyl alcohol (9 mL), RT, 1 h. [b)] Isolated yield. [c)] Determined by GC using $PhNO_2$ or PhBr as internal standard. [d)] Determined by chiral HPLC. [e)] Absolute (+)-*2R,3R* configuration determined by comparing the sign of the optical rotation of the isolated product with literature data. [f)] Literature data.[2] [g)] Reaction time 24 h, 3 mol% tetramer ligand. [h)] Double loading of the iron catalyst and oxidant.

To find out the reasons for such a distinctive catalytic behaviour of the DPEN ligands before and after immobilization, several model ligands were designed (Figure 1). These ligands are represented by three isomeric trimethylsilyl (TMS) appended DPEN ligands (*S,S*-**4a-c**) and a dimeric ligand (*S,S*-**4d**) formed by two *S,S*-BnTsDPEN fragments tethered *via* the shortest possible carbosilane linker (see Supporting Info for details on synthesis and characterization).

No induction periods were observed in the kinetic profiles of the oxidation reaction of *trans*-stilbene using either the *para*- or *meta*-TMS-appended DPEN ligands *S,S*-**4a** and *S,S*-**4b**, while the parent *S,S*-**1** ligand demonstrated at least a 10 min lag time. Full substrate consumption was achieved within 45 min, *i.e.* 15 min prior to complete delivery of 2.0 equiv. of the oxidant (Figure 2A). *S,S*-**4a** and *S,S*-**4b** also demonstrated a marginal effect on the chemo- and enantio-selectivity of the reaction. Catalytic epoxidations carried out with these ligands yielded quite consistent amounts of *trans*-stilbene oxide (*R,R*-**3a**) of 86, 83 and 95% with corresponding *ee* values of 38, 42 and 41%, using *S,S*-**4a**, *S,S*-**4b** and *S,S*-**1**, respectively (Table 2). Further screening of the substituted *trans*-stilbenes **2b-d** also did not reveal a great difference in chemoselectivity between these ligands, however, the optical purity of the substituted stilbene oxides **3c** and **3d** produced by *S,S*-**4b** was somewhat lower than those obtained with the ligands *S,S*-**4a** and *S,S*-**1**.

Positioning the TMS-group in the *ortho*-position (*S,S*-**4c**) had a dramatic effect on the DPEN catalyst activity. No conversion was detected at all for the substituted stilbenes **2b-d** in the presence of *S,S*-**4c**, and only 11% of **2a** was consumed. In the latter case, the epoxide *R,R*-**3a** was isolated in 11% yield and low *ee* of 12%. ESI-MS analysis of a catalyst mixture based on *S,S*-**4c** only revealed the protonated ligand and its numerous clusters $[X(S,S\text{-}\mathbf{4c})_n(HCl)_{m-1}]^+$ (where {n, m} = 1, 2, 3 and X = H or Na), whereas no iron-containing ions were observed.

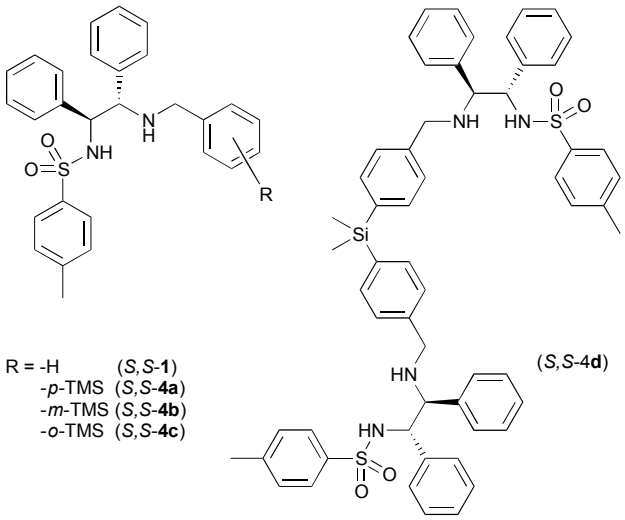

Figure 1. TMS-decorated ligands *S,S*-**4a-c** and the „dimer" *S,S*-**4d.**

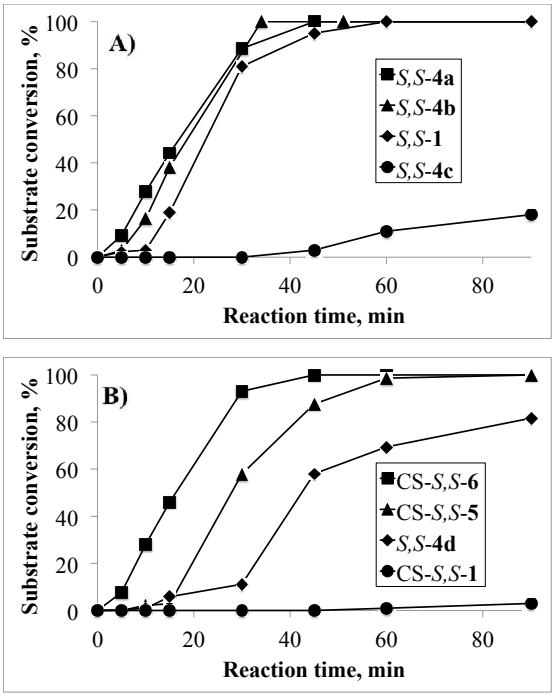

Figure 2. *Trans*-stilbene conversion *vs* time plots for A) *S,S*-**1**, *S,S*-**4a-c** and B) *S,S*-**4d**, CS-*S,S*-**1**, CS-*S,S*-**5** and CS-*S,S*-**6** ligands.

Probably, the ortho-positioning of the carbosilane moiety interferes with the formation of the catalytically active $[Fe^{III}Cl_2(L)_2(H_2PDC)]^+$ species, resulting in a lower activity, in particular with sterically demanding substrates such as **2b-d**. While the *ortho*-positioning of a carbosilane moiety has detrimental effects on the overall performance of the DPEN

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ligand in catalysis, positioning the carbosilane moiety at either the *meta*- or in particular the *para*-position, like in CS-*S,S*-**1**, seems to exert a minor steric or electronic effect on the catalytic performance.

Table 2. Olefin epoxidation with *S,S*-**4a-d** ligands.[a)]

Entry	Substrate	Ligand	Yield [%][b)] / Conv. [%][c)]	*ee* [%][d,e)]
1	**2a**	*S,S*-**4a**	86/99	38
2	**2a**	*S,S*-**4b**	83/99	42
3	**2a**	*S,S*-**4c**	11/11	12
4[f)]	**2a**	*S,S*-**4d**	54/69	21
5	**2b**	*S,S*-**4a**	88/99	54
6	**2b**	*S,S*-**4b**	79/99	nd
7	**2b**	*S,S*-**4c**	0/0	-
8[f)]	**2b**	*S,S*-**4d**	49/58	18
9	**2c**	*S,S*-**4a**	85/99	76
10	**2c**	*S,S*-**4b**	77/99	60
11	**2c**	*S,S*-**4c**	0/0	-
12[f)]	**2c**	*S,S*-**4d**	42/45	48
13	**2d**	*S,S*-**4a**	39/99	71
14	**2d**	*S,S*-**4b**	32/99	63
15	**2d**	*S,S*-**4c**	0/0	-
16[f)]	**2d**	*S,S*-**4d**	24/41	55

[a-e)] See Table 1. [f)] 6 mol% of ligand *S,S*-**4d**.

In turn, the *S,S*-**4d**-based catalytic system demonstrated only a moderate oxidative activity (Figure 2B, Table 2). The best substrate conversion within 1 h was achieved with *trans*-stilbene **2a** (69%). The reaction chemoselectivity with *S,S*-**4d** and *S,S*-**1** did not differ that much in the epoxidation of substrates **2a-c** (78-93 and 86-96%, respectively). Moreover, oxidation of **2d** using the *S,S*-**4d** ligand proceeded with 59% selectivity towards the epoxide, while *S,S*-**1** ligand was less chemoselective (46%). This variation can be attributed to different substrate conversion levels reached with *S,S*-**4d** (41-69%) and *S,S*-**1** (over 99%) catalysts. Unfortunately, not only was the activity of the *S,S*-**4d** catalyst lower compared to that of *S,S*-**1**, the epoxidation stereoselectivity with *S,S*-**4d** decreased as well. For instance, *R,R*-**3a** was obtained with 21% *ee* using *S,S*-**4d**, against 41% using the parent *S,S*-**1** ligand. Using *S,S*-**4d**, a maximum *ee* value of 55% was achieved in the epoxidation of **2d**, while epoxidation of **2b** gave the lowest *ee* value of 18% for the *R,R*-**3b** oxide.

These observations for the 'dimeric' ligand *S,S*-**4d** contrast the fact that the use of an excess of monomeric ligand *S,S*-**1** with respect to the iron salt (L/Fe = 2.4/1) positively affects the oxidation rate and, to a lesser extent, product stereoselectivity.[6] In addition, ESI-MS analysis of the *S,S*-**1**-based catalytic system showed the iron-containing ions $[Fe^{III}Cl_2(S,S\text{-}\mathbf{1})_2(H_2PDC)]^+$ (previously reported)[6] and $[Fe^{III}(PDC)(S,S\text{-}\mathbf{1})_2(H_2PDC)]^+$ (this work) with *m/z* values of 1205.2715 (calcd. 1205.2690) and 1300.3287 (calcd. 1300.3373), respectively, in which the 2:1 L/Fe ratio supports the necessity of a high ligand loading over the iron precursor for successful catalysis. In the case of catalytic mixtures containing the dimeric ligand *S,S*-**4d**, ESI-MS analysis revealed the analogously composed ion $[Fe^{III}Cl_2(S,S\text{-}\mathbf{4d})(H_2PDC)]^+$ with *m/z* 1261.2788 (calcd. 1261.2770). If these similar species, containing two DPEN ligands combined with one Fe ion, indeed participate in the catalytic cycle, it is not their composition that determines their catalytic properties. Considering the respective ligand structures, both the overall geometry and the electronics of the active species formed in the case of *S,S*-**1** and *S,S*-**4d** will be different. Where in the case of *S,S*-**1** coordination of two DPEN ligands to the iron centre is likely to result in a complex in which two identical N-donors are positioned *trans* with respect to each other, the connectivity within *S,S*-**4d** will force these donors to be *cis* to each other. Yet, a more specific explanation cannot be given because of the need for further structural information required to build a more detailed model for the active species in this catalytic system.

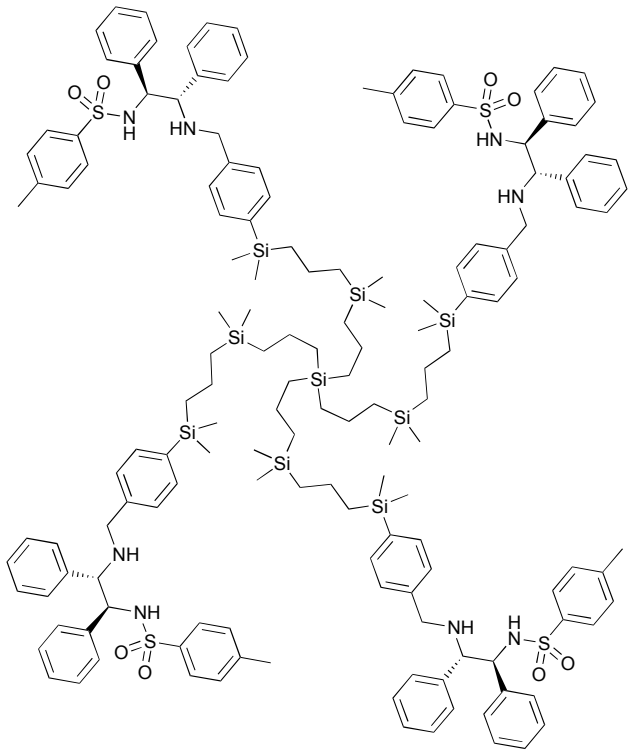

Figure 3. Optically pure elongated carbosilane-linked CS-*S,S*-**5** ligand.

Further inspection of ESI-MS data of the *S,S*-**4d**-based system showed a complex ion with *m/z* 1168.2155, which can be assigned to an ion of overall formula $[Fe^{III}Cl_2(S,S\text{-}\mathbf{4d})(HCl)_2]^+$ (calcd. 1261.2056). Such an ion can correspond to a tetrachloroferrate salt of *S,S*-**4d** $([(S,S\text{-}\mathbf{4d})H]^+[FeCl_4]^-$ or $[(S,S\text{-}\mathbf{4d})H_2]^{2+}X^-[FeCl_4]^-$, where X = chloride or tetrachloroferrate). Related ions in the case of monomeric DPEN ligands, *e.g.* $[(S,S\text{-}\mathbf{1})H]^+$ $[FeCl_4]^-$, would appear as $[(S,S\text{-}\mathbf{1})H]^+$ in ESI-MS and would be indistinguishable from the singly protonated *S,S*-**1** ligand. Importantly, carrying out the catalytic reaction with these ligands in the absence of H_2PDC showed no conversion.

ESI-MS spectra of CS-*S,S*-**1** premixed with ferric chloride and H_2PDC in *tert*-amyl alcohol were more complex. A number of anticipated iron-containing doubly charged ions with *m/z* 1272.9475 (calcd. 1272.9414) and 1225.9098 (calcd. 1225.9185) were observed, which correspond to partially metallated CS-*S,S*-**1** species of the formula $[HFe^{III}Cl_2(CS\text{-}S,S\text{-}\mathbf{1})(H_2PDC)]^{2+}$ and $[HFe^{III}Cl_2(CS\text{-}S,S\text{-}\mathbf{1})(HCl)_2]^{2+}$, respectively. The species derived from the exhaustively metallated CS-*S,S*-**1** molecule, $[(Fe^{III}Cl_2)_2(CS\text{-}S,S\text{-}\mathbf{1})(H_2PDC)_2]^{2+}$ with calcd. *m/z* 1418.8835, was observed at a very low intensity.

Keeping in mind that CS-*S,S*-**1** bears four DPEN units per molecule, these species are characterized by DPEN/Fe ratios of 4/1 and 2/1, respectively. The low abundance of dimetallated

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species and the presence of H_2PDC-free complexes might explain the observed lower catalytic activity of the carbosilane-linked ligand CS-*S,S*-**1**. The oxidation stereoselectivity in this case, presumably, is affected by the distorted geometry of immobilized active sites enforced by the carbosilane support structure. Tentatively, the molecules with a higher concentration of TsDPEN units at their periphery than in CS-*S,S*-**1** will be even less active in catalysis.[16]

In order to overcome the ligand proximity and orientation issue it was decided to anchor the *S,S*-**1** ligand to a more elongated carbosilane molecule and to a carbosilane wedge (Figure 3 and 4). These organic supports were prepared following general protocols for carbosilane tetramer preparation and modification, reported by Van Koten,[14] and Van Leeuwen[17,18]. Subsequently these compounds were treated with *S,S*-TsDPEN and sodium triacetoxyborohydride to accomplish the reductive amination coupling. The immobilization progress was monitored by IR, ^{1}H and ^{13}C-NMR. Approximately after 24 h all starting materials and intermediates had disappeared. Purification of CS-*S,S*-**5** bearing four DPEN units was achieved using passive membrane dialysis, whereas the monomeric ligand CS-*S,S*-**6** was subjected to column chromatography. Purity of these molecularly enlarged ligands was confirmed by NMR, ESI-MS, and SEC (PDI 1.03 and 1.02 for CS-*S,S*-**5** and CS-*S,S*-**6**, respectively; Page 45 and 46 in Supporting Info). In ESI-MS, CS-*S,S*-**5** appeared predominantly as the corresponding doubly charged ion with *m/z* 1326.6398 (calcd. for M+2H$^+$ 1326.6400). The CS-*S,S*-**6** ligand appeared as an ion with *m/z* 929.5128 (calcd. for M+H$^+$ 929.5161).

The CS-*S,S*-**5** ligand comprises enlarged carbosilane branches compared to CS-*S,S*-**1** and, hence, the anchored DPEN units are more mobile in space. As it turned out, this modification of the carbosilane support structure completely restored the initial catalytic activity of the *S,S*-**1** system. The epoxidation of *trans*-stilbene reached 98% conversion within 1 h and yielded 79% of the *R,R*-**3a** epoxide (Table 3). In this reaction, CS-*S,S*-**5** also demonstrated an improved stereoselectivity compared to CS-*S,S*-**1**, *i.e.* the *R,R*-**3a** epoxide was formed with an increased *ee* of 25% (which is still lower than the value obtained using the parent *S,S*-**1** ligand, see Table 1). Epoxidation of the substituted stilbenes **2b-d** with CS-*S,S*-**5** proceeded smoothly as well, reaching nearly complete substrate conversion. The *R,R*-**3b** and **3c** products were isolated with good yields above 80% and *ee*'s of 38 and 63%, respectively. *R,R*-**3d** was also obtained with 63% *ee*, whereas the low chemoselectivity (35%) is inherent to the epoxidation of this particular substrate.

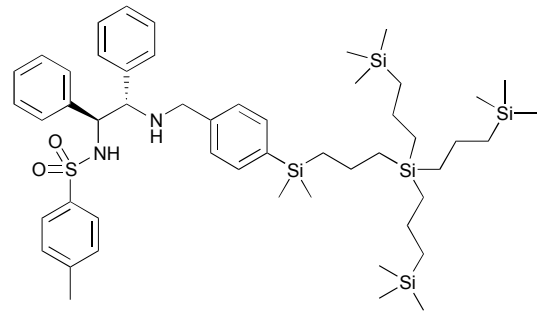

Figure 4. Optically pure CS-*S,S*-**6** ligand.

Only one iron-containing ion was identified in the ESI-MS spectrum of the CS-*S,S*-**5** catalyst mixture at *m/z* 1473.5658 (calcd. 1473.5833), corresponding to [HFe^{III}Cl$_2$(CS-*S,S*-**5**)(H_2PDC)]$^{2+}$. Besides this ion with an L/Fe ratio of 4/1, no exhaustively metallated or H_2PDC-free species were found in this case. This observation suggests that the enlarged carbosilane support does not hamper interactions between CS-*S,S*-**5**, ferric chloride and, especially, H_2PDC, and that the reactivity of the catalyst sites located at partially metallated carbosilane-linked ligands (with L/Fe = 4) is only slightly affected by neighbouring peripheral DPEN fragments. Accordingly, the pre-orientation of DPEN fragments on the carbosilane support is more crucial for catalysis than the peripheral ligand concentration. On the other hand, the relatively restricted mobility of the anchored DPEN ligands within the CS-*S,S*-**5** structure results in a lower stereoselectivity of the epoxidation reaction than demonstrated by *S,S*-**1**.

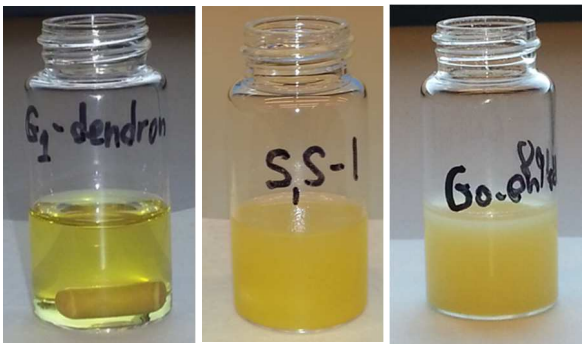

Figure 5. Catalyst mixtures with CS-*S,S*-**6** (left), *S,S*-**1** (middle) and CS-*S,S*-**5** (right).

In turn, the activity, chemo- and enantioselectivity of CS-*S,S*-**6** closely resembled that of the parent catalyst (Table 3). For example, *trans*-stilbene **2a** was quantitatively converted within 45 min into *R,R*-**3a** with an *ee* of 38% using CS-*S,S*-**6**. Like in the case of the original *S,S*-**1** ligand, even the crude reaction mixture analysed by ^{1}H-NMR was free of by-products. With CS-*S,S*-**6**, a complex product mixture was obtained only in the epoxidation of **2d**. The *R,R*-**3d** epoxide was isolated in 41% yield and 73% ee, nearly reproducing the original *S,S*-**1**-catalyzed reaction outcome. The highest epoxide *ee* 80% and almost quantitative yield 92% were observed when oxidizing **2c** in the presence of CS-*S,S*-**6**.

Table 3. Olefin epoxidation with CS-*S,S*-**5** and CS-*S,S*-**6** ligands.[a)]

Entry	Substrate	Ligand	Yield [%][b)] / Conv. [%][c)]	*ee* [%][d,e)]
1[f)]	**2a**	CS-*S,S*-**5**	79/98	25
2		CS-*S,S*-**6**	99/99	38
3[f)]	**2b**	CS-*S,S*-**5**	80/95	38
4		CS-*S,S*-**6**	95/99	55
5[f)]	**2c**	CS-*S,S*-**5**	83/99	63
6		CS-*S,S*-**6**	92/99	80
7[f)]	**2d**	CS-*S,S*-**5**	35/99	63
8		CS-*S,S*-**6**	41/99	73

[a-e)] See Table 1. [f)] 3 mol% of ligand CS-*S,S*-**5**.

While all other DPEN ligands described here, including *S,S*-**1**, formed highly turbid solutions upon mixing with ferric chloride and H_2PDC, the CS-*S,S*-**6** catalyst mixture remained completely transparent (Figure 5). *Trans*-stilbene and the other tested substrates are moderately soluble in the reaction solvent (*tert*-

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amyl alcohol), while the epoxide products possess a fair solubility, allowing for the oxidation progress using CS-*S,S*-**6** to be monitored visually as the reaction medium gradually turned clear and transparent.

Catalyst recycling studies

It was found that the carbosilane-appended DPEN ligands are fairly soluble in common organic solvents (DCM, $CHCl_3$, EtOAc, THF, MeOH, Et_2O, toluene and acetone), however, their solubility in hexanes varies. For instance, the parent ligand *S,S*-**1** and the other monomeric ligands **4a-c** are partially soluble, the "dimer" **4d** and the "tetramers" CS-*S,S*-**1** and CS-*S,S*-**5** are hardly-soluble, while CS-*S,S*-**6** is completely soluble in hexanes. Basing on this observation we attempted the separation of the catalyst CS-*S,S*-**5** from the reaction medium *via* precipitation using hexanes. Ferric chloride and 2,6-pyridinedicarboxylic acid are also known to have a poor solubility in hexanes, while all the obtained epoxides **3a-d** and the corresponding *trans*-stilbenes, except for **2b**, easily go into solution in hexanes. By selecting **2c** as a model substrate for the epoxidation with CS-*S,S*-**5** it was envisioned to separate the catalyst and the reaction products using their drastic solubility difference in hexanes.

In order to investigate the recycling of the CS-*S,S*-**5** catalyst, the epoxidation of **2c** was performed as usual in a batch-wise mode. After oxidant addition was completed, the reaction mixture was concentrated under reduced pressure at RT until most of the *tert*-amyl alcohol solvent was removed and a very viscous brownish residue was obtained. Some hexanes were added to this and the mixture was thoroughly shaken. The obtained suspension was centrifuged to form a dense solid phase and a transparent product solution in hexanes. The organic supernatant was decanted from solids and concentrated under reduced pressure yielding a brownish oil, which solidified upon standing. The resulting epoxide product was essentially pure according to GC and ^{1}H-NMR analysis. It was further decolorized by passing it through a short column of silica gel with EtOAc to give 92% of the *R,R*-**3c** product with 62% *ee* (Table 4).

Table 4. Study of the CS-*S,S*-**5** catalyst recycling *via* precipitation and reuse in batch mode with **2c** as a substrate.[a)]

Entry	Run	Yield [%][b)]	Conv. [%][c)]	*ee* [%][d,e)]
1	1	92	99	62
2[f)]	2	95	99	42
3[f)]	3	34	41	25
4	1	95	99	63
5[f,g)]	2	96	99	51
6[f,g)]	3	69	78	30

[a)] *Reaction conditions:* **2c** (1.0 mmol), H_2O_2 (2.0 mmol), $FeCl_3{\cdot}6H_2O$ (5.0 mol%), H_2PDC (5.0 mol%), CS-*S,S*-**5** (3.0 mol%), *tert*-amyl alcohol (18 mL), RT, 1 h. [b-e)] See Table 1. [f)] A precipitate from the former reaction cycle was used as a catalyst instead of the ligand, ferric chloride and H_2PDC. [g)] In addition $FeCl_3{\cdot}6H_2O$ (1.0 mol%), H_2PDC (1.0 mol%) were introduced.

The solid precipitate was used in the next oxidation run as a replacement for the ligand, ferric chloride and 2,6-pyridinedicarboxylic acid, and only fresh solvent, substrate, and oxidant were added. A full substrate conversion was achieved in the second reaction cycle and the epoxide *R,R*-**3c** was isolated in 95% yield. The recovered CS-*S,S*-**5** catalyst demonstrated a lower enantioselectivity (42% *ee*) in this run. In the third catalyst run most of the **2c** substrate (59%) remained unreacted. The corresponding epoxide *R,R*-**3c** was isolated in 34% yield and only 25% *ee*.

It was previously observed while optimizing the conditions for *trans*-stilbene oxidation with the parent *S,S*-**1** ligand that the reaction stereoselectivity remained unchanged in a broad L/Fe ratio from 0.5/1 to 2.4/1 at a constant concentration of iron.[6] In addition, the oxidation rate was found to be rather low under ligand-deficient conditions and an essential loss of the reaction stereoselectivity was found under iron-deficient conditions. The recycling of CS-*S,S*-**5** catalyst is likely to be accompanied by a significant iron leaching from the catalytically active species, due to processes related to ferric chloride hydrolysis and further condensation of iron hydroxides. These side-reactions will shift the actual reaction conditions towards iron-deficient, *i.e.* low stereoselective, conditions upon catalyst recycling. The drop in substrate conversion in the third catalyst run along with the further decrease of the product *ee* point at an extremely low concentration of catalytically active species and a high L/Fe ratio. ESI-MS analysis of the recovered CS-*S,S*-**5** containing catalyst mixture showed the presence of the initial ligand and of several new and, so far, unidentified ions, but did not show previously assigned iron-containing species.

In order to compensate for iron loss during catalysis and recycling, the same recycling experiment was carried out with the addition of ca. 20% of the initially introduced amount of $FeCl_3{\cdot}6H_2O$ and H_2PDC in every subsequent reaction run. In doing so, complete substrate conversion was reached in the second catalytic run and 96% of *R,R*-**3c** was isolated, which is comparable to the value obtained in the initial recycling experiment. At the same time, the stereoselectivity in the second run improved from 42 to 51% *ee*, confirming that iron depletion was the main issue affecting the enantiomeric product outcome. Extra ferric chloride and H_2PDC were added again to the precipitate obtained in this experiment and the obtained mixture was used in the epoxidation of **2c** for the third time. Incomplete substrate consumption of 78% was observed in this case and 69% of **3c** was isolated. This is roughly two times more than the yield in the initial recycling experiment. The recovered catalyst stereoselectivity was also higher; it rose slightly from 25 to 30% *ee* of the *R,R*-**3c** product. Overall this protocol, involving batch-wise catalyst recovery and reuse combined with an extra feed of iron(III) chloride and H_2PDC, allowed us to obtain three times more of the **3c** epoxide, compared to the conventional reaction work-up. Nevertheless, the average *ee* of *R,R*-**3c** was 49% against 62% after the first reaction cycle.

While CS-*S,S*-**5** was recycled based on its poor solubility in hexanes, recovery and reuse of the carbosilane-linked monomeric CS-*S,S*-**6** ligand were carried out using its high affinity to apolar solvents. In this case a hexanes-acetonitrile biphasic solvent system was considered to separate the ligand and the reaction products. It was found that both *trans*-stilbene **2a** and its epoxide **3a** preferably (above 80%) reside in the MeCN phase allowing for their effective extraction. Thus, **2a** was oxidized following a standard catalytic protocol and using the CS-*S,S*-**6** ligand. The reaction mixture was dried at the end and, subsequently, partitioned between MeCN and hexanes. The top layer was further washed with acetonitrile, water containing

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ethylenediamine to scavenge iron and H_2PDC, and dried. The isolated material, according to ^{1}H-NMR, consisted of mainly stilbene oxide and carbosilane wedge residues. However, the characteristic pattern of the chiral DPEN backbone in the ^{1}H-NMR spectrum drastically changed (See supporting information for the details). A new group of multiplets with 1:1 integral ratio appeared at 5.1 and 4.4 ppm. The observed NMR shift to the weak field may be caused by ligand oxidation; however, no assignment to any definite structure has been made.

In the next step, the amount of hydrogen peroxide was reduced from 2.0 to 0.6 equiv. in order to avoid ligand oxidation by the excess of oxidant. Also the oxidant addition time was scaled to 30 min instead of 1 h. Under these oxidant limiting conditions conversion of **2a** reached 57% and the epoxide *R,R*-**3a** (in the MeCN layer) was isolated in a 48% substrate-based yield and 40% ee (Table 5). The apolar phase contained the unchanged CS-*S,S*-**6** ligand and **3a** and **3b** as impurities (in total ca. 5-10% by weight). After the first reaction run CS-*S,S*-**6** was recovered in approx. a 75% yield as a slightly turbid colourless oil. In the next run, the substrate, ferric chloride and H_2PDC loading were complimentary decreased to maintain the right proportions with respect to the recovered ligand. In this case, the epoxide was isolated in 53% yield and 37% ee; ca. 80% of the CS-*S,S*-**6** ligand was recovered. The third catalyst cycle provided 46% of *R,R*-stilbene oxide with 38% ee and 83% of the ligand was isolated. The ESI-MS analysis of this recovered ligand revealed except for the anticipated *m/z* 929.5195 $[M+H]^+$ also a mono-charged ion of a low intensity with a 16 units higher *m/z* value of 945.5385, which could be attributed to a $[M+O+H]^+$ ion (calcd. *m/z* 945.5128), i.e. a hydroxylation product of CS-*S,S*-**6**.

Table 5. Study of the CS-*S,S*-**6** catalyst recycling *via* phase separation and reuse in batch mode with **2a** as a substrate.[a)]

Run	Ligand recovered, %	Yield [%][b)]	Conv. [%][c)]	*ee* [%][d,e)]
1	75	48	57	40
2[f)]	80	53	60	37
3[f)]	83	45	55	38

[a)] *Reaction conditions:* **2a** (1.0 equiv.), H_2O_2 (0.6 equiv.), $FeCl_3{\cdot}6H_2O$ (5.0 mol%), H_2PDC (5.0 mol%), CS-*S,S*-**6** (12 mol%), *tert*-amyl alcohol, RT, 30 min. [b-e)] See Table 1. [f)] The ligand isolated in the previous run was used; the substrate, $FeCl_3{\cdot}6H_2O$ and H_2PDC amounts were adjusted in proportion to the recovered ligand quantity.

Overall, the carbosilane wedge in CS-*S,S*-**6** was shown to be quite oxidatively robust under oxidant limiting conditions. Moreover, by introducing it into the parent ligand structure, the solubility of catalyst species was immensely increased, allowing for the epoxidation to occur faster compared to the parent *S,S*-**1** catalyst without sacrificing the stereoselectivity in epoxidations. Furthermore, the lipophilic nature of the CS-*S,S*-**6** ligand allowed for a simple recovery and reuse of the expensive DPEN ligand. In addition, by isolating the CS-*S,S*-**6** ligand after its use in catalysis confirmed its stability during catalytic stilbene epoxidations. This feature is not obvious for nitrogen ligands used in iron-mediated oxidations and has not been documented before for the DPEN ligand framework.

Finally, ultrafiltration can be considered as an appealing technique that allows for the (continuous) separation of size-enlarged molecules from a reaction medium. Within our study its application could further simplify product purification and allow for an efficient catalyst reuse, avoiding, for instance, superfluous solvent exchange steps, required for precipitation. Most of the relevant publications in the field emphasize on the fact that the commercial membranes are often not compatible with organic solvents required for the reported catalytic transformations (olefin metathesis, cross-coupling etc.)[19,20] and in some cases the membrane material interacts with a catalyst, causing its deactivation.[14] Especially when using hydrogen peroxide the membrane choice is limited. We selected a MILLIPORE Ultrafiltration Membrane made of regenerated cellulose with molecular weight cut-off (MWCO) of 1000 Da and of 47 mm in diameter. In the case of solvents like CH_2Cl_2 and EtOAc a stable flow rate of 25-45 mL/h was observed under an external pressure of 3-4 atm. Pure methanol often caused this membrane to suddenly leak, while the preferred reaction solvent (*tert*-amyl alcohol) even under 4.5 atm. of external pressure oozed through this membrane with only 0.3-0.7 mL/h.

Accordingly, the retention of CS-*S,S*-**5** by the membrane was tested using CH_2Cl_2 as a solvent and it was estimated to be above 99.90%, as 400/400 mg of CS-*S,S*-**5** stayed behind the membrane and no ligand was found in the permeate. Then, the oxidation of **2c** was carried out as usual with CS-*S,S*-**5** and the reaction mixture was concentrated to remove *tert*-amyl alcohol. The residue was dissolved in CH_2Cl_2, passed through a paper filter first and then filtered through the MILLIPORE membrane. This filtration was repeated three times to wash out the epoxide product entirely. After drying the epoxide *R,R*-**3c** was obtained in 96% yield with *ee* 64% and was shown to be analytically pure.

Conclusions

We have presented the immobilization of *S,S*-DPEN-derived ligands for the homogeneous epoxidation of stilbenes and demonstrated a determining role of the structure of the soluble carbosilane support on the catalytic behaviour. This study emphasizes, once more, that even when having a perfectly operating and optimized homogeneous catalytic system, along with a large number of catalyst heterogenization strategies at hand, it is still not a trivial task to transfer the single site properties of the parent homogeneous catalyst onto its immobilized and, in this case, molecularly enlarged version. The initially selected carbosilane support turned out to be inappropriate and lead to a devastating activity of the linked *S,S*-DPEN ligand. In order to understand this observation, several aspects of the support structure were investigated.

Catalytic stilbene epoxidation experiments with the TMS-substituted ligands *S,S*-**4a-c** showed that linking of the DPEN ligand to the carbosilane support through the *para*-position (as in *S,S*-**4a**) had a minor impact on catalyst activity, chemo- and stereoselectivity in *trans*-stilbene epoxidation. The diminished catalytic activity of the "dimeric" ligand *S,S*-**4d** pointed to the importance of the formation of the proper single site active species. The enlarged carbosilane-linked CS-*S,S*-**5** was then studied in order to investigate the preorientation of the peripheral *S,S*-DPEN ligands by adjusting the flexibility of the support, which showed that ligand preorientation has a more pronounced influence on the epoxidation reaction outcome than the proximity of the neighbouring DPEN units.

The recovery and reuse of the carbosilane-appended DPEN

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ligands was investigated next. The catalytic system derived from CS-*S,S*-**5** can be efficiently separated from product mixtures *via* precipitation with hexanes or ultrafiltration. Both approaches facilitate epoxide synthesis and raise the isolated product yield to near quantitative in the initial run. Moreover, the recovered CS-*S,S*-**5** catalyst was shown to be active in three subsequent batch oxidation experiments, where feeding the system with fresh ferric chloride and H_2PDC lead to better results. A gradual loss of the catalyst stereoselectivity and, to a lesser extent, activity was still observed though. This can be attributed to a partial catalyst deactivation as well as catalyst loss due to the required manipulations in between catalytic runs. In order to overcome these problems, the application of CS-S,S-**5** in a continuous flow membrane reactor is currently under investigation.

The carbosilane wedge linked DPEN ligand CS-*S,S*-**6** has shown the best performance in epoxidation reactions of the *trans*-stilbenes **2a-d**. This molecularly enlarged ligand closely mimics the catalytic properties of the parent *S,S*-**1** ligand by providing full flexibility to the ligand. Moreover, this ligand has superior solubility properties and remains entirely in solution upon mixing with the other vital reaction ingredients ferric chloride and H_2PDC, allowing for its potential application in micro-reactors. In contrast to the parent *S,S*-**1** ligand, CS-*S,S*-**6** can be efficiently recovered unchanged from the reaction medium and reused afterwards. Still, the applied ligand recovery strategy in a biphasic acetonitrile-hexanes system is accompanied by about 20% ligand loss per reaction run and requires the oxidation to be carried out at moderate substrate conversion levels. Although it was not exhaustively explored in this study, the size of this molecularly enlarged ligand would allow for its separation from reaction mixture by means of nanofiltration using a membrane with MWCO lower than 1000 Da.[20]

Overall, this study has shown the delicacy in designing the proper soluble supporting material for single-site homogeneous catalysts. Where earlier we had shown that proximity effects can be detrimental for the catalytic activity of preformed catalysts,[16b] the current study has shown that care should be taken in the immobilization of chiral ligands used for the *in-situ* formation of catalysts. These and other considerations are currently employed in the design of advanced supported versions of homogeneous oxidation catalysts based on iron, where reuse of precious ligands is more important than reuse of the metal.

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