

# Highly Enantioselective Transfer Hydrogenation of Prochiral Ketones Using Ru(II)-Chitosan Catalyst in Aqueous Media

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Unprecedentedly high enantioselectivities are obtained in the transfer hydrogenation of prochiral ketones catalyzed by a Ru complex formed *in situ* with chitosan chiral ligand. This biocompatible, biodegradable chiral polymer obtained from the natural chitin afforded good, up to 86% enantioselectivities, in the aqueous-phase transfer hydrogenation of acetophenone derivatives using HCOONa as hydrogen donor. Cyclic ketones were transformed in even higher, over 90%, enantioselectivities, whereas further increase, up to 97%, was obtained in the transfer hydrogenations of heterocyclic ketones. The chiral catalyst precursor prepared *ex situ* was examined by scanning

electron microscopy, FT-mid- and -far-IR spectroscopy. The structure of the *in situ* formed catalyst was investigated by <sup>1</sup>H NMR spectroscopy and using various chitosan derivatives. It was shown that a Ru pre-catalyst is formed by coordination of the biopolymer to the metal by amino groups. This precursor is transformed in water insoluble Ru-hydride complex following hydrogen donor addition. The practical value of the developed method was verified by preparing over twenty chiral alcohols in good yields and optical purities. The catalyst was applied for obtaining optically pure chiral alcohols at gram scale following a single crystallization.

## Introduction

During the last few decades the increased demand of optically pure fine chemicals accelerated the development of asymmetric catalytic procedures.<sup>[1]</sup> Among the most convenient stereoselective reactions are the enantioselective hydrogenations of prochiral compounds. A huge variety of metal complexes and heterogeneous chiral catalysts have been developed and successfully applied in asymmetric hydrogenations of diverse unsaturated chemicals.<sup>[2]</sup> The operational simplicity brought by the use of organic or inorganic hydrogen donors instead of H<sub>2</sub> gas promoted studies aimed at designing chiral catalysts efficient in enantioselective transfer hydrogenations (ETH) of various prochiral compounds.<sup>[3]</sup> In their pioneering work Noyori, Ikariya and co-workers developed efficient ruthenium complexes using sulfonamides derived from optically pure diamines for these purposes.<sup>[4]</sup> According to recent trends in the fine

chemical industry efforts are devoted to replace the synthetic, expensive ligands with natural, renewable chiral compounds.

Chitosan (CS, Figure 1) is obtained by deacetylation from chitin (CT),<sup>[5]</sup> which is the second most abundant chiral natural polymer available in large quantities from food industry wastes. This biocompatible and biodegradable polymer has multiple applications in food, pharmaceutical and medicinal industry, in separation and purification processes, water treatment, cosmetics, and as biosensors.<sup>[6]</sup> It is also a proper candidate for developing cheap and stereoselective catalysts. CS has been used for the preparation of chiral organocatalysts either by coupling with catalytically active molecules or just using the natural chirality of this biopolymer.<sup>[7]</sup> Its ability to chelate metal cations was exploited to prepare catalytically active metal complexes and supported metal particles.<sup>[8]</sup> These materials were also applied as asymmetric catalysts employing the chirality of the CS.<sup>[9]</sup> Among these applications the enantioselective hydrogenations and transfer hydrogenations were the most studied. Early attempts on using such catalysts in enantioselective hydrogenations of prochiral ketones gave uncertain, irreproducible results,<sup>[10]</sup> whereas moderate enantioselectivities were reached in ETH even following chemical modification of chitosan used as chiral ligand.<sup>[11]</sup> At best 78%

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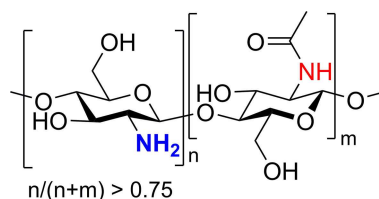


Figure 1. Structure of chitosan (CS).

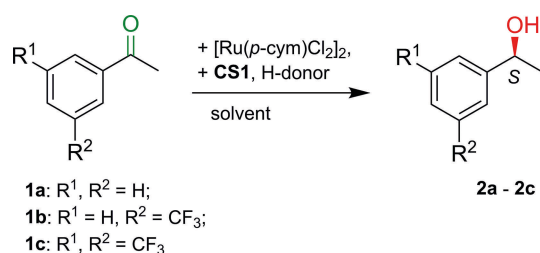
enantiomeric excess (ee) was obtained in the transfer hydrogenation of aromatic ketones using the Ru complex of 6-O-pivalate derivative of CS.<sup>[12]</sup>

In the present study our goal was to develop a simple, environmentally benign method for the ETH of prochiral ketones in aqueous media using unmodified CS from commercial source as degradable, renewable, chiral ligand.

## Results and Discussion

We commenced our experiments with the transfer hydrogenations of acetophenone (**1a**) and its two substituted derivatives (**1b** and **1c**, Scheme 1) using *in situ* formed chiral Ru complex from a high molecular weight chitosan (CS1, see Experimental section) and [Ru(*p*-cym)Cl<sub>2</sub>]<sub>2</sub> (*p*-cym: *para*-cymene) (see Table 1). Initially sodium formate was applied as hydrogen donor (H-donor). The reaction of **1a** in water resulted in similar ee as described previously (entries 1–3).<sup>[12]</sup> However, using 20 vol % isopropanol (*i*PrOH) the ee increased up to 78 %, reaching the highest value obtained up to now in ETH using CS derived ligand. Even higher ee values were obtained under identical conditions in the ETH of **1b** and **1c** (entries 5, 10), however, the reaction of the latter had to be extended to 70 h for reaching good conversion (entry 11). By increasing the amount of *i*PrOH in the mixture the ee slightly decreased (compare entries 11–13). Replacement of *i*PrOH with other polar, water miscible solvents (MeOH, EtOH or *N,N*-dimethylformamide (DMF)) decreased both the conversion and the ee (entries 14–16). HCOONa and HCOOK were similarly efficient H-donors (entries 5, 6), whereas using HCOONH<sub>4</sub> or HCOOH/Et<sub>3</sub>N 5/2 mixture resulted in low conversions (entries 7, 9). The attempt of using *i*PrOH as H-donor in the presence of a strong base (KOH) provided moderate conversion and lower ee even at higher reaction temperature (entry 8).

Chiral Ru catalyst formed with CS1 ligand was also prepared *ex situ* in water by slow evaporation of the solvent using the same ratio of ligand/metal precursor as in the transfer hydrogenations (see Experimental section). An orange film-like material was obtained (denoted as Ru-CS1), which was easily cut or broken in pieces (Figure 2). This material provided similar results as the *in situ* formed catalyst in the reactions of all three compounds (Table 1, entries 4, 5, 10) even after a long-time storage (close to one year).

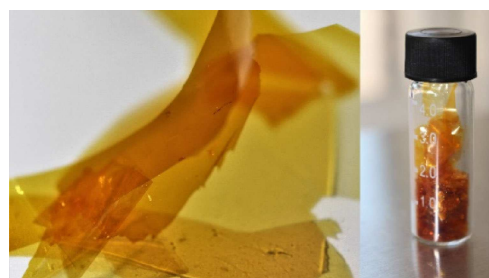


**Scheme 1.** Asymmetric transfer hydrogenation of acetophenones **1a**, **1b** and **1c** using chitosan CS1 as chiral ligand.

**Table 1.** Investigation of the solvent and H-donor effect on the transfer hydrogenation of **1a**, **1b** and **1c** using chitosan CS1 as ligand.<sup>[a]</sup>

Entry	Ketone	Solvent	H-donor; amount [mmol]	Conv <sup>[b]</sup> [%]	ee <sup>[c]</sup> [%]
1	<b>1a</b>	H <sub>2</sub> O	HCOONa; 0.75	66	71
2	<b>1a</b>	H <sub>2</sub> O	HCOONa; 1.25	87	71
3	<b>1a</b>	H <sub>2</sub> O	HCOONa; 2.50	99	70
4	<b>1a</b>	H <sub>2</sub> O/ <i>i</i> PrOH 4/1	HCOONa; 1.25	99; 92 <sup>[d]</sup>	78; 77 <sup>[d]</sup>
5	<b>1b</b>	H <sub>2</sub> O/ <i>i</i> PrOH 4/1	HCOONa; 1.25	99; 98 <sup>[d]</sup>	85; 85 <sup>[d]</sup>
6	<b>1b</b>	H <sub>2</sub> O/ <i>i</i> PrOH 4/1	HCOOK; 1.25	> 99	85
7	<b>1b</b>	H <sub>2</sub> O/ <i>i</i> PrOH 4/1	HCOONH <sub>4</sub> ; 1.25	3	5
8	<b>1b</b>	H <sub>2</sub> O/ <i>i</i> PrOH 4/1	KOH; 0.25 <sup>[e]</sup>	55	75
9	<b>1b</b>	H <sub>2</sub> O/ <i>i</i> PrOH 4/1	HCOOH/Et <sub>3</sub> N 5/2; 0.1 cm <sup>3</sup>	3	4
10	<b>1c</b>	H <sub>2</sub> O/ <i>i</i> PrOH 4/1	HCOONa; 1.25	62; 63 <sup>[d]</sup>	86; 85 <sup>[d]</sup>
11 <sup>[f]</sup>	<b>1c</b>	H <sub>2</sub> O/ <i>i</i> PrOH 4/1	HCOONa; 1.25	90	86
12 <sup>[f]</sup>	<b>1c</b>	H <sub>2</sub> O/ <i>i</i> PrOH 3/2	HCOONa; 1.25	98	83
13 <sup>[f]</sup>	<b>1c</b>	H <sub>2</sub> O/ <i>i</i> PrOH 2/3	HCOONa; 1.25	99	83
14 <sup>[f]</sup>	<b>1c</b>	H <sub>2</sub> O/MeOH 4/1	HCOONa; 1.25	25	73
15 <sup>[f]</sup>	<b>1c</b>	H <sub>2</sub> O/EtOH 4/1	HCOONa; 1.25	40	79
16 <sup>[f]</sup>	<b>1c</b>	H <sub>2</sub> O/DMF 4/1	HCOONa; 1.25	32	72

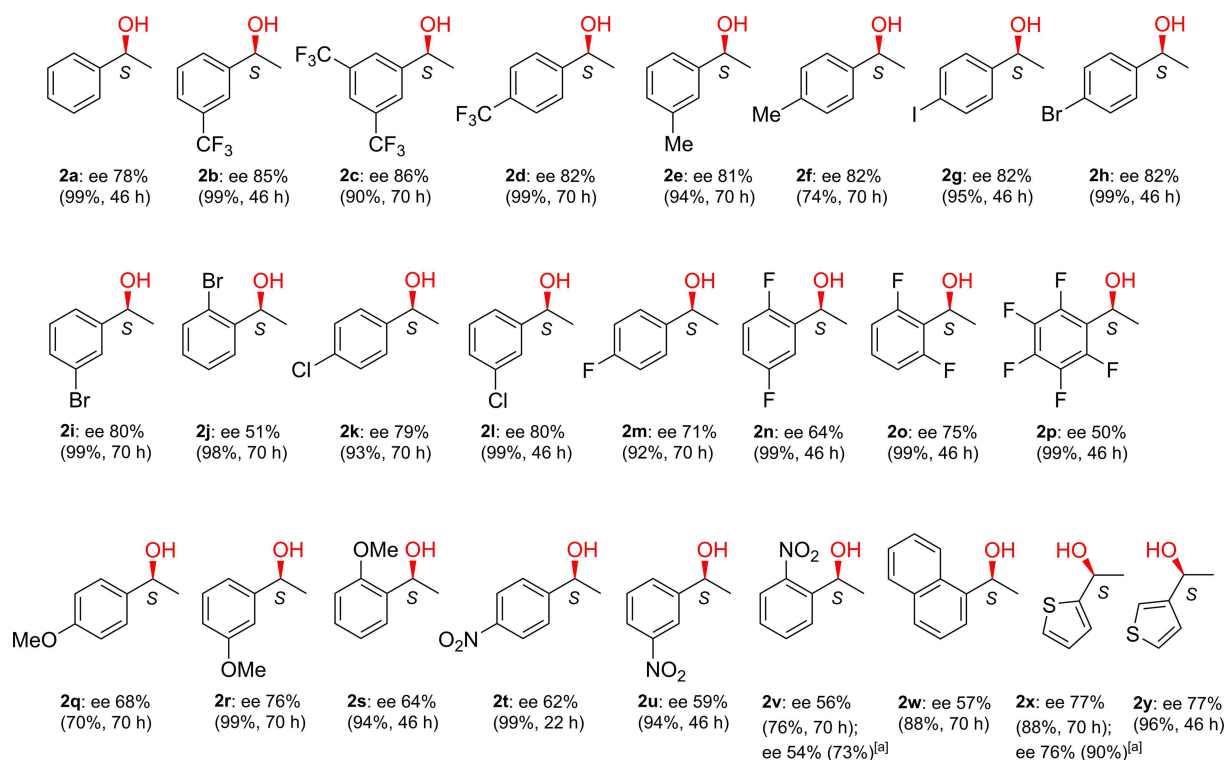
[a] Reaction conditions: 0.00625 mmol [Ru(*p*-cym)Cl<sub>2</sub>]<sub>2</sub>, 2 mg CS1, 1 cm<sup>3</sup> solvent, 0.25 mmol ketone, room temperature (rt, 24 ± 1 °C), 46 h; [b] Conversion of **1a**, **1b** or **1c**; [c] The ee determined by gas-chromatography (GC), configuration of the excess enantiomers were assigned as *S* based on the optical rotation of the isolated products and literature data;<sup>[13]</sup> [d] Using 5 mg pre-prepared Ru-CS1 complex; [e] Reaction temperature 50 °C; [f] Reaction time 70 h.



**Figure 2.** Photographs of the *ex situ* prepared Ru-CS1.

### Scope of the Catalytic System: ETH of Acetophenone Derivatives

Encouraged by the enantioselectivities obtained in the ETH of the above ketones, we examined the effect of various substituents on the phenyl ring and the ETH of other aryl methyl ketones. Selected results obtained in reactions of **1b–1y** as compared with **1a**, resulting in 1-arylethanol **2b–2y** are shown in Figure 3.



**Figure 3.** Enantioselectivities obtained in the ETH of aryl methyl ketones using *in situ* formed Ru-chitosan complex (conversions and reaction times are in brackets). Reaction conditions: 0.00625 mmol [Ru(*p*-cym) $\text{Cl}_2$ ] $_2$ , 2 mg CS1, 0.25 mmol ketone, 1.25 mmol HCOONa, 1 cm<sup>3</sup> H<sub>2</sub>O/*i*PrOH 4/1, rt. [a] Results obtained using 5 mg *ex situ* prepared Ru-CS1.

Substituents with both electron withdrawing and releasing inductive effects, such as CF<sub>3</sub>, Me, I, Br, Cl in *meta* or *para* positions (**1b–1i**, **1k**, **1l**), increased the ee value as compared with acetophenone. In contrast, in the presence of substituents having electron withdrawing and releasing mesomeric effects, *i.e.* NO<sub>2</sub> or OMe (**1q**, **1r**, **1t**, **1u**), the ee values decreased.

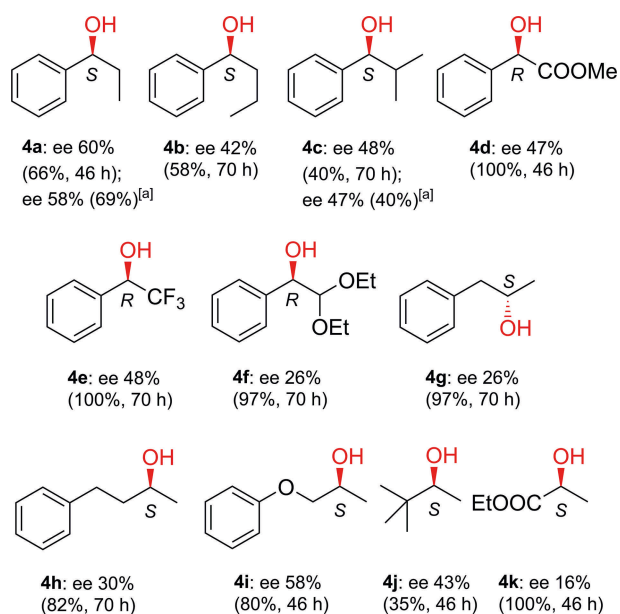
Substituents in *ortho* positions irrespective of their character decreased significantly the enantioselectivity (**1j**, **1s**, **1v**, **1w**), ascribed to their unfavorable steric effects. This is supported by the lower decrease obtained in the ETH of **1o** substituted with fluorine in both *ortho* positions as compared with bulkier functional groups, such as Br, OMe or NO<sub>2</sub>. The heteroaromatic ketones **1x**, **1y** gave similar enantioselectivities as **1a**. The *ex situ* prepared material Ru-CS1 also provided similar results as the *in situ* obtained catalyst in the ETH of ketones **1v** and **1x**.

The above results showed that this asymmetric catalytic system has broad applicability and can afford fairly good enantioselectivities in the ETH of several acetophenone derivatives. It must be mentioned that in the reaction of many derivatives the ee surpassed the previously reported highest values obtained using chitosan or its derivatives as chirality source.

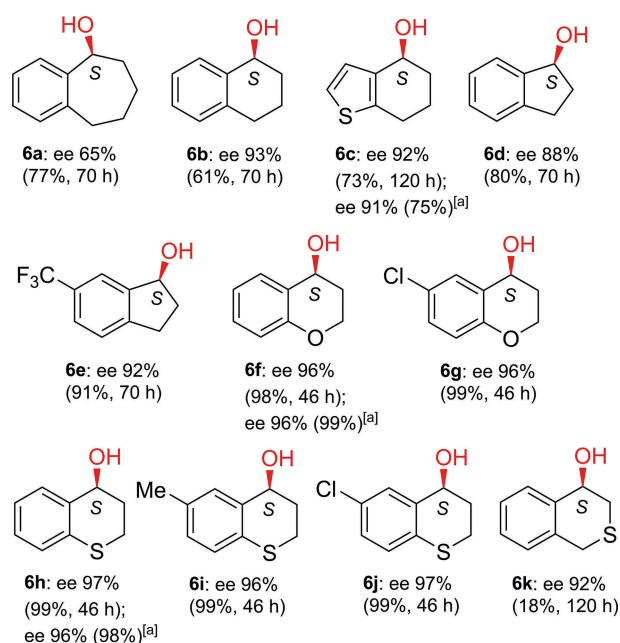
### Scope of the Catalytic System: ETH of Various Ketones

Next, we attempted the ETH of prochiral ketones of various structures using ketones **3a–3k**, resulting in chiral alcohols **4a–4k** (Figure 4). Increasing the alkyl chain from Me to Et and further to Pr gradually decreased the conversion and the ee (see **4a**, **4b**) as well as the  $\alpha$ -branched alkyl chain in isobutyrophenone **3c**. The *ex situ* prepared Ru-CS1 also gave poor results in the ETH of both **3a** and **3c**. Aromatic ketones activated by electron withdrawing groups, such as COOMe, CF<sub>3</sub> or CH(OEt)<sub>2</sub> (**3d–3f**), were hydrogenated in low, up to 48% enantioselectivities. Distancing the keto group from the aromatic moiety (**3g**, **3h**) also decreased the ee, however, by inclusion of an oxygen between the phenyl and the ketone moieties the ee slightly increased (**3i**) as compared with **3h**. In the ETH of aliphatic prochiral methyl ketones both bearing electron releasing (*t*Bu, **3j**) or electron withdrawing (COOEt, **3k**) groups low ee values were reached.

According to these results, although the enantioselective transfer hydrogenation of structurally very diverse prochiral ketones is possible using the *in situ* formed chiral Ru-chitosan complex, good ee values were obtained only in reactions of properly substituted aryl methyl ketones.



**Figure 4.** Enantioselectivities obtained in the ETH of various ketones using *in situ* formed Ru-chitosan complex (conversions and reaction times are given in brackets). Reaction conditions: 0.00625 mmol [Ru(*p*-cym)Cl<sub>2</sub>]<sub>2</sub>, 2 mg CS1, 0.25 mmol ketone, 1.25 mmol HCOONa, 1 cm<sup>3</sup> H<sub>2</sub>O/*i*PrOH 4/1, rt. [a] Results obtained using 5 mg *ex situ* prepared Ru-CS1.

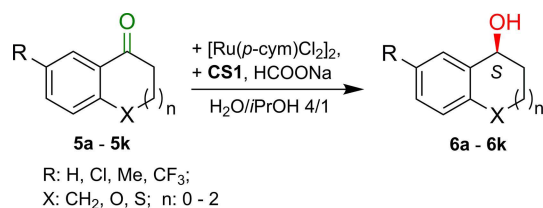


**Figure 5.** Enantioselectivities obtained in the ETH of cyclic ketones using *in situ* formed Ru-chitosan complex (conversions and reaction times are given in brackets). Reaction conditions: 0.00625 mmol [Ru(*p*-cym)Cl<sub>2</sub>]<sub>2</sub>, 2 mg CS1, 0.25 mmol ketone, 1.25 mmol HCOONa, 1 cm<sup>3</sup> H<sub>2</sub>O/*i*PrOH 4/1, rt. [a] Results obtained using 5 mg *ex situ* prepared Ru-CS1.

### Scope of the Catalytic System: ETH of Cyclic Ketones

Although, increasing the alkyl chain length of aryl alkyl ketones resulted in diminished ee values as compared with **1a**, we hoped that closing this chain in a rigid ring condensed with the aromatic moiety may have beneficial effect on the enantioselectivity. Thus, we decided to investigate the ETH of cyclic aromatic ketones **5a–5k** (see Scheme 2).

Surprisingly high enantioselectivities were obtained in the ETH of six-membered carbocyclic ketones 1-tetralone (**5b**) and **5c**, respectively (Figure 5). Increase of the ring size to seven (1-benzosuberone, **5a**), lowered significantly the ee value, possibly due to the higher flexibility of this ring as compared with the six-membered cycle. The ee attained in the ETH of the five-membered cyclic ketone 1-indanone (**5d**) approached the value obtained with 1-tetralone, supporting the assumption that the rigidity of the aliphatic ring has crucial role in reaching high ee. Moreover, the presence of the trifluoromethyl substituent on the aromatic ring (**5e**) further increased the ee to over 90%. Delightfully, high enantioselectivities (ee 96–97%) were obtained in reactions of heterocyclic compounds, such as 4-



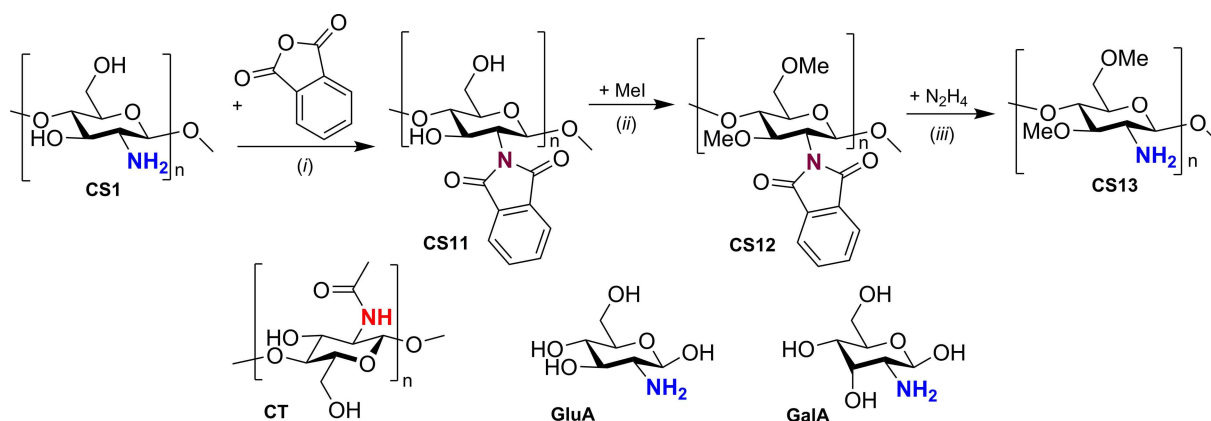
**Scheme 2.** Asymmetric transfer hydrogenation of cyclic ketones.

chromanone, 4-thiochromanone and their substituted derivatives (**5f–5j**) either with the *in situ* or with *ex situ* prepared catalyst (the latter in the ETH of **5c**, **5f** and **5h**). The position of the heteroatom was vital for obtaining high ee, evidenced by the lower value attained with 4-isothiochromanone (**5k**). Accordingly, we presume that the heteroatoms also interact with the chiral catalyst leading to an additional directing effect.

### Studies on the Structure of the Chiral Catalyst

We continued our studies with the goal of gathering information on the structure of the chiral Ru catalyst. For this purpose, we attempted to identify the requirements, which must suit the efficient ligand. Accordingly, we have used several types of commercially available chitosan (CS1, CS2 and CS3), D-glucosamine (GluA, the monomer of this biopolymer), D-galactosamine (GalA), chitin (CT), and several other CS derivatives (CS11, CS12 and CS13) having protected amino and/or hydroxyl groups, which were prepared from CS1 by known methods. The preparation procedures are shown in Scheme 3.<sup>[14]</sup> Transformation of CS1 was monitored by Fourier-transform infrared spectroscopy (FT-IR, Figure S11, Supporting Information).<sup>[15]</sup>

As test reaction the ETH of 4-chromanone (**5f**) was selected (Table 2), in which excellent enantioselectivity could be obtained using CS1 ligand (see Figure 5 and Table 2, entry 2). Without using chiral ligand the reaction did not proceed. The high molecular weight (CS1) and the low viscosity (CS3) chitosan performed similarly, with the former being slightly



**Scheme 3.** Preparation methods of chitosan derivatives and the structure of other ligands tested in the ETH of 4-chromanone; (i) DMF/H<sub>2</sub>O 95/5, 100 °C, 24 h; (ii) NaH, DMF, 0 °C, 15 h; (iii) MeOH/H<sub>2</sub>O 4/1, 80 °C, 24 h.

**Table 2.** ETH of **5f** using Ru complexes formed with various chitosan derived chiral ligands.<sup>[a]</sup>

Entry	Ligand	Conv [%] <sup>[b]</sup>	ee [%] <sup>[b]</sup>
1	–	3	0
2	CS1	> 99	96
3 <sup>[c]</sup>	CS1	> 99	95
4	CS2	60	89
5	CS3	94	96
6	CT	40	85
7	GluA-HCl	22	44
8	GalA-HCl	12	40
9	CS11	5	26
10	CS12	4	8
11	CS13	80	93

[a] Reaction conditions: 0.00625 mmol [Ru(*p*-cym)Cl<sub>2</sub>]<sub>2</sub>, 2 mg chitosan or 0.012 mmol ligand, 0.25 mmol ketone, 1.25 mmol HCOONa, 1 cm<sup>3</sup> H<sub>2</sub>O/*i*PrOH 4/1, rt, 46 h; [b] Conversions and enantioselectivities determined by GC-FID; the absolute configuration of the excess enantiomer was *S*; [c] 50 °C, 22 h.

more efficient (entries 2, 5). Accordingly, the molecular weight (viscosity) is not a crucial property for having an efficient chiral ligand. Using the former (CS1) the reaction took only 22 h at higher temperature (50 °C) with almost identical enantioselectivity.

The low molecular weight chitosan (CS2) having similar degree of deacetylation as CS1 (see Experimental section) was much less appropriate ligand, giving lower conversion and ee (entry 4). A single chitosan monomer (GluA) was found much less efficient, than chitosan (entry 7), similarly with its stereoisomer GalA (entry 8).

To trace down the role of the functional groups in bonding the metal cation three chitosan derivatives were prepared. As a consequence of transforming the amino group of CS1 to phthalimide (CS11) and further protecting the hydroxyl groups by methylation (CS12) the conversions were similar as without

any ligand (entries 9, 10), attributable to lack of complex formation with these derivatives. By deprotecting the amino group again, we obtained an efficient ligand (CS13), which had a performance approaching CS1 (entry 11). Accordingly, free amino groups are essential to form active complex, whereas the hydroxyl groups are not crucial, however their role in the formation of the active complex with CS may not be excluded, knowing that chiral 1,2-aminoalcohol ligands are also efficient in ETH.<sup>[4c,16]</sup> The complex formed with commercial chitin also had some activity (entry 6), which may be ascribed either to some degree of deacetylation of this material or to weak binding to the metal by amide and/or hydroxyl groups.

In the ETH of various ketones the material prepared *ex situ* (Ru-CS1, Figure 2) gave very similar results with those obtained with the catalyst formed *in situ* (see Table 1, Figures 3, 4 and 5). The SEM micrograph of the Ru-CS1 showed the formation of a film-like material having smooth surface, which could be crushed giving sharp edges (Figure 6 (a)). The SEM-EDX elemental map showed uniformly distributed N in the sample. The distribution of the Ru was less uniform with areas of CS where metal could be barely detected (Figure 6 (b)). The atomic ratio of N/Ru introduced during preparation was close to one (0.94). Accordingly, even under these conditions (Ru in slight excess) the metal bonding capacity of CS1 was not fully exploited. This indicated that besides the predominant formation of a pre-catalyst with a monomer/Ru 1/1 ratio, unreacted Ru precursor or species in which one monomer bonded more cations may exist in this material. The EDX spectrum of the sample indicated a Cl/Ru ratio close to 2, similarly with that of the precursor (Figure S12, Supporting Information). Hence no HCl was eliminated and mono-dentate coordinative bonding of the biopolymer to the metal may be assumed in the pre-catalyst.

Subsequently, we examined the interaction of the CS and Ru by Fourier-transform mid-infrared (FT-IR) and far-infrared spectroscopy (FT-far-IR) using this *ex situ* prepared pre-catalyst. The FT-IR spectra of the Ru precursor, chitosan and Ru-CS1, respectively are shown in Figure 7. Alterations detected in the spectrum of the Ru-CS1 material as compared with that of CS1,

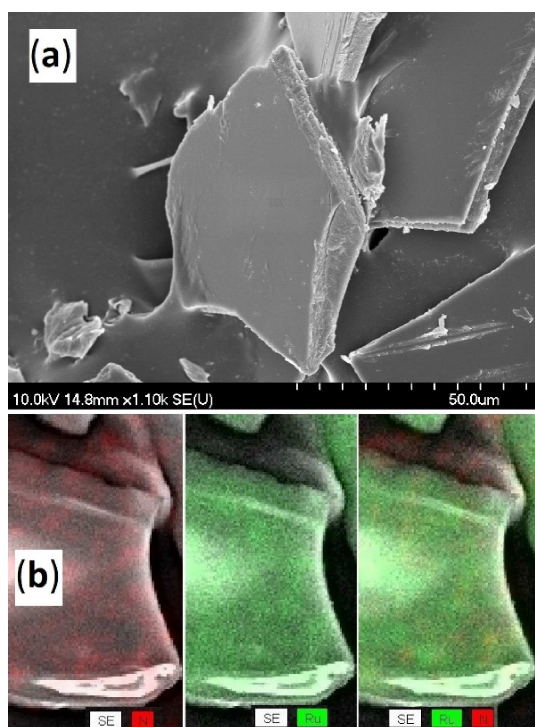


Figure 6. SEM micrograph (a) and SEM-EDX elemental maps (b) (N: red, Ru: green) of the *ex situ* prepared Ru-CS1.

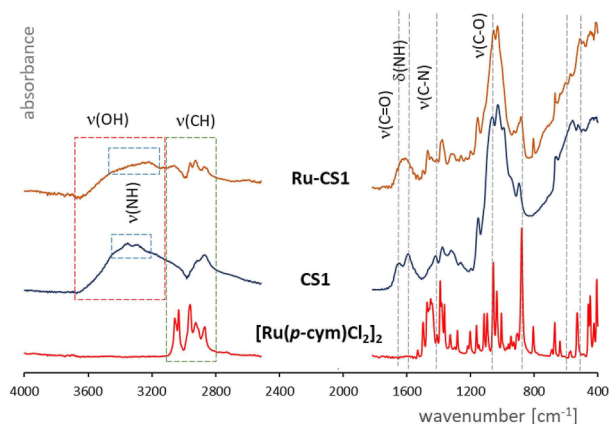


Figure 7. FT-IR spectra of  $[\text{Ru}(p\text{-cym})\text{Cl}_2]_2$ , chitosan CS1 and Ru-CS1.

were similar with those described previously for metal-chitosan complexes.<sup>[15b,17]</sup> The intensity of the broad band at 3150–3600  $\text{cm}^{-1}$  corresponding to the overlapped  $\nu(\text{O-H})$  and  $\nu(\text{N-H})$  vibrations decreased and the latter shifted to lower wavenumbers. However, the hydroxyl groups still gave a strong band, indicating that most of these are not involved in bonding the Ru. In the spectrum of Ru-CS1 the  $\nu(\text{C-H})$  vibrations corresponding to the *p*-cym ligand also appeared, showing the formation of a half-sandwich type complex. The bands  $\delta(\text{N-H})$  at 1595  $\text{cm}^{-1}$  and  $\nu(\text{C=O})$  at 1655  $\text{cm}^{-1}$ , the latter attributed to the residual acetamido groups, disappeared and a broad band centered at 1620  $\text{cm}^{-1}$  developed, as a consequence of bonding

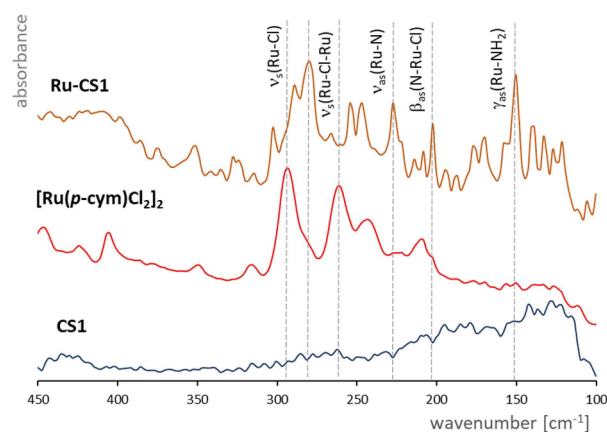


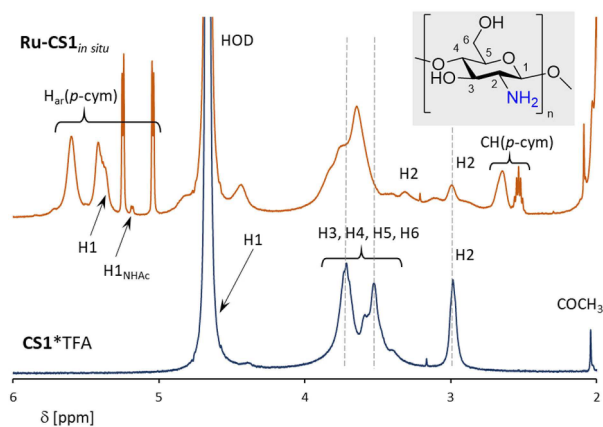
Figure 8. FT-far-IR spectra of CS1,  $[\text{Ru}(p\text{-cym})\text{Cl}_2]_2$  and Ru-CS1.

the Ru by amino groups. Similarly, the band in the spectrum of CS1 corresponding to  $\nu(\text{C-N})$  (at 1420  $\text{cm}^{-1}$ ) was shifted in that of Ru-CS1. Changes of the positions and the intensities of the bands in the  $\nu(\text{C-O})$  region (950–1150  $\text{cm}^{-1}$ ) were also detected. In the low wavenumber region low intensity bands appeared in the spectrum of Ru-CS1, previously assigned to vibrations of Ru–N or Ru–Cl bonds.<sup>[17b]</sup>

Identification of bonds formed between the metal and CS was attempted using FT-far-IR (Figure 8). Bands at 293  $\text{cm}^{-1}$  and 264  $\text{cm}^{-1}$  in the spectrum of the Ru precursor are attributed to the  $\nu_5(\text{Ru-Cl})$  stretching vibrations and the  $\nu_3(\text{Ru-Cl-Ru})$  symmetric vibration of the Cl bridges.<sup>[18]</sup> The former band shifted to lower wavenumber (279  $\text{cm}^{-1}$ ) in the spectrum of Ru-CS1, whereas the latter disappeared, due to splitting of the precursor dimer by interaction with CS1. The intense band appeared at 227  $\text{cm}^{-1}$  in the spectrum of Ru-CS1 may be ascribed to  $\nu_{\text{as}}(\text{Ru-N})$  vibrations based on far-IR studies of Ru halogenoammine complexes.<sup>[18c]</sup> Furthermore, bands at 202 and 150  $\text{cm}^{-1}$  were identified as  $\beta_{\text{as}}(\text{N-Ru-Cl})$  bending and  $\gamma_{\text{as}}(\text{Ru-NH}_2)$  torsional vibrations. In conclusion, the above IR studies indicated the predominant formation of half-sandwich Ru-chitosan complexes by Ru–N bonding, whereas the *p*-cym ligand and Ru–Cl bonds were still present in the pre-catalyst.

The structure of the Ru complex formed *in situ* in  $\text{D}_2\text{O}$  was examined by  $^1\text{H}$  NMR spectroscopy (Figure 9). A solution of CS1 obtained by addition of trifluoroacetic acid (TFA) was used as reference (CS1\*TFA). Signals corresponding to the ring H of CS1 were assigned based on literature, where the signal of the anomeric H (H1) was covered by that of HOD.<sup>[15a,19]</sup>

In the spectrum recorded in the presence of Ru (monomer-CS1/Ru 1.41) we detected two sets of signals in about 2/1 ratio corresponding to the *p*-cym ligand. The major, broad, unresolved set of signals (5.60, 5.41, 2.64 ppm) showed formation of a flexible complex with the *p*-cym in its composition (signals corresponding to the two  $\text{CH}_3$  groups showed similar pattern). We assigned these signals to H of complexes in which amino groups are coordinated to the Ru, based on previously proposed interaction of aminosaccharide derivatives with Pd.<sup>[19d]</sup> The well-resolved signal set (5.24, 5.03, 2.53 ppm) may



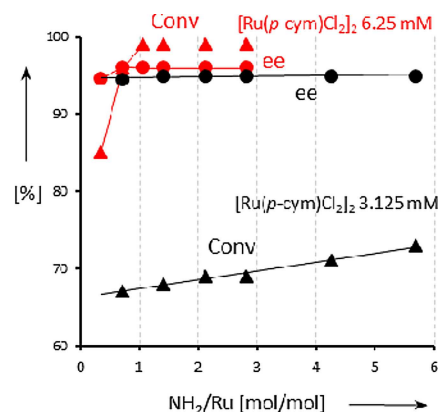
**Figure 9.**  $^1\text{H}$  NMR spectra of  $\text{CS1}^*\text{TFA}$  and of the material formed from  $\text{CS1}$  (3 mg) and  $[\text{Ru}(\text{p-cym})\text{Cl}_2]_2$  (0.00625 mmol) in  $\text{D}_2\text{O}$ .

be attributed to formation of a more rigid half-sandwich type complex in which a glucosamine monomer may act as a bidentate ligand and is coordinated to the metal by two amino groups or by the involvement of hydroxyl and/or acetamido groups.<sup>[19d,20]</sup> Due to the overlapped signals it is not possible to identify certainly the ring Hs, however, one may observe the split of the H2 signal in two signals. Besides the broad one close to 3 ppm, another shifted downfield to 3.3 ppm may also be assigned to H2. The merged ring H signals between 3.4–4.0 ppm (H3, H4, H5, H6) gave a relative integral value of 4.5, accordingly we assume that the signal at 4.4 ppm also corresponds to the H3 of the complex.

The above characterization methods gave information on the possible structure of the pre-catalyst. However, the composition and the structure of the working chiral catalyst remained unclear. Transformation of this pre-catalyst was visible upon addition of the H-donor and further in the presence of the ketone. To determine the amount of the chiral ligand necessary to obtain the active catalyst we have investigated the effect of the  $\text{CS1}/\text{Ru}$  ratio on the conversion and ee in the ETH of **5f**. Results of these investigations are illustrated in Figure 10.

The  $\text{CS1}$  amount had significant influence on the conversion at 6.25 mM Ru-precursor concentration. The conversions increased until a  $\text{NH}_2/\text{Ru}$  of 1 was reached (calculated considering a 75% deacetylation degree for  $\text{CS1}$ ), when complete transformation is obtained and further changes cannot be monitored. Using halved metal concentration showed a slow linear increase of the conversion by raising the  $\text{CS1}$  amount.

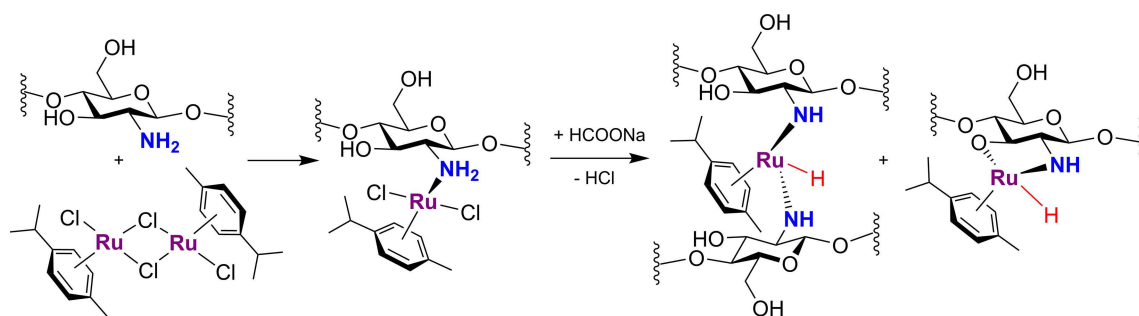
Importantly, at both Ru amounts even at the lowest  $\text{NH}_2/\text{Ru}$  ratios ( $< 1$ ), the ee reached values close to the best obtained in these experiments (95% and 96%, respectively). Accordingly, even at low  $\text{CS1}$  amount the enantioselective catalyst is already formed, though at high Ru concentrations the metal was not completely transformed to catalytically active species. The conversion may also be influenced by the solubility of the complex. A soluble pre-catalyst results by mixing the Ru-precursor and  $\text{CS1}$  (Figure 10 (a)), which is transformed to a yellow precipitate following addition of  $\text{HCOONa}$  (Figure 10 (b)).



**Figure 10.** Effect of the  $\text{CS1}/\text{Ru}$  ratio on the conversion (triangles) and ee (circles) in the ETH of **5f**. Reaction conditions:  $[\text{Ru}(\text{p-cym})\text{Cl}_2]_2$  concentration 6.25 mM and 3.125 mM (red and black symbols), 0.25 mmol **5f**, 1.25 mmol  $\text{HCOONa}$ , 1  $\text{cm}^3$   $\text{H}_2\text{O}/i\text{PrOH}$  4/1, 30 °C, 24 h; below are the photographs of the *in situ* formed soluble pre-catalyst (a), the complex resulted following addition of  $\text{HCOONa}$  (b) and the product mixture after 24 h reaction (c) using 3.125 mM Ru-precursor and  $\text{NH}_2/\text{Ru}$  2.1.

This complex is further transformed during ETH shown by the solubilized catalyst, which also changed its color to pale orange (Figure 10 (c)). When high amounts of  $\text{CS1}$  were used, the excess polymer remained undissolved.

According to the widely accepted concerted outer-sphere type mechanism of the transfer hydrogenation of prochiral ketones with half-sandwich complexes, Ru-hydride is formed by addition of the H-donor.<sup>[21]</sup> Thus, the yellow precipitate (Figure 10 (b)) could be a similar Ru-hydride complex formed from the Ru-chitosan pre-catalyst. The heterogeneous nature of this complex makes difficult to determine its composition based on the above results, however, the continuous increase in the conversion with the  $\text{CS1}$  amount showed the possible participation of more than 1 monomer in the formation of the catalyst. Based on previous studies on the structure of chitosan complexes formed with metals and the above described results we assume the formation of a pre-catalyst and active hydride complexes having structures as illustrated in Scheme 4.



**Scheme 4.** Suggested structure of the pre-catalyst formed from chitosan and  $[\text{Ru}(p\text{-cym})\text{Cl}_2]_2$  and the probable active species resulted by addition of  $\text{HCOONa}$ .

### Preparative Applicability of the Chiral Ru-CS1 Catalyst

Having in hand a catalytic system, which affords good enantioselectivities in the ETH of several acetophenone derivatives and cyclic ketones we examined the practical value of the Ru complex bearing unmodified CS1 as ligand. For this purpose, we carried out reactions at 1 mmol scale (4-fold) increasing proportionally the metal precursor and the solvent amount and using doubled quantities of H-donor. The yields of the isolated optically enriched products are summarized in Table 3.

**Table 3.** ETH of ketones at one mmol scale with *in situ* formed Ru-CS1 complex.<sup>[a]</sup>

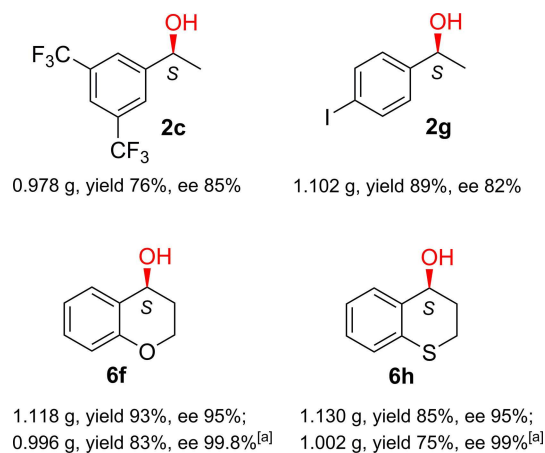
Entry	Product	Reaction time [h]	Conv <sup>[b]</sup> [%]	Yield <sup>[c]</sup> [%]	ee <sup>[d]</sup> [%]
1	2a	48	99	84	79
2	2b	72	99	85	84
3	2c	96	85	73	85
4	2d	48	98	82	83
5	2e	75	92	80	82
6	2f	96	75	72	81
7	2g	72	93	83	82
8	2h	72	99	86	82
9	2i	72	99	85	79
10	2k	96	92	81	79
11	2l	72	99	95	78
12	2m	96	90	75	72
13	2o	72	99	80	73
14	2r	96	90	84	75
15	6b	168	65	60	91
16	6c	168	80	66	91
17	6d	96	80	64	86
18	6e	96	90	68	93
19	6f	48	98	87	95
20	6g	72	98	86	95
21	6h	48	99	88	96
22	6i	72	99	87	96
23	6j	72	99	90	97

[a] Reaction conditions: 0.025 mmol  $[\text{Ru}(p\text{-cym})\text{Cl}_2]_2$ , 10 mg CS1, 1 mmol ketone, 2.5 mmol  $\text{HCOONa}$ , 4 cm<sup>3</sup>  $\text{H}_2\text{O}/i\text{PrOH}$  4/1, rt; [b] Conversions determined by GC; [c] Isolated product yields determined following purification by flash chromatography; [d] The ee determined by gas-chromatography (GC), the configuration of the excess enantiomers was assigned as *S*.<sup>[13]</sup>

Under the above conditions the reactions needed more time, however similar conversions and very close ee values were reached as compared with the runs carried out at lower scale (0.25 mmol). Accordingly, the optically enriched alcohols were isolated in good yields. Further the ETH of **1c**, **1g**, **5f** and **5h** were also carried out at gram scale with 5 or 8 mmol ketones, under identical conditions, using proportionally increased catalyst, chitosan and H-donor amounts. The corresponding alcohols were prepared in high yields following flash chromatographic purification (Figure 11). Moreover, close to optically pure (*S*)-**6f** and (*S*)-**6h** were obtained in good yields following a single recrystallization of the products in hexane.

### Conclusions

Our attempts to develop a green and sustainable reduction method using the biocompatible and degradable biopolymer chitosan of natural origin led to an aqueous catalytic system in which high enantioselectivities were obtained in the asymmetric transfer hydrogenation of prochiral ketones using an *in situ* formed chiral Ru complex as catalyst and  $\text{HCOONa}$  as hydrogen donor. Acetophenone derivatives were reduced to the corre-



**Figure 11.** Products prepared at gram scale (using 5 mmol **1c**, **1g** or 8 mmol **5f** or **5h**) purified by flash-chromatography; [a] products obtained following an additional recrystallization from hexane.



sponding 1-arylethanol in up to 86% ee, unprecedented until now in the presence of natural CS as chirality source. Moreover, cyclic aryl ketones were hydrogenated in surprisingly high, over 90% ee, the best results, up to 97%, being obtained in reactions of heterocyclic compounds, such as 4-chromanone or 4-thiochromanone and their substituted derivatives. These outstanding results may be rationalized by the rigidity of the cyclic ketones, *i.e.* the steric hindrances imposed by the ring. In case of the heterocyclic compounds this effect could be complemented by possible interactions of the heteroatoms with the catalyst, which may also have a directing effect on the substrate during ETH.

A pre-catalyst prepared from the Ru-precursor and CS was equally efficient as the *in situ* formed complex, was much easier to handle and could be stored for several months. This material was characterized using scanning electron microscopy, infrared and NMR spectroscopy. Although coordination of the CS to Ru could be demonstrated, it was shown the presence of complexes of both high and low rigidity in the presence of excess CS. In these complexes CS interacts with the metal through amino groups, however, in some species the role of the hydroxyl or even acetamido groups in bonding to the Ru could not be excluded. Based on results obtained using CS derivatives and that of a study on the CS/metal ratio we reached to the conclusion, that the amino groups have crucial role in the formation of the active complex and probably the metal interacts with two glucosamine monomers to form the active complex. Results obtained in the present study and previously published data were used to suggest possible structures for the pre-catalyst and the active complex. However, further examination of the catalyst composition and structure will be carried out in the near future and will be reported in due course.

## Experimental Section

### Materials and methods

High molecular weight chitosan (CS1,  $M_w$ : 310,000–375,000 Da,  $\geq 75\%$  deacetylated,  $\mu$  800–2000 cP of 1 wt.% in 1% acetic acid), low molecular weight chitosan (CS2,  $M_w$ : 50,000–190,000 Da, 75–85% deacetylated,  $\mu$  20–300 cP of 1 wt.% in 1% acetic acid) and low viscosity chitosan (CS3,  $\mu < 200$  cP of 1 wt.% in 1% acetic acid) were purchased from Sigma-Aldrich and used as received. The Ru-precursor  $[\text{Ru}(p\text{-cym})\text{Cl}_2]_2$  was used as received (Sigma-Aldrich). Ketones used in this study were all commercial products and used without purification. The hydrogen donors and analytical grade organic solvents were obtained from commercial sources and used as received. The *ex situ* prepared material Ru-CS1 was obtained by stirring 38 mg  $[\text{Ru}(p\text{-cym})\text{Cl}_2]_2$  and 20 mg CS1 chitosan in 40 cm<sup>3</sup> water for 24 h. The solution was transferred into a Petri dish of 10 cm diameter and the solvent was let to evaporate slowly under ambient conditions. 53 mg dry orange material could be recovered and was used in reaction within 1 year.

FT-IR measurements were recorded on a Bio-Rad Digilab Divison FTS-65 A/896 IR spectrophotometer operating in diffuse reflectance mode between 4000–400 cm<sup>-1</sup> using 2 cm<sup>-1</sup> resolution by averaging 256 scans. FT-far-IR (far-infrared) spectra were recorded on a Bio-Rad Digilab Divison FTS-40 vacuum IR spectrophotometer in

the 500–100 cm<sup>-1</sup> range accumulating 256 scans with 2 cm<sup>-1</sup> resolution using the Nujol mull technique. SEM measurements were carried out on a Hitachi S-4700 Type II FE-SEM microscope with 10 kV accelerating voltage. The samples were mounted on a conductive carbon tape and sputter coated by a thin Au/Pd layer in Ar atmosphere prior to measurements. For obtaining the SEM-EDX (energy dispersive X-ray) analysis of the sample Ru-CS1 a Röntec QX2 spectrometer coupled to the microscope was used.

<sup>1</sup>H and <sup>13</sup>C NMR spectra of the purified products were recorded on a Bruker AVANCE DRX 400 spectrometer using CDCl<sub>3</sub> solvent (see Supporting Information). Products were isolated by flash chromatography on silica gel 60, 40–63  $\mu\text{m}$ , using hexane isomers/ethyl acetate (EtOAc) mixtures (as indicated in the Supporting Information). The purity of the fractions was checked by thin-layer chromatography on Kieselgel-G (Merck Si 254 F) layers. Optical rotations of the products were measured using Perkin-Elmer 341 polarimeter. The <sup>1</sup>H NMR spectrum of CS1 in presence of the Ru-precursor or TFA following 24 h stirring in D<sub>2</sub>O was recorded on a Bruker Ascend 500 instrument at 500 MHz.

Gas-chromatographic analysis of the reaction products were carried out using Agilent Techn. 6890 N GC-5973 MSD (GC-MSD) equipped with 30 or 60 m long HP-1MS capillary columns for mass spectrometric identification of the products. For quantitative analysis Agilent 7890 A GC-FID (GC-FID) chromatograph equipped with chiral capillary column (Cyclodex-B 30 m, J&W; Cyclosil-B 30 m, J&W or HP-Chiral 30 m, J&W from Agilent or Hydrodex g-TBDAC, 25 m from Macherey-Nagel) was used.

### Transfer Hydrogenation: General Procedure

The reactions were carried out in 4 cm<sup>3</sup> closed glass vials. The slurries were stirred magnetically (800 rpm). If higher than rt was necessary the vials were immersed in a heated oil bath. In a typical reaction the given amounts of  $[\text{Ru}(p\text{-cym})\text{Cl}_2]_2$ , chitosan and 1 cm<sup>3</sup> solvent were introduced into the vial and stirred at rt 1 h followed by addition of the required amount of HCOONa (typically 1.25 mmol) and further stirred 1 h. Finally, the prochiral ketone (0.25 mmol) was added to the mixture and stirred for the given time. Following the reactions, the products were extracted in 3 cm<sup>3</sup> EtOAc, the aqueous phase was washed twice with 2 cm<sup>3</sup> EtOAc, the unified organic phase was dried using MgSO<sub>4</sub> (sicc) and analyzed by gas-chromatography (GC-MSD and GC-FID). Reactions at 1 mmol ketone scales were carried out similarly as above in 8 cm<sup>3</sup> vials using the amounts given in Table 3. Reactions at gram scale (5 or 8 mmol) were carried out under identical conditions increasing the reaction components proportionally. Following GC analysis of the crude products the solvent was removed by evaporation and the pure products were obtained by flash chromatography. These products were analyzed by GC-MSD, GC-FID, <sup>1</sup>H and <sup>13</sup>C NMR spectroscopy and their optical rotations were measured (see Supporting Information). Products obtained at 8 mmol scale were crystallized in hexane to obtain the optically pure alcohols.

Conversions (Conv) and enantioselectivities (as enantiomeric excess, ee) were calculated based on the relative concentrations determined from chromatograms using the formulae given in the Supporting Information. The absolute configuration of the excess enantiomers was assigned based on the optical rotation sign of the isolated products and literature data,<sup>[13,22]</sup> or based on chromatographic analysis and comparison with samples of known configurations.

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## Conflict of Interest

The authors declare no conflict of interest.

**Keywords:** enantioselective · transfer hydrogenation · chitosan · ketones · ruthenium

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