THE MECHANOCHEMICAL IMPLEMENTATION OF THE ENVIRONMENTALLY FRIENDLY ASYMMETRIC TRANSFER HYDROGENATION OF KETONES

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Abstract

Optically pure compounds are essential in the synthesis of pharmaceuticals, fragrances and pesticides. Asymmetric catalytic reactions are the most favorable methods to achieve high conversions and enantiomeric excesses in fast reactions, using only catalytic amount of the chirality sources. Hydrogenations and transfer hydrogenations are well-studied procedures to obtain optically pure chiral alcohols. The transfer hydrogenation is convenient, as it ensures the possibility to use a hydrogen donor compound instead of hydrogen gas to provide the necessary H atom. In the past few decades several synthetic chiral compounds were used as the ligand of the catalyst complex, however these days more environmentally friendly implementations are favored. The use of natural chiral compounds would provide great opportunities to carry out asymmetric catalytic reactions using less organic solvents and producing less hazardous waste.

In our previous studies, we have developed an asymmetric catalytic system for the transfer hydrogenation of prochiral ketones using an *in situ* prepared Ru-chitosan complex in aqueous media. The catalyst prepared using the readily and easily available, biodegradable and inexpensive biopolymer provided good result in the transfer hydrogenation of various prochiral ketones in aqueous-phase reactions. In order to increase the preparative value of this method for preparing optically pure alcohols, we decided to use mechanical energy transmission instead of conventional thermally activated reactions carried out in magnetically stirred batch reactors. With the former method the reaction time can be reduced, as well as the volume of the used solvent and the produced waste. After the optimization of the reaction conditions in the transfer hydrogenation of 4-chromanone, we examined the reaction of various ketones and the obtained results were compared with those reached in reactions carried out conventionally. All the examined ketones were transformed in similar degrees and the chiral alcohols were obtained in high enantiomeric excesses (ee). The reactions were scaled up as well, to prepare the optically enriched compounds in mmol quantities.

Introduction and aims

During the last few decades the protection of the environment, the application of sustainable and economical solutions play major role in science. Although the synthesis of optically pure compounds is well studied and successful as well, researchers have to develop greener and more sustainable methods to meet the standards of the environmental regulations. Optically pure compounds are widely used in pharmaceuticals, agrochemicals, flavors and fragrances. Asymmetric catalytic transfer hydrogenations are convenient methods to transform prochiral unsaturated compounds into essential optically pure chemicals. Large variety of chiral complexes have been developed to catalyze these reactions [1]. Although excellent results were achieved, synthetic ligands do not meet the requirements of the recent economic and ecologic trends.

The use of chiral ligands from natural sources became essential, to develop new, economically and environmentally advantageous methods. Shell food industry produces great volume of chitin as waste, which could be further used in catalysis. In alkali solution chitin can be deacetylated to obtain chitosan [2], which may replace the expensive, synthetic ligands. Due to the presence of the free amino groups, this biopolymer is able to form complexes with metal cations to catalyze several types of organic transformations [3]. Furthermore, it can be used in aqueous media as a result of its hydrophilic character. In our previous studies, we used chitosan as a chiral ligand to *in situ* form Ru-chitosan complex in aqueous media, which catalyzed the asymmetric transfer hydrogenations of prochiral ketones. Using this method several phenyl ethanol derivatives, cyclic and heterocyclic alcohols and even amino alcohols were obtained with high conversions (90-99%) and enantioselectivities (ee: 88-97%). Based on the results achieved in the reactions of different ketones we reached to numerous conclusions about the secondary bonds formed between the complex and the ketones in the transition state. We have also examined the pre-prepared Ru-chitosan complex, which gave identical results even after several months' of storage. The NMR and IR characterization of the complex provided enough information to determine the possible structure of the complex and that of the transition state [4,5].

Although, the use of the natural ligand gave excellent results, similar to the synthetic compounds, the mechanochemical implementation could open new opportunities to the development of greener, more sustainable methods [6,7]. Our aim was to investigate the transfer hydrogenation of prochiral ketones catalyzed by a chiral Ru-chitosan complex prepared from unmodified, commercially available chitosan in aqueous solvents, using a mixing mill to provide the necessary energy for the reaction. We chose the transfer hydrogenation of 4-chromanone to determine the optimal reaction conditions, then we planned to implement the method to other, previously studied prochiral compounds as well. Practical use is essential in science, so our goals included the scale-up of the reactions as well.

Experimental

The prochiral ketones, the hydrogen donor (HCOONa), the metal precursor ([Ru(*p*-cymene)Cl]$_2$Cl$_2$) and the chitosan were obtained from commercial sources and were used as received. Transfer hydrogenations were carried out in closed 10 mL ZrO_2 grinding jars with grinding balls made from the same material with the diameter of 3; 5; 12 and 15 mm (Figure 1.). In a typical run all the compounds were measured into to the jars, then the necessary amount of balls was counted and added to the system. The mixture then was mixed in a Retsch Mixing Mill MM 400 instrument at the chosen frequency for the desired time. When the reaction was completed 2 mL ethyl acetate was added into the jar to dissolve the organic compounds from the ZrO_2 surfaces. The system then was washed 2 times with 1 mL ethyl acetate. The organic phases were combined, then filtered to remove the solid remnants. The products were analyzed by GC-MSD and GC-FID using chiral capillary columns, and NMR spectroscopy. The products of the serial and the scale up measurements were easily purified by column chromatography using desired mixture of hexane and ethyl acetate as eluent, or in the cases of the solid products recrystallization from pure hexane was also efficient.

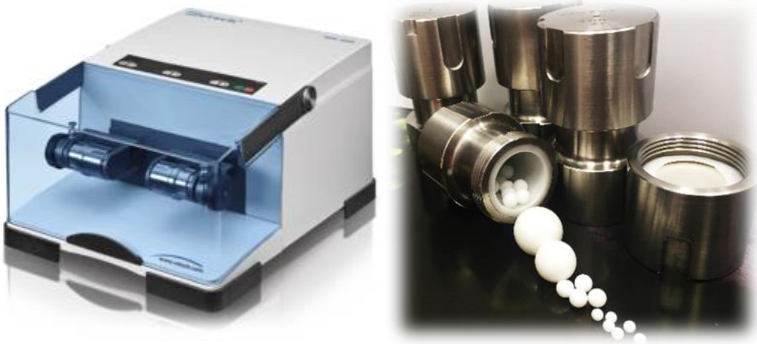

Figure 1. Retsch Mixing Mill MM400 Instrument, and the used ZrO_2 grinding jars and balls

Results and discussion

First, based on the results of our previous studies the transfer hydrogenation of 4-chromanone was carried out in the new catalytic system. The optimization of the instrument parameter such as the size and the quantity of the balls, the used frequency and the reaction time led us to the conclusion that 100 grinding balls with 3 mm diameter, at 30 Hz gave the best result after 120 min of reaction time (Figure 2.). Then the reaction parameters – the volume of solvent, the amount of the hydrogen donor and the catalyst – were optimized. 0.2 mL water/^{i}PrOH gave the best result with 10 eq. of HCOONa and 5% catalyst. We would like to stress out that under these conditions we were able to decrease significantly the reaction time, from 48 h to 2 h, thus, the turn-over frequency (TOF) has increased twenty-fourfold (from 0.41 h^{-1} to 10 h^{-1}).

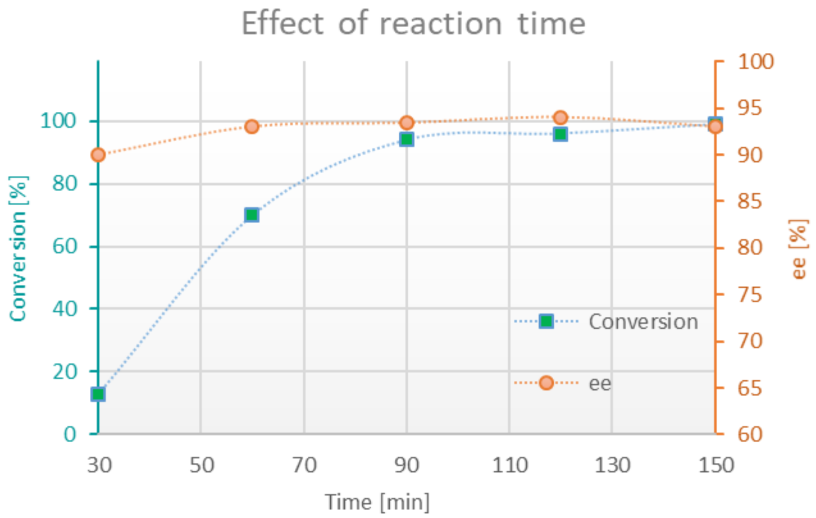

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Figure 2. The effect of reaction time. 100 grinding balls with 3 mm diameter, 30 Hz, 0.2 mL solvent, 2 eq. hydrogen donor, 5% catalyst

Next we examined the possibility of scale up by adding 1 mmol 4-chromanone to the system. In this case the reaction was slower, and at the same frequency the amount of the solvent, the catalyst and the hydrogen donor had to be increased to achieve 98 % conversion with 91 % ee. Although, the amount of the catalyst and the hydrogen donor had to be increased, to our delight the reaction required less equivalents of these components as compared to the ketone than in the serial measurements.

In our following experiments, other ketones were used in the catalytic system. Further compounds – 7 acetophenone derivatives, 9 cyclic ketones and 10 heterocyclic ketones – were chosen based on the results obtained in our previous studies [4,5]. Although the above conditions were set for the transfer hydrogenation of 4-chromanone, some of the prochiral ketones' reactions were slower in the magnetically stirred reactions. Based on this observation further optimizations were needed in the reaction of some of these compounds. Following these optimizations all of the desired chiral alcohols were obtained with excellent conversion (90-99,9 %) in this catalytic system (Figure 3.). As our previous studies showed, the enantiomeric excess highly depends on the structure of the prochiral ketones. In this system all the achieved ee values were similar to the ee obtained in our previous experiments carried out in batch system using magnetic stirring (67-96%). A few percent of decrease can be observed. Probably the heat produced by repetitive impact energy causes the faster degradation of the catalyst complex or the racemization of the product. This effect was known from previous, high temperature measurements, although, in the mechanochemial reactions it didn't seem to be as significant as in the magnetically stirred ones.

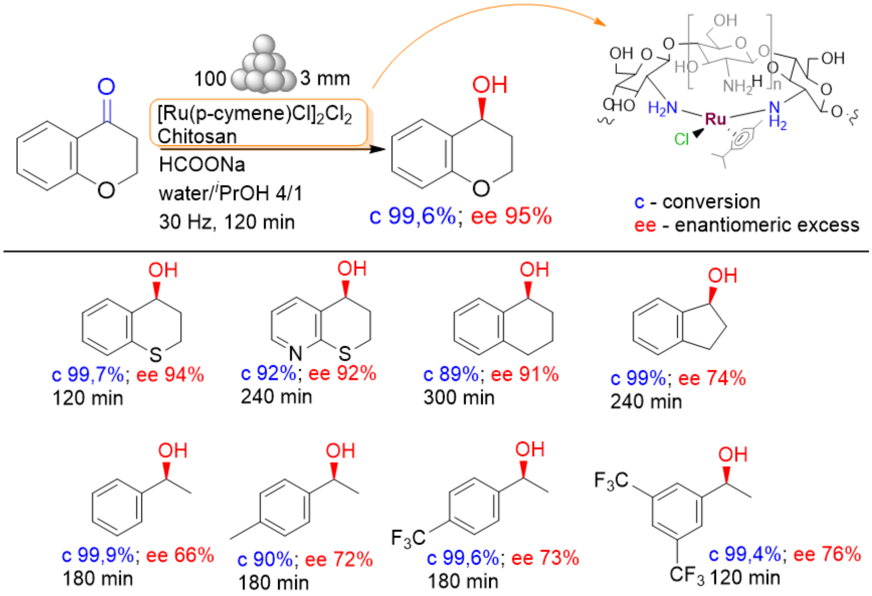

Figure 3. The transfer hydrogenation of 4-chromanone with the previously determined catalyst structure and a few examples of starting compounds with the achieved conversions and ee values

Conclusions

In summary, we have developed a sustainable and green method, using the biopolymer chitosan as a chiral ligand to *in situ* form a Ru complex in aqueous catalytic system, in which high enantioselectivities were obtained in the asymmetric transfer hydrogenation of prochiral ketones by mechanical energy transmission in a mixing mill. The enantiomeric excess and conversion values were similar to the values achieved in magnetically stirred reactions, although significantly less solvent and shorter reaction times were necessary. In consequence, the TOF of the catalyst could be increased twenty-fourfold. The product alcohols were easily separable from the reaction mixture and were purified by column chromatography or recrystallization. The latter method has many advantages, such as greener and less organic solvent was used during the work-up process. The reaction was easily scaled-up in this system. Accordingly, with this new system optically pure alcohols can be obtained with the use of natural chiral ligand in aqueous media using mechanical energy transmission following an environmentally benign procedure.

Acknowledgements

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