

Ru-catalyzed mechanochemical asymmetric transfer hydrogenations in aqueous media using chitosan as chirality source

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ABSTRACT

As the demand for sustainable methods increases, synthetic chemistry is focusing on the application of environmentally benign methods, such as fast reactions induced by alternative energy transmission. Chitosan is a chiral biopolymer of natural origin, which can be used in asymmetric catalysis. The application of Ru-chitosan complexes along with the mechanochemical activation may open great opportunities for sustainable preparation of optically pure alcohols. In the present study, we optimized the mechanochemical asymmetric transfer hydrogenation of 4-chromanone, carried out in a mixing mill. The reaction was catalyzed by the *in situ* formed Ru-chitosan complex, applying HCOONa as the hydrogen donor in aqueous media. We examined the mechanical effects of different grinding media sizes, then explored the scope of the system using 24 prochiral ketones, which ranged from hetero- and carbocyclic ketones to acetophenone derivatives. In most of the cases, the reactions were successfully scaled up to 1 mmol and the products were isolated in good yields and outstanding enantioselectivities. Our present study is a significant step forward to the development of environmentally benign and sustainable enantioselective processes, as the alternative activation method provided optically enriched alcohols using a biodegradable chirality source in aqueous media.

1. Introduction

The importance of chiral compounds in the pharmaceutical industry is rapidly increasing. Nowadays over 90% of the available drugs are chiral, optically pure chemicals [1]. Since the 90s' catalytic asymmetric processes have become preferred methods for the synthesis of optically pure building blocks [2]. Among these are various secondary chiral alcohols. Accordingly, their stereoselective preparation is in the focus of synthetic chemistry. Reduction of ketones in the presence of chiral auxiliaries provide high enantiomeric excesses (ee) [3], however, catalytic reactions are more favorable as smaller amounts of optically pure compounds are necessary [4]. The most efficient methods to produce chiral alcohols are the catalytic hydrogenations of the corresponding unsaturated carbonyl compounds. Various chiral metal complexes had been developed, which efficiently catalyze asymmetric hydrogenations (AH), reaching outstanding conversions and ees [5–7]. Despite the great success of the AHs, easy-to-operate systems are more preferable on laboratory and even on industrial scale. Gaseous H₂ can be replaced by cheap hydrogen donors, such as alcohols, formic acid or its salts [6]. Ru

complexes formed with the bifunctional chiral ligands developed by Noyori et al., which provide optically pure alcohols under mild conditions represented a breakthrough in the research of ATH [8–11]. Due to the wide applicability and simplicity of the asymmetric transfer hydrogenations (ATH), the development of chiral catalysts designed for these purposes accelerated [12].

Today's expectations of applying environmentally benign methods demand solutions that may provide high value-added fine chemicals using cheap and less hazardous compounds. The preparation of the tailored chiral synthetic ligands is time and energy-consuming and produces large quantities of waste. Hence, recent studies are focusing on using natural compounds from renewable sources. Chitosan, which is a chiral biopolymer from natural sources, has diverse applications [13–16]. Beside its utilization in the pharmaceutical industry, it can be employed in asymmetric catalytic processes as catalyst support, organocatalyst or chiral ligand [16–20]. Chitosan can be obtained by the alkaline deacetylation of chitin under different reaction conditions [21]. Due to its free amine and hydroxyl groups, this polymer forms Ru complexes, which catalyze the ATH of ketones, similarly with the

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ligands developed by Noyori and Hashiguchi [11]. Although the reaction is slower with chitosan than with the highly efficient synthetic ligands, the environmental footprint of the reaction may be decreased due to the use of the natural, biodegradable ligand. Moreover, high conversions and enantioselectivities can be achieved in the ATH of acetophenone derivatives, and outstanding results are obtained in the reduction of carbocyclic and O, S or N-heterocyclic ketones [22,23].

Alternative energy transmission methods have a central role in developing greener chemical processes. Numerous examples can be found in the literature on asymmetric reactions induced by microwave, ultrasound or milling [24–27]. The application of mechanochemistry in asymmetric catalytic processes has numerous advantages. May shorten the reactions, which can be carried out solventless or in the presence of a small amount of liquid [28,29]. In a mixing mill, the collision and friction of the grinding balls provide the energy to carry out the reaction [30,31], however, the efficiency can be increased significantly by applying a liquid energy transmitting media, termed as liquid assisted grinding (LAG) [32,33]. A wide range of organic catalytic reactions was carried out by dry milling or by the LAG method, such as Suzuki, Heck and Sonogashira couplings, Cu-catalyzed click reactions, aldol, Baylis-Hillmann and oxidation reactions, Michael additions and cascade reactions [34]. Various pharmacologically active compounds were also efficiently synthesized using mechanochemical activation [35]. Among the examined processes are a large number of asymmetric catalytic reactions, such as enantioselective organocatalytic aldol, Michael additions and anhydride ring openings, asymmetric alkylations, Cu-catalyzed couplings and halogenations [36–42].

Due to their industrial importance, reductions of unsaturated compounds were also carried out by mechanochemical activation, for example in the synthesis of the antidepressant fluoxetine using NaBH_4 [43]. The hydrogen or deuterium necessary for transfer hydrogenations could be *in situ* generated from water by applying metal grinding media or metal additives [44–46]. A variety of aldehydes and ketones were reduced by catalytic mechanochemical transfer hydrogenations using silica-supported tert-butyl ammonium fluoride catalyst in the presence of polymethylhydrosiloxane donor [47]. Portada et al. studied the Pd/C catalyzed transfer hydrogenation of aromatic nitro compounds in a mill. Their work focused on investigating the efficiency of the LAG method in the chosen system [48]. These studies and the numerous publications on asymmetric mechanochemical reactions motivated us to develop a mechanochemical system for the ATH of ketones.

In our previous work, we have investigated the Ru-TsDPEN (TsDPEN: *N*-(*p*-toluenesulfonyl)-1,2-diphenylethane-1,2-diamine) catalyzed ATH of various ketones in a mixing mill [49]. Due to the relatively low rate of the Ru-chitosan catalyzed batch transfer hydrogenations, we aimed to examine the possibility of using mechanochemical activation to increase the efficiency of the process. The environmental impact of the catalytic system was also in our focus. Thus, beside the application of the cheap and easily available hydrogen donor (HCOONa) and the natural, biocompatible and biodegradable chiral ligand, the amount of organic solvent used was also minimized.

2. Experimental

2.1. Materials and methods

The Ru-precursor: $[\text{Ru}(p\text{-cym})\text{Cl}_2]_2$ (*p*-cym: *para*-cymene) and the chiral ligand: high molecular weight chitosan (CHMw) were used as received (Sigma Aldrich). The chitosan flakes were pre-milled at 30 Hz for 10 min in 500 mg portions, in 10 cm^3 ZrO_2 grinding jars with 1 pc (piece) of $\varnothing 12\text{ mm}$ ZrO_2 grinding ball (\varnothing : diameter). The obtained powder was characterized by scanning electron microscopy (SEM) measurements using 10 kV accelerating voltage performed on a Hitachi S-4700 Type II FE-SEM instrument, and by X-ray diffractometry (XRD) on a Rigaku Miniflex-II diffractometer using $\text{Cu K}\alpha$ radiation ($\lambda = 0.1548\text{ nm}$) at a scanning rate of 4° min^{-1} between 5 and $40^\circ 2\theta$ angles.

Ketones (**1a** – **24a**) and the hydrogen donor (HCOONa) used in this study were all commercial products (except **6a**, which was prepared, as described previously [23]) and were used without purification. Analytical grade organic solvents were obtained from commercial sources and were applied as such.

Gas-chromatographic analysis of the reaction mixtures was carried out using Agilent Techn. 6890N GC-5973 MSD (GC-MSD) equipped with 30 m long HP-1MS capillary column for mass spectrometric identification of the products. For quantitative analysis, Agilent 7890A GC-FID (GC-FID) chromatograph equipped with chiral capillary columns (Cyclodex-B 30 m, J&W; Cyclosil-B 30 m, J&W; HP-Chiral 30 m, J&W from Agilent Technol. or Astec Chiraldex B-DA 30 m from Sigma-Aldrich) was used. Products were isolated by flash chromatography on silica gel 60, 40–63 μm , using hexane isomers/ethyl acetate (EtOAc) 4/1 – 8/1 mixtures or by crystallization in hexane. The purity of the fractions was checked by thin-layer chromatography on Kieselgel-G (Merck Si 254 F) layers. ^1H and ^{13}C NMR spectra of the purified products were recorded on a Bruker Ascend 500 instrument at 500 and 125 MHz using CDCl_3 solvent.

2.2. Reactions in mixing mill (by grinding)

The mechanochemically activated reactions were carried out in 10 cm^3 ZrO_2 inner-coated grinding jars and ZrO_2 grinding balls ($\varnothing 3, 5, 12, 15\text{ mm}$). In a typical reaction, the given amounts of $[\text{Ru}(p\text{-cym})\text{Cl}_2]_2$, CHMw, water/ $^i\text{PrOH}$ 4/1 mixture, the necessary amount of HCOONa donor and ketone were introduced into the jar, then the chosen number of balls were added to the system. The jars were placed into a Retsch MM400 mixing mill and agitated at the chosen frequency for the given time. Following reactions, the products were dissolved in 2 cm^3 EtOAc , the jars and balls were washed twice with 2 cm^3 EtOAc , the unified organic phase was filtrated on a short silica pad to separate the remaining water and solid residues from the product, which was analyzed by gas-chromatography using *n*-dodecane as internal standard (GC-MSD and GC-FID). Conversions (Conv) and enantioselectivities (as enantiomeric excess, ee) were calculated based on the relative concentrations determined from chromatograms using the formulae given in the Supplementary material (SM). The TOF values were determined based on the conversions by the formulae given in the SM as well. The experiments were repeated at least 3 times, the reproducibility of the product composition was found to be within $\pm 1\%$. The absolute configuration of the excess enantiomers was assigned based on chromatographic analysis. The samples were compared to that resulted in our previous studies using the same Ru-chitosan catalyst [22,23], and to the results obtained by applying Ru-(*R,R*)-TsDPEN catalyst, which afforded the opposite *R* enantiomer in excess in all these reactions [49].

Reactions at 1–2.5 mmol ketone scales were carried out similarly as above using the indicated amounts of the components. Following GC analysis of the crude products, the solvent was removed by evaporation and the pure products were obtained by crystallization or flash chromatography. These products were analyzed by GC-MSD, GC-FID, ^1H and ^{13}C NMR spectroscopy, their analytical and spectroscopic data were analogous with the previously published results and are included in the SM [22,23].

2.3. Batch reactions

The reactions were carried out in 4 cm^3 closed glass vials. The slurries were stirred magnetically (800 rpm). If higher than room temperature (rt ; $24 \pm 1^\circ\text{C}$) was necessary the vials were immersed in a pre-heated oil bath. In a typical reaction the given amounts of $[\text{Ru}(p\text{-cym})\text{Cl}_2]_2$, CHMw, solvent and the required amount of HCOONa and pro-chiral ketone (0.25 mmol) were introduced into the vial and stirred for the given time at the chosen temperature. Following reactions the products were extracted in 2 cm^3 EtOAc , the aqueous phase was washed twice with 2 cm^3 EtOAc , the unified organic phase was dried using

MgSO₄ (sicc.) and analyzed by gas chromatography (GC-MSD and GC-FID). The ultrasound activated reactions were carried out similarly. After the addition of the reaction components, the vial was immersed in a Branson 150 ultrasonic bath, which irradiated the reaction system at 40 kHz. The microwave-assisted reactions were carried out in 8 cm³ vials using a CEM Discover microwave reactor at 50 °C. Mixing of the slurry was ensured by magnetic stirring. The work-up of these reactions were similar to that of the traditional batch reactions.

3. Results and discussions

3.1. Ru-chitosan catalyzed ATH using different activation methods

In the past few years, we have developed an asymmetric catalytic system for the transfer hydrogenation of acetophenone derivatives, carbo- and heterocyclic ketones, catalyzed by *in situ* formed Ru-chitosan complex using HCOONa as the hydrogen donor [22,23]. Recently, we have reported the effective mechanochemical (MC) ATH of prochiral ketones catalyzed by Ru-TsDPEN complexes. High conversion and ee values were achieved in the reduction of various prochiral ketones [49]. We started the present study by comparing several activation methods, such as conventional magnetically stirred (MS), ultrasound, microwave or mechanical energy-assisted reactions using 4-chromanone (**1a**) as a test molecule. Pre-milled high molecular weight chitosan (CHMw_p) was applied as the chiral ligand (Table 1).

Reactions carried out by MS in 1 cm³ water/ⁱPrOH 4/1 mixture gave similar results as in our previous report [22]. The use of less solvent accelerated the MS reaction reaching higher TOF values in 0.2 cm³ compared to 1 cm³ under identical conditions. Thus, the TOF reached 9.1 h⁻¹, when the system was heated to 60 °C. Decrease of the solvent amount slightly decreased the enantioselectivity as well. The ultrasound activated ATHs gave lower conversion and ee values, probably due to the inefficient mixing of the system. If the water bath was heated to 50 °C the TOF increased significantly. The magnetically stirred microwave-assisted ATH gave slightly better conversion, but the

enantioselectivity decreased compared to the ultrasound-induced reaction. The mechanochemical activation using a mixing mill, 10 cm³ jars and Ø 5 mm grinding balls provided the best results. Almost full conversion and high ee were achieved after 2 h of milling. This opens up the possibility to carry out efficiently the ATH by this method using chitosan as the chiral ligand.

3.2. Effect of the milling parameters

The commercially available chitosan was flake-like (Fig. 1, b.). The irregular size of the flakes caused difficulties in handling and reproducibility because the smaller flakes grind and distribute better, than the bigger ones. To eliminate this error, the chitosan used in the present experiments was pre-milled, to obtain a fine powder containing closely similar particle sizes, which was examined by SEM (Fig. 1, a.). During the milling process, the crystallinity of the chitosan changed, as the XRD measurements show (Fig. 1, c.). The high molecular weight chitosan used as received (CHMw_{ar}) has 53% crystallinity degree (x_c), meanwhile, the milled chitosan powder (CHMw_p) has only 25%. However, our previous study showed no correlation between the crystallinity of the chitosan and the obtained conversion [21]. To check the validity of these observations in the mechanochemically activated system, we carried out the reaction with both forms of the biopolymer under the conditions given in Table 1. (MC). CHMw_p and CHMw_{ar} provided 70% and 67% conversions, respectively, which is close to the reproducibility error of the reaction. Thus, in our further reactions, we applied the pre-milled chitosan to simplify the handling of the chiral material.

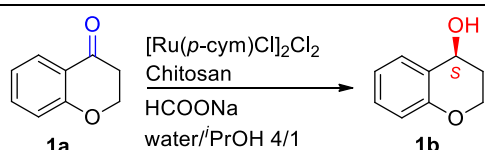
For the optimization of the reaction parameters, we started the experiments under the conditions found the best in our previous paper [49]. The appropriate solvent composition was determined in our prior study on using Ru-chitosan complex [22]. The volume of the solvent strongly influences the mechanochemical reactions, as it is necessary for the proper mixing of the reactants, though greater volumes may absorb the transmitted energy. In most mechanochemical reactions “solvent” is not the proper term as the added liquid has the role of the energy transmitting media (liquid assisted grinding, LAG) [32,33]. Thus, we examined the effect of solvent volume on the ATH of **1a**. As it is shown in Fig. 2 0.2 cm³ solvent was enough to ensure the proper mixing of the reaction components and the necessary uniform distribution of the Ru-CHMw_p catalyst, nonetheless was not too much to reduce the reaction promoting energy. The ee did not change significantly in these measurements if at least moderate conversions were obtained.

Further measurements were carried out using 0.2 cm³ water/ⁱPrOH 4/1 mixture. The conversion plotted as a function of time gave a saturation curve, whereas the ee was not affected significantly (Fig. SM-1). 90 min were enough to reach almost complete conversion in the reaction of **1a**, yet for our following experiments, we chose to agitate the system for 120 min, considering that the magnetically stirred ATH of some other ketones, catalyzed by the Ru-chitosan complex were slower than that of **1a** [22,23].

The decrease of the metal amount is essential from an economic point of view, thus we attempted to reduce the catalyst amount in the test reaction. The above used 5 mol% Ru complex provides full conversion with high ee. However, the application of less catalyst (3.76 mol %) is still efficient, similar conversion with slightly smaller ee was obtained (Fig. SM-2.). In the case of **1a** 2.4 mol% Ru-chitosan also gives acceptable results, though a small decrease in the Conv was observed. Accordingly, in the following mechanochemical ATH experiments, we decided to use at least 3.76 mol% catalyst. The effect of the amount of HCOONa was examined using 3.76 and 5 mol% Ru-chitosan catalyst. In both cases at least 8 eq of donor was necessary to achieve appropriate results. Full conversion was reached in the presence of 10 eq HCOONa (Fig. SM-3). The enantioselectivity was not significantly affected by this parameter.

Next, we examined the effect of the number of grinding balls with both Ø 3 and 5 mm balls in 60 and 120 min reactions (Fig. 3). The

Table 1
Transfer hydrogenation of **1a** to **1b** using various activation methods.^a



1a **1b**

[Ru(*p*-cym)Cl]₂Cl₂
Chitosan
HCOONa
water/ⁱPrOH 4/1

Activation method ^b	Reaction parameters	V ^c (cm ³)	t ^d (h)	Conv ^e (%)	TOF ^{f,g} (h ⁻¹)	ee ^g (%)
MS	800 rpm, 24 °C	1	46	97	0.42	95
	800 rpm, 50 °C	1	24	99.6	0.83	95
	800 rpm, 24 °C	0.2	24	99.5	0.83	93
	800 rpm, 24 °C	0.2	2	31	3.1	91
	800 rpm, 50 °C	0.2	2	68	6.8	91
	800 rpm, 60 °C	0.2	2	91	9.1	91
Ultrasound	40 kHz, 24 °C	0.2	2	39	3.9	87
	40 kHz, 50 °C	0.2	2	63	6.3	87
Microwave	20 W ^h , 50 °C	0.2	2	66	6.6	78
MC	30 Hz, ZrO ₂ Ø 5 mm ⁱ , 25 PCS	0.2	2	96	9.6	94

^a Reaction conditions: 0.00625 mmol [Ru(p-cym)Cl]₂Cl₂, 3 mg CHMw_p (5 mol% catalyst), 0.25 mmol **1a**, 2.5 mmol (10 eq) HCOONa, water/ⁱPrOH 4/1.

^b Abbreviations: MS – magnetically stirred; MC – mechanochemical.

^c V: volume of solvent.

^d t: reaction time.

^e Conversions determined by gas-chromatography (GC).

^f Turn over frequency.

^g Enantiomeric excess (ee) by GC-FID, the configuration of the excess enantiomer was S.

^h Maximum allowed irradiation power during the reaction.

ⁱ diameter of the grinding balls.

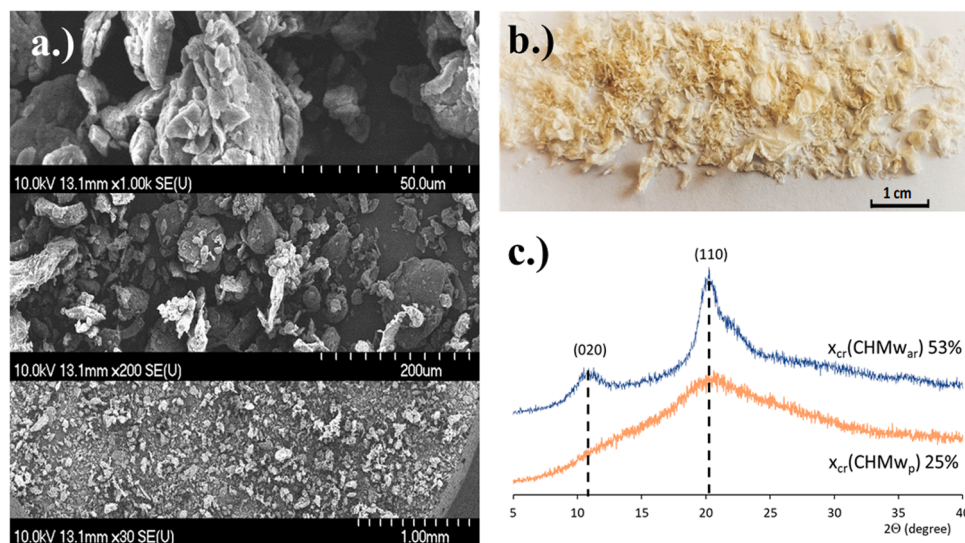


Fig. 1. SEM images of the powdered chitosan (a.) photograph of chitosan flakes (b.) and the X-ray diffractograms of the as-received (CHMw_{ar}) and powdered (CHMw_p) materials (c.).

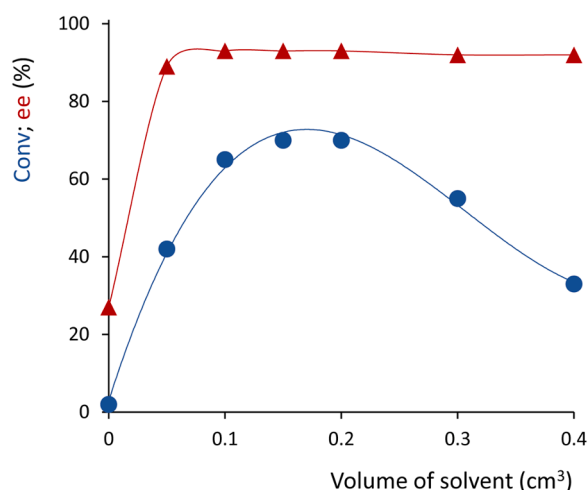


Fig. 2. Effect of the solvent volume on the ATH of **1a** carried out in a mixing mill. Reaction conditions: 0.00625 mmol [Ru(*p*-cym)Cl₂]₂, 3 mg CHMw_p (5 mol % catalyst), 0.25 mmol **1a**, 10 eq HCOONa, water/^tPrOH 4/1, 25 pcs Ø 5 mm ZrO₂ grinding balls, 30 Hz milling frequency, 90 min reaction time; Conv: ●, ee: ▲.

number of the balls was determined to have comparable total volumes of the Ø 5 and Ø 3 mm beads.

In the longer reactions, fewer grinding balls were enough to achieve full conversions. At lower total ball volume (V_{total}) the Ø 3 mm balls gave better results, although the Ø 5 mm balls provided a sharper increase of the conversion when the V_{total} was raised over $\sim 223 \text{ cm}^3$. To achieve similar V_{total} values, obviously the number of the Ø 3 mm beads must be higher than that of Ø 5 mm, which allows more collision points in the system [50]. However, if the necessary ball-ball contact is granted by the number of the milling media, the intensity of collision became the determining factor, i.e. using 1.5 cm^3 Ø 5 mm balls. We conclude, that if low V_{total} was applied, the pcs of the Ø 5 mm balls are not sufficient to provide the necessary number of ball-ball collisions to carry out the reaction, however the use of 3 mm beads (25 pcs) with the same V_{total} grants the required contacts.

Thus, we reached the conclusion that if small V_{total} is applied, the number of collisions is essential, but if the number of balls grants the demanded contacts, the velocity of the balls and the collision intensity

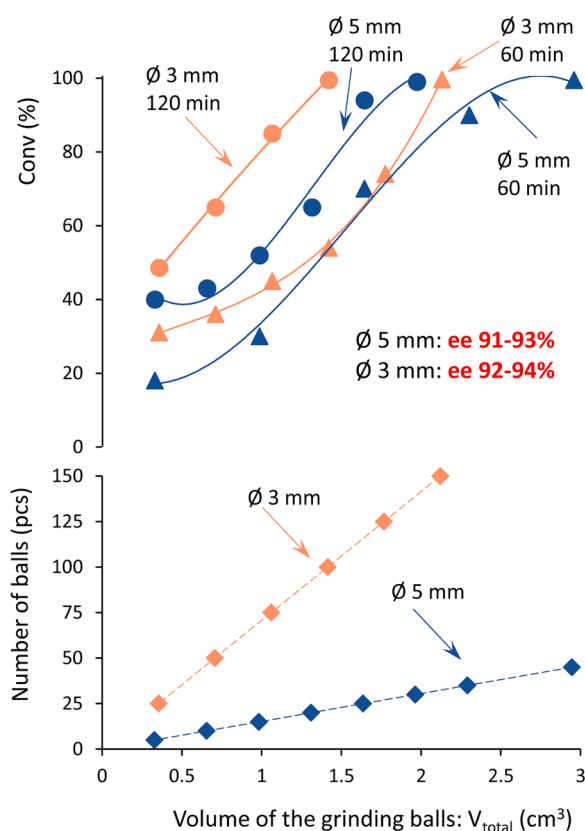


Fig. 3. Effect of the number of the grinding balls on the ATH of **1a** carried out in a mixing mill. Reaction conditions: 0.00625 mmol [Ru(*p*-cym)Cl₂]₂, 3 mg CHMw_p (5 mol% catalyst), 0.25 mmol **1a**, 10 eq HCOONa, 0.2 cm³ water/^tPrOH, 30 Hz milling frequency; ZrO₂ grinding balls: Ø 3 mm, 120 min: ●; Ø 5 mm, 120 min: ●; Ø 3 mm, 60 min: ▲; Ø 5 mm, 60 min: ▲; correlation between the number and total volume of the balls, Ø 3 mm: ◆, Ø 5 mm: ◆.

may become determining parameters. Prasad and Theuerkauf examined the latter parameters in a Spex mill, using grinding jars with different shapes [50,51]. The used mixer mill has a different shaking angle compared to our equipment, however, the modified grinding chamber and caps had a similar profile to the ones used in our study. They

concluded that the contact force, thus the collision intensity increases with the diameter of the used balls, as the weight of the beads raises [50]. This confirms our interpretation of the results presented in Fig. 3., that the small grinding media size has lower collision intensity, which can be compensated by the number of collisions, and the higher intensity of Ø 5 mm balls is less efficient in case of fewer collisions. As Fig. 3 shows, 25–30 pcs from the Ø 5 mm balls were enough to achieve closely full conversion in 120 min. Similar results with better ee values can be obtained using 100 pcs of the Ø 3 mm balls. Balls with higher intensity produce more heat by friction and collision, thus the system might warm up at a higher rate, which explains the slightly lower ee values obtained with Ø 5 mm balls, as was shown in our previous study on the effect of the temperature in the ATH using Ru-chitosan [22]. Fig. SM-4 shows well that the temperature of the system is significantly higher after only 30 min of grinding with Ø 5 mm, compared to the experiment using Ø 3 mm balls, which has an expected slightly negative effect on the ee.

Based on these results we further examined the effect of the ball size by applying bigger, Ø 12 and Ø 15 mm, balls as well. The reaction mixtures were agitated for 60 and 120 min, the obtained conversions and ees are presented in Fig. 4. The conversions after 60 min drastically decreased by increasing the ball diameters. The change of reaction rate (TOF value) correlates to the number of collisions, i.e. the ball numbers (Fig. 4). This may lead to the conclusion that the activation of the reaction highly depends on the energy generated by the collision number of the grinding media. After 120 min of milling, this trend is altered in the case when 2 pcs of Ø 12 mm balls were used, as the two balls hindered each other's motion in the Ø 19 mm jar. In conclusion, the best result was achieved by applying the Ø 3 mm grinding balls.

Last, the reaction was carried out at various agitation frequencies (Fig. SM-5). In these measurements we have used 27 pcs of Ø 5 mm and 125 pcs of Ø 3 mm ($V_{\text{total}} = 1.767 \text{ cm}^3$), which afforded full conversions in our previous experiments carried out at 30 Hz. Difference between the conversions was only observed at low frequency (10 Hz), at 15 Hz or higher agitation speed the two ball sizes performed similarly. However, at least 30 Hz milling frequency is necessary to obtain full conversion after 2 h of milling. At low frequencies the enantiodifferentiation was better with both ball sizes, explained by the more significant warm-up of the system at higher agitation speed.

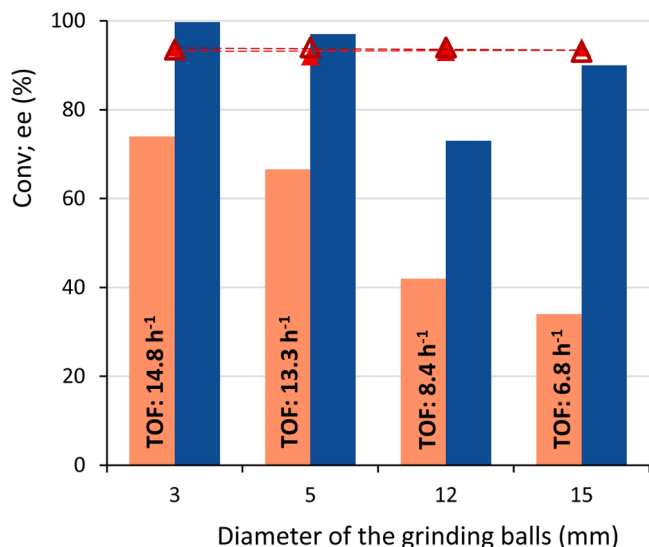


Fig. 4. Effect of the size of the grinding balls on the ATH of **1a** in a mixing mill. Reaction conditions: 0.00625 mmol [Ru(*p*-cym)Cl₂]₂, 3 mg CHMW_p (5 mol% catalyst), 0.25 mmol **1a**, 10 eq HCOONa, 0.2 cm³ water/ⁱPrOH, ZrO₂ grinding balls: Ø 3 mm: 125 pcs, $V=1.767 \text{ cm}^3$; Ø 5 mm: 27 pcs, $V=1.767 \text{ cm}^3$; Ø 12 mm: 2 pcs, $V=1.809 \text{ cm}^3$; Ø 15 mm: 1 pc $V=1.767 \text{ cm}^3$, 30 Hz frequency, Conv 60 min: ■; Conv 120 min: ■; ee 60 min: △; ee 120 min: ▲.

3.3. Scope of the mechanochemical ATH

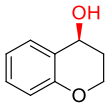
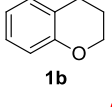
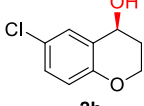
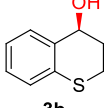
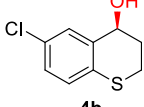
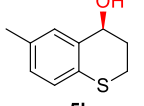
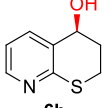
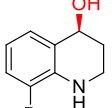
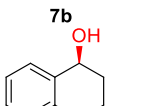
The ATHs of prochiral ketones catalyzed by the Noyori-Ikariya type catalysts are well-studied reactions. Greener methods have been developed aiming at the reduction of the amount of the used organic solvents and/or the reaction time [52,53], the applicability of environmentally benign hydrogen donors and natural ligands. In our previous studies, we examined the ATH of prochiral ketones to develop sustainable methods for the synthesis of optically pure alcohols [21–23]. For this, we have used the biodegradable polymer, chitosan as the chiral ligand without structural modification, in the ATH of acetophenone derivatives, carbo and heterocyclic ketones, which included valuable pharmaceutical intermediates. By the successful use of this biopolymer ligand in aqueous media with HCOONa donor a greener synthetic system was developed. However, the application of alternative activation methods may further increase the sustainability of this procedure [49]. Thus in the present study, we combined the use of chitosan chiral ligand in aqueous media with the mechanochemical activation of the reaction.

Following the above-presented optimizations using 4-chromanone, we aimed to examine the scope of the developed catalytic system using various prochiral ketones. The initial reactions were carried out using 0.25 mmol ketone, 3.75% and/or 5% catalyst, 5 eq HCOONa hydrogen donor, 0.2 cm³ water/ⁱPrOH 4/1 mixture, applying 100 pcs of Ø 3 mm ZrO₂ grinding balls. The reactions were milled for 2 h at 30 Hz to achieve high conversions, which were compared with results obtained in magnetically stirred batch reactions. Table 2 summarizes results achieved in the magnetically stirred (MS), mechanochemical (MC) and reactions scaled up (SU) to 1 mmol (with **1a** to 2.5 mmol as well). The ATH of 4-chromanone shows that the MC reaction is not just faster, but the amount of the used catalyst can be reduced from 5 to 3.75 mol% as well, still providing similar results. The MC reaction of the *O*- and *S*-heterocyclic ketones followed the same tendency, the reaction time was shortened from 1 to 2 days to only 2 h, and in almost every case 3.76 mol % of catalyst was enough to reach the expected results. The mechanochemical ATH of 6-methyl-4-thiochromanone (**5a**) gave lower conversion in this system, however, by applying 5 mol% catalyst full conversion can be achieved (SM, Scheme SM-1). The reactions of every *O*- and *S*-heterocyclic compounds were also carried out applying 5 mol% catalyst, and the results exceeded the ones obtained in the MS reactions (Scheme SM-1). The ATH of *N*-heterocyclic ketones were slower, in the MS reaction 5 mol% catalyst and a higher temperature is necessary to obtain optically enriched alcohols [23]. In the mechanochemical reactions, although the necessary amount of catalyst cannot be decreased, the reaction provided better results in a small fraction of the time needed for the MS-ATH (3,4 h vs 168 h).

By scale-up of the reaction of the test molecule (**1a**) we observed that it is not necessary to proportionally increase neither the mmol of the donor nor the solvent volume with the amount of the catalyst (Table 2). In the 1 mmol reaction of **1a** 1.87 mol% catalyst gave good results (Conv: 93%, ee 93%, entry 3), although to further scale up the reaction to 2.5 mmol **1a** it is advantageous to increase the catalyst amount to 2.5 mol%, which ensured 83% conversion (entry 5). The scale-up of the different heterocyclic compounds was also successful, however, the reaction time and the amount of catalyst and donor had to be optimized for each ketone.

The Ru-chitosan catalyzed ATH of carbocyclic ketones in magnetically stirred reactions are slower than those of the *O*- and *S*-heterocyclic compounds, probably due to the lack of additional hydrogen bonds between the heteroatom and the -NH₂ or -OH groups of the biopolymer, which may promote faster hydrogen transfer and improvement in the stereoselectivity [22]. Consequently, in the mechanochemical reactions of the carbocyclic ketones the amount of catalyst was not decreased. Thus, at least 5 mol% catalyst and longer milling times were necessary in these experiments. Table 3 shows the conversion and ee values achieved in the MS and MC system. In every case, the MC reactions provided higher conversion and similar or better

Table 2
Mechanochemical transfer hydrogenation of heterocyclic ketones (**1a–8a**)^a.

Entry	Product	Conditions	Conv (Yield) ^b (%)	TOF ^c (h ⁻¹)	ee (ee) ^d (%)
1		MS ^e : 50 °C, 24 h	>99	0.83	95
2		MC: 2 h	>99	13.3	93.5
3		SU ^f : 4 h	93 (66)	12.4	93 (99)
4		SU ^g : 5 h	98 (68)	7.8	91 (99)
5		SU ^h : 5 h	83 (75)	6.6	91 (99)
6		MS ^e : 50 °C, 24 h	>99	0.83	94.5
7		MC: 2 h	>99	13.3	93
8		SU ^f : 4 h	86 (62)	8.6	93 (97.5)
9		MS ^e : 50 °C, 24 h	99	0.83	96
10		MC: 2 h	96	11.5	92
11		SU ⁱ : 4 h	>99 (85)	4.9	93 (>99)
12		MS ^e : 24 °C, 46 h	99	0.41	96
13		MC: 2 h	90	11.9	94
14		SU ^j : 5 h	98 (70)	3.9	95 (>99)
15		MS ^e : 24 °C, 70 h	94	0.78	96
16		MC: 2 h	64	8.5	93
17		SU ^j : 4 h	97 (55)	4.8	92 (>99)
18		MS ^e : 24 °C, 70 h	87	0.12	90
19		MC ^k : 5 h	>99	3.9	92.5
20		MS ^e : 70 °C, 168 h	97	0.12	88
21		MC ^k : 4 h	97	4.8	88
22		MS ^e : 70 °C, 168 h	90	0.11	95
23		MC ^k : 3 h	94	6.3	93
24		SU ^g : 5 h	44 (32)	3.5	91

^a Reaction conditions: mechanochemical reaction (MC), 0.0047 mmol [Ru(p-cym)Cl₂]₂, 2.25 mg CHMW_p (3.76 mol% catalyst), 0.25 mmol ketone, 10 eq HCOONa, 0.2 cm³ water/ⁱPrOH 4/1, 10 cm³ ZrO₂ jar, Ø 3 mm 100 pcs grinding balls, 30 Hz.

^b Conversions determined by gas-chromatography (GC), yields obtained by crystallization in brackets.

^c Turn over frequency.

^d Enantiomeric excess (ee) by GC, in brackets the ee of the crystallized products; the configuration of the excess enantiomer was S.

^e Magnetically stirred reaction (MS); 0.00625 mmol [Ru(p-cym)Cl₂]₂, 3.0 mg CHMW_p (5 mol% catalyst), 0.25 mmol ketone, 10 eq HCOONa, 1 cm³ water/ⁱPrOH 4/1, 800 rpm.

^f Scale-up reaction (SU), 1.87 mol% catalyst, ketone 1 mmol, 5 eq HCOONa, 0.4 cm³ water/ⁱPrOH 4/1.

^g SU, 2.5 mol% catalyst.

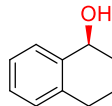
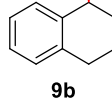
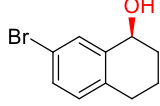
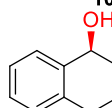
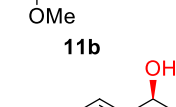
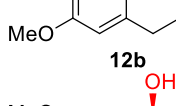
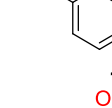
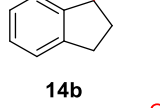
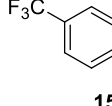
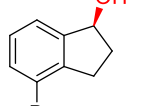
^h SU, 2.5 mol% catalyst, 2.5 mmol ketone, 4 eq HCOONa.

ⁱ SU, 5 mol% catalyst.

^j SU, 5 mol% catalyst, 1 mmol ketone, 10 eq HCOONa.

^k MC, 5 mol% catalyst.

Table 3
Mechanochemical transfer hydrogenation of carbocyclic ketones (**9a–17a**)^a.

Entry	Product	Conditions	Conv. (Yield) ^b (%)	TOF ^c (h ⁻¹)	ee (ee) ^d (%)
1		MS ^e : 24 °C, 70 h	61	0.81	93
2		MC: 4 h	79	3.95	91
3		SU ^f : 6 h	72 (66)	2.4	87
4		MS ^e : 24 °C, 168 h	90	0.11	95
5		MC ^g : 4 h	98	6.51	92.5
6		SU ^h : 5 h	63 (49)	5.04	92
7		MS ^e : 50 °C, 94 h	41	0.08	91
8		MC: 5 h	83	5.52	91.5
9		SU ⁱ : 5 h	25	2	89
10		MS ^e : 50 °C, 168 h	12	0.014	71
11		MC: 4 h	22	1.1	84
12		MS ^e : 24 °C, 168 h	59	0.07	93
13		MC: 4 h	79	3.95	94
14		MS ^e : 24 °C, 70 h	86	0.24	85
15		MC: 4 h	90	4.5	78
16		MS ^e : 24 °C, 70 h	91	0.52	91
17		MC: 5 h	99	3.96	87
18		SU ^j : 5 h	79 (62)	6.32	84
19		MS ^e : 50 °C, 70 h	98	0.27	88
20		MC: 4 h	>99	4.87	85
21		SU ^j : 5 h	92 (55) ⁱ	3.68	84 (97.5) ⁱ
22		MS ^e : 24 °C, 70 h	52	0.14	87
23		MC: 5 h	83	3.32	84

^a Reaction conditions: Mechanochemical reaction (MC), 0.00625 mmol [Ru(p-cym)Cl₂]₂, 3.0 mg CHMW_p (5 mol% catalyst), 0.25 mmol ketone, 10 eq HCOONa, 0.2 cm³ water/ⁱPrOH 4/1, 10 cm³ ZrO₂ jar, Ø 3 mm 100 pcs grinding ball, 30 Hz.

^b Conversions determined by gas-chromatography (GC), yields obtained by flash chromatography are given in brackets.

^c Turn over frequency.

^d Enantiomeric excess (ee) by GC, in brackets the ee of the crystallized products; the configuration of the excess enantiomer was S.

^e Magnetically stirred reaction (MS); 1 cm³ water/ⁱPrOH 4/1, 800 rpm.

^f Scale-up reaction (SU), 5 mol% catalyst, 1 mmol ketone, 10 eq HCOONa, 0.4 cm³ water/ⁱPrOH 4/1, 10 cm³ ZrO₂ jar, Ø 3 mm 100 pcs grinding ball, 30 Hz.

^g MC, 3.76 mol% catalyst.

^h SU, 2.5 mol% catalyst, 1 mmol ketone.

ⁱ Yield and ee obtained by crystallization in hexane.

enantioselectivity in short reactions (4–5 h compared to 72–168 h). The low conversion achieved in the ATH of **12a** can be improved slightly by adding 10 mol% catalyst to the system (not indicated). Due to the longer reaction times, and the more catalyst demand, we investigated the scale-up of the system only with a few compounds. The conversion obtained in the SU reaction of **11b** was not sufficient to isolate the product, however, **10b** and **15b**, was obtained in good, **16b** in outstanding conversion in the 1 mmol scale mechanochemical ATH, and were isolated with moderate yields by flash chromatography or crystallization (**16b**).

The ATHs of acetophenone derivatives are well-studied reactions in the Noyori-Ikariya catalytic system. These compounds were in the main focus of our previous publication on the mechanochemically activated ATH [49]. In the present study, by using chitosan ligand the mechanochemical ATHs of acetophenone and its selected six derivatives were also successful applying 3.76 mol% Ru-chitosan catalyst, as shown by the results summarized in Table 4. The bromine and methyl-substituted acetophenones (**23a**, **24a**) were less reactive, the conversion and ee values indicated in Table 4 were obtained using 5 mol% catalyst. The slight decrease in the enantioselectivity of the mechanochemical ATH compared to the magnetically stirred reductions may be due to the increase of the temperature at the collision points, as discussed in the previous subsection. The scale-up of the ATH of these compounds in a ball mill was easily carried out, at 1 mmol scale outstanding conversions and similar ee values as in the previous reactions were achieved. The products were isolated in good yields by flash chromatography.

Finally, we have to note that the effects of the substituents on the results of the mechanochemical reactions with all three types of prochiral ketones, i.e. aromatic heterocycloaliphatic and carbocycloaliphatic ketones and acetophenone derivatives, were similar to those observed in batch reactions carried out by magnetic stirring. Accordingly, we suggest that in the grinding systems the same complexes are formed and the reactions occur through the same intermediates, i.e. by the same mechanism, as was suggested in our previous reports [22,23]. The suggested structure of the Ru-chitosan complex and that of the intermediate of the ATH is illustrated in Scheme 1. Thus, these results may be interpreted analogously, considering the same steric and electronic effects of the substituents. However, the benefit of using mechanochemistry resides in the much more efficient energy transmission to the catalyst-hydrogen donor-reactant system, which results in the decrease of the reaction time from days to few hours, even with the less active Ru catalyst formed with the biocompatible, natural ligand, chitosan.

4. Conclusions

In our present work, we examined the mechanochemical ATH of prochiral ketones catalyzed by the *in situ* formed Ru-chitosan catalyst in order to increase the sustainability and decrease the environmental impact of the preparation of optically pure alcohols. The ATH of a test compound, 4-chromanone, carried out by ball milling provided better performances compared to the thermally activated, ultrasound and microwave-assisted reactions. The reaction parameters, i.e. the applied amount of solvent, catalyst and donor, the grinding time and frequency were optimized. We have also studied the effects of the size and quantity of the used milling balls. The results demonstrated the role of both the collision intensity and quantity. Conversions achieved using the Ø 3 mm balls had a linear correlation with the applied V_{total} , which shows that in this system the collision number was the determining. In contrast, with Ø 5 mm beads the collision intensity was higher, however, the necessary collision number was granted only if the V_{total} reached 1.5 cm³.

In the reaction of 0.25 mmol 4-chromanone 3.76 mol% Ru-chitosan complex with 10 eq HCOONa hydrogen donor in 0.2 cm³ water/ⁱPrOH 4/1 mixture were found to be efficient following 120 min milling at 30 Hz. The reaction time of the mechanochemical ATH was significantly shorter than that necessary in the magnetically stirred system. The scope of the MC reactions is wide, ranging from hetero- and carbocyclic ketones to acetophenone derivatives. The reaction conditions were

Table 4

Mechanochemical transfer hydrogenation of acetophenone derivatives (**18a–24a**)^a.

Entry	Product	Conditions	Conv. (Yield) ^b (%)	TOF ^c (h ^{−1})	ee ^d (%)
1		MS ^e : 50 °C, 24 h	>99	0.83	70
2		MC: 4 h	92	6.12	68
3		SU ^f : 4 h	86 (84) ^g	8.6	66
4		MS ^e : 50 °C, 24 h	>99	0.83	79
5		MC: 3 h	99	8.78	73
6		SU ^f : 5 h	>99 (84)	15.9	73
7		MS ^e : 50 °C, 24 h	>99	0.83	79
8		MC: 3 h	>99	8.83	74
9		SU ^f : 5 h	99 (81)	7.92	74
10		MS ^e : 50 °C, 24 h	>99	0.83	81
11		MC: 3 h	>99	8.83	78
12		SU ^f : 5 h	99 (77)	7.92	75
13		MS ^e : 50 °C, 24 h	98	0.81	78
14		MC: 4 h	>99	6.62	71
15		SU ^f : 5 h	88 (73)	3.52	67
16		MS ^e : 50 °C, 24 h	>99	08.3	74
17		MC ^h : 3 h	96	6.37	70
18		SU ^f : 3 h	95 (88)	12.67	69
19		MS ^e : 50 °C, 24 h	78	0.65	73
20		MC: 3 h	90	6	72
21		SU ^f : 5 h	90 (70)	3.6	68

^a Reaction conditions: Mechanochemical reaction (MC), 0.0047 mmol [Ru(*p*-cym)Cl₂]₂, 2.25 mg CHMw_p (3.76 mol% catalyst), 0.25 mmol ketone, 10 eq HCOONa, 0.2 cm³ water/ⁱPrOH 4/1, 10 cm³ ZrO₂ jar, Ø 3 mm 100 pcs grinding ball, 30 Hz.

^b Conversions determined by gas-chromatography (GC), yields obtained by flash chromatography are given in brackets.

^c Turn over frequency.

^d Enantiomeric excess (ee) by GC; the configuration of the excess enantiomer was *S*.

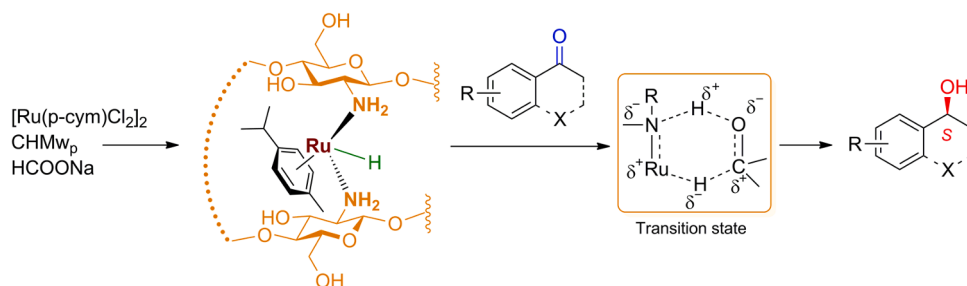
^e Magnetically stirred reaction (MS); 0.00625 mmol [Ru(*p*-cym)Cl₂]₂, 3.0 mg CHMw_p (5 mol% catalyst), 0.25 mmol ketone, 10 eq HCOONa, 1 cm³ water/ⁱPrOH 4/1, 800 rpm.

^f SU, 2.5 mol% catalyst, 1 mmol ketone.

^g SU, 5 mol% catalyst, ketone 1 mmol, 10 eq HCOONa.

^h MC, 5 mol% catalyst.

optimized for each prochiral ketone, moreover, the ATH in many cases was successfully carried out at 1 mmol scale, too. The present study showed the efficiency of chitosan, a biopolymer of natural origin, as a chiral ligand, which can be used successfully in mechanochemical ATH. This opens up the opportunity to further improve the sustainability of the previously reported Ru-catalyzed systems designed for the production of optically pure benzylic alcohols by transfer hydrogenation.



Scheme 1. ATH of prochiral ketones using chitosan as chiral ligand; suggested reaction pathway and structure of the active hydride complex and transition state.

Supplementary material: Formulae used for evaluating the results, additional experimental data obtained in the ATH and analytical data of the products are available in the supplementary material (SM).

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at [doi:10.1016/j.mcat.2022.112162](https://doi.org/10.1016/j.mcat.2022.112162).

References

- [1] A. Nag, *Asymmetric Synthesis of Drugs and Natural Products*, Taylor & Francis Group, CRC Press, Boca Raton, 2018.
- [2] I. Shinkai, Design and development of practical asymmetric synthesis of drug candidates, *Pure Appl. Chem.* 69 (1997) 453–458, <https://doi.org/10.1351/pac199769030453>.
- [3] S. Eagon, J. Kim, B. Singaram, Mild and practical reductions of prochiral ketones to chiral alcohols using the chiral boronic ester TarB-H, *Synthesis* (2008) 3874–3876, <https://doi.org/10.1055/s-0028-1083605> (Mass).
- [4] H.U. Blaser, E. Schmidt, *Asymmetric Catalysis On Industrial Scale: Challenges, Approaches and Solutions*, Wiley-VCH, Weinheim, 2004.
- [5] T. Ohkuma, M. Kitamura, R. Noyori, I. Ojima, *Catalytic Asymmetric Synthesis*, 2nd ed., John Wiley and Sons, Hoboken, NJ, 2000, pp. 1–110, chapter 1.
- [6] J.G. de Vries, C.J. Elsevier, *The Handbook of Homogeneous Hydrogenation*, Wiley-VCH, Weinheim, 2007.
- [7] G. Shang, W. Li, X. Zhang, I. Ojima, *Catalytic Asymmetric Synthesis*, 3rd ed., John Wiley and Sons, Hoboken, NJ, 2010, pp. 343–435, chapter 7.
- [8] S. Hashiguchi, A. Fujii, J. Takehara, T. Ikariya, R. Noyori, Asymmetric transfer hydrogenation of aromatic ketones catalysed by chiral Ruthenium(II) complexes, *J. Am. Chem. Soc.* 117 (1995) 7562–7563, <https://doi.org/10.1021/ja00133a037>.
- [9] A. Fujii, S. Hashiguchi, N. Uematsu, T. Ikariya, R. Noyori, Ruthenium(II)-catalyzed asymmetric transfer hydrogenation of ketones using a formic acid-triethylamine mixture, *J. Am. Chem. Soc.* 118 (1996) 2521–2522, <https://doi.org/10.1021/ja954126l>.
- [10] J. Takehara, S. Hashiguchi, A. Fujii, S. Inoue, T. Ikariya, R. Noyori, Amino alcohol effects on the Ruthenium(II)-catalysed asymmetric transfer hydrogenation of ketones in propan-2-ol, *ChemComm* (1996) 223–224, <https://doi.org/10.1039/CC9600000233>.
- [11] R. Noyori, S. Hashiguchi, Asymmetric transfer hydrogenation catalysed by chiral ruthenium complexes, *Acc. Chem. Res.* 30 (1997) 97–102, <https://doi.org/10.1021/ar950234l>.
- [12] D. Wang, D. Astruc, The golden age of transfer hydrogenation, *Chem. Rev.* 115 (2015) 6621–6686, <https://doi.org/10.1021/acs.chemrev.5b00203>.
- [13] S.P. Davis, *Chitosan: Manufacture, Properties and Usage*, Nova Science Publishers, New York, USA, 2011.
- [14] P.K. Dutta, *Chitin and Chitosan for Regenerative Medicine*, Springer, New Delhi, India, 2016.
- [15] G.L. Dotto, S.P. Campana-Filho, L.A. de Almeida Pinto, *Chitosan Based Materials and its applications*, 3, Mentha Science Publishers, Sharjah, UAE, 2017. *Frontiers in Biomaterials*.
- [16] J. Li, X. Tian, T. Hua, J. Fu, M. Koo, W. Chan, T. Poon, Chitosan natural polymer material for improving antibacterial properties of textiles, *ACS Appl. Bio Mater.* 4 (2021) 4014–4038, <https://doi.org/10.1021/acsabm.1c00078>.
- [17] E. Khor, A.C.A. Wan, *Chitin Fulfilling a Biomaterial Promise*, 2nd ed., Elsevier, Ltd., Oxford, UK, 2014.
- [18] S.K. Kim, *Chitin and Chitosan derivatives: Advances in Drug Discovery and Developments*, CRC Press, Taylor & Francis Group, Boca Raton, USA, 2014.
- [19] A. Ajavakon, S. Supsvetson, A. Somboot, M. Sukwattanasinitt, Products from microwave and ultrasonic wave assisted hydrolysis of chitin, *Carbohydr. Polym.* 90 (2012) 73–77, <https://doi.org/10.1016/j.carbpol.2012.04.064>.
- [20] D.L. Bertuzzi, T.B. Becher, N.M.R. Capreti, J. Amorim, I.D. Megiatto, C. Ornelas, General protocol to obtain D-glucosamine from biomass residues: shrimp shells, cicada sloughs and cockroaches, *Global Challenges*, 2 (2018) 180046 (1–6), [doi:10.1002/gch2.201800046](https://doi.org/10.1002/gch2.201800046).
- [21] V.J. Kolcsár, G.Y. Szöllösi, Chitosan as a chiral ligand and organocatalyst: preparation conditions-property-catalytic performance relationship, *Catal. Sci. Technol.* 11 (2021) 7652–7666, <https://doi.org/10.1039/D1CY01674A>.
- [22] G.Y. Szöllösi, V.J. Kolcsár, Highly enantioselective transfer hydrogenation of prochiral ketones using Ru(II)-chitosan catalyst in aqueous media, *ChemCatChem* 11 (2019) 820–830, <https://doi.org/10.1002/cctc.201801602>.
- [23] V.J. Kolcsár, F. Fülöp, G.Y. Szöllösi, Ruthenium(II)-chitosan, an enantioselective catalyst for the transfer hydrogenation of N-heterocyclic ketones, *ChemCatChem* 11 (2019) 2725–2731, <https://doi.org/10.1002/cctc.201900363>.
- [24] P.J. Dunn, A.S. Wells, M.T. Williams, *Green Chemistry in the Pharmaceutical Industry*, Wiley-VCH, Weinheim, 2010.
- [25] A. Patti, *Green Approaches to Asymmetric Catalytic Synthesis*, Springer, Dordrecht, 2011.
- [26] M.M. Pereira, M.J.F. Calvete, *Sustainable Synthesis of Pharmaceuticals Using Transition Metal Complexes as Catalyst*, The Royal Society of Chemistry, Cambridge, 2018.
- [27] R.S. Varma, Greener and sustainable trends in synthesis of organic and nanomaterials, *ACS Sustain. Chem. Eng.* 4 (2016) 5866–5878, <https://doi.org/10.1021/acssuschemeng.6b01623>.
- [28] B. Ranu, A. Stolle, *Ball Milling Towards Green Synthesis: Applications, Projects, Challenges*, Royal Chemical Society, Cambridge, 2015.
- [29] D. Margetic, V. Strukul, *Mechanochemical Organic Synthesis*, Elsevier, Amsterdam, 2016.
- [30] S.Y. Lu, Q.J. Mao, Z. Peng, X.D. Li, J.H. Yan, Simulation of ball motion and energy transfer in a planetary ball mill, *Chin. Phys. B* 21 (1–9) (2012), 078201, <https://doi.org/10.1088/1674-1056/21/7/078201>.
- [31] K.S. McKissic, J.T. Caruso, R.G. Blair, J. Mack, Comparison of shaking versus baking: further understanding the energetics of a mechanochemical reaction, *Green Chem.* 16 (2014) 1628–1632, <https://doi.org/10.1039/C3GC41496E>.
- [32] S.L. James, C.J. Adams, C. Bolm, D. Braga, P. Collier, T. Friščić, F. Grepioni, K.D. M. Harris, G. Hyett, W. Jones, A. Krebs, J. Mack, L. Maini, A.G. Orpen, I.P. Parkin, W.C. Shearouse, J.W. Steed, D.C. Waddell, Mechanochemistry: opportunities for new and cleaner synthesis, *Chem. Soc. Rev.* 41 (2012) 413–447, <https://doi.org/10.1039/C1CS15171A>.
- [33] J. Yu, P. Ying, H. Wang, K. Xiang, W. Su, Mechanochemical asymmetric cross-dehydrogenative coupling reaction: liquid-assisted grinding enables reaction acceleration and enantioselectivity control, *Adv. Synth. Catal.* 362 (2020) 893–902, <https://doi.org/10.1002/adsc.201901363>.
- [34] G.W. Wang, Mechanochemical organic synthesis, *Chem. Soc. Rev.* 42 (2013) 7668–7700, <https://doi.org/10.1039/C3CS35526H>.
- [35] M. Pérez-Venegas, E. Juaristi, Mechanochemical and mechanoenzymatic synthesis of pharmacologically active compounds: a green perspective, *ACS Sustain. Chem. Eng.* 8 (2020) 8881–8893, <https://doi.org/10.1021/acssuschemeng.0c01645>.
- [36] B. Rodríguez, A. Bruckmann, C. Bolm, A highly efficient asymmetric organocatalytic aldol reaction in a ball mill, *Chem. Eur. J.* 13 (2007) 4710–4722, <https://doi.org/10.1002/chem.200700188>.
- [37] P. Chauhan, S.S. Chimni, Mechanochemistry assisted asymmetric organocatalysis: sustainable approach, *Beilstein J. Org. Chem.* 8 (2012) 2132–2141, <https://doi.org/10.3762/bjoc.8.240>.
- [38] Z. Li, Z. Jiang, W. Su, Fast, solvent-free, highly enantioselective three-component coupling of aldehydes, alkynes, and amines catalysed by the Copper(II)pybox

- complex under high-vibration ball-milling, *Green Chem.* 17 (2015) 2230–2234, <https://doi.org/10.1039/C5GC00079C>.
- [39] Y. Wang, H. Wang, Y. Jiang, C. Zhang, J. Shao, D. Xu, Fast solvent-free and highly enantioselective fluorination of β -keto esters catalysed by chiral copper complexes in a ball mill, *Green Chem.* 19 (2017) 1674–1677, <https://doi.org/10.1039/C6GC03306G>.
- [40] C. Bolm, J.G. Hernández, From synthesis of amino acids and peptides to enzymatic catalysis: a bottom-up approach in mechanochemistry, *ChemSusChem* 11 (2018) 1410–1420, <https://doi.org/10.1002/cssc.201800113>.
- [41] D. Kristoffiková, M. Mečiarová, E. Rakovský, R. Šebesta, Mechanochemically activated organocatalytic domino Mannich reaction-fluorination, *ACS Sustain. Chem. Eng.* 8 (2020) 14417–14424, <https://doi.org/10.1021/acssuschemeng.0c04260>.
- [42] I.N. Egorov, S. Santra, D.S. Kopchuk, I.S. Kovalev, G.V. Zyryanov, A. Majee, B. C. Ranu, V.L. Rusinov, O.N. Chuakhin, Ball milling: an efficient and green approach for asymmetric organic syntheses, *Green Chem.* 22 (2020) 302–315, <https://doi.org/10.1039/C9GC03414E>.
- [43] R. Solà, O.B. Sutcliffe, C.E. Banks, B. Macià, Ball mill and microwave assisted synthetic routes to Fluoxetine, *Sustain. Chem. Pharm.* 5 (2017) 14–21, <https://doi.org/10.1016/j.scp.2016.11.003>.
- [44] Y. Sawama, T. Kawajiri, M. Niikawa, R. Goto, Y. Yabe, T. Takahashi, T. marumoto, M. Itoh, Y. Kimura, Y. Monguchi, S.-I. Kondo, H. Sajiki, Stainless-steel ball-milling method for hydro-/deuteration using $\text{H}_2\text{O}/\text{D}_2\text{O}$ as a hydrogen/deuterium source, *ChemSusChem* 8 (2015) 3773–3776, <https://doi.org/10.1002/cssc.201501019>.
- [45] Y. Sawama, N. Yasukawa, K. Ban, R. Goto, Niikawa M, Y. Monguchi, M. Itoh, H. Sajiki, Stainless steel-mediated hydrogen generation from alkanes and diethyl ether and its application for arene reduction, *Org. Lett.* 20 (2018) 2892–2896, <https://doi.org/10.1021/acs.orglett.8b00931>.
- [46] Y. Sawama, M. Niikawa, H. Sajiki, Stainless steel ball milling for hydrogen generation and its application for reduction, *J. Synth. Org. Chem. Jpn.* 77 (2019) 1070–1077, <https://doi.org/10.5059/yukigoseikyokaishi.77.1070>.
- [47] A.Y. Li, A. Segalla, C.J. Li, A. Moores, Mechanochemical metal-free transfer hydrogenation of carbonyls using polymethylhydrosiloxane as the hydrogen source, *ACS Sustain. Chem. Eng.* 5 (2017) 11752–11760, <https://doi.org/10.1021/acssuschemeng.7b03298>.
- [48] T. Portada, D. Margetić, V. Štrukil, Mechanochemical catalytic transfer hydrogenation of aromatic nitro derivatives, *Molecules* 23 (1–18) (2018) 3163, <https://doi.org/10.3390/molecules23123163>.
- [49] V.J. Kolcsár, G.Y. Szöllösi, Mechanochemical, water-assisted asymmetric transfer hydrogenation of ketones using ruthenium catalyst, *ChemCatChem* (2021), <https://doi.org/10.1002/cctc.202101501>.
- [50] D.V.N. Prasad, J. Theuerkauf, Effect of grinding media size and chamber length on grinding in a Spex mixer mill, *Chem. Eng. Technol.* 32 (2009) 1102–1106, <https://doi.org/10.1002/ceat.200900035>.
- [51] D.V.N. Prasad, J. Theuerkauf, Improvement in the collision intensity of grinding media in high energy impact mills, *Chem. Eng. Technol.* 33 (2010) 1433–1437, <https://doi.org/10.1002/ceat.200900392>.
- [52] X. Wu, X. Li, W. Hems, F. King, J. Xiao, Accelerated asymmetric transfer hydrogenation of aromatic ketones in water, *Org. Biomol. Chem.* 2 (2004) 1818–1821, <https://doi.org/10.1039/B403627A>.
- [53] X. Wu, X. Li, A. Zanotti-Gerosa, A. Pettman, J. Liu, A.J. Mills, J. Xiao, Rh^{III} - and Ir^{III} -catalyzed asymmetric transfer hydrogenation of ketones in water, *Chem. Eur. J.* 14 (2008) 2209–2222, <https://doi.org/10.1002/chem.200701258>.