ChemCatChem
Research Article
doi.org/10.1002/cctc.202101501
Chemistry Europe
European Chemical Societies Publishing
www.chemcatchem.org

Mechanochemical, Water-Assisted Asymmetric Transfer Hydrogenation of Ketones Using Ruthenium Catalyst

Vanessza Judit Kolcsár[a] and György Szőllősi*[b]

Dedicated to the memory of Prof. Ferenc Fülöp

Asymmetric catalytic reactions are among the most convenient and environmentally benign methods to obtain optically pure compounds. The aim of this study was to develop a green system for the asymmetric transfer hydrogenation of ketones, applying chiral Ru catalyst in aqueous media and mechanochemical energy transmission. Using a ball mill we have optimized the milling parameters in the transfer hydrogenation of acetophenone followed by reduction of various substituted derivatives. The scope of the method was extended to carbo- and heterocyclic ketones. The scale-up of the developed system was successful, the optically enriched alcohols could be obtained in high yields. The developed mechanochemical system provides TOFs up to 168 h^{-1}. Our present study is the first in which mechanochemically activated enantioselective transfer hydrogenations were carried out, thus, may be a useful guide for the practical synthesis of optically pure chiral secondary alcohols.

Introduction

Since the last two decades, the importance of environmental protection in the pharmaceutical industry is notably increasing, which requires the development of sustainable production methods. A large scale of reaction conditions contributes to reach a green process, such as the use of different catalysts, solvent-free or aqueous reactions and alternative energy transmissions as well.[1,2] Accordingly, microwave-assisted and mechanochemically activated reactions, have been integrated already into the toolbox of the pharmaceutical industry. As in the current decade, it is expected that approximately 95% of the pharmaceuticals will be chiral,[3] various methods have been developed in the past years to increase the sustainability and diminish the environmental impact of the preparation of optically pure intermediates.

Asymmetric catalytic reactions are among the most important and efficient processes to prepare enantiomerically enriched chemicals using small amounts of the often costly chirality sources.[4] Among the enantioselective catalytic reactions, hydrogenations and transfer hydrogenations are convenient procedures to synthesize chiral alcohols from ketones. Nevertheless, transfer hydrogenations have several advantages compared to traditional hydrogenations, such as the use of easily available hydrogen donors instead of gaseous H_2 and the application of simple equipment to carry out reductions.[5]

Numerous studies have been reported on the use of mostly Rh, Ru and Ir complexes bearing chiral ligands of various structures as catalysts in asymmetric transfer hydrogenations (ATH).[6] Privileged ligands are the optically pure 1,2-diphenylethane-1,2-diamine (DPEN) derivatives, among which the *para*-tosylated compounds, *i.e.* *N*-(4-toluenesulfonyl)-1,2-diphenylethane-1,2-diamines (TsDPEN), developed by Noyori, Ikariya *et al.* were the first highly effective.[6,7] Using the Ru(II)-arene-TsDPEN complexes outstanding conversions (Conv) and enantiomeric excesses (ee) were obtained in the ATH of acetophenone derivatives and carbocyclic ketones with isopropanol, as the hydrogen source. Further studies showed that these catalysts can be used under neat reaction conditions, applying formic acid/triethylamine ($HCOONa/Et_3N$) 5/2 azeotrope donor[8] and in aqueous media, using HCOONa as the hydrogen donor leading to increased rates, thus affording good conversions and ee values in few hours.[9] Aqueous ATH became of great significance, as allows the application of less amounts of organic solvents and cheap and easily available hydrogen sources (formates), which does not generate hazardous wastes. In addition, the process requires mild reaction conditions and is easy to control. Water enables easy catalyst/product separation, allows the reduction to be pH-controlled and according to Xiao *et al.* stabilizes the active catalyst. It was suggested that in the aqueous ATH the reduction takes place "on water" rather than in water, which provides an elevated reaction rate due to the higher concentration of the substrate.[9]

The application of alternative energy transmission methods in asymmetric catalytic processes may improve the sustainability and efficiency of these synthetic procedures. Thus, mechanochemical organic reactions are becoming increasingly important due to their favourable properties, such as shortened reaction times, simple equipment and wide applicability.[2,10] Mechanochemical activation of a wide range of organic

[a] *V. J. Kolcsár*
Department of Organic Chemistry
University of Szeged
6720 Szeged, Dóm tér 8 (Hungary)
[b] *Prof. G. Szőllősi*
Stereochemistry Research Group
Eötvös Loránd Research Network
University of Szeged
6720 Szeged, Eötvös utca 6 (Hungary)
E-mail: szollosi@chem.u-szeged.hu

Supporting information for this article is available on the WWW under https://doi.org/10.1002/cctc.202101501

reactions, such as C–C couplings, condensations, carbon-heteroatom bond-forming reactions, cycloadditions, oxidations and reductions had been carried out by grinding in mixing mills.[10] Often a small amount of liquid is necessary to reach optimal mixing in the mill and to transmit the mechanical energy, therefore the term liquid assisted grinding (LAG) is used for these processes.

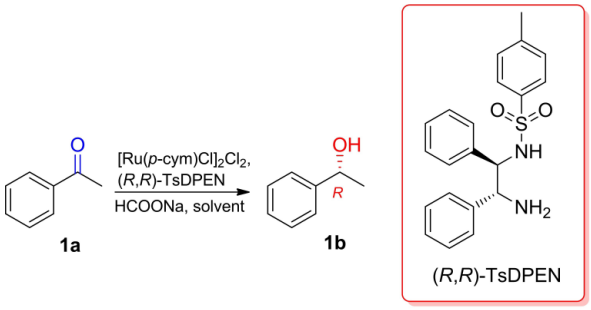
The mechanochemical reduction of various unsaturated compounds has been studied as well.[10–16] Thus, the solvent-free reductive benzylation of malonitrile and 4-methylaniline by various aromatic aldehydes was carried out in a ball mill using Hantzsch ester as the reductant.[11] Sajiki *et al.* used *in situ* generated hydrogen or deuterium for the saturation of various compounds, such as alkynes, alkenes, haloarenes, ketones, azides and nitroarenes. The hydrogen (deuterium) was generated under milling conditions from water, alkanes or diethyl ether either by metals added to the reaction mixture or by the material of the stainless-steel grinding equipment.[12] Aldehydes and ketones were selectively transfer hydrogenated using tetrabutylammonium fluoride on silica catalyst and polymethylhydrosiloxane donor,[13] whereas, the reduction step in the preparation of fluoxetine, an active pharmaceutical ingredient, was carried out by $NaBH_4$ in mixer mills.[14] The efficiency of LAG was studied by Štrukil and co-workers in the catalytic transfer hydrogenation of aromatic nitro compounds on Pd/C catalyst and $HCOONH_4$ hydrogen donor.[15] These examples showed that organic compounds may be reduced efficiently using mechanochemical activation.

Mechanochemistry has also been used in asymmetric catalytic reactions. In their pioneering works, Bolm *et. al.* studied the cinchona alkaloid-catalyzed ring-opening of cyclic *meso*-anhydrides and the proline catalyzed aldol addition in a planetary ball mill.[17] Since the publication of these studies, a variety of enantioselective catalytic reactions have been carried out under milling conditions.[10,18] Among these, chiral alcohols could be prepared by enzymatic acylative kinetic resolution of the corresponding racemic alcohols under ball-milling conditions.[19] However, the pharmaceutical importance of optically pure secondary alcohols justifies the development of enantioselective hydrogenation methods using this activation procedure. To the best of our knowledge, mechanochemical asymmetric hydrogenations or transfer hydrogenations have not yet been reported. The aim of our present study was to examine the applicability of the mechanochemistry in the above-discussed ATH of ketones with classical Noyori-Ikariya Ru-TsDPEN catalyst. We have optimized the milling and reaction conditions, and explored the scope of the procedure on a variety of ketones along with the scale-up of the system.

Results and Discussion

We started our investigations with the ATH of acetophenone (**1 a**) to 1-phenylethanol (**1 b**), a well-studied model reaction to examine the performance of different catalysts and the effect of the reaction conditions. The optically pure (1*S*,2*S*)- or (1*R*,2*R*)-TsDPEN are the simplest commercially available ligands used in the ATHs (Scheme 1.). Results obtained with catalyst formed *in situ* using $[Ru(p\text{-cym})Cl]_2Cl_2$ (*p*-cym: *para*-cymene) precursor and (1*R*,2*R*)-TsDPEN in aqueous media with HCOONa donor using different activation modes are summarized in Table 1.

In the traditional magnetically stirred (**MS**) system at room temperature (rt) low conversions (Conv) were obtained in 15 or even 60 min reactions (entries 1, 2). The transformation of **1 a** was complete after 22 h. In 1 cm^3 solvent the reaction afforded 61% Conv in 60 min. The highest turnover frequency (TOF) in the magnetically stirred batch system was reached at 50 °C, however, the enantiomeric excess (ee) decreased (entry 5). The transfer hydrogenation activated by ultrasound (**US**) at rt gave lower Conv compared to the **MS** reaction (entry 6), probably due to insufficient mixing. In the microwave (**MW**) assisted reaction, which was also stirred **1 a** was transformed with a high TOF value (entry 7), however, the enantioselectivity was much lower (ee 87%) than in the case of the former **MS** reaction at 50 °C. The reaction carried out by ball milling (**BM**) using Retsch MM 400 mixer mill and 10 cm^3 grinding jars with ZrO_2 lining and ZrO_2 balls, gave good results, both as concerns the activity and enantioselectivity (entry 8). High TOF and ee values, which surpassed even the ones obtained at 50 °C in batch system,



Scheme 1. Asymmetric transfer hydrogenation (ATH) of acetophenone (**1 a**) to (*R*)-1-phenylethanol (**1 b**) using Ru-(*R*,*R*)-TsDPEN complex.

Table 1. Transfer hydrogenation of **1 a** to **1 b** with Ru-TsDPEN catalyst using various activation methods.[a]

Entry	Reaction conditions[b]	t[c] [min]	Conv[d] [%]	TOF[e] [h^{-1}]	ee[f] [%]
1	**MS**, 800 rpm, 24 °C	15	30	48.0	95
2	**MS**, 800 rpm, 24 °C	60	72	28.8	96
3	**MS**, 800 rpm, 24 °C	22 h	99.9	–	94
4[g]	**MS**, 800 rpm, 24 °C	60	61	24.4	96
5	**MS**, 800 rpm, 50 °C	15	84	134.4	93
6	**US**, 40 kHz, 24 °C	15	18	28.8	95
7	**MW**, 20 W[h], 50 °C	15	88	140.8	87
8	**BM**, 30 Hz, Ø 5 mm, 28 pcs	15	87	139.2	94

[a] Reaction conditions: $[Ru(p\text{-cym})Cl]_2Cl_2$ 0.00625 mmol, (*R*,*R*)-TsPDEN 0.0125 mmol (2.5 mol% catalyst), acetophenone 0.5 mmol, HCOONa 4 equivalent (eq), H_2O 0.2 cm^3. [b] Abbreviations: magnetically stirred (**MS**), ultrasound activated (**US**), microwave activated (**MW**), mechanochemical activation using Retsch MM400 mill and ZrO_2 jars and balls (**BM**). [c] Reaction time. [d] Conversion determined by gas-chromatography (GC-FID). [e] Turn over frequency. [f] The ee determined by GC-FID, excess of *R*-**1 b**. [g] Reaction in 1 cm^3 water. [h] Maximum value of power allowed during the reaction.

were achieved without optimization of the reaction conditions. This latter observation gave us the possibility to develop a fast and green method for the ATH of prochiral ketones using mechanochemical activation. Our first step was to optimize the milling and reaction parameters using the same compound, **1 a**.

Effect of the milling parameters

First, the effect of the balls' size was examined using ZrO_2 balls with 3, 5, 12 and 15 mm diameters (Figure 1). In each case, the number of these was determined in order to have similar total volumes ($V_{balls} = 1.80 \pm 0.03$ cm^3). As can be seen, the diameter of the balls did not affect the enantioselectivity (ee 94–95%). In every case outstanding TOF values were achieved, however, the use of balls with 5 mm diameters (Ø5 mm) gave the best results, thus, in our further optimization studies this size was used.

The number of the Ø5 mm grinding balls had no effect on the enantioselectivity, whereas, the conversion increased significantly by applying more pieces (Figure 2). Under the given conditions, full conversion can be achieved using 42 pcs. For our further measurements, we chose 42 and 28 pcs, the former to achieve the best possible results, the latter to make the effects of the studied parameters visible.

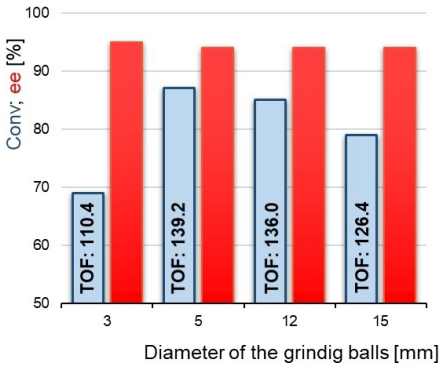


Figure 1. Effect of the size of the grinding balls on the ATH of **1 a** in Retsch MM400 mixer mill. Reaction conditions: $[Ru(p\text{-cym})Cl]_2Cl_2$ 0.00625 mmol, (*R*,*R*)-TsPDEN 0.0125 mmol (2.5 mol% catalyst), **1 a** 0.5 mmol, HCOONa 4 eq, 0.2 cm^3 H_2O, ZrO_2 grinding balls: Ø3 mm: 128 pcs; Ø5 mm: 28 pcs; Ø12 mm: 2 pcs; Ø15 mm: 1 pcs, frequency 30 Hz, reaction time 15 min., Conv: ■, TOF in h^{-1}; ee: ■.

The effect of the milling frequency was studied with both 28 and 42 pcs of balls (see Supporting information (SI), Figure SI-1). Full conversion can be achieved after 15 minutes only if the milling frequency is at least 30 Hz with 42 pcs grinding balls in the system. The conversions achieved with 28 balls were slightly lower, compared to the use of 42 pcs at each frequency, except at very low agitation speed (5 Hz), at which we obtained equally low transformations of **1 a** (Conv ≈40%) with both amounts of balls. The effect of the milling time was examined at both 20 and 30 Hz agitation speed, at each frequency 28 and 42 pcs of balls were used as well (Figure 3). In the case of higher milling frequency, a shorter reaction time was enough to achieve closely full conversion, even if fewer balls were used. The ee slightly decreased after longer reaction times, probably due to the warming-up of the system caused by the friction and collision of the grinding balls, as evidenced by the temperature of the final reaction mixture (see SI, Figure SI-2 for the temperatures of the mixtures at the end of reactions as a function of time).

Under mild conditions (20 Hz, 7.5 min, 28 or 42 pcs of balls) when the temperature increased only with 1.2-1.9 °C, the ee was high, 97%. The highest temperature was measured after 20 min milling at 30 Hz with 42 pcs of grinding balls. The system reached 49 °C and the ee decreased to 94% which is close to that obtained in the batch reaction carried out at 50 °C (Table 1, entry 5). Based on the above results, for further optimization of the reaction parameters, 28 pcs of Ø 5 mm grinding balls were chosen and the apparatus was operated at 30 Hz frequency for 15 min.

In this mechanochemical system water has primarily an energy mediating role. However, previous studies on the ATH of prochiral ketones in aqueous systems indicated that the water may also participate in the formation of the intermediate responsible for the highly selective reaction.[20] It also provides a

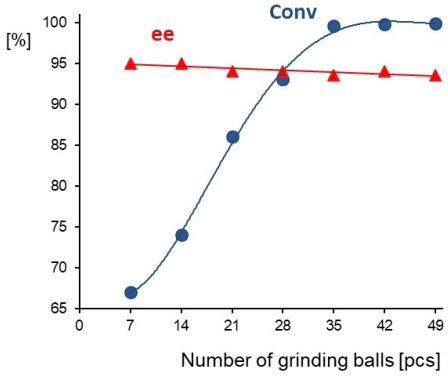


Figure 2. Effect of the number of grinding balls on the ATH of **1 a** carried out in a mixing mill. *Reaction conditions*: see Figure 1, grinding balls: Ø 5 mm, milling time 15 min, Conv: ●; ee: ▲.

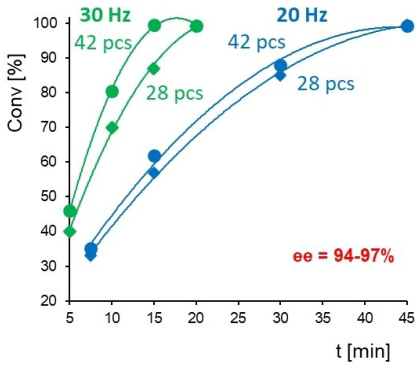


Figure 3. Effect of the milling time at different agitation frequencies on the ATH of **1 a**. Reaction conditions: see Figure 1, ZrO_2 grinding balls: Ø 5 mm, at 20 Hz 28 pcs: ◆, 42 pcs: ●; at 30 Hz, 28 pcs: ◆, 42 pcs: ●.

soluble form of formate and stabilizes the active form of the catalyst. Nevertheless, the reaction may take place on water, leading to faster reactions.[9] In our test ATH, when no or only a small amount of water was added to the system the components could not mix properly during the milling. Possibly the donor was not dissolved and the transmission of the energy was not sufficiently effective, thus only low conversions were observed, as illustrated by the data presented in Figure 4. However, too much liquid in the system absorbs the energy, preventing the activation of the components. Based on the above result obtained under the given conditions 0.2 cm^3 of water was the most efficient liquid volume to achieve high conversion. Under these conditions, 3.75 mol% of catalyst and 4 eq of HCOONa can provide full conversion after 15 min of milling (see SI, Figure SI-3 and SI-4). Although these results are outstanding, our main goal was to develop an environmentally benign and sustainable system, in which less catalyst and donor are used. 98% conversion and 94% ee can be achieved in the ATH of **1a** employing as little as 2.5 mol% catalyst with only 2 eq HCOONa hydrogen donor when we performed reactions with more grinding balls (42 pcs) and increasing the milling time with only 5 minutes. Neither the volume of water nor the amount of the catalyst or the hydrogen donor affected significantly the ee.

The formation of the active catalyst under milling conditions was examined as well (Table 2). The dry milling of the precursor and ligand was less efficient in the formation of the active pre-catalyst (entry 1), possibly because the elimination of the HCl and formation of the complex with the chiral ligand is not promoted in the absence of a base.[21] However, the use of a water additive was able to ensure the formation of the complex, leading to an increase in the conversion (entry 2).

The best results can be achieved if the active catalyst complex is pre-prepared by the milling of the precursor, the ligand and the hydrogen donor (HCOONa), the latter also acting as a base additive (entry 3). However, without any pre-treatment (entry 4) the TOF was only slightly lower than in the reaction mentioned before. Accordingly, the additional 10 min pre-treatment did not have a significantly advantageous contribution, thus, we have decided to carry out the following reactions similarly as before, by omitting this time consuming pre-milling step.

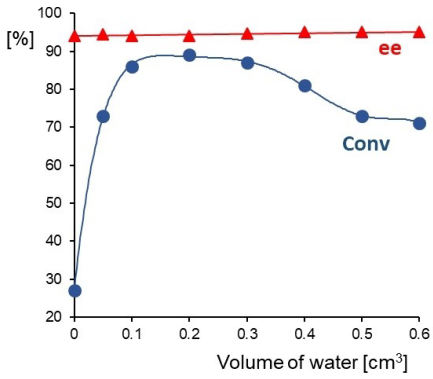


Figure 4. Effect of the volume of water on the ATH of **1a** carried out in a mixing mill. Reaction conditions: $[Ru(p\text{-cym})Cl]_2Cl_2$ 0.00625 mmol, (*R*,*R*)-TsPDEN 0.0125 mmol, **1a** 0.5 mmol, HCOONa 4 eq, ZrO_2 grinding balls: Ø 5 mm 28 pcs, milling frequency 30 Hz, reaction time 15 min; Conv: ●, ee: ▲.

Table 2. The effect of the pre-treatment on the ATH of **1a**.[a,b]

Entry	Pre-treated components	Conv [%]	TOF [h^{-1}]	ee [%]
1	Ru-precursor, ligand	37	59.2	96
2	Ru-precursor, ligand, H_2O	70	112.0	95
3	Ru-precursor, ligand, HCOONa	80	128.0	95
4	–	76	121.6	95

[a] Pre-treatment: the indicated components were milled 10 min at 30 Hz using 42 pcs Ø 5 mm grinding balls; Ru-precursor: $[Ru(p\text{-cym})Cl]_2Cl_2$ 0.00625 mmol, ligand: (*R*,*R*)-TsPDEN 0.0125 mmol (2.5 mol% catalyst), HCOONa 2 eq, 0.2 cm^3 H_2O. [b] Reaction conditions: all the additional components were added: **1a** 0.5 mmol, ball milling at 30 Hz, 15 min.

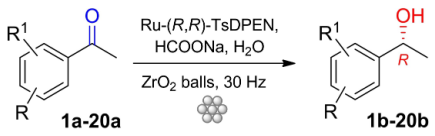
Scope of the mechanochemical ATH

Next we examined the extension of the scope of the mechanochemically activated ATH. The initial reactions were carried out using 0.5 mmol ketone, 2.5 mol% catalyst, 2 eq HCOONa hydrogen donor adding 0.2 cm^3 water and 42 pcs of Ø 5 mm ZrO_2 balls. The mixtures were milled at 30 Hz for 20 min, thus smaller amount of catalyst and donor were enough to achieve good conversions. Furthermore, longer reaction times ensured the reduction of less active ketones as well. Numerous substituted 1-phenylethanols are reachable by this method, with good conversions and enantioselectivities, as summarized in Table 3.

In the case of the electron withdrawing trifluoromethyl substituted derivative (**2a**), the conversions and ee-s decreased, compared to **1a**. The ATH of the bis-CF_3-acethophenone (**3a**) was even slower, and the enantiodifferentiation was weaker. In the reaction of the latter compound it was possible to reach close to complete conversion by increasing the reaction time to 30 min and using 3 eq hydrogen donor. However, decrease in the ee was also detected (84%) owing to the increase of the temperature, as observed previously in the reaction of **1a** (Figure SI-2).

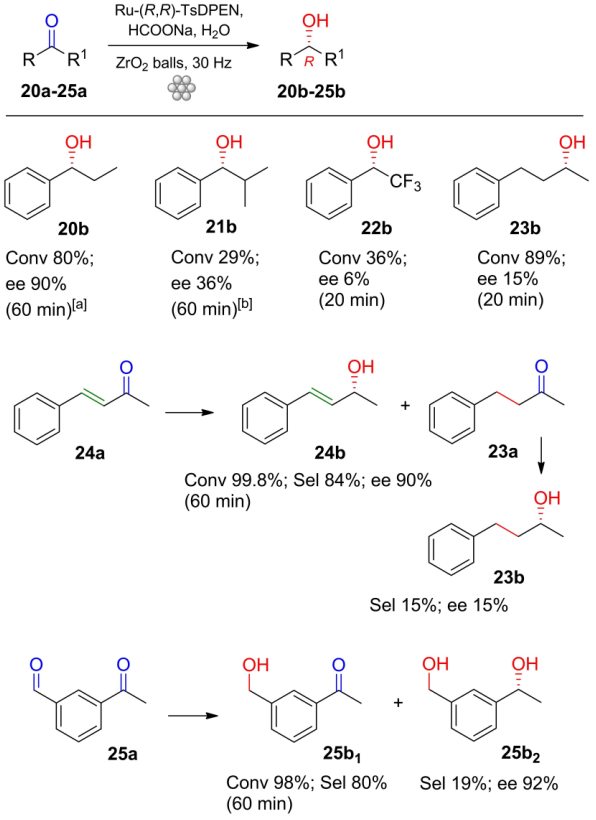
The inductive electron-withdrawing halogen group has a similar effect on the enantioselectivity as the CF_3 substituent, *i.e.* slightly decreased ee-s were observed when compared to **1a**. The increase of the size of the halogen in *meta* and *para* positions had almost no effect on the degree of transformation, except in the case of iodine (**12a**), which due to its significant steric hindrance decreased the conversion. However, similarly to the ATH of **3a**, high conversion could be reached in that of **12a** in prolonged milling. The difluoro-substituted alcohols (**5b**, **6b**) were obtained with lower enantioselectivities, which can also be traced back to the electron-withdrawing properties of the substituents. Due to the mesomeric electron-donating property of the methoxy group the reaction of **16a** took place much slower as a consequence of the increased electron density of the carbonyl C atom. In contrast, the mesomeric electron-withdrawing effect of the nitro group activated the

Table 3. Mechanochemical ATH of acetophenone derivatives (**1a–19a**).[a]



Entry	Product	R	R[1]	Conv[b] [%]	ee[c] [%]
1	**1b**	H	H	98	94
2	**2b**	3′-CF_3	H	87	91
3	**3b**	3′-CF_3	5′-CF_3	75	87
4[d]	**3b**	3′-CF_3	5′-CF_3	99	84
5	**4b**	4′-F	H	95	92
6	**5b**	2′-F	5′-F	99.9	71
7	**6b**	2′-F	6′-F	98	89
8	**7b**	3′-Cl	H	90	92
9	**8b**	4′-Cl	H	95	92
10	**9b**	2′-Br	H	88	90
11	**10b**	3′-Br	H	97	91
12	**11b**	4′-Br	H	95	91
13	**12b**	4′-I	H	54	91
14[d]	**12b**	4′-I	H	87	92
15	**13b**	4′-CH_3	H	82	94
16	**14b**	2′-CH_3O	H	70	73
17	**15b**	3′-CH_3O	H	88	93
18	**16b**	4′-CH_3O	H	60	94
19[d]	**16b**	4′-CH_3O	H	79	94
20	**17b**	2′-NO_2	H	87	89
21	**18b**	3′-NO_2	H	99.9	77
22	**19b**	4′-NO_2	H	99.9	84

[a] Reaction conditions: $[Ru(p\text{-cym})Cl]_2Cl_2$ 0.00625 mmol, (*R*,*R*)-TsPDEN 0.0125 mmol (2.5 mol% catalyst), ketone (**1a**-**19a**) 0.5 mmol, HCOONa 2 eq, 0.2 cm^3 water, 10 cm^3 ZrO_2 jar, 42 pcs Ø 5 mm balls, 30 Hz, 20 min. [b] Conversions determined by gas-chromatography (GC-FID). [c] Enantiomeric excess (ee) by GC-FID, the configuration of the excess enantiomer was *R*.[22] [d] After 30 min milling using 3 eq HCOONa.



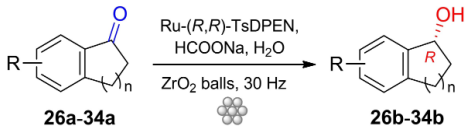
Scheme 2. ATH of various prochiral ketones by milling. Reaction conditions: $[Ru(p\text{-cym})Cl]_2Cl_2$ 0.00625 mmol, (*R*,*R*)-TsPDEN 0.0125 mmol (2.5 mol% catalyst), **20a**-**25a** 0.5 mmol, HCOONa 2 eq, 0.2 cm^3 H_2O, milling with 42 pcs Ø 5 mm balls, 30 Hz, milling time in parentheses. [a] HCOONa 3 eq. [b] Using $[Ru(p\text{-cym})Cl]_2Cl_2$ 0.0125 mmol, (*R*,*R*)-TsPDEN 0.025 mmol (5 mol% catalyst) and 3 eq HCOONa donor.

carbonyl moiety, thus both **18a** and **19a** were completely transformed under the given initial conditions. However, in the ATH of these compounds, a significant decrease in the ee was observed. The transformation of the *ortho*-substituted derivatives was the slowest, possibly due to the disadvantageous steric effect of the substituents in this position. This was illustrated by the conversions obtained in the ATH of **9a** and **17a**.

The modification of the aliphatic chain had an overall negative effect on the ATH (Scheme 2.). The reaction of propiophenone (**20a**) was slower than the ATH of **1a**, and the enantioselectivity was lower as well. The branching aliphatic chain of isobutyrophenone (**21a**) had a steric inhibiting effect on the reaction, decreased conversion and enantioselectivity were achieved even under harsher reaction conditions as compared to **20a**. The strong inductive electron-withdrawing CF_3 group in α-position also reduced the conversion and the ee values (**22a**). If the ketone group is distanced from the aromatic ring (**23a**), the reaction afforded low enantioselectivity (ee 15%). In the case of **24a** the re-established conjugation, between the aromatic ring and the ketone group, by the C=C double bond, was essential to achieve close to full conversion. The main product, the unsaturated alcohol (**24b**), was obtained with good chemoselectivity and high enantioselectivity. As a by-product the saturated alcohol (**23b**) was formed in low amount. The low selectivity and ee of **23b** (15%) suggest that the side product is formed by the reduction of the saturated ketone intermediate (**23a**), which may form in low amount parallel with **24b**. The ATH of 3′-acetylbenzaldehyde (**25a**) shows that the aldehyde group is saturated faster, however, after longer milling the ketone group of the intermediate **25b$_1$** is also reduced in high enantioselectivity.

In continuation, we extended the application of the mechanochemical method on the ATH of aliphatic cyclic ketones fused with the aromatic ring. Initially, we examined the reduction of carbocyclic compounds (see Table 4). The ATH of these ketones were slower, than the reaction of the acetophenone derivatives. Due to the seven membered ring of 1-benzosuberone (**26a**) this compound was coordinated less efficiently to the active center of the catalyst, thus 60 minutes of milling was necessary to achieve high conversion. The reaction of 1-tetralone (**27a**) was longer as well, compared to acetophenone, similarly to 1-indanone (**31a**), the milling time had to be increased to 30 min to reach closely full conversions in the ATH of both. However, the longer milling time did not affect the enantioselectivity considerably.

Table 4. Mechanochemical ATH of carbocyclic ketones (**26a–34a**).[a]

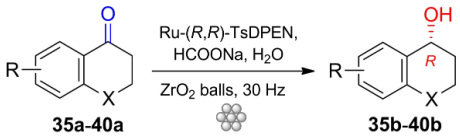


26a-34a 26b-34b

Entry	Product	n	R	t[b] [min]	Conv[c] [%]	ee[c] [%]
1	**26b**	3	H	20	34	88
2	**26b**	3	H	60	98	89
3	**27b**	2	H	20	85	95
4	**27b**	2	H	30	97	94
5	**28b**	2	5-CH_3O	40	99	95
6[d]	**29b**	2	6-CH_3O	60	< 1	nd
7	**29b**	2	6-CH_3O	60	54	95
8[e]	**29b**	2	6-CH_3O	120	97	94
9	**30b**	2	7-Br	30	93	95
10	**31b**	1	H	20	79	96
11	**31b**	1	H	30	96	97
12	**32b**	1	6-CF_3	30	95	97
13	**33b**	1	4-Br	30	98	95
14	**34b**	1	5-Br	30	83	97

[a] Reaction conditions: [Ru(*p*-cym)Cl]$_2$Cl$_2$ 0.00625 mmol, (*R*,*R*)-TsPDEN 0.0125 mmol (2.5 mol% catalyst), **26a–34a** 0.5 mmol, HCOONa 2 eq, 0.2 cm^3 H_2O, milling with 42 pcs Ø 5 mm balls, 30 Hz. [b] Milling time. [c] Conversion and enantiomeric excess determined by GC-FID, the excess enantiomer was *R*;[22] nd: not determined. [d] **MS** reaction (800 rpm). [e] Using [Ru(p-cym)Cl]$_2$Cl$_2$ 0.0125 mmol, (*R*,*R*)-TsPDEN 0.025 mmol (5 mol% catalyst) and 3 eq HCOONa.

Table 5. Mechanochemical ATH of heterocyclic ketones (**35a–40a**).[a]



35a-40a 35b-40b

Entry	Product	X	R	Conv[b] [%]	ee[b] [%]
1	**35b**	O	H	99	96
2	**36b**	O	6-Cl	75	97
3	**37b**	S	H	99	95
4	**38b**	S	6-Cl	94	95
5[c]	**39b**	NH	8-Br	95	93
6[c]	**40b**	N-Boc	H	88	95

[a] Reaction conditions: [Ru(*p*-cym)Cl]$_2$Cl$_2$ 0.00625 mmol, (*R*,*R*)-TsPDEN 0.0125 mmol (2.5 mol% catalyst), **35a–40a** ketone 0.5 mmol, HCOONa 2 eq, 0.2 cm^3 H_2O, milling with 42 pcs Ø 5 mm balls, 30 Hz, 20 min. [b] Conversion and enantiomeric excess determined by GC-FID, the excess enantiomer was *R*.[22] [c] 40 min milling time.

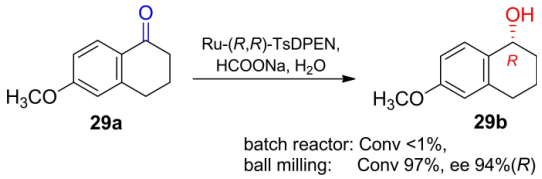
The mesomeric electron-donating methoxy group of the 1-tetralon derivatives **28a** and **29a** had a negative effect on the mechanochemical ATH, similarly to the methoxy-substituted acetophenone derivatives. Longer reaction time and harsher conditions were necessary to achieve high conversion especially if the substituent was located in position 6 (**29a**). In the ATH of the latter, no transformation was observed in the magnetically stirred batch reactor under similar reaction conditions (Table 4; entry 6), which showed the benefit of the mechanochemical activation. In the presence of an inductive electron-withdrawing group in position 7 (**30a**) the product was formed in a shorter reaction, similar to **27b**. The ATH of the 1-indanone derivatives bearing inductive electron-withdrawing substituents (**32a–34a**) was also fast, moreover, high ee values were obtained.

Finally, we examined the mechanochemical ATH of some heterocyclic ketones, too (see Table 5). We obtained outstanding results in the ATH of 4-chromanone (**35a**) and 4-thiochromanone (**37a**) after the same milling time which was used in the reaction of **1a**, however, the 6-chlorine-substituted derivatives (**36a**, **38a**) gave lower conversions, though accompanied with high enantioselectivities.

The reactions of the *N*-heterocyclic ketones (**39a**, **40a**) were somewhat slower. Probably the bulky Br substituent or the large *tert*-butoxycarbonyl (Boc) protecting group on the N atom inhibited to some extent the coordination of these molecules, compared with the *O*- and *S*-heterocyclic ketones and decelerated these reactions, thus 40 min milling times were necessary, to reach good conversions. However, as described in our previous publication the presence of these bulky substituents makes possible the ATH of *N*-heterocyclic ketones, inhibiting the strong (irreversible) coordination of these compounds to the catalyst by the NH group.[22]

The ATH in batch reactors of several prochiral ketones used in the above study (**1a**, **8a**, **13a**, **14a**, **15a**, **16a**, **20a**, **27a**, **31a**) was examined previously under similar reaction conditions.[9a] The reactions described in the literature were performed at 40 °C, in water using HCOONa as the hydrogen donor and afforded high conversions and enantioselectivities in 2–3 hours.

Our results show that using mechanochemical activation could shorten the reaction times to 20–60 min to reach similar results by employing less hydrogen donor. Moreover, the enantioselectivities obtained in the mechanochemical ATHs were similar to or better than those obtained in reactions carried out traditionally. Overall it can be stated, that the implementation of mechanochemistry has several advantages over the traditional batch reactions, such as high conversions and high enantioselectivities can be achieved after shorter reaction times using small amounts of hydrogen donor and water. The remarkable advantage of this activation method is illustrated by the ATH of 6-methoxytetralone (**29a**), which could not be reduced in the batch system, whereas high conversion and ee were obtained in the ball mill (Scheme 3.). This is attributed to the efficient mixing of the reaction components by grinding in case of water-insoluble, solid reactants, which allows the reduction to occur in contrast with magnetic stirring under aqueous conditions.



Scheme 3. The ATH of 6-methoxytetralone **29a** in batch and in mixing mill. Reaction conditions: see Table 4.

Table 6. Scale-up of the mechanochemical ATH of **1 a**, **19 a** and **37 a**.[a]

Entry	Ketone; amount [mmol]	Catalyst amount [mol%]	HCOONa amount [eq]	V[b] [cm^3]	t[c] [min]	Conv[d] [%]	TOF [h^{-1}]	ee[d] [%]	Yield[e] [%]
1	**1 a**; 1	1.25	2	0.3	20	70	168	94	–
2	**1 a**; 1	1.88	2	0.3	20	92	147	95	–
3	**1 a**; 2	1.88	2	0.3	30	99.9	107	94	–
4	**1 a**; 4	1.41	1.5	0.4	30	99	141	94	–
5[f]	**1 a**; 4	1.41	1.5	0.4	30	99.9	142	93	89
6	**1 a**; 8	1.41	1.5	0.8	90	99.9	47	93	86
7	**19 a**; 2	1.41	2	0.4	40	99.9	120	83	88
8	**37 a**; 2	1.41	2	0.4	40	98	118	94 (98)[g]	92 (72)[g]

[a] Reaction conditions: catalyst precursor: $[Ru(p\text{-}cym)Cl]_2Cl_2$, ligand: (*R*,*R*)-TsPDEN, ball milling in 10 cm^3 ZrO_2 jar with 42 pcs Ø 5 mm grinding balls, 30 Hz. [b] Volume of added H_2O. [c] Milling time. [d] Conversion and enantiomeric excess (*R*) determined by GC-FID. [e] Yields after purification by flash chromatography using hexane/EtOAc 4/1-8/1 eluent. [f] Reaction using (*S*,*S*)-TsPDEN ligand resulting in the *S*-**1 b** enantiomer in excess. [g] ee and yield following additional recrystallization from hexane.

Scale-up of the mechanochemically activated ATH

The scale-up of the developed catalytic system was optimized for the ATH of acetophenone, using 0.5–8 mmol ketone (Table 6, entries 1–6). The ratio of catalyst, hydrogen donor and solvent were not necessary to be increased proportionally with the amount of **1 a** in order to achieve similar results as with 0.5 mmol. Generally, higher amount of water was necessary, and the milling time was increased as the amount of **1 a** was gradually raised to 2, 4 or 8 mmol. More importantly, the catalyst amount could be decreased to 1.41 mol% and only 1.5 eq HCOONa was sufficient to reach full conversions. The reaction carried out using (*S*,*S*)-TsDPEN at 4 mmol scale (entry 5) provided the *S* alcohol in similarly good ee, as its previously used enantiomer. Following purification by flash chromatography, the *S*- and *R*-**1 b** obtained by the ATH of 4 and 8 mmol **1 a** were isolated in good yields.

The mechanochemical transfer hydrogenation of 4′-nitroacetophenone and 4-thiochromanone was carried out with 2 mmol of ketones (entries 7, 8). After 40 min milling, high conversions and ee values were reached. After purification by flash chromatography, the chiral alcohols were obtained in high yields. Moreover, the optical purity of *R*-4-thiochromanol could be increased by crystallization from hexane. Accordingly, the mechanochemical method used in the present work for the ATH of various prochiral ketones may be scaled-up easily to obtain the corresponding optically pure alcohols at a few gram scale.

Conclusions

In this study our aim was to develop a sustainable and environmentally benign catalytic system for the ATH of ketones using chiral Ru(II)-TsDPEN catalyst in aqueous system and HCOONa hydrogen donor. After the examination of different activation methods, such as thermally activated, magnetically stirred batch reactions, ultrasound or microwave assisted and ball milling, the latter method was found the most promising to reaching our goal. The thorough optimization of the reaction conditions was carried out in the mixing mill using the ATH of acetophenone. The effect of the size and number of milling balls along with the milling frequency and time were examined. These results led to the conclusion that the use of 42 pcs of Ø 5 mm balls at 30 Hz for 15 minutes provided good conversions, although at high frequencies after longer milling the warm-up of the system was observed, which had a slightly detrimental effect on the enantioselectivity. Further, other reaction conditions were optimized as well, such as the amount of added water, catalyst and donor. The goal of minimizing the amount of the components, such as the Ru precursor, the chiral ligand and the hydrogen donor was achieved by applying more grinding balls and the slight extension of the reaction time.

In this new mechanochemical catalytic system, numerous acetophenone derivatives, carbo- and heterocyclic ketones were transformed to the corresponding chiral alcohols with high conversions and enantioselectivities. In a few reactions further optimization of the conditions was necessary, but in every case similar or better results were achieved in shorter reaction times than in the previously reported batch reactions. An outstanding example is the ATH of 6-methoxytetralone, which cannot be reduced with Ru-TsDPEN and HCOONa using aqueous media under batch conditions, yet the mechanochemically activated reaction gave good conversion and high ee value.

Our study shows that the system can be easily scaled-up reaching remarkable TOF values, only the size of the grinding jar may limit the used quantities. In our hands, the 10 cm^3 jar was sufficient to carry out the ATH of up to 8 mmol ketone effectively.

Unprecedentedly, the achieved results prove that the mechanochemical activation is efficient to carry out asymmetric transfer hydrogenations using a simple mixing mill. The short reaction times and the easy scale-up of the method provides a unique opportunity to obtain high amounts of optically pure chiral building blocks for pharmaceutical use in a sustainable and environmentally friendly manner.

Experimental Section

Materials and methods

The Ru-precursor: $[Ru(p\text{-cym})Cl]_2Cl_2$, the chiral ligands: (*R*,*R*)- and (*S*,*S*)-*N*-(*p*-toluenesulfonyl)-1,2-diphenylethane-1,2-diamine (TsDPEN) were used as received (Alfa Aesar and Sigma-Aldrich). Ketones and the hydrogen donor (HCOONa) used in this study were all commercial products and used without purification. Analytical grade organic solvents were obtained from commercial sources and were applied as such.

Gas-chromatographic analysis of the reaction products were carried out using Agilent Techn. 6890 N 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 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 Technol.) was used. For purification of products by flash chromatography silica gel 60, 40–63 μm, and hexane isomers/ethyl acetate (EtOAc) 4/1–8/1 mixtures were applied. 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.

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

Mechanochemical transfer hydrogenations

The mechanochemically activated reactions were carried out in 10 cm^3 ZrO_2 coated grinding jars and ZrO_2 grinding balls (Ø 3, 5, 12, 15 mm). In a typical reaction, the given amount of $Ru(p\text{-cym})Cl]_2Cl_2$, (*R*,*R*)-TsDPEN, 0.2 cm^3 water, the necessary amount of HCOONa and 0.5 mmol ketone were introduced into the jar, than the chosen number of balls were added to the system. The closed jars were placed into a Retsch MM 400 mixing mill and agitated at the chosen frequency for the given time. Following the reactions, the products were dissolved in 2 cm^3 EtOAc, the jars and balls were washed twice with additional 2 cm^3 EtOAc, the unified organic phase was filtrated on silica to separate the remaining water and solid residues, and was analysed 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 (see SI). The TOF values were determined based on the conversions by the formulae given in the SI as well. The experiments were repeated at least 3 times, the reproducibility of the product composition was found to be within $\pm 1\%$.

Reactions at 1–8 mmol ketone scales were carried out similarly as above using the indicated amounts. Following GC analysis of the crude products the solvent was removed by evaporation and the pure products were obtained by flash chromatography. The purified products were analysed 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 shown in the SI.[9,22,23]

Batch transfer hydrogenations

Reactions were carried out in 4 cm^3 closed glass vials. The slurries were stirred magnetically (800 rpm). If higher than room temperature (rt) was necessary the vials were immersed in a preheated oil bath. In a typical reaction the given amounts of $[Ru(p\text{-cym})Cl]_2Cl_2$, (*R*,*R*)-TsDPEN, water, HCOONa and the prochiral ketone (0.5 mmol) were introduced into the vial and stirred for the given time at the indicated temperature. Following reactions, the products were extracted in 2 cm^3 EtOAc, the aqueous phase was washed twice with additional 2 cm^3 EtOAc, the unified organic phase was dried using $MgSO_4$ (sicc.) and analysed by gas-chromatography (GC-MSD and GC-FID). The ultrasound activated reaction was carried out similarly. After the addition of the reaction components the vial was immersed in a Barson 150 ultrasonic bath, which irradiated the reaction system at 40 kHz. The microwave assisted reactions were carried out in 8 cm^3 reactor tubes using a CEM Discover microwave reactor. Mixing of the slurry was ensured by magnetic stirring at 50 °C. The work-up of these reactions were similar as that of the traditional batch reactions.

Acknowledgements

Financial support by the Hungarian Ministry of Human Capacities through NTP-NFTÖ-20-B-0186 (V. J. Kolcsár) and through grant 20391-3/2018/FEKUSTRAT is highly appreciated. Financial support of the Hungarian National Science Foundation through OTKA Grant K 138871 is acknowledged.

Conflict of Interest

The authors declare no conflicts of interest.

Keywords: enantioselective · ketones · mechanochemistry · ruthenium · transfer hydrogenation

[1] a) *Green Chemistry in the Pharmaceutical Industry* (Eds.: P. J. Dunn, A. S. Wells, M. T. Williams), Wiley-VHC, Weinheim, **2010**; b) A. Patti, *Green Approaches to Asymmetric Catalytic Synthesis*, Springer, Dordrecht, **2011**; c) *Sustainable Synthesis of Pharmaceuticals Using Transition Metal Complexes as Catalyst* (Eds.: M. M. Pereira, M. J. F. Calvete), Green Chemistry Series No. 54, The Royal Society of Chemistry, Cambridge, **2018**.

[2] a) H. C. Erythropel, J. B. Zimmerman, T. M. de Winter, L. Petitjean, F. Melnikov, C. H. Lam, A. W. Lounsbury, K. E. Mellor, N. Z. Janković, Q. Tu, L. N. Pincus, M. M. Falinski, W. Shi, P. Coish, D. L. Plata, P. T. Anastas, *Green Chem.* **2018**, *20*, 1929–1961; b) K. J. Ardila-Fierro, J. G. Hernández, *ChemSusChem* **2021**, *14*, 2145–2162.

[3] *Asymmetric Synthesis of Drugs and Natural Products* (Ed.: A. Nag), Taylor & Francis Group, CRC Press, Boca Raton, **2018**.

[4] a) *Asymmetric Catalysis on Industrial Scale: Challenges, Approaches and Solutions* (Eds.: H. U. Blaser, E. Schmidt), Wiley-VCH, Weinheim, **2004**; b) *New Frontiers in Asymmetric Catalysis* (Eds.: K. Mikami, M. Lautens), John Wiley & Sons, Hoboken, NJ, **2007**; c) *Catalytic Asymmetric Synthesis* (Ed.: I. Ojima), John Wiley & Sons, Hoboken, NJ, 3rd ed., **2010**; d) *Catalytic Methods in Asymmetric Synthesis: Advanced Materials, Techniques and Applications* (Eds.: M. Gruttadauria, F. Giacalone) John Wiley & Sons, Hoboken, NJ, **2011**; e) *Science of Synthesis: Asymmetric Organocatalysis* (Eds.: B. List, K. Maruoka) Thieme, Stuttgart, **2012**; f) *Comprehensive Enantioselective Organocatalysis: Catalysts, Reactions, and Applications* (Ed.: P. I. Dalko) Wiley-VCH, Weinheim, Vol. 1–3, **2013**; g) J. Tan, N. Yasuda, *Org. Process Res. Dev.* **2015**, *19*, 1731–1745; h) Gy. Szőllősi, *Catal. Sci. Technol.* **2018**, *8*, 389–422; i) M. Tavakolian, S. Vahdati-Khajeh, S.

Asgari, *ChemCatChem* **2019**, *11*, 2943–2977; j) H. Pellissier, *Adv. Synth. Catal.* **2020**, *362*, 2289–2325; k) X. Xiao, B.-X. Shao, Y.-J. Lu, Q.-Q. Cao, C.-N. Xia, F.-E. Chen, *Adv. Synth. Catal.* **2021**, *363*, 352–387; l) V. A. Larionov, B. L. Feringa, Y. N. Belokon, *Chem. Soc. Rev.* **2021**, *50*, 9715–9740.

[5] a) *The Handbook of Homogeneous Hydrogenation* (Eds.: J. G. de Vries, C. J. Elsevier) Wiley-VCH, Weinheim, **2007**; b) D. Wang, D. Astruc, *Chem. Rev.* **2015**, *115*, 6621–6686; c) *Asymmetric Hydrogenation and Transfer Hydrogenation* (Eds.: V. Ratovelomanana-Vidal, P. Phansavath) Wiley-VCH, Weinheim, **2021**.

[6] a) R. Noyori, S. Hashiguchi, *Acc. Chem. Res.* **1997**, *30*, 97–102; b) S. Gladiali, E. Alberico, *Chem. Soc. Rev.* **2006**, *35*, 226–236; c) T. Ikariya, A. J. Blacker, *Acc. Chem. Res.* **2007**, *40*, 1300–1308; d) R. Malacea, R. Poli, E. Manoury, *Coord. Chem. Rev.* **2010**, *254*, 729–752; e) J. Václavik, P. Kačer, M. Kuzma, L. Červeny`, *Molecules* **2011**, *16*, 5460–5495; f) W. Zuo, A. J. Lough, Y. F. Li, R. H. Morris, *Science* **2013**, *342*, 1080–1083; g) Y.-Y. Li, S.-L. Yu, W.-Y. Shen, J.-X. Gao, *Acc. Chem. Res.* **2015**, *48*, 2587–2598; h) P.-G. Echeverria, T. Ayad, P. Phansavath, V. Ratovelomanana-Vidal, *Synthesis* **2016**, *48*, 2523–2539; i) A. Mezzetti, *Isr. J. Chem.* **2017**, *57*, 1090–1105; j) A. E. Cotman, *Chem. Eur. J.* **2021**, *27*, 39–53; k) A. A. Mishra, B. M. Bhanage, *Chirality* **2021**, *33*, 337–378; l) V. Ritleng, J. G. de Vries, *Molecules* **2021**, *26*, art.no. 4076.

[7] a) S. Hashiguchi, A. Fujii, J. Takehara, T. Ikariya, R. Noyori, *J. Am. Chem. Soc.* **1995**, *117*, 7562–7563; b) K. Matsumura, S. Hashiguchi, T. Ikariya, R. Noyori, *J. Am. Chem. Soc.* **1997**, *119*, 8738–8739.

[8] a) A. Fujii, S. Hashiguchi, N. Uematsu, T. Ikariya, R. Noyori, *J. Am. Chem. Soc.* **1996**, *118*, 2521–2522; b) M. Watanabe, K. Murata, T. Ikariya, *J. Org. Chem.* **2002**, *67*, 1712–1715.

[9] a) X. Wu, X. Li, W. Hems, F. King, J. Xiao, *Org. Biomol. Chem.* **2004**, *2*, 1818–1821; b) X. Wu, X. Li, F. King, J. Xiao, *Angew. Chem. Int. Ed.* **2005**, *44*, 3407–3411; *Angew. Chem.* **2005**, *117*, 3473–3477; c) X. Wu, J. Xiao, *Chem. Commun.* **2007**, 2449–2466; d) X. Wu, X. Li, A. Zanotti-Gerosa, A. Pettman, J. Liu, A. J. Mills, J. Xiao, *Chem. Eur. J.* **2008**, *14*, 2209–2222; e) X. Wu, C. Wang, J. Xiao, *Platinum Met. Rev.* **2010**, *54*, 3–19.

[10] a) 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, *Chem. Soc. Rev.* **2012**, *41*; 413–447; b) G.-W. Wang, *Chem. Soc. Rev.* **2013**, *42*, 7668–7700; c) *Ball Milling Towards Green Synthesis: Applications, Projects, Challenges* (Eds.: B. Ranu, A. Stolle), RSC Green Chemistry No. 31, The Royal Society of Chemistry, Cambridge, **2015**; d) D. Margetić, V. Štrukil, *Mechanochemical Organic Synthesis*, Elsevier, Amsterdam, **2016**.

[11] Z. Zhang, J. Gao, J.-J. Xia, G.-W. Wang, *Org. Biomol. Chem.* **2005**, *3*, 1617–1619.

[12] a) 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, *ChemSusChem* **2015**, *8*, 3773–3776; b) Y. Sawama, N. Yasukawa, K. Ban, R. Goto, M. Niikawa, Y. Monguchi, M. Itoh, H. Sajiki, *Org. Lett.* **2018**, *20*, 2892–2896; c) Y. Sawama, M. Niikawa, H. Sajiki, *J. Synth. Org. Chem. Jpn.* **2019**, *77*, 1070–1077.

[13] A. Y. Li, A. Segalla, C.-J. Li, A. Moores, *ACS Sustainable Chem. Eng.* **2017**, *5*, 11752–11760.

[14] R. Solá, O. B. Sutcliffe, C. E. Banks, B. Maciá, *Sustain. Chem. Pharm.* **2017**, *5*, 14–21.

[15] T. Portada, D. Margetić, V. Štrukil, *Molecules* **2018**, *23*, art.no. 3163.

[16] C. Bolm, J. G. Hernández, *Angew. Chem. Int. Ed.* **2019**, *58*, 3285–3299; *Angew. Chem.* **2019**, *131*, 3320–3335.

[17] a) B. Rodríguez, T. Rantanen, C. Bolm, *Angew. Chem. Int. Ed.* **2006**, *45*, 6924–6926; *Angew. Chem.* **2006**, *118*, 7078–7080; b) B. Rodríguez, A. Bruckmann, C. Bolm, *Chem. Eur. J.* **2007**, *13*, 4710–4722.

[18] a) P. Chauhan, S. S. Chimni, *Beilstein J. Org. Chem.* **2012**, *8*, 2132–2141; b) Z. Li, Z. Jiang, W. Su, *Green Chem.* **2015**, *17*, 2330–2334; c) Y. Wang, H. Wang, Y. Jiang, C. Zhang, J. Shao, D. Xu, *Green Chem.* **2017**, *19*, 1674–1677; d) C. Bolm, J. G. Hernández, *ChemSusChem* **2018**, *11*, 1410–1420; e) P. Staleva, J. G. Hernández, C. Bolm, *Chem. Eur. J.* **2019**, *25*, 9202–9205; f) C. G. Avila-Ortiz, M. Pérez-Venegas, J. Vargas-Caporali, *Tetrahedron Lett.* **2019**, *60*, 1749–1757; g) J. Andersen, J. Brunemann, J. Mack, *React. Chem. Eng.* **2019**, *4*, 1229–1236; h) I. N. Egorov, S. Santra, D. S. Kopchuk, I. S. Kovalev, G. V. Zyryanov, A. Majee, B. C. Ranu, V. L. Rusinov, O. N. Chupakhin, *Green Chem.* **2020**, *22*, 302–315; i) M. Pérez-Venegas, E. Juaristi, *ACS Sustainable Chem. Eng.* **2020**, *8*, 8881–8893; j) J. Yu, P. Ying, H. Wang, K. Xiang, W. Su, *Adv. Synth. Catal.* **2020**, *362*, 893–902; k) D. Krištofíková, M. Mečiarová, E. Rakovsky, R. Šebesta, *ACS Sustainable Chem. Eng.* **2020**, *8*, 14417–144204.

[19] J. G. Hernández, M. Frings, C. Bolm, *ChemCatChem* **2016**, *8*, 1769–1772.

[20] a) X. Wu, J. Liu, D. Di Tommaso, J. A. Iggo, C. R. A. Catlow, J. Bacsa, J. A. Xiao, *Chem. Eur. J.* **2008**, *14*, 7699–7715; b) P. A. Dub, T. Ikariya, *J. Am. Chem. Soc.* **2013**, *135*, 2604–2619.

[21] K.-J. Haack, S. Hashiguchi, A. Fujii, T. Ikariya, R. Noyori, *Angew. Chem. Int. Ed.* **1997**, *36*, 285–288; *Angew. Chem.* **1997**, *109*, 297–300.

[22] a) Gy. Szőllősi, V. J. Kolcsár, *ChemCatChem* **2019**, *11*, 820–830; b) V. J. Kolcsár, F. Fülöp, Gy. Szőllősi, *ChemCatChem* **2019**, *11*, 2725–2731.

[23] V. Stepanenko, M. De Jesús, W. Correa, L. Bermúdez, C. Vázquez, I. Guzmán, M. Ortiz-Marciales, *Tetrahedron: Asymmetry* **2009**, *20*, 2659–2665.

Manuscript received: October 4, 2021
Revised manuscript received: December 3, 2021
Accepted manuscript online: December 7, 2021
Version of record online: December 28, 2021