RESEARCH ARTICLE

Mechanochemical Deracemization: A Novel and Sustainable Approach to Enantiopurity

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Abstract: We introduce mechanochemical deracemization (MCDR) as a novel strategy for obtaining enantiopure compounds. This study demonstrates the successful transposition of six archetypical deracemization reactions from a solvent-based to a solvent-minimized ball milling environment. The scope includes a ketone, isoindolinones, imines, an ester, and an inorganic compound, all of which deracemized successfully. Key parameters such as milling material, ball number and size, the use of a bulk material and liquid-assisted grinding (LAG) were systematically investigated, revealing their crucial role. Quantitative enantiomeric excesses (e.e.) were achieved, while reaction times were reduced by up to 97 % and solvent consumption by as much as 100 %. This work establishes MCDR as a versatile, sustainable pathway to enantiopure compounds. By highlighting the generalizability of this approach and its huge potential for minimizing waste, this study provides the foundation for future advancements in mechanochemical deracemization.

Introduction

Asymmetry is a fundamental property of life that results in stereoisomers interacting differently with biological systems.[1] An

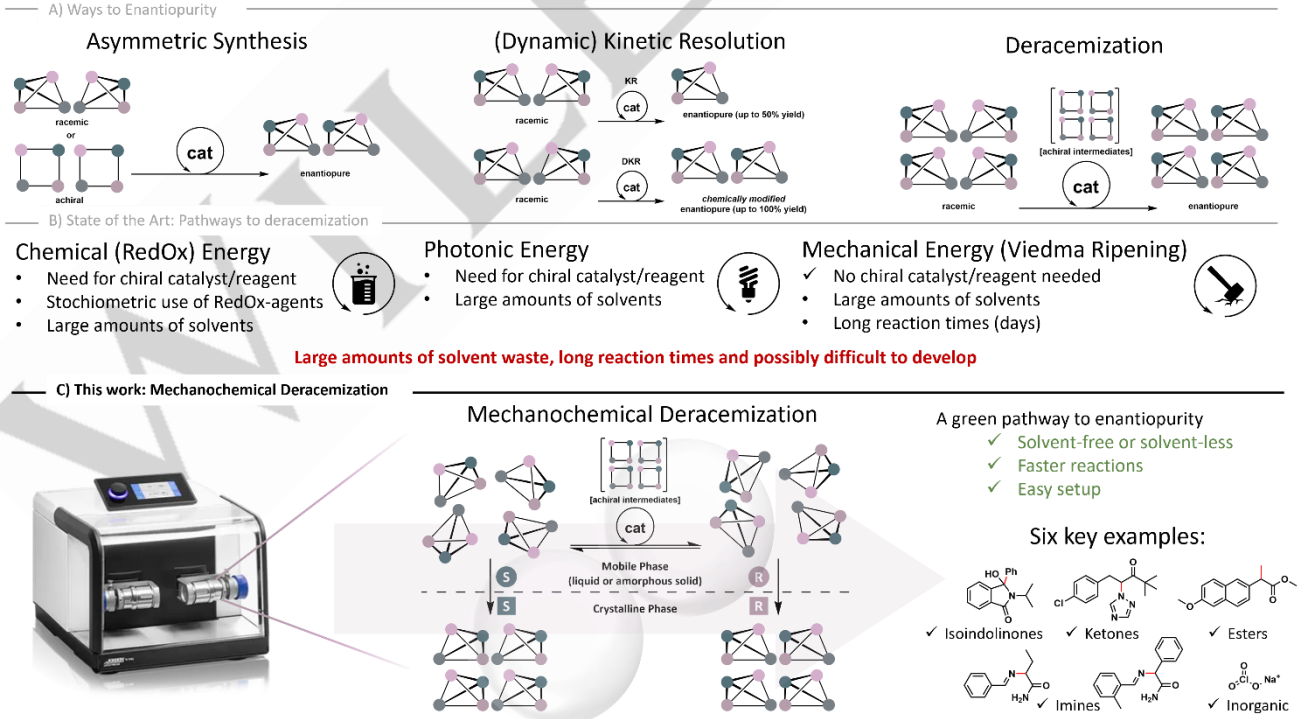


Figure 1. A) Major pathways to obtain enantiopure compounds: Asymmetric Synthesis, (Dynamic) Kinetic Resolution and Deracemization. B) Different energy sources for deracemization and their main drawbacks: Chemical (RedOx), photonic and mechanical energy.[5] C) This work: Mechanochemical deracemization (MCDR). MM400 ball mill used for MCDR (left), possible mechanism for MCDR similar to VR[17] (middle), advantages of MCDR and examples studied (right). The representation of chirality was inspired by literature.[10]

enantiomeric pair can have strongly differing effects, with the most infamous example being Thalidomide. This racemic drug was administered to pregnant women and caused birth defects in over 10.000 children.[2] Today, over 50 % of pharmaceuticals are chiral.[3] Although many are still sold as racemic mixtures, a recent study found only 10 racemates were approved by the FDA and EMA between 2013-2022.[4] Enantiopurity is thus of paramount importance in the pharmaceutical industry and the demand for economically viable yet sustainable pathways to obtain enantiopure compounds is higher than ever.

Despite important advances in asymmetric synthesis, a prominent way to enantiopure compounds remains formation and subsequent resolution of a racemate, with the distomer being discarded. However, if the distomer is racemizable, it can be converted into the eutomer in a deracemization process, with a theoretical yield and enantiomeric excess (e.e.) of 100 % while simultaneously having a high atom-economy (**Erreur ! Source du renvoi introuvable.**, A).[5] Unfortunately, deracemization is challenging to develop as there are major thermodynamic and kinetic obstacles.[6,7] The energy required to induce deracemization can be of (redox) chemical, photonic or mechanical origin (**Erreur ! Source du renvoi introuvable.**, B).[5] Reactions driven by chemical energy usually require sacrificial redox agents in stochiometric amounts thereby tarnishing the atom-economy of the process. Since 2018 remarkable works on photochemical deracemization have been reported.[8–10] However, these reactions require highly sophisticated photocatalysts. The last approach relies on mechanical energy. In 2005, Viedma reported the deracemization of $NaOCl_3$ merely by grinding a suspension with glass beads.[11] Since then, this approach has been extended to organic compounds.[12–20] This Viedma-Ripening (VR) process can only be applied to compounds that racemize and crystallize as a conglomerate (each enantiomer crystallizes in a separate crystal).[17,21] As the racemization reaction takes place in solution, major drawbacks of VR are large amounts of toxic solvents and the need for solubility. Furthermore, the process requires very long reaction times (days).

In recent years mechanochemistry has emerged as a sustainable alternative to classical solvent-based reactions.[22,23] Ball mills serve as reactors which operate at high frequencies and generate collisions between milling balls and particles thereby generating mechanical energy that allows solids to react directly with each other in the absence of solvents. Mechanochemical reactions are further often faster than conventional reactions, with new reactivities unique to mechanochemistry also having been discovered.[24–29] Due to these advantages, mechanochemical reactions are increasingly used in organic[30–35], inorganic[36–39] or material synthesis[40–42] and especially the combination of mechanochemistry and other disciplines proved to be fruitful.[43–46] Recently, it was shown that enantiomerically pure compounds can be combined to form a racemic compound under mechanochemical conditions.[47] Last year, we reported for the first time on the considerably more challenging, opposing process of deracemization via ball milling.[48] Adding minute amounts of solvent, the deracemization took only a couple of hours, instead of days. To date, this is still the only report on deracemization using mechanochemistry. We here set out to show that this was not a rare exception but that mechanochemical deracemization (MCDR) is a new and general approach to enantiopurity, drastically reducing both reaction time and solvent use.

In this work, we focus on six archetypical examples not only highlighting the possibility to deracemize all via ball milling but also showcasing the drastic reduction in reaction time and solvent use. The scope of this contribution covers key organic functionalities like ketones, isoindolinones, imines and esters as well as an inorganic example. We here demonstrate the robustness and versatility of our method and expect this work to be the cornerstone for future works on the new platform technology of MCDR (**Erreur ! Source du renvoi introuvable.**, C).

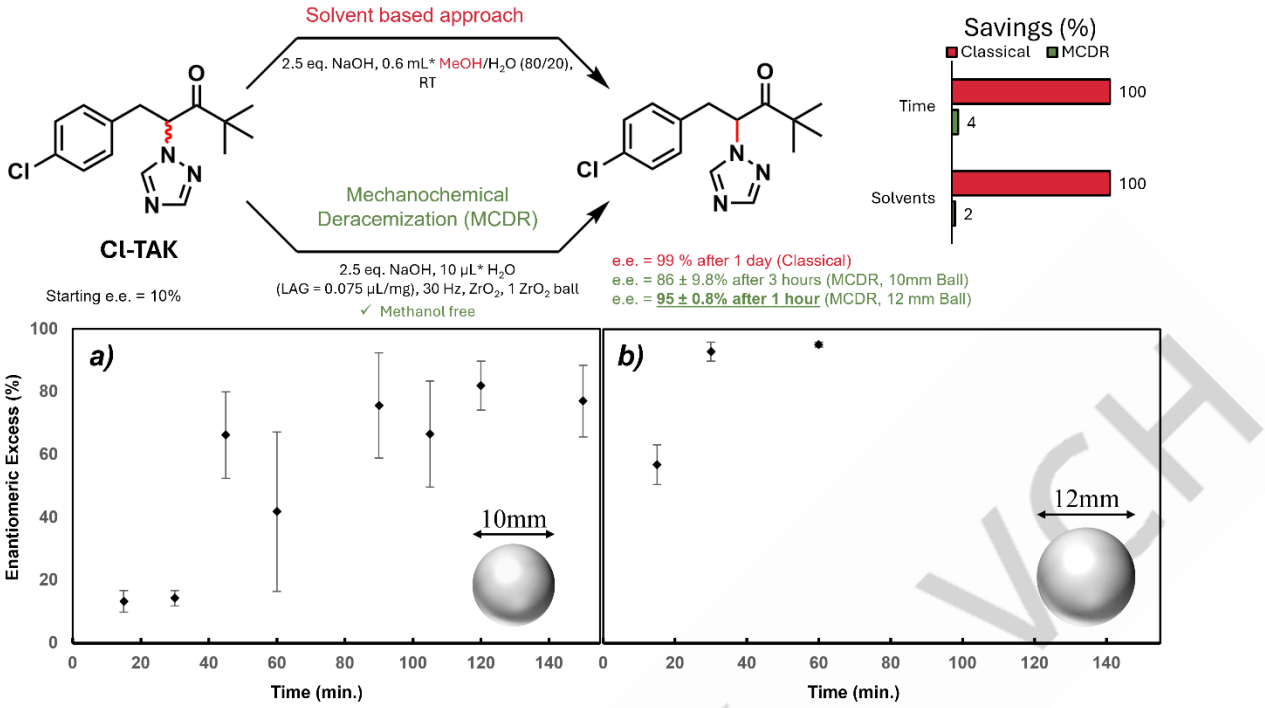
Results and Discussion

We here show MCDR to be a general approach to deracemization, enabling the technique for different compound families that are typically encountered in solution-based VR. As reaction conditions are family-dependent, we discuss each separately.

We believe the mechanism of MCDR to be similar to VR, with the racemization reaction, as many mechanochemical reactions, taking place in a non-crystalline intermediate phase.[49,50] Indeed, an amorphous phase can be formed by milling: Breaking of particles, mixing, introduction of defects and heating, which combines with a liquid phase through melting or liquid additives. In these phases, the mobility of the molecules is increased, which makes reactions possible. We will refer to the combination of amorphous and liquid phases as “mobile phase” (MP) in this article. We assume that in MCDR the racemization step takes place in this MP and its control is of crucial importance, as shown through the development of deracemization for each family of compounds (**Figure 1**, C).

Ketones

We recently reported the first deracemization via mechanochemistry.[48] A precursor of Paclobutrazol, 4,4-dimethyl-1-(4-chlorophenyl)-2-(1H-1,2,4-triazol-1-yl)-pentan-3-one (**Cl-TAK**) was successfully deracemized by ball milling with 2.5 eq. NaOH and 10 µL H_2O in a 10 mL ZrO_2 vessel using one 10 mm milling ball at a frequency of 30 Hz. Water was added as a liquid-assisted grinding (LAG) agent. It is well-known that LAG can have dramatic effects on mechanochemical reactions.[51–53] LAG is quantified by the η-parameter, which represents the ratio between the amount of liquid in µL and the amount of solid in mg.[54] In our study, we found that the addition of water (η = 0.075 µL/mg) is important to create a mobile phase in which racemization can take place. It is important to note that water does not act as a solvent in the reaction since the substrate is insoluble in water. Starting with 10 %e.e., an e.e. of ca. 86 % is reached in merely three hours, whereas the solvent-based deracemization process takes at least a day. MCDR process kinetics revealed an induction period of ca. 45 minutes during which no increase in e.e. was observed. After this period the e.e. increased drastically. We argued that this induction period corresponds to the time needed for the reaction mixture to change from a powder into a cohesive state which subsequently allows the racemization reaction to take



Scheme 1. Deracemization of Cl-TAK via the solvent-based approach (red) and MCDR (green) as well as a comparison of the savings (top). * The amount of solvent is per 100 mg of starting material. The e.e. for the classical approach is taken from literature. Kinetics of Cl-TAK deracemization via MCDR by using a) a 10 mm and b) a 12 mm diameter ZrO_2 milling ball (bottom). Each experiment was repeated at least four times, and the average value was plotted. Error bars correspond to the standard deviation.

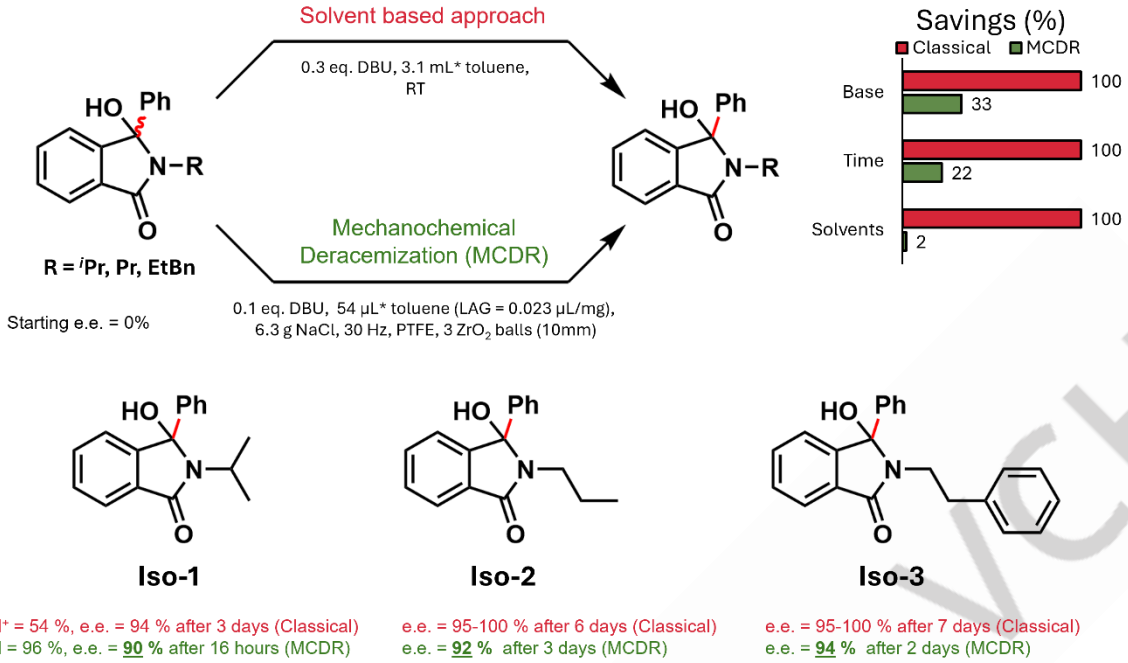
place. Such sigmoidal kinetics are known in mechanochemistry[49] and are also typical for classical VR. We found a relatively strong variability on the final e.e., which can be explained by the variation in kinetics (**Scheme 1**, a).

Using a single 12 mm milling ball instead of a 10 mm ball led to important changes in the reaction kinetics (**Scheme 1**, b). Deracemization occurs much more rapidly, leading to a final e.e. of ca. 95 % within one hour. Interestingly, the induction period has been strongly reduced and is almost undetectable. But most notably the reproducibility improved drastically, showing a standard deviation below 1 %. These results suggest that increasing the ball size (and therefore the amount of kinetic energy) not only has a positive impact on the rate of deracemization but also on the reproducibility. Using the 12 mm ball, MCDR achieves similar e.e. as the solvent-based approach while reducing the reaction time by 96 % and the amount of solvent by an astonishing 98 % (**Scheme 1**).

Isoindolinones

The next substance class we targeted were isoindolinones (**Scheme 2**, **Erreur ! Source du renvoi introuvable.**). These compounds exhibit strong biological activities, making them essential motifs in many drugs.[14] Compounds **Iso-1**, **-2** and **-3** crystallize as stable conglomerates and their classical deracemization via VR is carried out in toluene with 0.3 eq. of 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) over a period of 3-7 days.[14]

We initially milled 200 mg of **Iso-1** (e.e. = 20 %), 0.1 eq. of DBU and 100 µL of toluene in a 10 mL ZrO_2 milling vessel with one or two ZrO_2 milling balls (10 mm) for 90 minutes at a milling frequency of 30 Hz (**Erreur ! Source du renvoi introuvable.**, entry 1). Surprisingly, a racemic mixture was obtained. This can be explained by the high liquid-to-solid ratio (DBU is a liquid) in combination with low vessel loading. Indeed, sticking of the reaction mixture to the vessel walls was observed, a phenomenon well-known in mechanochemical reactions which hinders mixing and thus the transfer of mechanical energy. As racemization occurs in the MP, this can indeed explain the observed racemization and lack of deracemization. We added NaCl as an inert bulk material to improve the rheology of our system. This resulted in deracemization, observing an e.e. of 58 % (**Erreur ! Source du renvoi introuvable.**, entry 2). As expected, removing DBU did not lead to deracemization (**Table 1**, entry 3). Interestingly, for deracemization some amount of toluene is required, as its removal led again to racemization (**Table 1**, entry 4). Changing the milling material to PTFE leads to similar results as with ZrO_2 (**Erreur ! Source du renvoi introuvable.**, entry 5). PTFE was used for further investigations due to its non-adhesive properties which help to avoid sticking. We then optimized the amounts of added liquid, NaCl, DBU as well as the number of milling balls. We observed a maximum in the e.e. using 140 to 150 µL of toluene (**Erreur ! Source du renvoi introuvable.**, entries 5-7). Using lower or higher quantities, deracemization deteriorates. Such “sweet spots” are known in LAG mechanochemistry.[53] The role of LAG is rather complex, as it impacts the amount of MP, the racemization reaction, as well as the overall powder mobility (**Erreur ! Source du renvoi introuvable.**, entries 5-8). The amount of NaCl was found to be optimal at 6.3 g. This amount yields the ideal ratio between liquid and solid phase allowing optimal racemization as well as mixing of the reaction mixture (**Erreur ! Source du renvoi introuvable.**, entries 9-11). The number of milling balls is also a crucial parameter affecting mixing. Three balls were found to give the best tradeoff between reactive and inhibitory collisions between



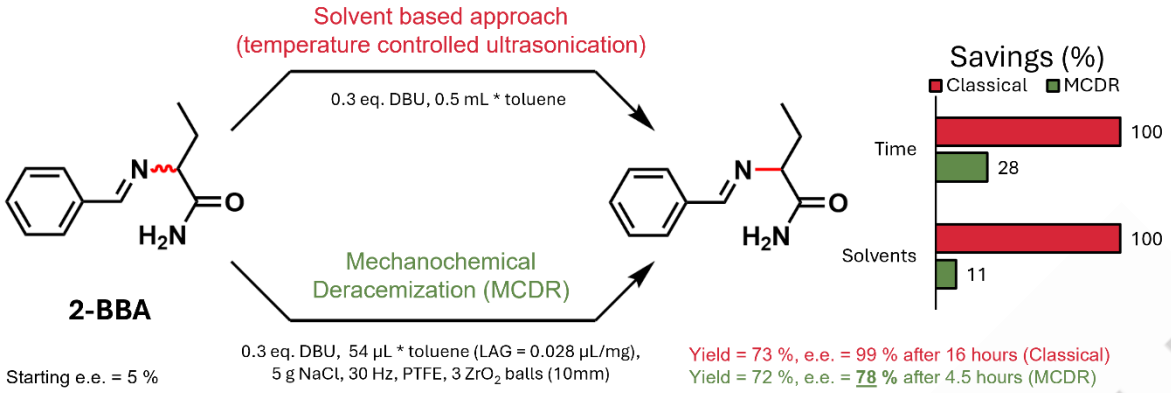
Scheme 2. Deracemization of isoindolinones via the solvent-based approach (red) and MCDR (green) as well as a comparison of the savings for **Iso-1**. * The amount of solvent is per 100 mg of starting material. + See supporting information regarding the method of yield determination. The e.e. for the classical approach is taken from literature.

balls and reaction mixture (**Erreur ! Source du renvoi introuvable.**, entries 12-14).[22] Lastly, we increased the amount of DBU to 0.3 eq., the same amount as the solvent-based VR process (**Erreur ! Source du renvoi introuvable.**, entry 15). The final e.e. decreased from 80 % to 60 %, once again likely due to too high proportion of the MP. Experiments 11 and 13 show the sensitivity to the reactor set-up, as the type of mixer mill (MM400 (Retsch) or IST400 (InSolido)) can have a strong influence on MCDR, once again highlighting how small process changes can have a large impact on the outcome of mechanochemical reactions.

Finally, the optimized conditions were tested on a racemic mixture (0 % e.e.) at varying reaction times (**Erreur ! Source du renvoi introuvable.**, entries 16-18). After 16h we observed a final e.e. of 90 % (96 % yield). A similar e.e. (92 %) is obtained after milling for 24 h in the IST400. This can be pushed to an e.e. of 98 % (97 % yield) after 87 h of milling. In comparison, classical VR yields an e.e. of 94 % after three days.

Table 1. MCDR optimization of Iso-1. An MM400 (Retsch) or an IST400 (InSolido)[a] ball mill was used at a frequency of 30 Hz. To transfer from the smaller ZrO_2 (10 mL) to the larger PTFE (14 mL) vessels the number of balls, the amount of NaCl, toluene and starting material were multiplied by 1.4 (compare entries 2 and 5). 200 mg of substrate for reactions in ZrO_2 vessels; 280 mg of substrate for reactions in PTFE vessels. The e.e. is slightly higher with 140 µL of toluene compared to 150 µL. This is likely due to different batches of starting material used (see SI). The following sets of experiments were performed using the same starting material (2 and 5; 1, 3 and 4; 6 to 8; 9 to 11; 12 to 15). Starting from a racemic mixture the final e.e. can be enriched in either enantiomer.[b] If a yield was determined, this is given in parentheses. Optimized conditions are highlighted.

Nr.	Milling Material	# of ZrO_2 balls (10mm)	m_{NaCl} [g]	$V_{Toluene}$ [µL]	Base [eq.]	Time [h]	Initial e.e.	Final e.e.
1	ZrO_2	1 or 2	-	100	0.1	1.5	20%	0%
2	ZrO_2	2	3.8	100	0.1	1.5	20%	58%
3	ZrO_2	2	3.8	100	-	1.5	20%	20%
4	ZrO_2	2	3.8	-	0.1	1.5	20%	0%
5	PTFE	3	5.3	140	0.1	1.5	20%	50%
6	PTFE	3	5.3	100	0.1	1.5	20%	36%
7	PTFE	3	5.3	150	0.1	1.5	20%	42%
8	PTFE	3	5.3	200	0.1	1.5	20%	30%
9[a]	PTFE	3	3.8	150	0.1	1.5	20%	22%
10[a]	PTFE	3	5.0	150	0.1	1.5	20%	24%
11[a]	PTFE	3	6.3	150	0.1	1.5	20%	36%
12	PTFE	2	6.3	150	0.1	1.5	20%	64%
13	PTFE	3	6.3	150	0.1	1.5	20%	80%
14	PTFE	4	6.3	150	0.1	1.5	20%	70%
15	PTFE	3	6.3	150	0.3	1.5	20%	60%
16	PTFE	3	6.3	150	0.1	16	0%	90%(1) (96%)



Scheme 3. Deracemization of **2-BBA** via the solvent-based approach (red) and MCDR (green) as well as a comparison of the savings. * The amount of solvent is per 100 mg of starting material. The e.e. and the yield for the classical approach are taken from literature.

17[a]	PTFE	3	6.3	150	0.1	24	0%	92%(2)
18[a]	PTFE	3	6.3	150	0.1	87	0%	98%(2) (97%)

[a] IST400 ball mill was used. [b] Starting from a racemic mixture the final e.e. can be enriched in either enantiomer. This is indicated by the exponent (1) or (2).

Reproducing the classical solvent-based VR using the same conditions reported in the literature[14] gave a yield of only 54 % (**Scheme 2**). This significant difference in yield can be explained by the solubility of the compound. In classical VR, the dissolved (racemic) powder is discarded upon filtration, and only the solid powder is recovered. In our approach, all the material is recovered. Overall, the optimal conditions for this system are 280 mg of **Iso-1**, 0.1 eq. DBU, 6.3 g NaCl and 150 µL toluene in a 14 mL PTFE milling vessel with three ZrO_2 milling balls (10 mm) in an MM400 ball mill leading to a yield of 96 % with an e.e. of 90 % after 16 h or a yield of 97 % with an e.e. of 98 % after 87 h of milling at 30 Hz (**Erreur ! Source du renvoi introuvable.**, entries 16 and 18).

We investigated the robustness of our methodology by deracemizing **Iso-2** and **Iso-3** under the same conditions as entries 17 and 18, achieving a final e.e. of 92 % for **Iso-2** after three days and of 94 % for **Iso-3** after two days.

These results demonstrate that MCDR has several advantages for isoindolinones over classical VR. Most Importantly, while achieving a similar e.e., the yield is significantly higher since no racemic product remains in solution. Furthermore, our method saves 78 % time and 98 % solvents while reducing the amount of base by 66 %.

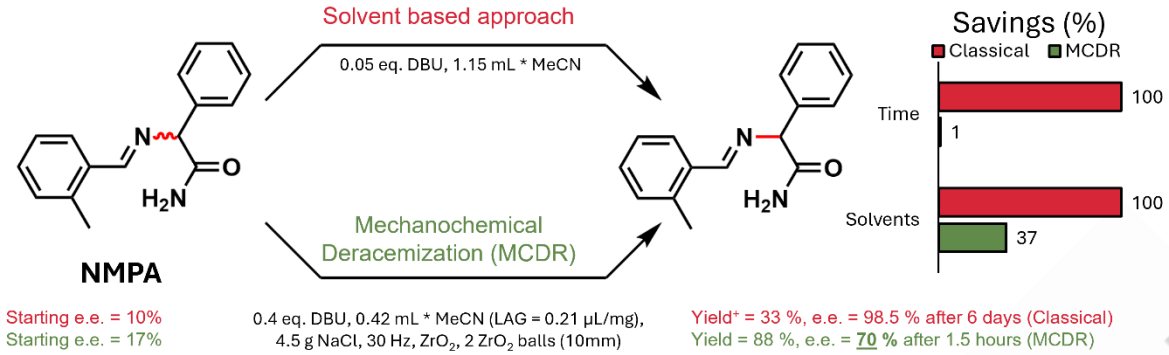
Imines

We then turned our attention to the deracemization of imines. Imines are a key functionality for the generation of enantiomerically pure building blocks. Recently, conglomerate 2-(benzylideneamino)butanamide (**2-BBA**) was deracemized via VR which allowed access to enantiomerically pure (S)-2-aminobutyramide, a key intermediate in the generation of levetiracetam and brivaracetam. VR of this compound is executed, in an ultrasonic bath, with 0.3 eq. of DBU in toluene overnight and starts from a mixture with 5 % e.e.[15] We chose this reaction to test whether imines can also be deracemized more sustainably and efficiently using our methodology.

Using the same parameters as for the isoindolinone system, no deracemization occurred (**Erreur ! Source du renvoi introuvable.**, entries 1-2). Increasing the amount of DBU we were able to deracemize, pushing the e.e. to 50 % (**Erreur ! Source du renvoi introuvable.**, entry 6). Next, we evaluated the influence of LAG. First, we used ZrO_2 vessels and obtained the highest e.e. with 50 µL of toluene (**Erreur ! Source du renvoi introuvable.**, entries 3-7). Remarkably, deracemization also occurred without the addition of a liquid additive leading to an e.e. of 38 %. Since the imine is soluble in DBU (see SI), we assume that the liquid base also acts as the LAG agent.

Table 2. Parameter optimization for the MCDR of 2-BBA. Reactions were carried out in an MM400 (Retsch) ball mill at a milling frequency of 30 Hz. The number of balls as well as the amount of NaCl, toluene and starting material come from the optimization of Iso-1 (see Table 1), depending on the material used (ZrO_2 or PTFE). 200 mg of substrate for reactions in ZrO_2 vessels; 280 mg of substrate for reactions in PTFE vessels. If a yield was determined, this is given in parentheses. Optimized conditions are highlighted.

Nr.	Milling Material	# of ZrO_2 balls (10mm)	m_{NaCl} [g]	$V_{Toluene}$ [µL]	Base [eq.]	Time [h]	Initial e.e.	Final e.e.
1	ZrO_2	2	3.8	100	0.1	1.5	20%	20%
2	PTFE	3	6.3	150	0.1	1.5	20%	20%
3	ZrO_2	2	3.8	0	0.3	1.5	20%	38%
4	ZrO_2	2	3.8	25	0.3	1.5	20%	30 %
5	ZrO_2	2	3.8	50	0.3	1.5	20%	60 %
6	ZrO_2	2	3.8	100	0.3	1.5	20%	50 %
7	ZrO_2	2	3.8	150	0.3	1.5	20%	42 %
8	PTFE	3	6.3	25	0.3	1.5	20%	50 %



Scheme 4. Deracemization of NMPA via the solvent-based approach (red) and MCDR (green) as well as a comparison of the savings. * The amount of solvent is per 100 mg of starting material + See supporting information regarding the method of yield determination. The e.e. for the classical approach is taken from literature.

9	PTFE	3	6.3	50	0.3	1.5	20%	50 %
10	PTFE	3	6.3	100	0.3	1.5	20%	58 %
11	PTFE	3	6.3	150	0.3	1.5	20%	56 %
12	PTFE	3	6.3	200	0.3	1.5	20%	46%
13	PTFE	3	6.3	150	0.3	4.5	5%	78% (72 %)
14	PTFE	3	6.3	150	0.3	9	5%	82%

We performed a similar investigation with PTFE and found the reaction mixture to be less sensitive to the variation of LAG compared to ZrO_2 (**Erreur ! Source du renvoi introuvable.**, entries 8-12).

In solvent-based VR, temperature-controlled ultrasonication is employed to enrich a mixture overnight starting from an e.e. of 5 % to a final e.e. of 99 % (73 % yield). Using the same starting enrichment, we obtained a final e.e. of 78 % (72 % yield) after 4.5 hours, while longer reaction times not having a significant impact (**Erreur ! Source du renvoi introuvable.**, entries 13-14). The lower e.e. in MCDR can likely be attributed to the amount of MP. As racemization occurs in this phase, the racemate present contributes to an overall lowering of the e.e., limiting it to 80 % (20 % of MP) under the current conditions. As demonstrated with the isoindolinones, MCDR can achieve even higher enrichments given an optimal parameter set. We believe that also for this system the e.e. can be further increased by a more elaborate optimization. However, this is beyond the scope of this study.

A second compound bearing the imine moiety is N-(2-methylbenzylidene)-phenylglycine amide (**NMPA**). **NMPA** is a derivative of the amino acid phenyl glycine and was deracemized in suspension via VR, using DBU and MeOH or MeCN as solvent.[55] Starting from an initial e.e. of 10 % **NMPA** was deracemized in six days (**Scheme 4**).

Using the conditions from **2-BBA**, we started with 240 mg of **NMPA** (e.e. = 17 %), 4.4 g NaCl and 0.3 eq. DBU in a 10 mL ZrO_2 vessel with two ZrO_2 milling balls (10 mm) for a milling time of 90 minutes (**Erreur ! Source du renvoi introuvable.**, entries 1-2). As for **Iso-1**, the absence of a liquid additive led to racemization. Adding 2.4 ml of MeCN as LAG-agent allowed deracemization yielding a final e.e. of 38 %. Addition of MeOH did not allow deracemization. This is surprising, as MeOH is used as a solvent in classical VR (**Erreur ! Source du renvoi introuvable.**, entry 3).[55] Reducing the amount of MeCN to 1 ml led to an e.e. of 69 % (**Erreur ! Source du renvoi introuvable.**, entry 4). Increasing the amount of DBU (**Erreur ! Source du renvoi introuvable.**, entries 5-7) or the amount of bulk material (**Erreur ! Source du renvoi introuvable.**, entries 10-11) was found to be detrimental to deracemization.

Interestingly, prolonging the milling time to 8 h resulted in a lower e.e. (**Table 3**, entries 5 and 10). This once more seems coherent with an increased amorphization of the reaction mixture upon longer reaction times.

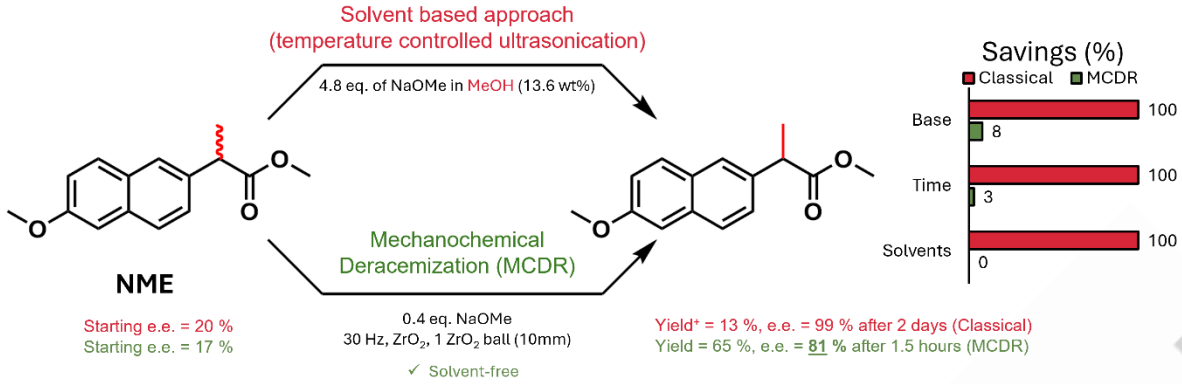
Results for **2-BBA** and **NMPA** show that deracemization of imines is possible by MCDR. Although both systems still require further optimization, we are already able to achieve enrichments of 78 % and 70 % respectively. MCDR therefore enables deracemization for these systems while reducing the reaction time by at least 72 % and the solvent usage by 63 % to 89 %.

Esters

Next, we studied naproxen methyl ester (**NME**). The parent compound is commonly used as a non-steroidal anti-inflammatory drug (NSAID) and is on the list of essential drugs in 44 countries.[56] It has been the subject of several deracemization studies as the respective methyl and ethyl esters crystalize as stable conglomerates.[16,57–59] Noorduin et al. were able to deracemize **NME** (e.e. of 1.5 %) over five days using VR in a MeOH slurry with NaOMe (~5 eq.). Starting from 20 % e.e. deracemization was already achieved in 2 days (**Scheme 5**).[16]

Table 3. Parameter optimization for the mechanochemical deracemization of NMPA. The reactions were carried out in an MM400 (Retsch) ball mill using a ZrO_2 milling vessel (10 ml) at a milling frequency of 30 Hz. 240 mg of NMPA. If a yield was determined, this is given in parentheses. Optimized conditions are highlighted.

Nr.	Milling Material	# of ZrO_2 balls (10mm)	m_{NaCl} [g]	V_{MeCN} [µL]	Base [eq.]	Time [h]	Initial e.e.	Final e.e.
1	ZrO_2	2	4.4	-	0.3	1.5	17 %	3 %
2	ZrO_2	2	4.4	2.4	0.3	1.5	17 %	38 %



Scheme 5. Deracemization of NME via the solvent based approach (red) and MCDR (green) as well as a comparison of the savings. + See supporting information regarding the method of yield determination. The e.e. for the classical approach is taken from literature.

3	ZrO_2	2	4.4	2.4 (MeOH)	0.3	1.5	17 %	18 %
4	ZrO_2	2	4.3	1.0	0.3	1.5	19 %	69 %
5	ZrO_2	2	4.5	1.0	0.4	1.5	17 %	70 % (88 %)
6	ZrO_2	2	4.5	0.9	0.4	1.5	17 %	52 %
7	ZrO_2	2	4.4	1.0	0.6	1.5	17 %	41%
8	ZrO_2	2	4.0	1.0	0.4	1.5	18 %	38 %
9	ZrO_2	2	5.5	1.0	0.4	1.5	19 %	53 %
10	ZrO_2	2	4.5	1.0	0.4	8	17 %	40 %

Based on our previous examples, we initially considered DBU as base. We used 240 mg of **NME**, 0.2 eq. of DBU in a 10 mL ZrO_2 milling vessel with one milling ball (10 mm) of the same material and an initial e.e. of 17 %. Under these conditions, no deracemization occurred (**Erreur ! Source du renvoi introuvable.**, entry 1). In literature, a solution of NaOMe in MeOH serves as base.[16] Using this reagent an e.e. of 28 % was obtained (**Erreur ! Source du renvoi introuvable.**, entry 2). To elucidate the influence of the amount of solvent, we performed the experiment using solid NaOMe adding 50 µL and 20 µL MeOH, respectively (**Erreur ! Source du renvoi introuvable.**, entries 8-9). Increasing the amount of solvent is detrimental for deracemization. Interestingly, the use of solid NaOMe led to even higher enrichments, with 0.4 eq. of NaOMe giving an e.e. of 81 % (**Erreur ! Source du renvoi introuvable.**, entries 3-6). Increasing the milling time further did not increase the level of deracemization (**Erreur ! Source du renvoi introuvable.**, entry 12). Using PTFE vessels, deracemization is less effective (**Erreur ! Source du renvoi introuvable.**, entry 7). The use of LAG or a bulk material led to deterioration of the reaction performance. While toluene yielded a liquid paste, NaCl might have diluted the powder too strongly. It is possible that solid NaOMe in our example not only serves as a base, but also acts as bulk material.

As expected, reducing the initial e.e. leads to a lower final e.e. under the same conditions due to the autocatalytic nature of the process (**Erreur ! Source du renvoi introuvable.**, entries 5, 13-14). Starting from a racemic (e.e. = 0 %) mixture we were able to successfully break symmetry and achieve deracemization after a reaction time of two days (**Erreur ! Source du renvoi introuvable.**, entry 15).

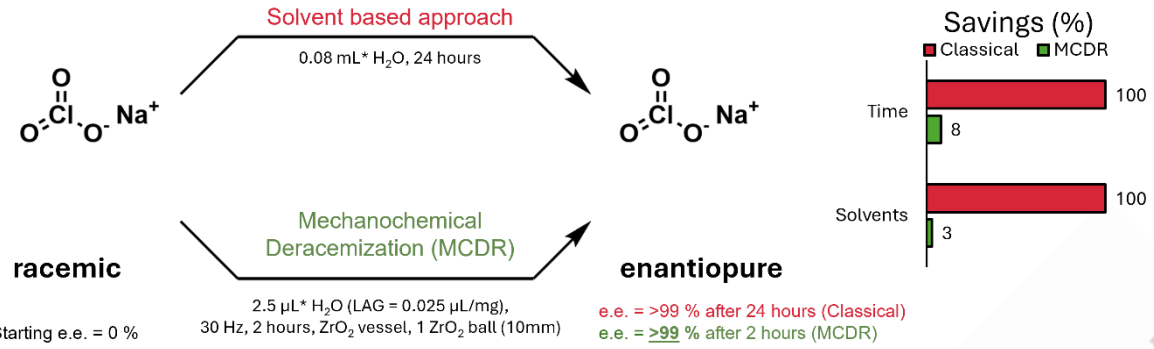
Compared to the literature, we reach a yield of 65 % with an e.e. of 78 % in only 1.5 hours using 0.4 eq. of base (**Scheme 5**). Whereas the literature procedure, albeit leading to a 99 %e.e., only shows a yield of 13 %. Thus, we can obtain the desired enantioenriched product in far higher yield while simultaneously reducing the amount of base by 92 % and the required reaction time by as much as 97 %. Most notably, all of this is achieved without the addition of any solvent thereby dramatically reducing the amount of generated waste during deracemization.

Supramolecular Chirality

After exploring five different organic examples, we were intrigued to apply our method to an inorganic compound. The first example of deracemization via VR was performed on $NaClO_3$ by Viedma in 2005.[11] Even though $NaClO_3$ possesses no molecular chirality, it is optical active as it crystallizes in the $P2_13$ space group, generating a pair of enantiomorphs. This optical activity is a property of the solid-state which is lost in solution.

Table 4. Parameter optimization for the mechanochemical deracemization of NME. The reactions were carried out in an MM400 (Retsch) ball mill using a ZrO_2 milling vessel (10 ml) or PTFE milling vessel (14 ml), with a ZrO_2 ball (1x10mm) at a milling frequency of 30 Hz. 240 mg of Naproxen methyl ester. If a yield was determined, this is given in parentheses. Optimized conditions are highlighted.

Nr.	Milling Material	Additive	Base [eq.]	Time [h]	Initial e.e.	Final e.e.
1	ZrO_2		DBU – 0.2	1.5	17 %	17 %
2	ZrO_2		NaOMe (30 wt% in MeOH) – 0.2	1.5	16 %	28 %
3	ZrO_2		NaOMe – 0.2	1.5	18 %	75 %
4	ZrO_2		NaOMe – 0.4	1.5	18%	81%



Scheme 6. Deracemization of $NaClO_3$ via the solvent-based approach (red) and MCDR (green) as well as a comparison of the savings. * The amount of solvent is per 100 mg of starting material. The e.e. for the classical approach is taken from literature.

5	ZrO_2		NaOMe – 0.7	1.5	16 %	78% (65%)
6	ZrO_2		NaOMe – 1.8	1.5	16 %	22%
7	PTFE		NaOMe – 0.7	1.5	16 %	32%
8	ZrO_2	50 µL MeOH	NaOMe – 0.7	1.5	18 %	24%
9	ZrO_2	20 µL MeOH	NaOMe – 0.7	1.5	16 %	57%
10	ZrO_2	100 µL toluene	NaOMe – 0.7	1.5	17%	19 %
11	ZrO_2	5 g NaCl	NaOMe – 0.7	1.5	19%	29%
12	ZrO_2		NaOMe – 0.7	2	17%	77%
13	ZrO_2		NaOMe – 0.7	1.5	9 %	56%
14	ZrO_2		NaOMe – 0.7	1.5	2 %	11%
15	ZrO_2		NaOMe – 0.7	48	0%	68%

Viedma demonstrated that, when starting from a racemic mixture, total enantiopurification of the solid is reached after 24 h of stirring a supersaturated water solution.

MCDR was performed by neat milling as well as by LAG with water. After two hours of neat milling, no change in enantiopurity was observed. In contrast, LAG led to complete enantiopurity (see SI). It is likely that neat milling inhibits enantioconversion due to the absence of an MP. On the other hand, LAG enables dissolution and recrystallization. Thus, we not only show that MCDR can be applied to inorganic compounds but also that we can achieve full enantiopurity in 92 % less time and 97 % less solvents compared to the conventional approach. Furthermore, we prove that MCDR is not only applicable to molecular chirality, but also to supramolecular chirality (**Scheme 6**).

Conclusion

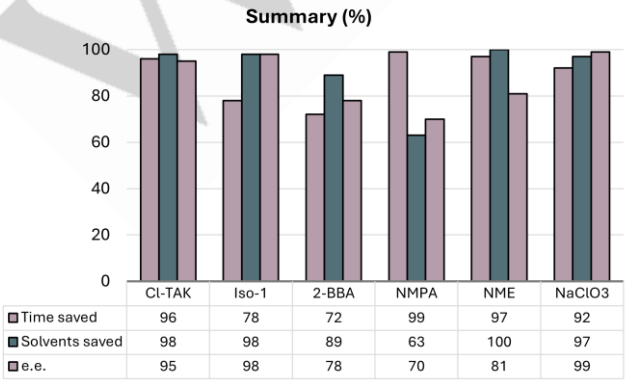


Figure 2: Comparison of saved time and solvents as well as the e.e. for the systems investigated.

In summary, we here showcase a general and more sustainable approach to deracemization using mechanochemistry. By transferring the deracemization of six archetypal examples from the classical solvent-based VR to a mechanochemical environment, we identified critical aspects of this new technique. We show that the size and number of milling balls, the milling material, the addition of a bulk material and LAG strongly influence MCDR. Furthermore, we show that these parameters affect each system to varying degrees, necessitating a deep understanding of the different systems. By precisely controlling these parameters, we were not only able to deracemize all compounds, but also to reduce the reaction time and solvent consumption by orders of magnitude. In all examples, the amount of solvent was reduced by 63-100 % compared to conventional VR, while the reaction time was reduced by 72-99 % (see **Figure 2**). Using MCDR for the deracemization of key functionalities such as ketones, isoindolinones, imines, esters and an inorganic example, we were able to demonstrate the generalizability of our approach. We are convinced the presented work lays the foundation for the establishment of MCDR as a new platform technology for the synthesis of enantioenriched compounds and will stimulate further studies.

Supporting Information

The authors have cited additional references within the Supporting Information.[60–63]

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