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# Scalable and Sustainable Mechanochemical Deracemisation by Resonant Acoustic Mixing

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Resonant Acoustic Mixing (RAM) is introduced as a solvent-minimised, scalable approach to deracemisation, achieving enantiomeric excesses of up to 91%. The influence of processing parameters such as amount and nature of liquid additive on the deracemisation outcome were systematically investigated. RAM furthermore shows 5-fold upscaling ability, facilitating near-gram-scale deracemisation with minimal solvent use ($\eta$ = 0.02) and reduced reaction times without the need for milling media. Notably, a racemic mixture was deracemised to 73% *ee* in 1.5 hours, showing enhanced efficiency compared to ball-milling and solvent-based deracemisation approaches. Mechanochemical deracemisation by RAM is a significant advancement, offering a faster, waste-minimising and scalable method, enabling a pathway to large-scale deracemisation processes while reducing waste.

## Introduction

The majority of syntheses of enantiopure compounds involves at least one chiral resolution step.[1] This is not only expensive, but also unsustainable, as 50% of the compound is discarded as unwanted enantiomer while large quantities of solvent waste are produced. In conjunction with the solvents used during synthesis, up to 90% of pharmaceutical production waste can be attributed to solvent use.[2] This issue is of particular concern in the context of green chemistry and the necessity of reducing the environmental footprint of industries.[3]

A more sustainable strategy is the conversion of the distomer, the enantiomer with the undesired activity, into the eutomer, the enantiomer with the desired activity, not only avoiding the solvent-consuming resolution process, but also inherently implying recovery of the otherwise lost distomer. Deracemisation processes, such as Viedma Ripening (VR), offer a promising route to this goal.[4] VR enables the conversion of racemic mixtures into enantiopure compounds in suspension through a combination of racemisation, Ostwald ripening, enantioselective incorporation, and mechanical attrition.[5] However, VR processes often require several days to complete, utilise substantial amounts of solvents, and suffer from low yields.[6,7]

As noted above, solvents constitute a major source of waste in chemistry. This issue persists across the entire field, ranging from small-scale laboratory experiments to large-scale industrial operations. Moreover, solvents are often environmental pollutants and pose a risk to human health. The reduction or elimination of solvents is a cornerstone of the 12 Principles of Green Chemistry.[8,9] In this context, mechanochemistry has gained interest as a solvent-free alternative to conventional chemistry.[10–13]

Mechanochemical reactions are the direct result of the absorption of mechanical energy, for example in ball milling devices in which the reactants are subjected to impacts from milling balls.[14–16] Using mechanical force to drive reactions has facilitated several solvent-free or solvent-minimised processes in various fields, including organic and inorganic synthesis, materials science, supramolecular synthesis and pharmaceuticals.[17–24] The employment of mechanochemistry enables unprecedented reactivities or selectivities. Recent important developments include direct mechanocatalysis or the direct activation of zero-valent metals.[25–39] Observing the wide applicability of mechanochemistry, we herein explored its potential in the field of deracemisation.

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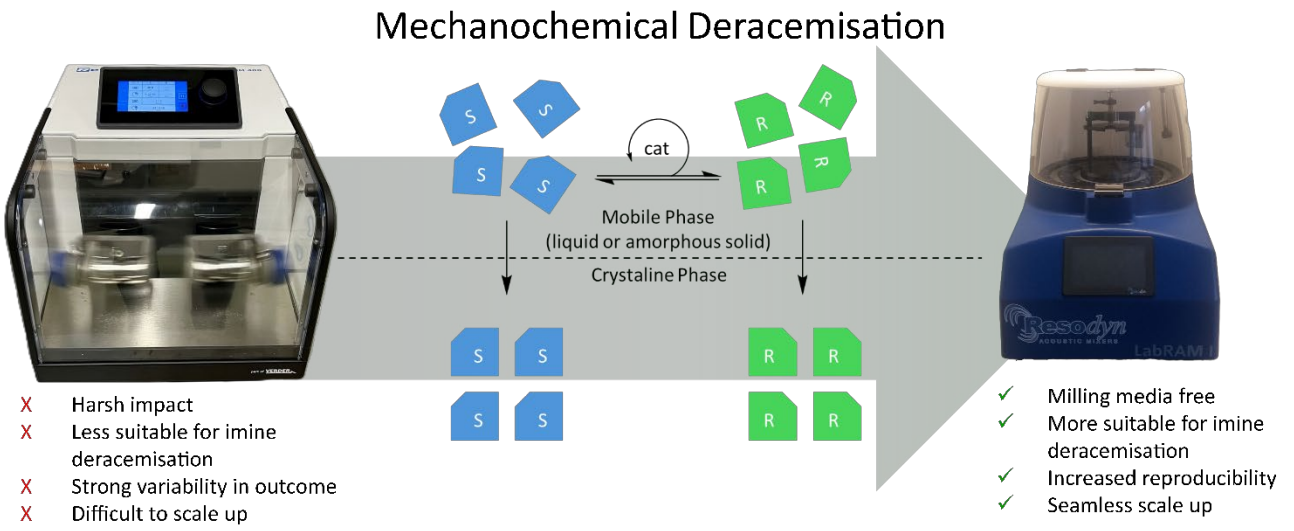



**Figure 1:** Schematic view on mechanochemical deracemisation by ball milling (MCDR-BM) and by resonant acoustic mixing (MCDR-RAM) together with advantages of RAM over ball-milling.

Some of us have recently demonstrated the viability of mechanochemistry for deracemisation processes.[40,41] We showed that mechanochemical deracemisation (MCDR) by ball milling not only accelerates reaction rates and enhances yields, but it also dramatically reduces the amount of solvents used compared to conventional suspension-based approaches. An essential element in MCDR is the mobile phase (MP), which can form through partial dissolution in the liquid additives, sublimation, amorphisation or mechanical events during milling.[18,42] Racemisation nucleation and crystal growth occur in this MP.[5] Therefore, the quantity and nature of the mobile phase (i.e., its polarity, acidity etc.) exerts a significant influence on the deracemisation process.

Unlike ball milling, Resonant Acoustic Mixing (RAM) is a milling media-free technique that employs high-energy vibrations to generate acoustic waves. The lack of milling media generates a milder reaction environment (**Figure 1**). The acoustic waves induce vortices and three-dimensional convective flow patterns within the reaction vessel. These flow patterns create dynamic mixing zones, combining acoustic energy with particle collisions to drive chemical transformations (**Figure 2**).[43,44] RAM has already demonstrated its versatility and efficiency across a range of applications, including multigram-scale organic synthesis, organometallic catalysis, photochemistry, and multicomponent crystal formation.[45–54]

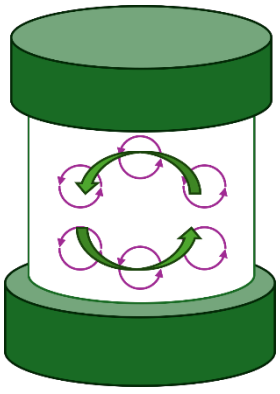


**Figure 2:** Example of the potential mixing zones generated by the acoustic waves in a jar during RAM. Note the overall circular flow of particles which requires enough volume to take place.

Key advantages of RAM versus ball milling include faster homogeneous mixing, reduced particle damage due to the elimination of shearing forces from milling media, the use of vessels that are too fragile for BM, such as glass vials and the ability to easily scale up.[43,44,51–58] The mild RAM conditions could provide an environment more conducive to crystal growth, thereby impacting the deracemisation process.[5] Recently, some of us, studied compared to use of RAM to ball-milling for the formation of a racemic compound starting from a physical mixture of enantiomers, identifying differences in outcome for both techniques. Considering all of this, we decided to investigate the potential of RAM for mechanochemical deracemisation.

To do so, we decided to focus on N-(2-methylbenzylidene)-phenylglycine amide (compound **1**) and 2-(benzylideneamino)butanamide (compound **2**) (**Figure 3**), as these were found more challenging in ball-mill based deracemisation.[40] With these systems, we included 2-[(2-methyl)-benzylideneamino]butanamide (compound **3**). We focused on these three compounds, as they form conglomerates, a mechanical mixture of crystals, each of which

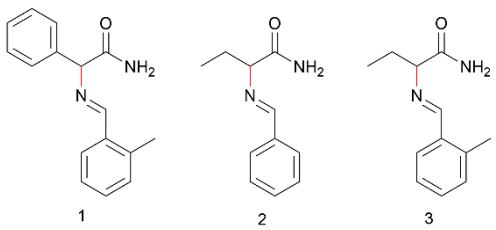



**Figure 3:** Structures of compounds deracemised in this work: N-(2-methylbenzylidene)-phenylglycine amide (**1**), 2-(benzylideneamino)-butanamide (**2**) and, 2-((2-methylbenzylidene)amino)butanamide (**3**).


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contains only one enantiomer. This property is a requirement for deracemisation by abrasive grinding and only occurs for about 10% of compounds.[59] For this reason, each synthesized compound was analysed by X-ray powder diffraction (XRPD) to confirm the conglomerate is obtained (**Figures S8-S10**).

## Results and Discussion

### Solvent screening for MCDR-BM

In our previous work, DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) was used as a racemisation agent for the imines (**Figure 4**). DBU deprotonates these substrates, generating an achiral intermediate and, thus, enabling interconversion between the two enantiomers. The best deracemisation conditions of our previous work in the ball mill for compounds **1** and **2**, led to a final *ee* of 70% using MeCN as liquid-assisted grinding (LAG) additive ($\eta$ = 0.21 µL/mg) and 0.66 equiv. of DBU; and 56% using toluene as LAG-additive ($\eta$ = 0.02 µL/mg) and 0.3 equiv. of DBU after 90 min. of milling starting with an *ee* of 20%. Since these conditions varied for both compounds, we extended the BM study here, varying amount and nature of LAG-additive, as well as milling material, before moving to RAM experiments to enable a coherent comparison.

Toluene, MeCN, *n*-hexane, MeOH and DCM were used as LAG-additives, covering a broad range of solvent properties: polar/apolar, protic/aprotic, and chlorinated/non-chlorinated. Based on our previous work, we tested two $\eta$-values (0.02 and 0.21 µL/mg).[40] Here, $\eta$ represents an empirical parameter that describes the ratio between volume of added liquid (in µL) and the weight of all solid reactants (in mg).[60] The reactions were carried out starting from 20% *ee* using both $ZrO_2$ (10 mL) and PTFE (14 mL) jars.

For all three systems, toluene and MeCN were found to be the most effective LAG-additives for deracemisation, particularly in the PTFE jar (**Figure 5**). The other LAG-additives showed markedly lower or no deracemisation efficiency (Tables

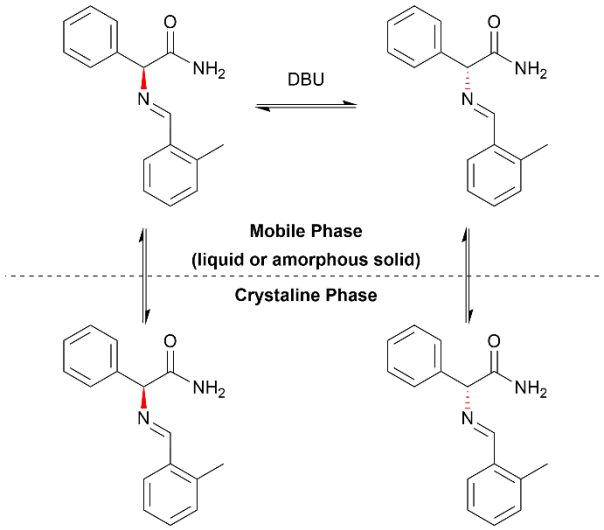



**Figure 4:** A general example of deracemisation mechanism using compound **1**. Through random fluctuations the initial symmetry is broken. Via an autocatalytic process this imbalance is then amplified to result in enantioenrichment.[5,6]

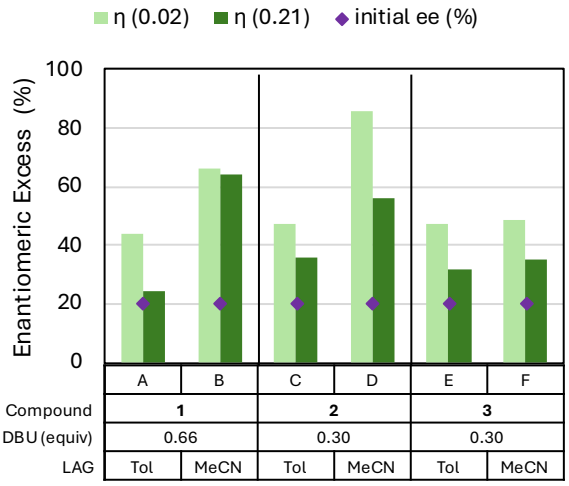



**Figure 5:** MCDR-BM *ee* obtained for compounds **1**, **2**, and **3** starting from an enantioenriched mixture (20% *ee*, indicated by purple diamonds) using toluene or MeCN as LAG-additives. The table directly below the graph lists, from top to bottom: compound, DBU equivalents, and LAG-additive. PTFE jars (14 mL) were charged with imine (280 mg), NaCl (6.3 g) and $ZrO_2$ balls (3x10 mm) and milled, in a vibrational ball-milling device, at 30 Hz for 1.5 h. Each experiment was performed once. (detailed results in tables S1–S3).

S1-S3). With toluene (**Figure 5**: exp. A, C, E), all compounds exhibited increased deracemisation efficiency at low (final *ee* between 44% and 48%) compared to high $\eta$ (final *ee* between 24% and 36%). A similar observation was made using MeCN (**Figure 5**: exp. B, D, F), with the lower $\eta$ experiments showing increased deracemisation, which is particularly noticeable for compound **2,** showing a final *ee* of 86% at low $\eta$, compared to 56% at high $\eta$ (**Figure 5**: exp. D). Overall, MeCN appeared to improve the deracemisation outcome over the use of toluene.

Subsequently, the process was performed starting from racemic mixtures instead of an initial 20% *ee*, using MeCN at low $\eta$-values (**Table 1**). For compounds **1** and **2**, a final *ee* of 84% and 85% was achieved, respectively, while for compound **3** a final 74% *ee* was obtained, with compounds **2** and **3** requiring a longer reaction time (24 h and 46 h, respectively). For compound **1**, the process takes a mere 17 h. Irrespective of the compound, MCDR-BM is substantially faster compared to suspension-based deracemisation processes, which typically take several days.[61,62] We then set out to investigate the potential of RAM for mechanochemical deracemisation. To allow comparison with the ball mill results, we used MeCN and toluene as liquid-assisted-RAM additives (LA-RAM-additives[63]) with $\eta$-values of 0.02 and 0.21 µL/mg (**Figure 6**).

**Table 1:** *Ee* obtained for compounds **1**, **2**, and **3** starting from a racemic mixture (*ee* = 0%) using MeCN as LAG-additive in MCDR-BM. PTFE jars (14 mL) were charged with imine

(280 mg), NaCl (6.3 g), LAG-additive (150 µL; $\eta$ = 0.02 µL/mg) and $ZrO_2$ balls (3x10 mm), and milled in a vibrational ball-milling device at 30 Hz.

| Compound | DBU [equiv.] | Time [h] | final *ee* |
|---|---|---|---|
| **1** | 0.66 | 17 | 84% |
| **2** | 0.30 | 24 | 85% |
| **3** | 0.30 | 46 | 74% |


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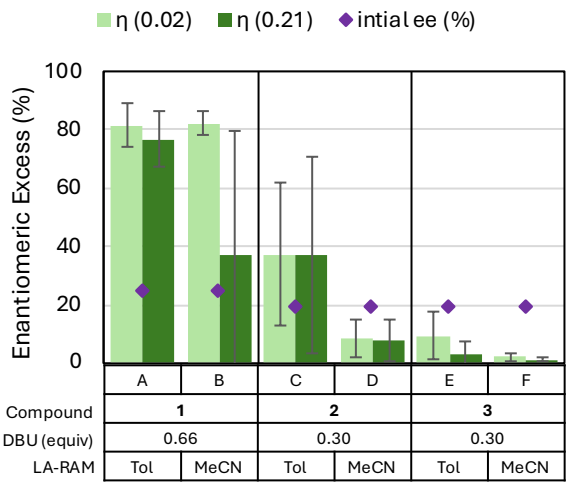



**Figure 6:** *Ee* obtained for compounds **1**, **2**, and **3** from an enantioenriched mixture (initial *ee* indicated by purple diamonds) using toluene or MeCN as LA-RAM-additives. The table directly below the graph lists, from top to bottom: compound, DBU equivalents, and LA-RAM-additive. Glass vials (5 mL) with plastic caps were charged with imine (140 mg) and NaCl (3.15 g). Reactions took place at 100 *g* for 1.5 h. Error bars represent the standard deviation from three independent experiments (detailed results in tables S6–S8).

**MCDR-RAM**

Initially, we used 5 mL glass vials, containing 140 mg of imine (20% *ee*), 3.15 g of NaCl as bulk material, DBU (0.66 equiv. for **1**, 0.30 for **2** and **3**), and the LA-RAM-additive (75 or 700 µL). With this reaction mixture, the vial was filled to approximately 50% of its capacity. Samples were subjected to an acceleration of 100 *g* for 1.5 h. Unexpectedly, for compounds **2** and **3**, this induced racemisation for six of the eight conditions (**Figure 6**: exp. D, E, F), contrasting with the ball milling processes (**Figure 5**, exp. D, E, F). However, for compound **1** deracemisation occurred successfully in all cases, with a final *ee* of 82% using an *η*-value of 0.02 µL/mg (**Figure 6**: exp. B). Mechanochemical deracemisation with RAM is, as the BM process, strongly parameter sensitive. As shown in **Figure 6**, increasing the amount of MeCN led to a less efficient deracemisation with a mere final *ee* of 37% *ee* (**Figure 6**: exp. B). To the best of our knowledge, these are the first examples of deracemisation using RAM technology. Extending the reaction time from 1.5 h to 3 h further improved the *ee* for compound **1** to 89-91% (see Table S6, using MeCN at an *η*-value of 0.02 µL/mg). Furthermore, this result is clearly different from the 66% *ee* obtained using MCDR-BM (**Figure 5**: exp. B), highlighting that MCDR-BM and MCDR-RAM can effectively lead to different outcomes when using seemingly identical conditions.

This is further highlighted by the toluene-based experiments. Whereas the use of toluene at low *η*-values in the ball-mill led to 50% *ee* irrespective of the compound used, a strong difference according to the nature of the compound was observed when using toluene as LA-RAM-agent. For compound **3**, racemisation occurred (**Figure 6**: exp. E); whereas for compounds **1** and **2**, deracemisation was achieved. Compound **2** showed moderate deracemisation at both *η*-values (final *ee* of about 37%) (**Figure 6**: exp. C), whereas compound **1** showed substantial deracemisation with a final *ee* of 82% (at low *η*) or 77% (at high *η*), clearly surpassing ball-milling deracemisation results for this compound, highlighting the potential of RAM-deracemisation (**Figure 6**: exp. A). As shown by the large error bars in **Figure 6**, variability can be significant. This is potentially due to the efficiency of the mixing process. In certain instances, a residue of powder was indeed found adhering to the interior surfaces of the vial. This possibly modified the mixing process, strongly impacting the process outcome.

To assess the importance of the LA-RAM-additive and the use of bulk material, control experiments were performed (**Table 2**). As observed in our previous work on BM, the absence of a liquid additive only allows limited deracemisation (40% and 32% *ee* for compounds **1** and **2,** respectively). This can be explained by the fact that the liquid agent impacts the nature and amount of the mobile phase, which is crucial to the process. Nevertheless, even without a liquid additive, deracemisation using RAM remains possible. The lack of bulk material resulted in racemisation using toluene as the LA-RAM-additive, whereas a slight level of deracemisation was still observed using MeCN. This can be explained by the rheology of the mixture. In the latter case, the imine remains a free-flowing powder, whereas the use of toluene in the absence of bulk material led to a sticky mixture hindering efficient mixing and thereby limiting the effective operation of the process.

**Table 2:** *Ee* obtained for compounds **1** and **2** from an enantioenriched mixture (*ee* = 20%) studying the impact of bulk material and LA-RAM-agent on MCDR-RAM. Glass vials (5 mL) with plastic caps were charged with imine (140 mg) and, depending on the experiment, NaCl (3.15 g) or LA-RAM-additive (75 µL), and mixed at 100 *g* for 1.5 h (detailed results in Tables S4–S5).

| Compound | Bulk material | LA-RAM-Agent | final *ee* |
|---|---|---|---|
| **1** | NaCl | - | 40% |
| **1** | - | Tol | 15% |
| **1** | - | MeCN | 31% |
| **2** | NaCl | - | 32% |
| **2** | - | Tol | 11% |
| **2** | - | MeCN | 49% |

After having successfully established RAM deracemisation of compounds **1** and **2** starting from an initial 20% *ee*, we attempted deracemisation starting from a racemic mixture (0% *ee*) (**Figure 7**). For compound **3**, using both LA-RAM-additives, a nearly racemic composition (≤10% *ee*) was observed, in agreement with the observations made in the experiments with enantioenriched mixtures (**Figure 7**: exp. G, H). Deracemisation was observed for compounds **1** and **2**, albeit at a lower level. For compound **1**, the use of MeCN gave a final *ee* of 27% at low *η* and of 40% at high *η* (**Figure 7**: exp. A-D). In contrast, compound **2** reached a final *ee* of 27% using toluene as LA-RAM-agent (**Figure 7**: exp. E). Achieving this enantioenrichment from a racemic mixture in only 17 h shows

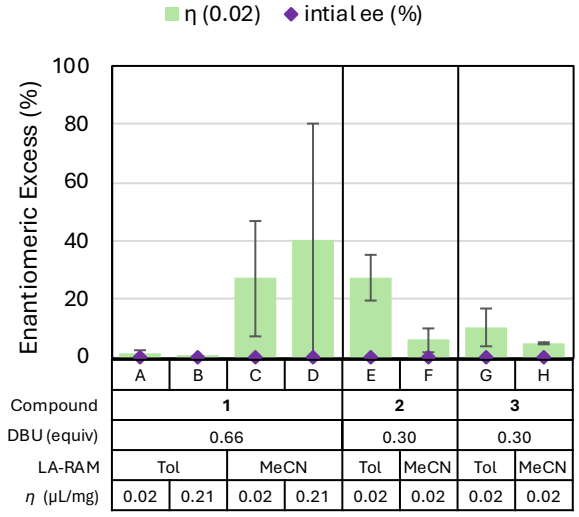



**Figure 8:** *Ee* obtained for compounds **1**, **2**, and **3** from a racemic mixture (initial *ee* indicated by purple diamonds) using toluene or MeCN as LA-RAM-additives. The table directly below the graph lists, from top to bottom: compound, DBU equivalents, and LA-RAM-additive. Glass vials (5 mL) with plastic caps were charged with imine (140 mg) and NaCl (3.15 g) and mixed at 100 *g* for 17 h. Error bars represent the standard deviation from three independent experiments (detailed results in Tables S6–S8).

that the timescale for symmetry breaking is significantly shorter in MCDR-RAM than in solvent-based VR processes.

The strong variability observed when starting from racemic compositions is also found in solvent-based processes, as well as the MCDR-BM process, and is explained by the stochastic induction period required for an enantiomeric population imbalance to occur; Furthermore, in these conditions the system can evolve randomly toward either enantiomer as found here also (**Tables S6-8**).[41,64,65]

Having demonstrated the feasibility of using RAM for deracemisation, we next wanted to explore one of its biggest advantages, namely its straightforward scalability compared to ball milling. To demonstrate this, a fivefold scale-up was performed, increasing the reaction volume from 5 mL to 25 mL, using low $\eta$, keeping all ratios constant and the filling factor at 50%, corresponding to an imine loading of 700 mg compared to 140 mg at the lower scale (**Figure 8**: left).

MeCN only produced positive results with compound **1**. A azeotropic mixture of toluene and MeCN (22:78 (v/v)) was tested with compound **1** to determine if a synergistic effect would produce a higher *ee*.[66] However, no difference was observed. Astonishingly, using toluene as LA-RAM-additive and starting from an initial *ee* of 20%, we were able to reach final enrichments of at least 80% *ee* for all compounds (**Figures S11-13**), including compound **3**, for which deracemisation was unsuccessful using RAM at smaller scale (compound **1**: 84%; compound **2**: 85%; compound **3**: 82%) without solid form transformation (**Figures S8-10**). Furthermore, this was achieved in a reaction time of only 90 minutes. On top, reduced variability with respect to the small-scale experiments was found. This is likely due to differences in intrinsic mixing zones at both scales. Furthermore, as for ball-milling, RAM can create substantial temperature increases during milling. Even though not measured explicitly, the temperature increase was felt stronger on the small vials, potentially also explaining the stronger variability at this scale. Ideally, future efforts should orient towards achieving full temperature control during the mixing process.

We then explored higher values of η using compound **1** (**Figure 8**: right). At η = 0.10 µL/mg we obtain similar *ee* to η = 0.02 µL/mg. Increasing to η = 0.21 µL/mg began to reduce the

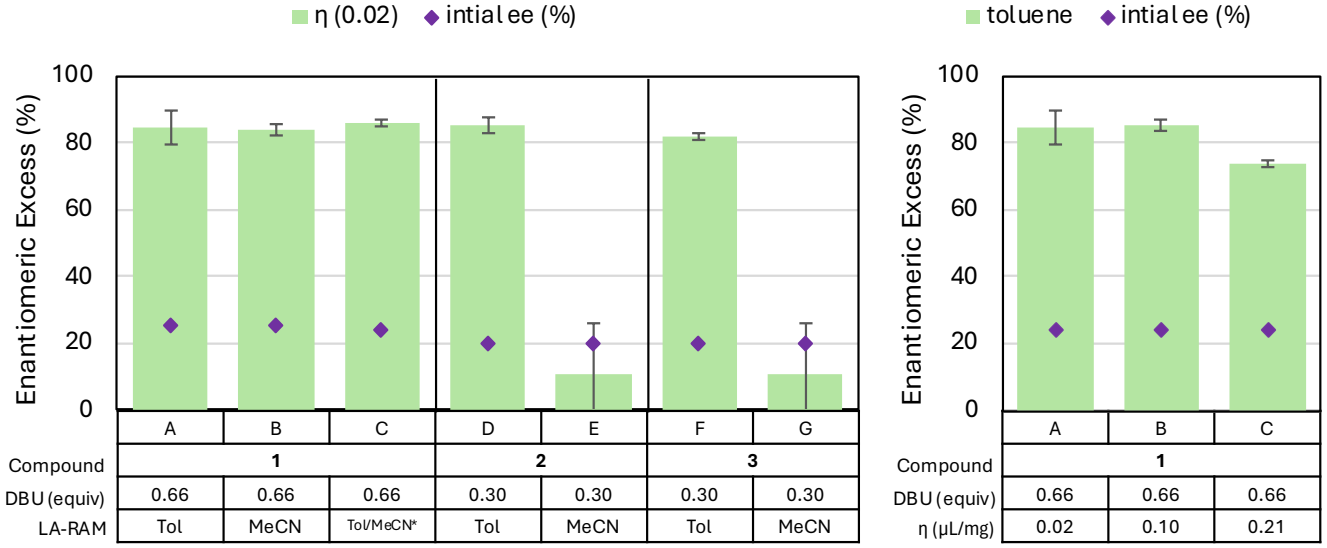



**Figure 7 Left:** *ee* obtained for compounds **1**, **2**, and **3** (initial *ee* indicated by purple diamonds) using toluene and/or MeCN as LA-RAM-additives. The table directly below the graph lists, from top to bottom: compound, DBU equivalents, and LA-RAM-additive. Glass vials (25 mL) with plastic caps were charged with imine (700 mg), NaCl (15.75 g), and the LA-RAM-additive (375 µL, $\eta$ = 0.02 µL/mg) and subjected to milling at 100 *g* for 1.5 h. Error bars represent the standard deviation from three independent repetitions of each experiment (detailed results in Tables S6–S8). **Right**: *ee* obtained for compound 1 (initial *ee* indicated by purple diamond) using toluene as LA-RAM-additive. The table directly below the graph lists, from top to bottom: compound, DBU equivalents, and toluene as LA-RAM-additive. Glass vials (25 mL) with plastic caps were charged with imine (700 mg), NaCl (15.75 g), and the η factor and subjected to milling at 100 *g* for 1.5 h. Error bars represent the standard deviation from three independent repetitions of each experiment (detailed results in Table S6).


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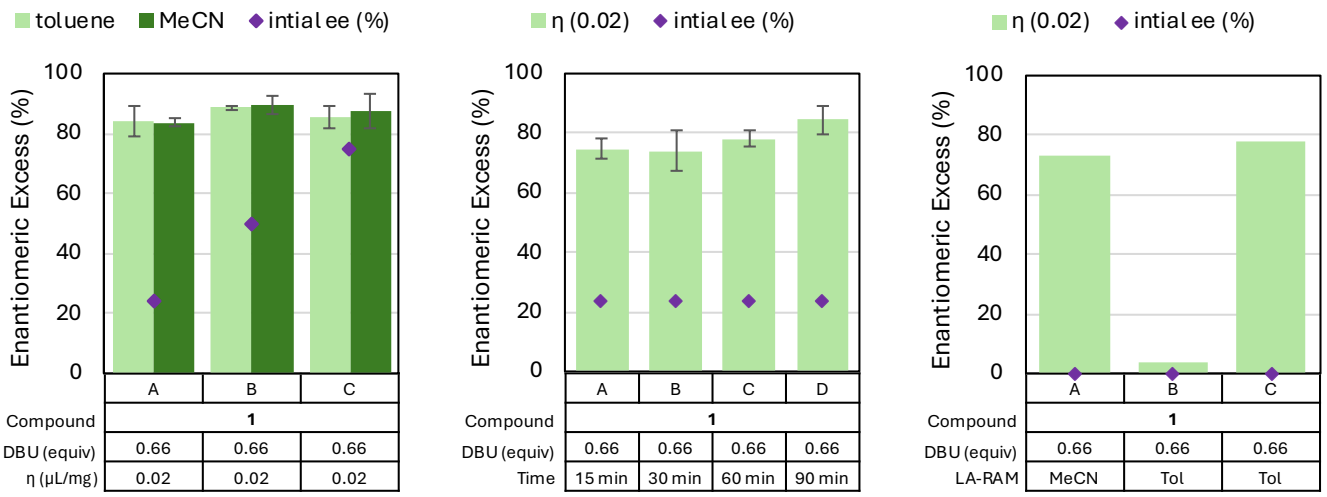



**Figure 9 Left:** *ee* obtained for compounds **1**, (initial *ee* indicated by purple diamonds) using toluene or MeCN as LA-RAM-additives. The table directly below the graph lists, from top to bottom: compound, DBU equivalents, and LA-RAM-additive. Glass vials (25 mL) with plastic caps were charged with imine (700 mg), NaCl (15.75 g), and the η factor and subjected to milling at 100 *g* for 1.5 h. Error bars represent the standard deviation from three independent repetitions of each experiment (detailed results in Table S6. **Middle:** *ee* obtained for compounds **1**, (initial *ee* indicated by purple diamonds) using toluene as LA-RAM-additive. The table directly below the graph lists, from top to bottom: compound, DBU equivalents, and LA-RAM-additive. Glass vials (25 mL) with plastic caps were charged with imine (700 mg), NaCl (15.75 g), and the η factor and subjected to milling at 100 *g* for 1.5 h. Error bars represent the standard deviation from three independent repetitions of each experiment (detailed results in Table S6. **Right:** *ee* obtained. *ee* obtained for compounds **1**, (initial *ee* indicated by purple diamonds) using toluene as LA-RAM-additive. The table directly below the graph lists, from top to bottom: compound, DBU equivalents, and LA-RAM-additive. Glass vials (25 mL) with plastic caps were charged with imine (700 mg), NaCl (15.75 g), and the η factor and subjected to milling at 100 *g* for 1.5 h. (detailed results in Table S6.

obtained *ee*, though maintaining a low level of variance. The lower *ee* can be attributed to a greater proportion of the compound being in the racemic MP. Higher η values could not be investigated, as the required liquid volume exceeded the absorption capacity of the bulk material. Next, we investigated whether starting from higher *ee* would affect the final ratio obtained. Starting from a higher ee led to similar final *ee*s of 85%. Based on the results in the left graph of **Figure 9** there is no benefit to starting at higher ee, as the results are within the margin of error of each other. This is consistent with the autocatalytic behaviour observed in classical VR and MC-DR reactions.[41,67] Starting higher along the curve only shortens the time to completion, but does not change the final *ee* reached. This is further reinforced by the kinetic study done on compound **1** with toluene as LA-RAM (η = 0.02 µL/mg),(**Figure 9**: middle) showing that after 15 minutes, the *ee* has already increased to more than 75% with only a slight further increases to reach the final level of around 85% *ee*, once more in alignement with the autocatalytic behavior.

Our final achievement was to upscale the deracemisation of compound **1** starting from a racemic mixture (*ee* = 0%). BM and small-scale RAM deracemisation experiments starting from a racemate typically required over 17 h to break symmetry and reach *ee*-values comparable to those of experiments that started from enantioenriched samples. For the upscaled experiments, two out of three trials successfully broke symmetry, achieving a 73% *ee* and 75% *ee* in just 1.5 h (**Figure 9**: right). This was possible with both toluene and MeCN as LA-RAM. When starting from a racemic mixture, this symmetry breaking is stochastic, as confirmed by the repeat experiment using toluene, for which the symmetry did not break in 1.5h. A deep statistical study would be required to understand the full stochastic aspect of this phenomenon, which is beyond the scope of this paper. To our knowledge, deracemization of a fully racemic mixture (0% ee) reaching an enantioenrichement of 76% *ee* in a mere 1.5 h has not been reported before, leaving the RAM experiment to be amongst the fastest deracemisation processes reported so far.

Overall, our findings clearly establish RAM as a sustainable approach to deracemisation, combining minimal solvent use, reduced reaction times, and scalability, all key aspects in line with the principles of green chemistry.

## Conclusions

In this work, we report the first RAM process for deracemisation, which achieved enantiomeric excesses of up to 91%. The technique furthermore enabled 5-fold upscaling, facilitating near-gram-scale deracemisation, while substantially reducing reaction times. These combined features render RAM a promising green chemistry approach to deracemisation: minimizing solvent use, accelerating reaction rates, and showing ease of scalability. Using RAM, we were ultimately able to transform a racemic mixture into a scalemic mixture of 73% *ee* in a mere 1.5 hours, representing a significant improvement in both efficiency and sustainability compared to conventional solvent-based methods.

## Author contributions

J. G. and G. W. led the experimental work, performed both BM and RAM experiments, analysed the reactions, and wrote the manuscript. Z. E. K. performed experiments in the ball mill. L. H. supervised the RAM experiments and assisted in writing the manuscript. T. L., T. W. and C. B. assisted in writing the manuscript. D. M. B. conceptualised and led the project and the writing of the manuscript. All authors participated in the

discussion and interpretation of the data and commented on the manuscript.

## Conflicts of interest

There are no conflicts to declare.

## Data availability

All data supporting the findings of this study are available within the article and its supplementary information (SI). Supplementary information is available. See DOI:

## Acknowledgements

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