

## ENVIRONMENTALLY BENIGN ASYMMETRIC MICHAEL ADDITION TO MALEIMIDES USING MECHANOCHEMICAL ACTIVATION

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### Abstract

The preparation of chiral *N*-substituted succinimides is highly important since they are widely used intermediates in the pharmaceutical industry. Such compounds can be obtained by the Michael addition of nucleophiles to different maleimides. Since the environmental awareness is rising nowadays, there is a huge demand for sustainable synthetic methods that can be applied industrially. Carrying out reactions using efficient alternative activation is key to achieve environmentally friendly procedures. Asymmetric catalytic processes have been developed for Michael additions on maleimides using organocatalysts under batch conditions. Our aim was to carry out the implementation of mechanochemical activation in these reactions because of its huge benefits over the conventional methods, *i.e.* solvent-free conditions and significantly reduced reaction times. In the present study, we examined the impact of milling parameters through the test reaction of isobutyraldehyde and *N*-methylmaleimide. We set the goal to achieve similar conversion and enantioselectivity values as were obtained using thermal activation but without the addition of a solvent and under much less time. As a result of our studies, optimal conditions were determined to carry out the preparation of an *N*-substituted succinimide, which may be a significant step in the development of sustainable industrial synthetic methods of important pharmaceutical fine chemicals.

### Introduction

The synthesis of optically pure compounds is crucial for the pharmaceutical industry to produce effective drugs. For that reason, asymmetric catalytic methods have a huge significance and are often used in the production of chiral building blocks [1]. Among these catalytic procedures, because of their environmental benefits, numerous organocatalytic methods have been developed. Asymmetric Michael additions of aldehydes to maleimides catalysed by bifunctional organocatalysts result in products containing quaternary or tertiary stereogenic carbons, which are valuable pharmaceutical intermediates [2]. Outstanding conversion and enantiomeric excess values can be reached using amino acids, their simple derivatives and oligopeptides as organocatalysts in these reactions [3-9]. Out of several examined amino acids, L-phenylalanine (L-Phe) was found to be the most advantageous because of its natural occurrence and provided both great conversion and enantioselectivity. These experiments were carried out in conventional batch reactors, using various solvents and needed long reaction times. However, numerous alternative activation methods can be applied, such as microwave or ultrasound assisted reactions or mechanochemical energy transmission, in order to decrease the necessary time and to increase the sustainability of the processes.

Mechanochemistry bears several advantages over the conventional thermal activation from which the significantly reduced reaction time and the solvent free conditions must be highlighted. It is considered to be a green chemical method; hence it implies great industrial relevance. In the last few decades mechanochemical activation was efficiently applied in performing various organic reactions [10,11]. In these methods the necessary activation energy

is provided by the collisions and friction between the grinding media, the components and the wall of the mixing jar.

Although, a variety of asymmetric organic reactions, including stereoselective catalytic transformations, have been performed by milling [12-15], to our knowledge, enantioselective Michael additions to maleimides catalysed by simple bifunctional chiral organocatalysts, such as amino acids, have not yet been reported. Our aim was to examine the feasibility of asymmetric Michael addition reaction of an aldehyde to an *N*-substituted maleimide using mechanochemical activation. By screening the effect of different parameters, such as the number and size of the applied balls and the milling time and frequency, we hoped to reach the same conversion and enantiomeric excess values as under batch conditions but under environmentally friendly circumstances and significantly less time.

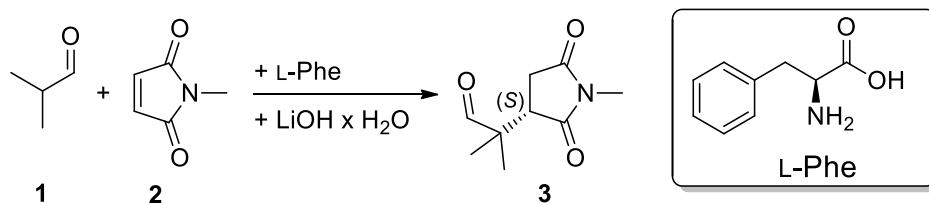
## Experimental

The isobutyraldehyde (**1**), *N*-methylmaleimide (**2**), L-phenylalanine (L-Phe) and LiOH x H<sub>2</sub>O were obtained from commercial sources and were used as received. The conventional magnetically stirred batch reactions were carried out in closed glass vials. After the given time the reactions were quenched by addition of 1 cm<sup>3</sup> aqueous NH<sub>4</sub>Cl solution and the products were extracted with 3 x 2 cm<sup>3</sup> ethyl acetate (EtOAc). The combined organic phases were dried over Na<sub>2</sub>SO<sub>4</sub> and analysed. Products were identified by mass spectrometry using a GC-MSD system. The conversion and enantiomeric excess (ee) were determined by gas-chromatography (GC-FID) using a chiral capillary column for the separation of the enantiomers.

The mechanochemical reactions were carried in 10 cm<sup>3</sup> ZrO<sub>2</sub> grinding jars with milling balls of 3, 5, 12 and 15 mm diameter made from the same material. In a typical run L-Phe, LiOH x H<sub>2</sub>O were measured into to the jars, then the necessary number of balls were added, followed by introducing the given amount of **2** and **1**. The mixture was agitated in a Retsch Mixing Mill MM 400 instrument at the desired frequency for the desired time. When the reaction was completed, the products were dissolved in 3 x 2 cm<sup>3</sup> EtOAc, the combined solutions were washed with 1 cm<sup>3</sup> aqueous NH<sub>4</sub>Cl solution, dried over Na<sub>2</sub>SO<sub>4</sub> and analysed using the same methods as in case of batch reactions.

## Results and discussion

As a test reaction we examined the addition of **1** to **2** resulting in the formation of the succinimide derivative 2-methyl-2-(1-methyl-2,5-dioxopyrrolidin-3-yl)propanal (**3**), using L-Phe as organocatalyst (Scheme 1.). In a similar addition it was found that the amino acid should be *in situ* transformed by reaction with a base in order to obtain high conversion and ee values. A previous study showed that with a β-amino acid the best results are obtained in the presence of LiOH [16].



**Scheme 1.** Michael addition of isobutyraldehyde (**1**) to *N*-methylmaleimide (**2**) catalysed by L-Phe in presence of LiOH.

Our first experiments were carried out in a conventional magnetically stirred system. Two different solvents, CH<sub>2</sub>Cl<sub>2</sub> and ethyl acetate (EtOAc) were used to screen the necessary reaction time under the conditions shown in Table 1. Although the ee values do not differ much,

high conversions were achieved only in few hours in both solvents, moreover in the latter solvent 24 hours were needed to reach the desired full transformation of **2** (entry 4). Under solvent-free conditions in batch system, the ee was maintained at high level (96%) and in 30 minutes 63% conversion was reached (entry 5). In order to reduce time and have the environmental benefit of a solvent-free method, it was worth trying to examine the test reaction using mechanochemical activation. By milling the reaction mixture for 30 minutes we have obtained over 90% conversion without loss in the enantioselectivity, *i.e.*, 96% (entry 6).

**Table 1.** Asymmetric Michael addition of isobutyraldehyde (**1**) to *N*-methylmaleimide (**2**) catalysed by L-Phe in batch system.<sup>a</sup>

Entry	Solvent; amount (cm <sup>3</sup> )	Time (h)	Conv. (%) <sup>b</sup>	ee (%) <sup>b</sup>
1	CH <sub>2</sub> Cl <sub>2</sub> ; 1	6	77	98
2	CH <sub>2</sub> Cl <sub>2</sub> ; 0.2	0.5	14	97
3	EtOAc; 1	4	40	96
4	EtOAc; 1	24	>99	97
5	–	0.5	63	96
6 <sup>c</sup>	–	0.5	92	96

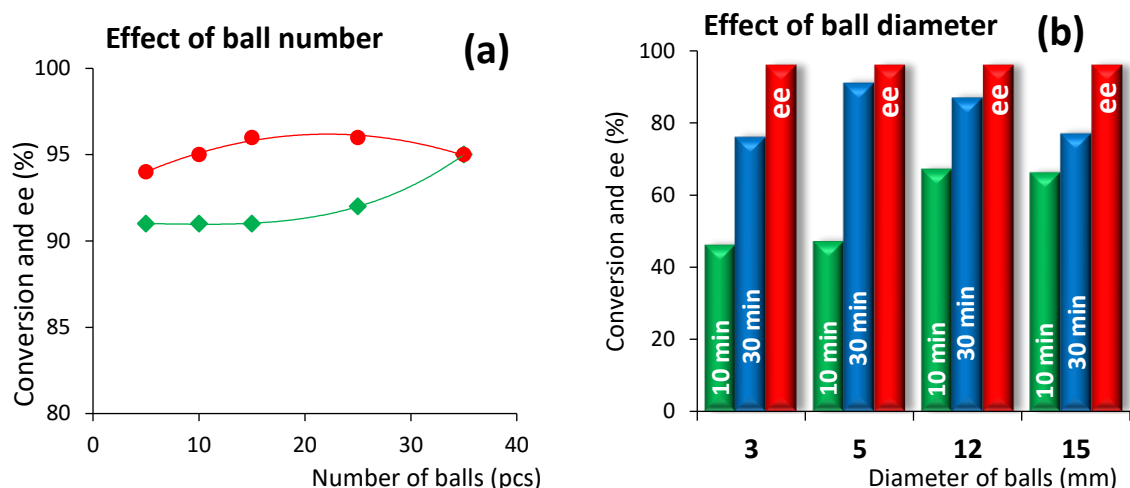
<sup>a</sup> Reaction conditions: L-Phe 0.03 mmol; LiOH x H<sub>2</sub>O 0.033 mmol, **2** 0.3 mmol, **1** 1.2 mmol.

<sup>b</sup> Conversion (Conv.) and enantiomeric excess (ee) determined by gas-chromatography (GC-FID), *S* enantiomer in excess.

<sup>c</sup> Mechanochemically activated reaction using 25 pieces of Ø 5 mm ZrO<sub>2</sub> grinding balls and 12 Hz milling frequency.

According to the above presented results, the mechanochemical realization of this asymmetric Michael addition is more efficient than the magnetically stirred reaction. Thus, in our further studies we attempted to improve the results of the reaction carried out in the ball-mill by examining the effect of some milling parameters. In the first step, we examined the influence of the applied number of balls on the conversion and ee (Figure 1. **a**). For these measurements we used grinding jars with walls made from ZrO<sub>2</sub> and grinding balls of the same material. We carried out the reactions using balls with the diameter of 5 mm. It was found that the conversion of **2** increased only slightly with the higher amount of grinding media starting from 91% with only 5 pieces (pcs) up to 95% with 35 pcs. However, the enantiomeric excess values reached a maximum of 96% by using 15 pcs. One can see that at high conversions obtained in our experiments the growing grinding surface that ensures the energy transfer has limited effect on the transformation of the maleimide, thus in our further experiments we have applied 15 pcs of balls, which afforded the best ee.

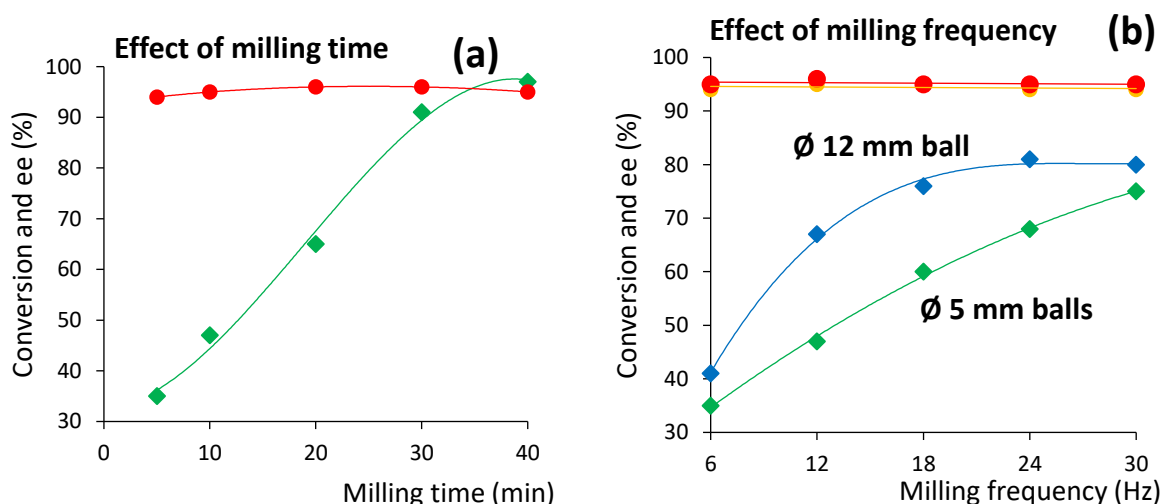
The next step was to examine the effect of the diameter of the applied balls (Figure 1. **b**). We chose the number of grinding balls as to have similar overall volumes, *i.e.*: 70 pcs of Ø 3 mm, 15 pcs of Ø 5 mm, 1 pc of Ø 12 mm and 1 pc of Ø 15 mm balls. The stereoselectivity was found to be the same (96% ee) regardless of the size of the balls and the milling time. The conversion however differed with the diameter. We set two different milling times for each ball size under otherwise identical conditions and found interesting results (Figure 1. **b**).



**Figure 1.** Effect of the number of  $\text{\O} 5$  mm balls on the conversion (◆) and ee (●) (a), and effect of the balls diameter on the conversion (green and blue bars) and ee (red bars) (b) in the mechanochemical Michael addition of **1** to **2**. Reaction conditions: L-Phe 0.03 mmol, LiOH  $\times$  H<sub>2</sub>O 0.033 mmol, **1** 1.2 mmol, **2** 0.3 mmol, 12 Hz, 30 min (10 min green bars).

In the 10 minutes reactions, the conversions were the highest with the  $\text{\O} 12$  mm (67%) and  $\text{\O} 15$  mm balls (66%). However, after 30 minutes milling, the  $\text{\O} 5$  mm balls were found to be the most effective, reaching a conversion of 91%. From these results it may be concluded that by shorter milling the decisive factor was the energy of the collisions, thus, the heavier balls performed better. When longer milling was applied, the effect of the increased number of collisions, *i.e.*, the increased number of the balls became more significant, except in case of  $\text{\O} 3$  mm, which although ensured the highest collision number, due to their low energy were less efficient compared to the  $\text{\O} 5$  mm balls.

After studying the impact of the balls on the conversion and ee, we have also examined the effect of the milling time (Figure 2. a).



**Figure 2.** Effect of the milling time (a) and milling frequency (b) on the conversion (◆, ◇) and ee (●, ●) using 15 pieces of  $\text{\O} 5$  mm balls (◆, ●) or one  $\text{\O} 12$  mm ball (◇, ●). Reaction conditions: L-Phe 0.03 mmol, LiOH  $\times$  H<sub>2</sub>O 0.033 mmol, **1** 1.2 mmol, **2** 0.3 mmol, 12 Hz (a), 10 min (b).

From these measurements, it could be seen that with a reaction time of 40 minutes a conversion of 97% and an ee of 96% could be reached, the latter did not change significantly regardless of the milling time. Furthermore, we examined the influence of the milling frequency (Figure 2. **b**). We used 10 minutes reaction times in order to detect the influence of this parameter. The Ø 12 mm balls provided greater conversions than the Ø 5 mm balls at the same frequency however the shape of the curves was different, and at higher agitation speed the conversion obtained with the latter approaches the value reached with the former. The applied milling frequency did not have an impact on the stereoselectivity, the ee was maintained at 95%.

## Conclusion

In summary, we have developed a sustainable method to carry out the asymmetric Michael addition of an aldehyde to an *N*-substituted maleimide by using mechanochemical activation. Compared to the conventional batch systems, we managed to achieve full conversion of the tested maleimide and high enantioselectivity in significantly less time and solvent-free conditions. The use of a natural organocatalyst also adds to the environmentally friendly character of the procedure. In this study the impact of the milling parameters on the reaction results was demonstrated. Based on these, the optimal conditions may be concluded under which the addition of different aldehydes to various *N*-substituted maleimides can be carried out. Our study is a significant step to develop in the future a sustainable method for the environmentally benign preparation of chiral succinimides.

## Acknowledgements

This research was supported by the Hungarian National Science Foundation through OTKA Grant K 138871.

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