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COMMUNICATION

Fast, solvent-free and hydrogen-bonding-mediated asymmetric Michael addition in a ball mill†

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The chiral squaramide derivatives as hydrogen bonding catalyst for the Michael addition reactions of 1,3-dicarbonyl compounds to nitroolefins under solvent-free conditions was developed using a planetary ball mill. High yields, high enantioselectivities and shorter reaction times were achieved with low catalyst loading.

Organocatalysis has been the subject of intensive development during the last decade due to its special features such as being environmentally benign, having atom economy and convenient operation.[1,2] However, there are still several drawbacks that are limiting industrial applications of organocatalysis; typical problems are the high catalyst loading, long reaction time and solvent limitations. In the pursuit of a more efficient and greener process, performing the reactions in the absence of any solvent appeared promising.[3] In this contribution, a solvent-free implementation of the Michael addition[4] of 1,3-dicarbonyl compounds to nitroolefins in a planetary ball mill is reported.

Ball milling as a mechanochemical technique in synthetic chemistry[5–7] has been received widespread research interest; among them catalyzed bond forming reactions has become particularly noteworthy, mainly including metal-mediated cross-coupling reactions[8–14] and organocatalysis.[15,16] The latter group of reactions caught our attention as it allows a significant decrease in the amount of harmful chemicals (toxic metals and solvent). However, to the best of our knowledge, their application in asymmetric organocatalysis was mainly limited to asymmetric aldol reactions[17–22] catalyzed by proline or its derivatives.

Hydrogen bonding is the most important of all directional intermolecular interactions determining molecular conformation, molecular aggregation in solid phase,[23,24] and introducing this function into solvent-free asymmetric catalysis may enhance the catalytic activity by the high concentration of the reagents and the avoidance of solvent interference to hydrogen bonding. We report here the successful results of H-bonding-mediated enantioselective organocatalysis under solvent-free conditions in a ball mill. Enantioselective Michael addition using a bifunctional cinchona-based squaramide organocatalyst[25,26] was dramatically accelerated in a ball mill compared to the reaction in organic solvents.[25] Remarkably, catalyst loading at 0.5 mol% was sufficient to complete most reactions within 30 min, affording the Michael adduct in up to 95% yield and >99% ee.

To investigate the effect of the solvent-free ball milling on the hydrogen bonding mediated asymmetric transformations, the addition of 2,4-pentanedione **1a** to β-nitrostyrene **2a** in the presence of differently substituted types of sqaramides was carried out in a ball mill (Fig. 1). A milling cycle consisting of a 10 min milling period at a rotational speed of 400 rpm, followed by a 5 min pause to avoid overheating, was used (Table 1). Gratifyingly, preliminary results showed that good yields and enantioselectivities were obtained when only 0.5 mol% of diaminocyclohexane/diphenylethylamino-derived squaramides used as catalysts after 4 cycles of milling (entries 1–2). To our delight, high enantioselectivity and especially high efficiency was achieved when cinchona-derived squaramides **IIa** and **IIb** were employed, which provided 87–89% yields and 89–95% ee values after only 1 cycle (entries 3–4). Further investigation of the effect of the substituent on one end of squaramide led to the discovery of the suitable catalyst **IIIg**, affording an excellent level of enantioselectivity (97% ee) and yield (91%) (entry 9). Notably, the reaction proceeds well even at 0.1 mol% catalyst loading with only slightly decreased result (entry 10). Further, the reaction rate of the hydrogen-bonding-mediated Michael

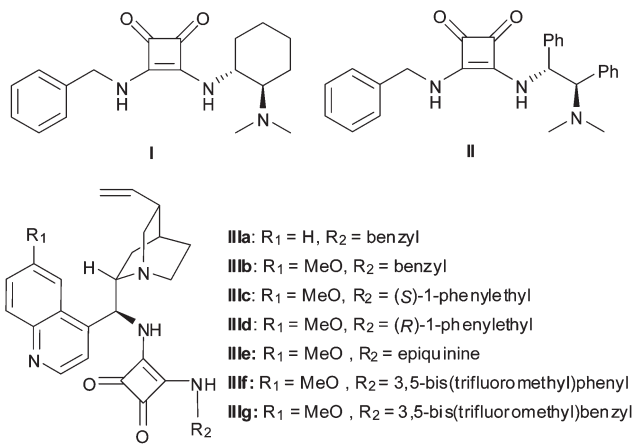

Fig. 1 Screened organocatalysts.

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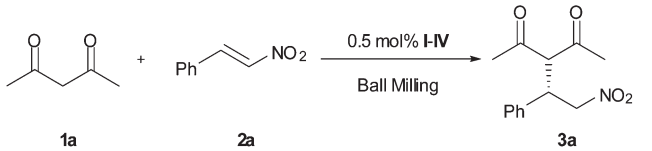
Table 1 Screening of the catalysts for the Michael reaction of 2,4-pentanedione with β-nitrostryrene[a]



1a 2a 3a

Entry	Catalyst	Time[b] (min)	Yield[c] (%)	ee[d] (%)
1	**I**	40	65	76
2	**II**	40	61	83
3	**IIIa**	10	87	89
4	**IIIb**	10	89	95
5	**IIIc**	10	86	80
6	**IIId**	10	87	81
7	**IIIe**	10	89	87
8	**IIIf**	10	49	73
9	**IIIg**	10	91	97
10[e]	**IIIg**	10	86	93
11[f]	**IIIg**	480	95	98

[a] Reactions were carried out with **2a** (8.00 mmol), **1a** (2.0 equiv.) and catalyst **I–III** (0.5 mol%); ball-milling conditions: 10 min at 400 rpm, and 5 min pause. [b] Time for milling. [c] Isolated yields. [d] Determined by HPLC analysis using a chiral stationary phase. [e] With 0.1 mol% catalyst loading. [f] Reaction was carried out with **2a** (0.5 mmol), **1a** (2.0 equiv.), and **IIIg** (0.5 mol%) in 1.5 mL of CH_2Cl_2.

Table 2 Optimization of the milling conditions for the Michael reaction of 2,4-pentanedione with β-nitrostryrene[a]

Entry	Milling speed (rpm)	Time (min)	Yield[b] (%)	ee[c] (%)
1	200	10	88	92
2	400	10	91	97
3	600	10	85	93
4	400	20	90	95
5	400	30	88	95
6	400	5	95	99

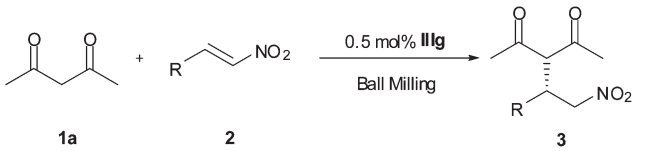
[a] Reactions were carried out with **2a** (8.00 mmol), **1a** (2.0 equiv.) and catalyst **IIIg** (0.5 mol%) in the ball mill. [b] Isolated yields. [c] Determined by HPLC analysis using a chiral stationary phase.

addition was remarkably accelerated due to the intense mixing by the ball milling and the absence of solvent interference, although the yield and enantioselectivity was slightly lower than the conventional process (entry 11).

With **IIIg** showing the best results, a screening of the milling conditions was performed. As shown in Table 2, varying the milling speed from 200 to 600 rpm (entries 1–3) reveals that neither decreasing nor increasing the milling speed resulted in better results. Further optimization of the milling times shows that even 5 min rotation is enough for the completion of the reaction with the excellent results (entry 6, 95% yield, 99% ee). The observed results are probably due to that the higher speed and longer milling time resulted in the temperature increase, and the lower speed led to the inefficient mixing.

Once the optimum reaction conditions were found, the scope and limitations of this methodology were explored (Tables 3 and 4). As shown in Table 3, a variety of substituted aromatic

Table 3 Variation of electrophiles[a]



1a 2 3

Entry	R	Product 3	Time[b] (min)	Yield[c] (%)	ee[d] (%)
1	Ph (**2a**)	**3a**	5	95	99
2	4-MeC_6H_4 (**2b**)	**3b**	5	93	96
3	2-$MeOC_6H_4$ (**2c**)	**3c**	25	94	98
4	4-$MeOC_6H_4$ (**2d**)	**3d**	5	89	98
5	4-FC_6H_4 (**2e**)	**3e**	10	88	99
6	2-ClC_6H_4 (**2f**)	**3f**	10	89	99
7	3-ClC_6H_4 (**2g**)	**3g**	10	93	99
8	4-ClC_6H_4 (**2h**)	**3h**	10	91	95
9	2-BrC_6H_4 (**2i**)	**3i**	20	83	98
10	3-BrC_6H_4 (**2j**)	**3j**	10	87	99
11	4-BrC_6H_4 (**2k**)	**3k**	10	93	94
12	2-$NO_2C_6H_4$ (**2l**)	**3l**	15	75	99
13	2, 4-$Cl_2C_6H_3$ (**2m**)	**3m**	30	72	98
14	naphthalen-2-yl (**2n**)	**3n**	10	86	91
15	furan-2-yl (**2o**)	**3o**	25	63	94
16	thien-2-yl (**2p**)	**3p**	30	92	92

[a] Reactions were carried out with **2** (8.00 mmol), **1a** (2.0 equiv.) and catalyst **IIIg** (0.5 mol%); ball-milling conditions: 5 min at 400 rpm, and 2 min pause. [b] Time for milling. [c] Isolated yields. [d] Determined by HPLC analysis using a chiral stationary phase.

β-nitroolefins, which bear electron-rich, electron–neutral and electron-withdrawing groups or heteroaryl β-nitroolefins as the electrophiles reacted smoothly with 2,4-pentanedione **1a** in a very short reaction time to afford the corresponding products **3a–3p** with high levels of yield (63–95%) and enantioselectivity (91–99% ee). Next, various 1,3-dicarbonyl compounds as nucleophiles was probed (Table 4). Of the cases studied, all give rise to the corresponding products in good yields and high enantioselectivities. Notably, some less active nucleophiles need relatively long milling time, and slightly erosion in yields and ee's was observed in these cases, perhaps as a result of temperature increasing during the long milling time.

In summary, a highly efficient H-bonding mediated enantioselective organocatalysis under solvent-free conditions in a ball mill was reported. The intense mixing of the reactants in the ball mill accelerates the reaction efficiently, but the diastereo- and enantioselectivities do not decrease.[25] The results suggest that H-bonding interactions, which are enhanced in the absence of solvents, are crucial for the course of the reaction. Simplicity of the reaction, solvent-free conditions, fast reaction times, high yields and selectivities lead us to conclude that the ball mill procedure is a significant version of the described reaction.

Acknowledgements

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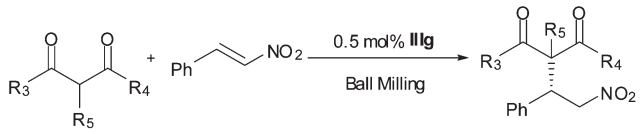
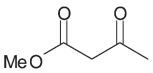
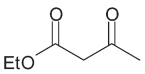
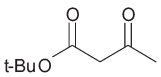
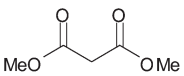
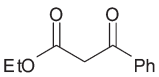
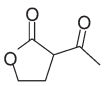
Table 4 Variation of nucleophiles[a]



1 2a 4

Entry	Nucleophile	Product **4**	Time[b] (min)	Yield[c] (%) (dr)[d]	ee[d] (%)
1		**4a**	10	90 1.6 : 1	99 99
2		**4b**	5	95 1.5 : 1	99 99
3		**4c**	25	86 1.4 : 1	90 93
4		**4d**	30	80	91
5		**4e**	50	75 1.7 : 1	96 85
6		**4f**	20	73 5.3 : 1	96 92

[a] Reactions were carried out with **2a** (8.00 mmol), **1** (2.0 equiv.) and catalyst **IIIg** (0.5 mol%); ball-milling conditions: 5 min at 400 rpm, and 2 min pause. [b] Time for milling. [c] Isolated yields. [d] Determined by HPLC analysis using a chiral stationary phase.

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