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Organocatalytic solvent-free hydrogen bonding-mediated asymmetric Michael additions under ball milling conditions†

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An efficient, solvent-free protocol for asymmetric Michael additions of α-nitrocyclohexanone to nitroalkenes using thiourea derivatives as hydrogen bonding catalysts has been developed. By performing the organocatalytic reactions in a planetary ball mill, high yields (up to 97%) and excellent enantioselectivities (er up to 98 : 2) were achieved in short reaction times with low catalyst loadings.

1. Introduction

The concept of organocatalysis has gained significant interest within the field of asymmetric organic synthesis over the last decade.[1,2] Besides its many advantages such as the use of air- and water-stable catalysts, the avoidance of toxic metals, and being environmentally benign in general, there are often still severe limitations, as for example, high catalyst loadings, a limited solvent choice and long reaction times, restricting the potential of asymmetric organocatalysis for industrial applications.[3] Attempts to overcome these boundaries include attempted syntheses of more efficient organocatalysts,[4] performing organocatalysed reactions in ionic liquids or water, the utilisation of solvent-free reaction conditions and the application of non-classical energy sources such as microwave irradiation, ultrasonication or high pressure and mechanochemical techniques.[5]

According to IUPAC, a mechanochemical reaction is defined as a "chemical reaction that is induced by the direct absorption of mechanical energy".[6] Ball milling is a well-established industrial technique,[7] and its method of mechanical activation is in accordance with this definition. It has been used for the grinding of minerals into fine particles and the preparation and modification of inorganic solids,[8] and more recently it was applied in solvent-free organic synthesis.[9] It has been argued that the latter is effective due to more efficient mixing and enhancement of reagent surfaces rather than the mechanical breaking of molecular bonds.[10]

Applications of ball milling in organic synthesis predominantly relate to catalytic C–C bond formations.[3,9,11–15] Although it was shown that, compared to the classical solution-based alternative, asymmetric organocatalytic reactions under ball milling conditions can be performed with lower catalyst loading and in shorter reaction times, only a few examples have so far been studied in depth. Respective reports include asymmetric anhydride openings,[12] aldol-[12,13] and alkylation reactions[14] and, only recently, Michael additions.[3,15]

Hydrogen bonding plays a major role in organocatalytic activations.[16] Many bifunctional organocatalysts that allow the simultaneous activation of two reactants rely on that concept.[17] Along those lines, we recently reported the asymmetric Michael addition of α-nitrocyclohexanone (**1**) to aryl nitroalkenes **2** catalysed by natural amino acid-derived bifunctional thioureas.[18] Combining these recent results with our long-lasting interest in asymmetric organocatalysis under (solvent-free) ball milling conditions,[12,13a,b] we envisioned that also this reaction could benefit from applying the mechanochemical technique. Three factors were expected to increase the reaction efficiency: first, the high local reagent concentration; second, the lack of solvent interference to hydrogen bonding; and third, the efficient reagent mixing in the solvent-free media. Here, we report on the validation of this hypothesis.

2. Results and discussion

To search for mechanochemical effects induced by ball milling on the aforementioned thiourea-catalysed asymmetric Michael addition reactions, the solvent-free coupling of α-nitrocyclohexanone (**1**) and 2-furyl-substituted nitroalkene **2a** was initially chosen as a test reaction. First experiments with

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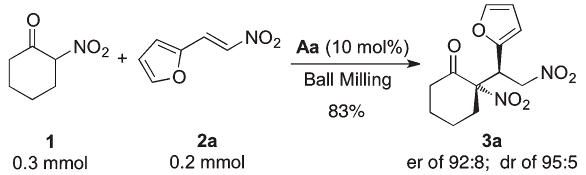
† Electronic supplementary information (ESI) available: Experimental procedures, results of the reaction condition screening, full characterization of new products, computational and experimental ECD and VCD spectra, and er determinations. See DOI: 10.1039/c2gc36906k



Scheme 1 Michael addition of α-nitrocyclohexanone (**1**) to 2-furyl-substituted nitroalkene **2a**; ball milling conditions: 2 × 15 min at 300 rpm and 15 min pause, 20 balls with a diameter of 0.4 cm.[19]

Table 1 Catalyst screening[a]

$$\mathbf{1} + \mathbf{2a} \xrightarrow[\text{Ball Milling}]{\text{cat. (10 mol\%)}} \mathbf{3a}$$

Entry	Catalyst	Yield[b] (%)	dr[c] (*anti* : *syn*)	er[c]
1	**Aa**	83	95 : 5	92 : 8
2	**B**	69	90 : 10	76 : 24
3	**Ca**	71	92 : 8	85 : 15
4	**Cb**	78	80 : 20	78 : 22
5	**Cc**	66	55 : 45	82 : 18
6	**Ab**	57	85 : 15	81 : 19
7	**Ac**	64	89 : 11	90 : 10
8	**Ad**	77	93 : 7	93 : 7
9	**Ae**	92	92 : 8	92 : 8
10	**Af**	85	96 : 4	95 : 5
11	**D**	67	95 : 5	20 : 80

[a] Reactions were carried out on a 0.2 mmol scale; ball milling conditions: 2 × 15 min at 300 rpm and 15 min pause. [b] After aqueous workup and flash chromatography.[19] [c] Determined by HPLC of the crude product using a chiral stationary phase.

piperidine-based thiourea **Aa** showed that the addition proceeded smoothly leading to product **3a** with an enantiomeric ratio of 92 : 8 and a diastereomeric ratio of 95 : 5 in 83% yield after only 30 min (Scheme 1).[19]

A subsequent screening of the reaction conditions including total milling time and milling speed revealed that this result could not be improved.[20] To avoid overheating, the reactions were typically carried out in milling cycles consisting of a 15 min milling period followed by a 15 min pause. The necessity of this procedure was validated following a 30 min test reaction without any pause, which afforded the resulting product with an er of 90 : 10 in a yield of only 66%.[19]

The use of neutral, acidic or basic additives as milling auxiliaries was tested as well as the addition of DCM for liquid-assisted grinding. However, none of those changes led to an improvement of the stereoselectivity and the yield.

Next, alternative thiourea catalysts were screened (Table 1, Fig. 1).[19] Compared to **Aa** the use of pyrrolidine-based thiourea **B** led to a lower yield of **3a** and a reduced enantioselectivity (entries 1 and 2). In the series of thiourea **Ca**, urea **Cb** and selenurea **Cc** (entries 3–5), the first gave the best stereoselectivities (er and dr).[20] None of those catalysts, however, reached the superior values obtained with thiourea **Aa** (entry 1).

Changing the substituent R^2 from 3,5-bis(trifluoromethyl)-phenyl (as in **Aa**) to 2-naphthyl or benzyl (as in thioureas **Ab** and **Ac**, respectively) lowered the yield and the stereoselectivities in the formation of **3a** (Table 1, entries 1, 6 and 7).[21] The latter, however, could be improved by applying piperidine-based thioureas with bulky substituents (such as *tert*-butyl) at the endocyclic nitrogen (Table 1, entry 1 *versus* entries 8 and 10). Consequently, the use of *N-tert*-butyl-containing thiourea **Af** having a benzyl group as R^2 gave the best results, affording product **3a** with an er of 95 : 5 in 85% yield (entry 10).[19]

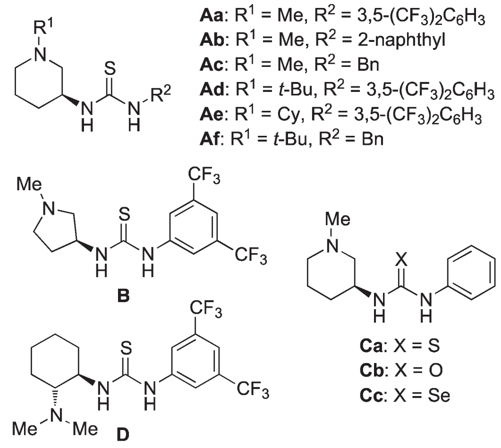


Fig. 1 Screened organocatalysts.

Finally, Takemoto's thiourea **D**[22] was included in the screening process, in order to compare the results obtained for **A**–**C** with those achievable with an established thiourea-type catalyst. With **D**, the diastereoselectivity remained high, but the yield and the enantioselectivity dropped (Table 1, entry 11). Based on all results, thiourea **Af** became the catalyst of choice for the subsequent investigations (Table 2).

The effect of the catalyst loading was studied next. To our delight, the enantioselectivity increased when the amount of the catalyst was reduced. Thus, with only 2.5 mol% (instead of the previously used 10 mol%) of **Af**, the er of **3a** was 96 : 4, and the product was obtained in 83% yield (Table 2, entry 3). Notably, the reaction proceeded with very high stereoselectivity (er of 96 : 4, dr of 97 : 3) even with a catalyst loading as low as 1 mol%, but under those conditions the yield dropped significantly to 57% (Table 2, entry 4).

To check for possible milling effects, the grinding balls in the vessel were exchanged for balls with a smaller diameter. While the stereoselectivity of the reaction remained high, lower yields of **3a** were obtained, probably due to blind spots in the vessel (Table 2, entries 5–7).[23]

In an attempt to overcome the problem of the α-nitrocyclohexanone traces in the final product, an investigation into the substrate ratio was carried out. Unfortunately, neither the use of stoichiometric reagent amounts nor applying an excess of nitroalkene **2a** proved superior to the aforementioned conditions, where an excess of α-nitrocyclohexanone (**1**) was employed. While the enantioselectivities remained high, the yield dropped to 52%–65% (Table 2, entries 8–11).

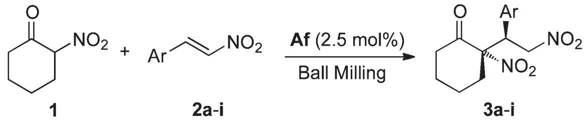
Table 2 Screening of reaction and milling conditions for the Michael addition of α-nitrocyclohexanone (**1**) to 2-furyl-substituted nitroalkene **2a**[a]

$$\mathbf{1} + \mathbf{2a} \xrightarrow[\text{Ball Milling}]{\textbf{Af}\text{ (cat.)}} \mathbf{3a}$$

Entry	Ratio of **1** : **2a**	Catalyst loading (mol%)	Milling balls diameter (cm)	Milling time (min)	Yield[b] (%)	dr[c] (*anti* : *syn*)	er[c]
1	1.5 : 1	10	0.4	30	85	96 : 4	95 : 5
2	1.5 : 1	5	0.4	30	70	93 : 7	96 : 4
3	1.5 : 1	2.5	0.4	30	83	96 : 4	96 : 4
4	1.5 : 1	1	0.4	30	57	97 : 3	96 : 4
5	1.5 : 1	2.5	0.1	30	47	97 : 3	94 : 6
6	1.5 : 1	2.5	0.2	30	66	97 : 3	96 : 4
7	1.5 : 1	2.5	0.3	30	35	96 : 4	96 : 4
8	1 : 1	2.5	0.4	30	63	96 : 4	96 : 4
9	1 : 1.5	2.5	0.4	30	65	95 : 5	96 : 4
10	1 : 1.5	2.5	0.4	60	61	94 : 6	93 : 7
11	1 : 1.5	2.5	0.4	80[d]	52	97 : 3	96 : 4
12[e]	1 : 1.5	2.5	0.4	30	86	94 : 6	96 : 4

[a] Reactions were carried out on a 0.4 mmol scale; ball milling conditions: 15 min at 300 rpm and 15 min pause. [b] After aqueous workup and flash chromatography.[19] [c] Determined by HPLC of the crude product using a chiral stationary phase. [d] Ball milling conditions: 8 cycles of 10 min at 300 rpm and 5 min pause. [e] Crude product was directly transferred to flash chromatography.

Table 3 Investigation of substrate scope[a]



Entry	Nitroalkene	Ar	Product	Yield[b] (%)	dr[c] (*anti* : *syn*)	er[c]
1	**2a**	2-Furyl	**3a**	86	94 : 6	96 : 4
2	**2b**	C_6H_5	**3b**	95	96 : 4	98 : 2
3	**2c**	*o*-FC_6H_4	**3c**	91	96 : 4	97 : 3
4	**2d**	*p*-FC_6H_4	**3d**	88	94 : 6	97 : 3
5	**2e**	*o*-ClC_6H_4	**3e**	91	96 : 4	99 : 1
6	**2f**	*p*-ClC_6H_4	**3f**	93	98 : 2	98 : 2
7	**2g**	*p*-BrC_6H_4	**3g**	86	96 : 4	97 : 3
8	**2h**	*p*-$MeOC_6H_4$	**3h**	80	95 : 5	97 : 3
9	**2i**	*p*-MeC_6H_4	**3i**	91	95 : 5	97 : 3

[a] Reactions were carried out on a 0.4 mmol scale with 1.5 equiv. of **2a**; ball milling conditions: 2 × 15 min at 300 rpm and 15 min pause. [b] After flash chromatography. [c] Determined by HPLC of the crude product using a chiral stationary phase.

The final solution for the product purification came from the work-up protocol. Pleasingly, we found that the yield and purity of the final product were improved by direct flash chromatography of the reaction mixture avoiding any additional aqueous work-up step. Thus, with 1.5 equivalents of nitroalkene **2a**, the final product was obtained in pure form in 86% yield (Table 2, entry 12).

To determine the substrate scope, the optimised reaction conditions were applied to a range of nitroalkenes. All compounds reacted well, and the corresponding addition products were obtained in yields ranging from 80% to 95% (Table 3). Neither electron-withdrawing nor electron-donating substituents on the aryl unit of the nitroalkenes appeared to significantly affect the overall yields. The diastereoselectivities were generally high, with dr values typically around 95 : 5. All enantiomeric ratios were above 96 : 4. In that respect, the *o*-chloro-substituted product **3e** provided the best result (er of 99 : 1).

Similar results could also be obtained when the reaction was run on a larger scale, whereby 1.024 g (97%) of product **3b** with an er of 98 : 2 was obtained from 3.6 mmol of α-nitrostyrene (**2b**).[24]

According to a comparison of calculated and measured ECD- and VCD-spectra of compound **3b** the absolute configuration of this product is very likely *S*,*S*.[25] This result is in accord with the one obtained previously by X-ray crystal structure analysis.[18]

In summary, we developed a new protocol for the hydrogen bond-mediated organocatalytic addition of α-nitrocyclohexanone to aryl nitroalkenes under solvent-free conditions in a ball mill providing the corresponding addition products in high yields and with excellent stereoselectivities. The reactions proceed with a remarkably low catalyst loading, and the products can be purified by direct flash chromatography (without aqueous work-up). In comparison to the results achieved in common solvent-phase reactions,[18,26] the ones performed (solvent-free) in a ball mill are faster and more stereoselective.

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