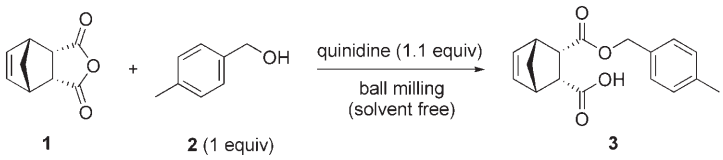
synthetic organic chemistry is relatively scarce, and the few reported examples include the functionalization of fullerenes,[2a] the reductive benzylation of malonitrile,[2b] the preparation of phosphorus ylides,[3] the protection of amines,[4] and Heck-type cross-coupling reactions.[5] The latter transformation caught our attention as it represents a scalable metal catalysis under solvent-free reaction conditions.[6] Utilizing otherwise cheap and simple starting materials, it allows a significant decrease in the amount of harmful organic reagents, thus leading to an improved and benign chemical synthesis.

As impressive advances have recently been achieved in asymmetric organocatalysis[7] and with the vision that such metal-free reactions could benefit from the inherent solvent-free conditions of the ball-milling technology, we initiated a program that studies a combination of both approaches.

The alkaloid-mediated asymmetric opening of a cyclic *meso* anhydride was studied as the initial organocatalytic test reaction in the ball mill (Scheme 1).[8] Usually this reaction is



Scheme 1. Alkaloid-mediated asymmetric opening of a cyclic *meso* anhydride.

performed at low temperatures (e.g., −60 °C) in an organic solvent, such as toluene or toluene/carbon tetrachloride mixtures, with methanol or benzyl alcohol as the nucleophile; products with high enantiomeric excess (up to 99 % *ee*) are formed after 24–48 hours in almost quantitative yields. The solvent-free variant was performed in a commercially available planetary micromill with two 45-mL grinding bowls containing 5-mm diameter balls, both composed of chemically inert and nonabrasive zirconium oxide. To allow comparison with previous results obtained in solution, structurally related, yet solid, starting materials (anhydride **1** and *p*-methylbenzyl alcohol (**2**) in combination with quinidine) were chosen. To prevent "overheating" of the reaction mixture, a milling cycle with a rotational speed of 250 rpm for 25 min followed by a 5-min cooling pause (to be repeated for 24–36 h until full consumption of the educts) was selected.[9] Under those conditions, the following observations were made: 1) The solvent-free asymmetric anhydride opening proceeded well and afforded hemiester **3** in high yield (91 %). 2) An enantioselective excess of 61 % *ee* was achieved, which compares well with reactions performed in solution at comparable temperatures (ambient and higher). 3) Whereas the reaction in solution generally requires three equivalents of the nucleophile to achieve high conversion after a reasonable reaction time, the ball-milling conditions allow the amount of this starting material to be lowered to one equivalent without significantly affecting the yield. As a consequence, a tedious extractive workup can be avoided and a simple acid wash to remove the alkaloid yields the hemiester in high purity.[10]

Organocatalysis

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Solvent-Free Asymmetric Organocatalysis in a Ball Mill**

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Ball milling is a mechanochemical technique, which is widely applied to the grinding of minerals into fine particles and the preparation and modification of inorganic solids.[1] Its use in

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Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

Whereas these initial results served as proof of concept for the applicability of the ball-milling technology in metal-free asymmetrically mediated reactions, its potential in organocatalytic enantioselective processes (with substoichiometric amounts of an organocatalyst) still needed to be demonstrated. The proline-catalyzed intermolecular aldol reaction is a well-studied and efficient C–C bond-forming reaction, which proceeds via enamine intermediates generated in situ, thus affording products with high chemo- and stereoselectivity under very mild conditions.[11] Generally, it is conducted in highly polar solvents, such as dimethyl sulfoxide (DMSO).[12]

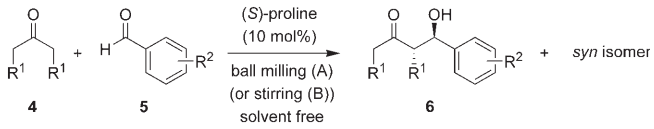
For the experiments in the ball mill, a 1.1:1 ratio of ketones **4** and aldehydes **5** in combination with 10 mol% of (*S*)-proline was used. All the reactants were ball milled, with a rotation speed of 250–400 rpm until the reaction was complete. The results are summarized in Table 1.

As shown in Table 1, the (solvent-free) ball-milling conditions allow a highly efficient catalysis to occur, and the use of simple (unmodified) (*S*)-proline leads to the formation of *anti*-aldol products with excellent stereoselectivities (up to >99% *ee*). A comparative study using conventional magnetic stirring revealed the beneficial effect of the ball milling. Although under those (solvent-free) conditions the aldol products were stereoselectively obtained in high yields as well, those reactions proceeded much more slowly, which indicates the advantage of the ball-milling technology.[13–15]

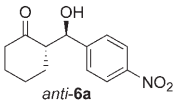
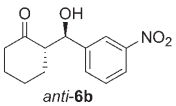
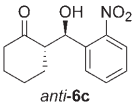
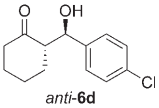
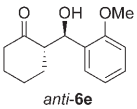
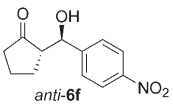
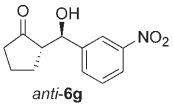
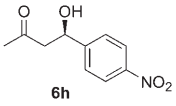
The generality of the organocatalytic aldol reaction in a ball mill was examined by varying the substrate combinations (Table 1). In reactions with cyclohexanone, aldehydes with electron-withdrawing substituents afforded products with high stereoselectivities in short reaction times (Table 1, entries 1–3). More electron-rich groups lowered both the reactivity and stereoselectivity (Table 1, entries 4 and 5). Cyclopentanone and acetone could also be used as keto components (Table 1, entries 6–8). In the former case, poor diastereoselectivities were observed, whereas the enantioselectivities were high (Table 1, >90–95% *ee*). In contrast, acetone afforded a product with only 56% *ee* (Table 1, entry 8). Note that the above-mentioned trends of the electronic effects and the dependence of the stereoselectivity on the substrate structure are analogous to those observed in aldol reactions under alternative reaction conditions (e.g., in organic or aqueous solvents and solvent-free conditions).[11,12]

In summary, ball milling has been used in solvent-free asymmetric organocatalysis for the first time. The mechanically induced desymmetrization of *meso* anhydrides mediated by quinidine leads to optically active hemiesters in high yields and with moderate enantioselectivities. Under the same conditions, a proline-catalyzed asymmetric aldol reaction proceed efficiently and *anti*-aldol products are formed with excellent diastereo- and enantioselectivities.

Table 1: Solvent-free enantioselective aldol reaction catalyzed by (*S*)-proline under ball-milling conditions.[a]



4 **5** **6**

Entry	Product	Method[b]	*t* [h]	Yield [%][c]	*anti*/*syn*[d]	*ee* [%][e]
1	 *anti*-**6a**	A	5.5	99	89:11	94
		B	96	98	87:13	94
2	 *anti*-**6b**	A	7	94	88:12	>99
		B	16	89 (10)	82:18	98
3	 *anti*-**6c**	A	7	97	93:7	97
		B	36	89	91:9	97
4	 *anti*-**6d**	A	20	87 (10)	74:26	75
		B	72	85 (9)	78:22	67
5	 *anti*-**6e**	A	36	65 (25)	66:34	63
		B	96	64 (26)	71:29	67
6	 *anti*-**6f**	A	5	53	57:43	95
		B	24	90	52:48	87
7	 *anti*-**6g**	A	5	93	50:50	90
		B	36	93	46:54	75
8	 **6h**	A[f]	19	73	–	56
		B	36	69	–	54

[a] Reaction conditions: ketone **4** (2.2 mmol), aldehyde **5** (2.0 mmol), and (*S*)-proline (0.2 mmol). [b] Method A: the grinding bowl containing the reaction mixture was rotated in the ball mill at a rotation speed of 250–400 rpm (see Experimental Section for details). Method B: the reaction mixture was stirred at room temperature using conventional magnetic stirring. [c] Combined yield of the isolated diastereomers. The data in parentheses indicate the amounts of recovered aldehyde. [d] Determined by ^{1}H NMR spectroscopic analysis of the crude product. [e] Determined by chiral-phase HPLC analysis of the *anti* isomer. [f] Acetone (4.0 mmol, 2.0 equiv) was employed.

Experimental Section

General procedure for the anhydride opening in the ball mill (Fritsch Planetary Micro Mill model "Pulverisette 7"): A ball-mill vessel was charged with 60 zirconium oxide balls, the anhy-

dride (1 mmol), the alkaloid (1.1 equiv of quinine or quinidine; 0.1 equiv of hydroquinone anthraquinone-1,4-diyl diether ($(DHQ)_2AQN$), and the alcohol (1.0 equiv). The vessel was closed, and the milling was started (milling time: 24–36 h at 250 rpm; sequential intervals of 25-min milling followed by a 5-min pause).[9] After completion of the reaction, the mixture was carefully washed with 2 N HCl and transferred into a separation funnel using EtOAc. The mixture was extracted three times with EtOAc, and the organic fractions were combined and dried ($MgSO_4$). The solvent was evaporated and if required, the product was purified by flash chromatography.

General procedure for the proline-catalyzed solvent-free aldol reaction: A reaction vessel was charged with aldehyde **5** (2.0 mmol, 1.0 equiv), ketone **4** (2.2 mmol, 1.1 equiv), and (*S*)-proline (23 mg, 0.2 mmol, 0.1 equiv). Stirring was either started in a grinding bowl using the ball mill with a rotation speed of 250–400 rpm (Table 1, method A), or in a round-bottomed flask using a conventional magnetic stirring bar (method B). After an appropriate reaction time, the crude product was washed off the reaction vessel with Et_2O (4 × 40 mL), and the combined organic fractions were filtered and concentrated in vacuo. The diastereoselectivity of the reaction was determined by ^1H NMR spectroscopic analysis of the crude product. Purification by flash chromatography on silica gel (pentane/EtOAc, 100:0→80:20) afforded the pure aldol product **6a–h** in the yields and enantioselectivities reported in Table 1. The identity and purity of the products were confirmed by ^1H and ^{13}C NMR spectroscopic analysis (see Supporting Information for full details).

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Keywords: aldol reaction · anhydrides · ball mill · organocatalysis · solvent-free reactions

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[13] Isolated examples of solvent-free organocatalytic aldol reactions can be found in references [11] and [12]. However, to the best of our knowledge, such approach has never been the focus of an intense study. It should also be noted that in these cases an excess of liquid ketone (≥ 5 equiv) appears essential for achieving both high yields and stereoselectivities.

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