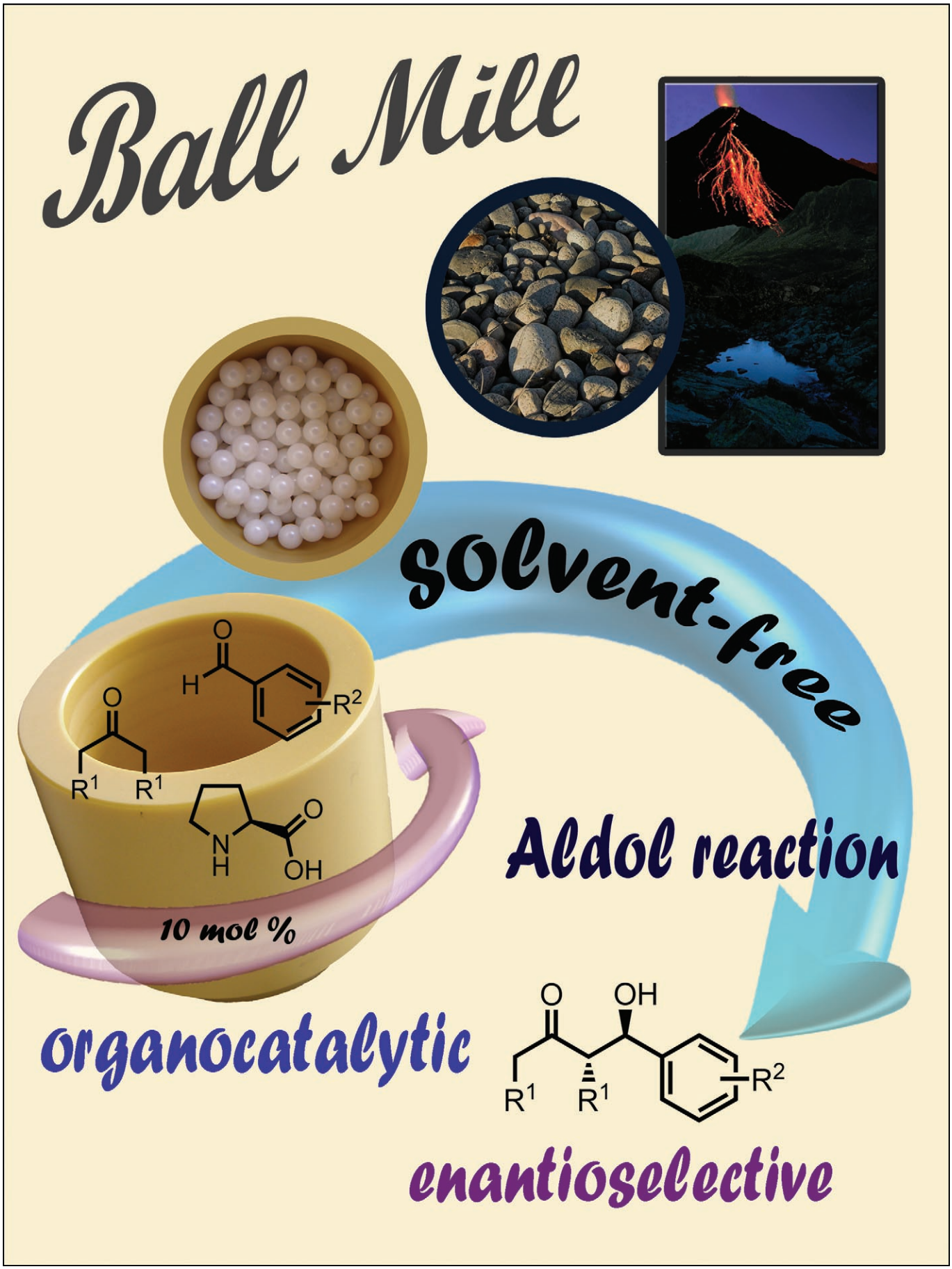
DOI: 10.1002/chem.200700188



A Highly Efficient Asymmetric Organocatalytic Aldol Reaction in a Ball Mill

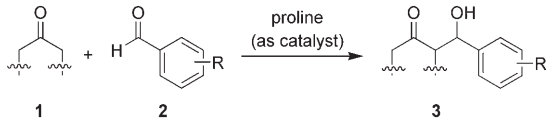
Belén Rodríguez, Angelika Bruckmann, and Carsten Bolm*[a]

Abstract: *Anti*-aldol products with up to >99% enantiomeric excess (*ee*) have been obtained by proline catalysis in excellent yields under experimentally simple solvent-free conditions. Efficient mixing of all the components is accomplished by applying a mechanochemical technique (ball milling). The catalysis is air and moisture tolerant and can be performed with non-purified starting materials. Even mixtures of solely solid compounds react, giving (mostly solid) products through a partially homogeneous (honey-like) intermediate melt. Since the reactant ratio is almost 1:1 (avoiding the common excess of ketone), the product isolation is easy leading to high aldol product yields.

Keywords: aldol reaction · ball milling · organocatalysis · proline · solvent-free

Introduction

The direct catalytic aldol reaction is a well-studied and broadly applicable C–C bond-forming reaction, which provides enantiomerically enriched β-hydroxy carbonyl compounds. Among other asymmetric catalytic methods, the proline-catalyzed version, which proceeds via in situ generated enamine intermediates, has attracted much attention, since it affords aldol products with high chemo- and stereoselectivity under very mild reaction conditions (Scheme 1).[1]



Scheme 1. Proline-catalyzed aldol reaction.

Besides the natural amino acid itself, various proline derivatives and many other small molecules have been successfully applied as catalysts.[2] Noticeably, several authors have referred to the "prebiotic" relevance of this transformation, because amino acid-catalyzed processes may have played a role in the evolution of homochirality.[3] However, since most of these studies have been performed in organic solvents and crucial factors such as appropriate solvation and reaction temperature are often not taken into account, this discussion appears somehow superficial.

Performing organic reactions in aqueous media has recently attracted considerable attention,[4] since water is nontoxic, environmentally friendly, nonflammable and inexpensive. Independent studies reported by Hayashi[5] and Barbas[6] revealed that high diastereoselectivities and enantioselectivities can be obtained, when organocatalyzed aldol reactions are performed in aqueous solution.[7–9] Generally, apolar organic molecules are only sparingly soluble in water, and presumably hydrophobic effects, which increase the effective concentration of the reagents by hydrophobic hydration,[10,11] lead to the observed distinctive rate accelerations and/or selectivity improvements.[8a,12,13] In this scenario, the reaction would occur either in the organic phase of a biphasic system[5a] or in an emulsion.[5b,6] Noteworthy, in the above-mentioned reports, unmodified proline, which is highly soluble in water, does not catalyze under those conditions, and only with hydrophobic proline derivatives significant reactivities have been achieved.[8a] As a whole, these results indicate that the main role of water is to bring the reactants closer together and *not* to act as a solvent. On that basis, performing the reaction *in the absence* of any solvent appeared promising.[14,15] By intense mixing of all reactants, phase separations could be overcome, and we hypothesized that such modified conditions would allow inexpensive and readily available proline to act as active catalyst. Hence, the use of lengthy procedures to prepare hydrophobic proline derivatives would be unnecessary and an environmentally benign process requiring a minimum amount of solvent (for

[a] Dr. B. Rodríguez, A. Bruckmann, Prof. Dr. C. Bolm
Institute of Organic Chemistry, RWTH Aachen University
Landoltweg 1, 52056 Aachen (Germany)
Fax: (+49) 241-809-2391
E-mail: Carsten.Bolm@oc.rwth-aachen.de

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

the work-up) would result.[16] Although a few isolated examples of organocatalytic aldol reactions performed in the absence of a solvent can be found in the literature,[17] to the best of our knowledge such approach has not been the focus of an intense study. Furthermore, in those previous examples high yields and acceptable stereoselectivities could only be achieved with an excess of liquid ketone ($\geq$5 equivalents), which appears to act as both reactant and reaction media. A solvent-free proline-catalyzed aldol reaction should avoid this disadvantage and provide good results with stoichiometric amounts of reactants.

In order to achieve a high conversion in solvent-free catalytic systems, an efficient mixing of all reagents and the catalyst is critical. In this respect, conventional magnetic stirring methods may prove insufficient. The mechanochemical technique of ball milling offers an alternative. Ball milling has widely been applied for the grinding of minerals into fine particles and for the preparation and modification of inorganic solids.[18,19] In synthetic organic chemistry it has seldomly been used, and the few reported examples include the functionalization of fullerenes,[20] the reductive benzylation of malonitrile,[21] the protection of amines,[22a] Knoevenagel[22b] and aldol[23] condensations, Michael additions,[22b] the preparation of phosphorus ylides,[24] the oxidative coupling of 2-naphthol,[25] and Heck-type cross-coupling reactions.[26]

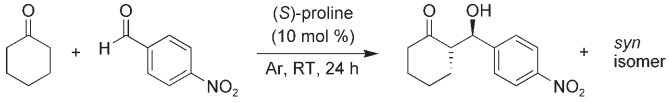
On that basis, a study was initiated focussing on the investigation of asymmetric organocatalytic reactions under (solvent-free) ball-milling conditions.[27] Besides enantioselective anhydride openings mediated by cinchona alkaloids,[28] proline-catalyzed asymmetric aldol reactions became research targets. For the latter, 10 mol% of (*S*)-proline were commonly applied as catalyst, and for comparison the reactions were performed under conventional magnetic stirring or ball-milling conditions. Here, the details of the study are disclosed.

Results and Discussion

In order to investigate the effect of the solvent-free ball milling on the proline-catalyzed aldol reaction, the reaction conditions were first optimized. Subsequently, comparative studies using either conventional magnetic stirring or ball milling were carried out for each substrate. As model system the reaction between cyclohexanone (**1a**) and *p*-nitrobenzaldehyde (**2a**) in the presence of 10 mol% of (*S*)-proline was chosen, and initially, conventional magnetic stirring was applied. Freshly purified starting materials were used under inert and dry conditions in order to avoid effects caused by water, air, and impurities. For the sake of consistency and to ensure optimal mixing, solid aldehyde **2a** was finely ground[29] and the resulting powder stirred with the ketone and the catalyst at a speed of 70–100 rpm at room temperature for 24 h. Furthermore, all reactions were conducted on a 2 mmol scale using the same round-bottom flask (10 mL) and magnetic stirring bar (prolate ellipsoid-shaped).[30] Then, using these established conditions, several experiments were performed in order to determine the effects of concentration, water and impurities on the reaction outcome.

Effect of concentration: In a solvent-free reaction the composition of the medium, in which the reaction occurs, is only determined by the ratio of reactants. Therefore, and with the goal to find the optimal reactant ratio, this crucial factor was focussed on first. The study was carried out under the conditions described above using various ratios of ketone **1a** to aldehyde **2a**, ranging from 1:1 to 5:1 (Table 1).

Table 1. Effect of the ratio of reactants on the solvent-free aldol reaction between cyclohexanone (**1a**) and *p*-nitrobenzaldehyde (**2a**) catalyzed by (*S*)-proline.[a]



1a **2a** *anti*-**3a**

Entry	Product	**1a**/**2a**	Yield [%][b]	*anti*/*syn*[c]	*ee* [%][d]
1	**3a**	1.0:1.0	77 (18)	82:18	95
2	**3a**	1.1:1.0	90 (8)	82:18	95
3	**3a**	1.5:1.0	93	80:20	94
4	**3a**	2.0:1.0	94	77:23	94
5	**3a**	3.0:1.0	91	72:28	93
6	**3a**	5.0:1.0	55 (38)	62:38	87

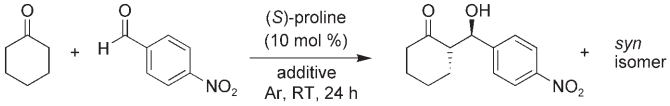
[a] Reaction conditions: under argon atmosphere, cyclohexanone (**1a**), *p*-nitrobenzaldehyde (**2a**, 2.0 mmol) and (*S*)-proline (0.2 mmol) were stirred for 24 h at room temperature using conventional magnetic stirring. [b] Combined yield of the isolated diastereomers. The data in parentheses indicate the amounts of recovered aldehyde. [c] Determined by ^{1}H NMR spectroscopic analysis of the crude product. [d] Determined by HPLC analysis of the *anti* isomer using a chiral stationary phase.

The first gratifying observation was that inexpensive and readily available (*S*)-proline was a highly efficient catalyst of the aldol reaction under solvent-free conditions. When stoichiometric amounts of reactants were used, the aldol product **3a** was obtained in 77% yield (along with 18% of recovered aldehyde), with an *anti*/*syn* ratio of 82:18 and with 95% *ee* (Table 1, entry 1). Improved conversions could be achieved by using 1.1 equivalents of ketone, leading to the desired product in 90% yield, without loss of selectivity (Table 1, entry 2).[31] As anticipated, the ratio of reactants was a crucial factor. It not only determined the rate of the reaction, but also the selectivity of the process. *It is particularly noteworthy that both reactivity and selectivity were higher in close to equimolar mixtures of reactants.* The best results were obtained when smaller excesses of cyclohexanone (between 0 and 50 mol%) were employed, affording products in high yields with both excellent diastereoselectivities and enantioselectivities ($\geq$80:20 *anti*/*syn*, $\geq$94% *ee*; Table 1, entries 1–3). The diastereoselectivity was lower ($\leq$77:23 *anti*/*syn*) when more than two equivalents of cyclohexanone were employed (Table 1, entries 4–6). Moreover, the use of a large excess of the liquid ketone, which was ex-

pected to favor the formation of a homogeneous mixture where the components can react more easily, not only decreased the selectivity of the process, but also slowed down the reaction. For example, when five equivalents of cyclohexanone were used (Table 1, entry 6), the desired adduct **3a** was obtained in only 55% yield (along with 38% of recovered aldehyde) and, additionally, the selectivity of the process was drastically diminished (62:38 *anti*/*syn*, 87% *ee*). Based on these results, subsequent experiments were carried out using a ketone to aldehyde ratio of 1.1:1.0.

Effect of water: In the proline-catalyzed aldol reaction the presence of water in an organic solvent was demonstrated to have positive effects increasing both reaction rate and enantioselectivity.[12] However, under solvent-free conditions water caused a deceleration of the reaction progress.[32] In order to determine the impact of water in our reaction system, catalyses were performed following the above-described methodology along with controlled additions of up to 5.0 equivalents of water (Table 2). It was observed

Table 2. Effect of water as additive on the solvent-free aldol reaction between cyclohexanone (**1a**) and *p*-nitrobenzaldehyde (**2a**) catalyzed by (*S*)-proline.[a]



1a **2a** *anti*-**3a**

Entry	H_2O [equiv]	Yield [%][b]	*anti*/*syn*[c]	*ee* [%][d]
1	0.15	78 (17)	90:10	97
2	0.5	63 (30)	93:7	98
3	1.0	17 (70)	88:12	90
4	2.0	<7	n.d.	n.d.
5	5.0	traces	n.d.	n.d.
6[e]	–	90 (8)	82:18	95

[a] Reaction conditions: under argon atmosphere, cyclohexanone (**1a**, 2.2 mmol), *p*-nitrobenzaldehyde (**2a**, 2.0 mmol), (*S*)-proline (0.2 mmol), and H_2O (if used) were stirred for 24 h at room temperature using conventional magnetic stirring. [b]–[d] As in Table 1. [e] Reaction run under air.

that even substoichiometric quantities of water (0.15 or 0.5 equivalents) led to reduced yields (78 and 63%, respectively) as a consequence of lower conversions (17 and 30% of recovered aldehyde, respectively; Table 2, entries 1 and 2). The stereoselectivities, however, improved giving *anti*-aldol products with up to 93:7 *anti*/*syn* ratio and 98% *ee* (Table 2, entry 2). In contrast, when stoichiometric amounts of water were added, the reaction was decelerated. Thus, by adding 1 equivalent of water, aldol product **3a** was obtained in only 17% yield, with an *anti*/*syn* ratio of 88:12 and with 90% *ee* (Table 2, entry 3). Besides, by adding $\geq$2 equivalents of water almost no reaction progress was detected (Table 2, entries 4 and 5). Probably, under those conditions proline is dissolved in the aqueous phase and thereby removed from the other reactants.

Gratifyingly, no difference in conversion, yield, or selectivity was observed between reactions run in air or under dry conditions (Table 2, entry 6 and Table 1, entry 2, respectively). Thus, this pleasing fact of "condition tolerance" allowed us to perform subsequent reactions without rigorously excluding air and moisture.

Direct use of commercial reagents—effect of acid: The established tolerance towards water indicated that neither dry reaction conditions nor strictly dried starting materials were required. However, the presence of other impurities in the commonly used commercially available reagents could also affect the reaction outcome. Therefore, a comparative experiment was carried out using all reagents as received from commercial suppliers, without further purification (Table 3, entry 1). Unlike in all previous cases, the initial heterogeneous reaction mixture rapidly evolved to a honey-like paste and after complete conversion a 95% yield of the aldol product with an *anti*/*syn* ratio of 89:11 and an *ee* of 94% resulted.

Table 3. Effect of *p*-nitrobenzoic acid (**4**) as additive on the solvent-free aldol reaction between cyclohexanone (**1a**) and *p*-nitrobenzaldehyde (**2a**) catalyzed by (*S*)-proline.[a]

Entry	**4** [equiv]	Yield [%][b]	*anti*/*syn*[c]	*ee* [%][d]
1[e]	–	95	89:11	94
2	0.005	92 (5)	85:15	90
3	0.01	90 (6)	87:13	87
4	0.02	92 (4)	88:12	82
5	0.04	93 (4)	86:14	82

[a] Reaction conditions: under argon atmosphere, cyclohexanone (**1a**, 2.2 mmol), *p*-nitrobenzaldehyde (**2a**, 2.0 mmol), (*S*)-proline (0.2 mmol), and acid **4** (if used) were stirred for 24 h at room temperature using conventional magnetic stirring. [b]–[d] As in Table 1. [e] All reagents were utilized as received from commercial suppliers, without further purification.

Taking into account the potential for aldehydes to be oxidized in air, the effect of small amounts of the corresponding acid, which could be present in commercial samples of aldehydes, was studied. In order to assure that only the impact of the acid (i.e., without other impurities or moisture present) was observed, the reactions were performed under argon using purified starting materials (ketone **1a** and aldehyde **2a**), and 0.5–4 mol% of *p*-nitrobenzoic acid (**4**) was added (Table 3, entries 2–5). Once again, almost complete conversions were achieved, and the products were obtained in high yields ($\geq$90%). For example, when 0.5 mol% of acid **4** was added, aldol product **3a** was obtained in 92% yield. With respect to the stereochemistry of the product, the acid had almost no effect on the *anti*/*syn* ratio (85:15), but the enantioselectivity decreased to only 90% *ee* (Table 3, entry 2). The latter was even reduced further by adding 1.0 mol% of acid **4** (87% *ee*; Table 3, entry 3). Upon use of $\geq$2 mol% of acid **4**, a dramatic decrease in the enantioselectivity was observed, leading to *anti*-aldol product **3a** with only 82% *ee* (Table 3, entries 4–5). Presumably, at this stage the acid catalysis of the aldol reaction became more dominate, promoting the (non-asymmetric) background re-

action. As a consequence, a larger fraction of racemic product was formed leading to a reduction of the final product *ee*. Fortunately, using reagents as received from commercial suppliers (without further purification) did not show this effect, and with them both high yields and excellent enantioselectivities were achieved.[33] Even more so, in all reactions with non-purified starting materials a more rapid formation of a melt favoring the stirring was observed, and perhaps the improved mixing of this partially homogenous intermediate phase favored higher yields after shorter times. The presence of small quantities of impurities (such as the corresponding acid) could promote this effect.

Based on these optimization studies, it can be concluded that: 1) using an excess of ketone is not advisable, since it causes a decrease in both yields and stereoselectivities; 2) neither dry conditions, nor inert atmosphere are required; 3) there is no advantage in using purified starting materials.

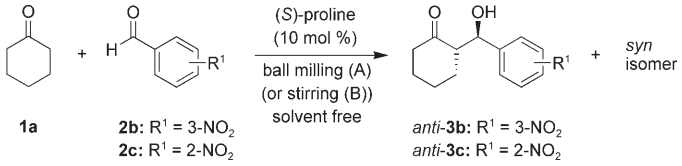
From these studies it became apparent that an efficient mixing method was vitally important in order to achieve high yields in this solvent-free reaction. In this respect, conventional magnetic stirring appeared insufficient, and to overcome this limitation, the mechanochemical technique of ball milling was considered.[18,19,27] With the aim to evaluate the effect of ball milling, comparative studies of the solvent-free aldol reaction using conventional magnetic stirring and ball milling were carried out for each substrate. Unless otherwise mentioned, the reactions were performed in an aerobic atmosphere, using all the reagents directly as received from commercial suppliers and a ratio of ketone to aldehyde of 1.1:1.

Studies in the ball mill: Ball milling is a mechanochemical technique, which can be applied as an alternative method of stirring. It involves milling (or grinding) of the reaction mixture with balls in a rotating vessel, both made of chemically inert and non-abrasive zirconium oxide.[34,35] The number of revolutions per minute (and therefore rate, temperature and degree of mixing) can be specified in a grinding cycle that includes a pause period to avoid overheating. Thereby, a selected cycle defined by the rotational speed, grinding time and pause period can be repeated until the reaction is completed.

First, the reaction between cyclohexanone (**1a**) and *p*-nitrobenzaldehyde (**2a**), in the presence of 10 mol% of (*S*)-proline as catalyst, was carried out in the ball mill. A milling cycle consisting of a 15 min milling period at a rotational speed of 400 rpm, followed by a 5 min pause, was used. This led to the desired aldol product **3a** in quantitative yield, with an *anti*/*syn* ratio of 89:11 and with 94% *ee*, after *only* 5.5 h. It is important to note that under typical ball-milling conditions, the mechanical agitation process led to a considerable heating of the reaction vessel (and as an extent, of the contents), in conjunction with increased pressure inside the vessel (detected when it was opened).[36]

As examples of the optimization of the milling cycle, the results of some selected experiments, in which cyclohexanone (**1a**) was treated with *m*-nitrobenzaldehyde (**2b**) or *o*-nitrobenzaldehyde (**2c**), are shown in Table 4. In these cases the optimum milling cycle for the formation of aldol products **3b** and **3c** consisted of a 15 min milling period at a rotational speed of 400 rpm, followed by a 5 min pause. Complete conversions were achieved after 7 h (Table 4, entries 3 and 7), and *anti*-aldol products **3b** and **3c** were formed in high yields (94 and 97%, respectively) and with excellent stereoselectivities (88:12 and 93:7 *anti*/*syn* ratio; >99 and 97% *ee*, respectively). It was observed that higher rotational speeds (≥500 rpm) resulted in lower *ee* values, together with decreased yields mainly due to the formation of by-products, both presumably as a result of the observed temperature increase (Table 4, entries 1, 2, 5 and 6). To minimize evolution of heat, shorter milling times, slower speeds and/or longer pause periods were programmed. However, in these systems lower rotational speed (300 rpm) led to lower substrate conversion as a result of inefficient mixing. Thus, long reaction times were required in order to achieve high yields (Table 4, entries 4 and 8).

Table 4. Optimization of the milling cycle for the aldol reaction between ketone **1a** and different aldehydes **2** catalyzed by (*S*)-proline performed in a ball mill.[a]



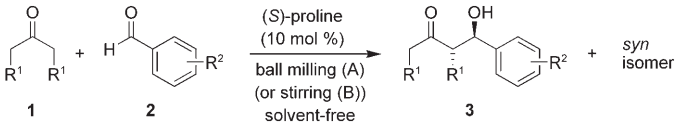
1a **2b**: R^1 = 3-NO_2; **2c**: R^1 = 2-NO_2; *anti*-**3b**: R^1 = 3-NO_2; *anti*-**3c**: R^1 = 2-NO_2

Entry	Product	Milling cycle	*t* [h]	Yield [%][b]	*anti*/*syn*[c]	*ee* [%][d]
1	**3b**	25 min at 700 rpm + 5 min pause	6.5	65	79:21	88
2	**3b**	5 min at 500 rpm + 5 min pause	5.5	87	82:18	97
3	**3b**	15 min at 400 rpm + 5 min pause	7	94	88:12	> 99
4	**3b**	30 min at 300 rpm + 15 min pause	16	92	84:16	95
5	**3c**	25 min at 700 rpm + 5 min pause	6.5	51 (16)	86:14	91
6	**3c**	5 min at 500 rpm + 5 min pause	5.5	76 (14)	89:11	94
7	**3c**	15 min at 400 rpm + 5 min pause	7	97	93:7	97
8	**3c**	30 min at 300 rpm + 15 min pause	16	83	90:10	96

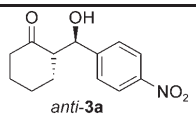
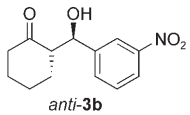
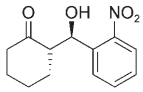
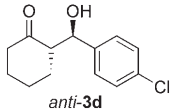
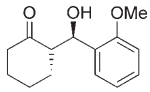
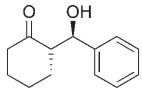
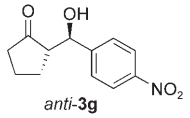
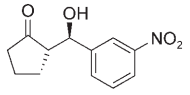
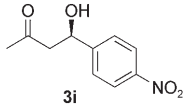
[a] Reaction conditions: cyclohexanone (**1a**, 2.2 mmol), aldehyde **2** (2.0 mmol), and (*S*)-proline (0.2 mmol) were stirred in the ball mill. [b]–[d] As in Table 1.

The generality of the ball-milling process was examined by varying the substrate combinations. Furthermore, a full comparative study revealed the beneficial effect of the ball milling with respect to conventional magnetic stirring (Table 5). Under solvent-free conditions the aldol products were generally obtained in high yields and with excellent stereoselectivities. By means of the ball mill the aldol reaction proceeded much faster, indicating the advantage of

Table 5. Scope of the solvent-free enantioselective aldol reaction catalyzed by (*S*)-proline under ball-milling conditions and under conventional magnetic stirring.[a]



1 2 3

Entry	Product	Method[b]	*t* [h]	Yield [%][c]	*anti*/*syn*[d]	*ee* [%][e]
1	 *anti*-**3a**	A	5.5	99	89:11	94
		B	24	95	89:11	94
2	 *anti*-**3b**	A	7	94	88:12	>99
		B	16	89 (10)	82:18	98
3	 *anti*-**3c**	A	7	97	93:7	97
		B	36	89	91:9	97
4	 *anti*-**3d**	A	20	87 (10)	74:26	75
		B	72	85 (9)	78:22	67
5	 *anti*-**3e**	A	36	65 (25)	66:34	63
		B	96	64 (26)	71:29	67
6	 *anti*-**3f**	A	11	53	81:19	45
		B	22	35	81:19	47
7	 *anti*-**3g**	A	5	53	57:43	95
		B	24	90	52:48	87
8	 *anti*-**3h**	A	5	93	50:50	90
		B	36	93	46:54	75
9	 **3i**	A	19	73	–	56
		B[f]	36	69	–	54

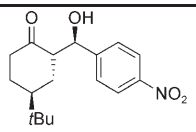
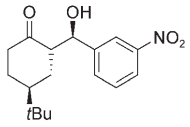
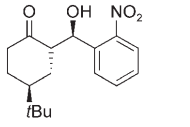
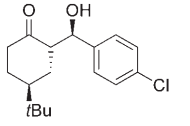
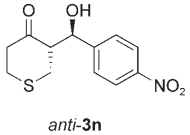
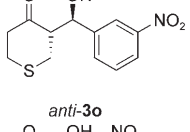
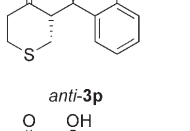
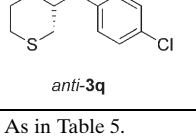
[a] Reaction conditions: ketone **1** (2.2 mmol), aldehyde **2** (2.0 mmol), (*S*)-proline (0.2 mmol). [b] Method A: the reaction mixture was stirred in the ball mill using a rotation speed of 250–400 rpm (see Supporting Information for details). Method B: the reaction mixture was stirred at room temperature using conventional magnetic stirring. [c] Combined yield of isolated diastereomers. The data in parentheses indicate the amounts of recovered aldehyde. [d] Determined by ^{1}H NMR spectroscopy of the crude product. [e] Determined by HPLC analysis of the *anti* isomer using a chiral stationary phase. [f] Acetone (4.0 mmol, 2.0 equiv) was employed.

using this mechanochemical technique.[37] As expected, while aldehydes with electron-withdrawing substituents afforded products with high stereoselectivities in short reaction times (Table 5, entries 1–3), more electron-rich groups lowered both the reactivity and stereoselectivity (Table 5, entries 4–6). Other liquid ketones such as cyclopentanone (**1b**) and acetone (**1c**) were also employed (Table 5, entries 7–9). In the former case, poor diastereoselectivities were observed, whereas the enantioselectivities were high (Table 5, 90–95% *ee*). In contrast, acetone afforded a product with only 56% *ee* (Table 5, entry 9). Notably, the abovementioned 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).[1,2,5a,6,12]

The excellent results obtained in the solvent-free aldol reaction, prompted us to further examine the advantages of the ball-milling technology by applying the method to a reaction between solely solid components, which additionally provided the opportunity to increase the range of cyclic ketones tested as donors. As such, 4-*tert*-butylcyclohexanone (**1d**) and tetrahydro-4*H*-thiopyran-4-one (**1e**) were treated with a variety of solid aromatic aldehydes. The results of this study, in conjunction with a comparative study using conventional magnetic stirring, are summarized in Table 6. We were pleased to observe that the reaction also proceeded efficiently between solely solid reagents under solvent-free conditions affording *anti*-aldol products **3j**–**q** with both excellent diastereoselectivities (up to 99:1 *anti*/*syn* ratio, Table 6, entry 8) and enantioselectivities (up to 98% *ee*, Table 6, entry 7). In the case of 4-*tert*-butylcyclohexanone (**1d**), the reaction produced mainly two diastereoisomers,[38] *anti*,*trans*-**3j**–**m** and *syn*,*trans*-**3j**–**m**, with high diastereocontrol (77:23 to 93:7 *anti*/*syn* ratio), obtaining the major *anti*,*trans*-(−)-**3j**–**m** in up to 95% *ee* (Table 6, entries 1–4). The relative stereochemistry of products **3j**–**m** was deduced from ^{1}H and ^{13}C NMR spectroscopic data: i) The characteristic ^{1}H NMR coupling constant between the protons COCHC*H*(OH) and COC*H*CH(OH) of the products ($^3J_{H,H}$ = 7.2 Hz) revealed the *anti*-aldol stereochemistry; ii) The 2,4-*trans* relationship was based on a comparison of the ^{13}C NMR data with those of the known *cis*- and *trans*-4-*tert*-butyl-2-hydroxymethylcyclohexanones.[39] Finally, the absolute configuration was assigned on the assumption of a similar reaction pathway.[40]

As expected, the reactions in the solid–solid system proceeded much slower than in the liquid–solid one (Table 5), presumably due to a more difficult mixing. In all these solid–solid reactions the application of a mechanochemical technique was particularly useful, and by means of ball milling high conversions were achieved in relatively short times (≤1.6 days), when compared with the use of conventional magnetic stirring (5–7 days). For example, while under conventional stirring the reaction between 4-*tert*-butylcyclohexanone (**1d**) and 4-nitrobenzaldehyde (**2a**) afforded aldol product **3j** in 58% yield after five days, ball milling led to the same product in 85% yield after only 1.4 days (Table 6, entry 1). In a similar way, reactions between ketone **1d** and nitrobenzaldehydes **2b**–**c** were faster under ball-milling conditions (Table 6, entries 2 and 3). As mentioned above, the

Table 6. Solvent-free enantioselective aldol reaction between solely solid reagents catalyzed by (*S*)-proline under ball-milling conditions.[a]

Entry	Product	Method[b]	*t* [d]	Yield [%][c]	*anti*/*syn*[d]	*ee* [%][e]
1	 *anti*-**3j**	A	1.4	85	91:9	91
		B	5	58 (24)	93:7	89
2	 *anti*-**3k**	A	1	80 (9)	78:22	92
		B	5	82	92:8	95
3	 *anti*-**3l**	A	1	66 (6)	81:19	88
		B	6	76 (6)	77:23	92
4	 *anti*-**3m**	A	1.6	75 (11)	92:8	93
		B	7	85 (10)	87:13	93
5	 *anti*-**3n**	A	1.4	79	96:4	90
		B	7	47 (32)	98:2	96
6	 *anti*-**3o**	A	1.5	75 (10)	88:12	89
		B	7	59 (18)	93:7	96
7	 *anti*-**3p**	A	1.5	59	82:18	96
		B	6	73	93:7	98
8	 *anti*-**3q**	A	1.4	72	95:5	85
		B	7	77	99:1	82

[a]–[e] As in Table 5.

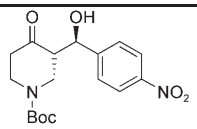
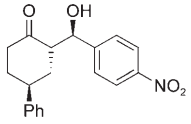
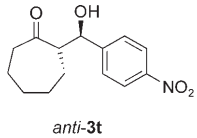
reactions were slower when aldehydes with more electron-rich substituents were utilized. Thus, after seven days under conventional stirring, the reaction between ketone **1d** and *p*-chlorobenzaldehyde (**2d**) afforded the aldol product **3m** in 85% yield. Remarkably, only 1.6 days under ball-milling conditions were required to obtain **3m** in 75% yield with excellent stereoselectivities (92:8 *anti*/*syn* and 93% *ee*; Table 6, entry 4). Due to the poor reactivity observed in these solid–solid systems, other aldehydes with more electron-rich substituents were not examined. Again in those reactions where solid 4-thiopyranone **1e** was employed, ball-milling conditions led to products in shorter reaction times without significant loss of stereoselectivities (Table 6, entries 5–8).

In the case of aldol reactions with purely solid reactants, it is of particular advantage to conduct the catalysis without using an excess of ketone (as required in solution). Besides the economical factor, practical issues are important, in particular, because purification of the products is simplified.

In solid–solid reactions two macroscopic solid particles interact directly and form a product (which can also be a solid) without the intervention of a liquid or vapor phase. Some proceed quantitatively without formation of waste, which makes them easily scalable. Furthermore, no solvent can be lost in an isolation step, making processes of this type sustainable and environmentally benign.[15,19] Although some reactions between solely solid compounds have been reported to proceed "in the solid phase", in most cases, mixing the solid reactants results in the formation of a liquid phase. Thus, some authors differentiate between purely solid-state reactions (also called solid–solid reactions)[15] and those that proceed via an intermediate melt.[41] When this liquefaction occurs at room temperature, it implies the existence of a eutectic mixture with T_{fusion} below ambient temperature (even when all reagents have higher than ambient melting points).[41] In our experiments performed at room temperature using conventional magnetic stirring, reactions between solely solid compounds *only* proceeded when a phase change to a melt occurred.[42] In a similar way, when solid aldol products **3a–i** were formed from liquid ketones **1a–c**, it was possible to observe that the initial (paste-likes) heterogeneous mixture of solid aldehyde **2** and proline dispersed in the liquid ketone **1** evolved to a partially homogeneous (honey-like) intermediate melt,[43] from which the aldol products crystallized as they were formed (Table 1 and Table 5). As a consequence of the continuous removal of the product from the reaction mixture, the aldol reaction is inherently irreversible under solvent-free conditions (unlike similar reactions in solution). In the ball-milling process the increased efficiency in mixing, the slightly elevated temperature and the pressure exhibited by the balls upon stirring are beneficial for a more rapid melt formation, which corresponds to the observed rate enhancement.

Additional evidence for the hypothesis that the existence of a liquid phase is a prerequisite for the reaction to occur is the observation that some reactions required heating (Table 7). When less reactive, solid ketones 1-Boc-4-piperidone (**1f**) and 4-phenylcyclohexanone (**1g**) were used as donors, no reaction or phase change was observed after stirring of the reaction mixture for eight days at room temperature (Table 7, entries 1 and 2). While the reaction components remained solids at room temperature, melting was observed at 60°C, which paralleled with some reaction progress. At this temperature, however, the enantioselectivity eroded (Table 7) and in some cases even racemates were obtained. Noteworthy, by means of ball milling these aldol reactions proceeded much faster (Table 7, entries 1 and 2), in-

Table 7. Solvent-free enantioselective aldol reaction catalyzed by (*S*)-proline.[a]

Entry	Product	Method[b]	*t* [d]	Yield [%][c]	*anti*/*syn*[d]	*ee* [%][e]
1	 *anti*-**3r**	A	1.5	50 (21)	86:14	55
		B	8	–	–	–
		B[f]	8	52 (6)	41:59	23
2	 *anti*-**3s**	A[g]	2	42 (29)	69:31	84
		B	8	–	–	–
		B[f,g]	8	42 (4)	45:55	rac
3	 *anti*-**3t**	A	3	traces	n.d.	n.d.
		B	8	traces	n.d.	n.d.
		B[f]	8	26 (60)	40:60	rac

[a]–[e] As in Table 5. [f] Reaction performed at 60 °C. [g] Depicted *anti*,*trans*-**3s** is the dominant isomer under ball-milling conditions. Conventional stirring at 60 °C leads predominantly to *syn*,*cis*-**3s**.

dicating once more the advantage of using this mechanochemical technique.[37]

Use of liquid cycloheptanone (**1h**) as donor showed that the existence of a liquid phase does not necessarily imply reactivity either at ambient temperature or in the ball mill (Table 7, entry 3). Indeed, this system was already known to be poorly reactive and unselective,[6] and here only low conversion was achieved when the mixture was stirred at 60 °C for eight days leading to product **3t** in 26 % yield without any stereoselectivity.

Only a few recently reported examples can be found in the literature where the solid ketones **1d**–**f** were used as donors in an organocatalyzed direct aldol reaction, all of them performed in organic solvents.[12,44] Among them, the study published by Pihko and co-workers attracted our attention, since there the proline-catalyzed enantioselective aldol reaction was also performed with stoichiometric amount of reactants.[12] This allowed us to directly compare their results obtained in DMF solution (with up to five equivalents of water, which was found to accelerate the catalysis) with ours achieved under solvent-free conditions. In their study, product **3n** was formed in 45 % yield after five days, and product **3q** in 54 % yield after three days. By means of a ball milling we obtained products **3n** and **3q** in 79 and 72 % yield, respectively, after only 1.4 days. The diastereoselectivities were similar to those described by Pihko and co-workers, while the enantioselectvities were somewhat lower (90 and 85 % *ee*, compared with 99 and 98 % *ee*, respectively). At least in terms of reactivity these results also highlight advantages of the ball-milling methodology.

It is fascinating to speculate on the correspondence between catalytic enantioselective reactions in a ball mill (which allow for the creation of conditions of high pressure and temperature, and, in the present case for crystallization of a highly enantiomerically enriched product from a melt) and reactions between achiral organic molecules in the presence of enantiomerically enriched amino acids in a presumably hot, geologically active prebiotic world. Such reactions are a possible source of complex molecules containing multiple stereocenters starting from a catalytic amount of enantiopure amino acid and similar processes could be implicated as steps in the evolution of homochirality.

Conclusion

In this study, proline-catalyzed aldol reactions have been investigated under solvent-free conditions. The effects of concentration, water and impurities on the reaction outcome have been established revealing that: 1) a reagent ratio close to 1:1 is optimal, and using an excess of ketone can cause a decrease in both yield and stereoselectivity; 2) neither dry conditions nor inert atmosphere are required; 3) there is no need to use purified starting materials.

For achieving optimal results in terms of yield and stereoselectivity an intense mixing of all reagents proved to be indispensable. Along these lines, ball milling has been used in asymmetric organocatalysis for the first time. The advantages of using this mechanochemical technique are: 1) Organocatalyzed asymmetric aldol reactions proceed faster than under commonly applied mechanical stirring leading to high yield of *anti*-aldol products **3** with excellent diastereoselectivities and enantioselectivities. 2) After optimization of milling cycles, the reactions are remarkably clean yielding mostly highly crystalline solids, which are easy to isolate. 3) Catalytic amounts of inexpensive proline can be used, and difficult to prepare catalysts are not required. 4) Almost equimolar amounts of the starting materials react well, avoiding the common uneconomical and impractical use of a large excess of ketone. As additional benefit, the isolation of the product from the reaction mixture becomes easier, since at that stage the entire starting materials are consumed.

Noteworthy, the preparation of **3a** can be performed in a 10 g scale in the ball mill without significant change in yield and with the same stereoselectivity.[45]

The results reported in this article may serve as useful guidelines for the development of other enantioselective organocatalytic carbon–carbon bond-forming reactions under solvent-free conditions.

Experimental Section

General information: All reagents were purchased from commercial suppliers. When purified reagents were used, cyclohexanone was distilled and *p*-nitrobenzaldehyde was sublimated before use. Reactions in the ball mill were conducted using a Fritsch Planetary Micro Mill model "Pulverisette 7". The milling instrument consists of a main disk which can rotate at a speed of 100–800 rpm and accommodates two grinding bowls. Both bowls (45 mL) and balls (5 mm diameter) are made of chemically inert and non-abrasive zirconium oxide. Grinding cycles (including a pause period) are programmed and repeated. Flash chromatography

was carried out with Merck silica gel 60 (63–200 mesh). For thin-layer chromatography (TLC), Merck 60 F_{254} silica gel plates were used and compounds were visualized by means of irradiation with UV light and/or by treatment with a solution of *p*-anisaldehyde (9.2 mL), concentrated H_2SO_4 (12.5 mL), acetic acid (3.8 mL), and ethanol (340 mL) followed by heating. ^{1}H NMR and ^{13}C NMR (300 or 400 MHz and 75 or 100 MHz, respectively) spectra were recorded in $CDCl_3$. Chemical shifts (δ) are reported in ppm using TMS as internal standard, and spin–spin coupling constants (J) are given in Hz. IR spectra were recorded on a Perkin-Elmer FT/IR 1760 as KBr pellets, neat or in $CHCl_3$ and are given in cm^{-1}. Melting points were measured in open glass capillaries and are uncorrected. Optical rotation measurements were determined at 22 °C using HPLC-grade solvents. Analytical HPLC measurements were carried out on a Gynkotek (Dionex) machine with autosampler GINA 50, UV/VIS detector UVD 170S, gradient pump M480G and degasser DG 503.

General experimental procedure for the solvent-free aldol reaction catalyzed by (*S*)-proline under inert and dry conditions: Under argon, a dry 10 mL round-bottomed flask charged with a magnetic stirring bar was filled with cyclohexanone (**1a**, 230 μL, 2.2 mmol, 1.1 equiv), *p*-nitrobenzaldehyde (**2a**, 302 mg, 2.0 mmol, 1.0 equiv), (*S*)-proline (23 mg, 0.2 mmol, 0.1 equiv), and an additive (if used). Stirring was started using a conventional magnetic stirring bar. After 24 h, the vessel was washed with Et_2O or CH_2Cl_2 (6×7 mL), and the combined organic fractions were filtered and concentrated in vacuo. Purification by flash chromatography on silica gel (pentane/EtOAc 100:0 → 80:20) afforded the pure aldol product **3a** in the yields and enantioselectivities reported in Tables 1–3 (see main Text). The identity and purity of the aldol product **3a** was confirmed by ^{1}H and ^{13}C NMR spectroscopic analysis. The diastereoselectivity of the reaction was determined by ^{1}H NMR spectroscopy of the crude product.

Typical experimental procedure for the solvent-free aldol reaction catalyzed by (*S*)-proline

Reaction performed in the ball mill (Method A): A ball-mill vessel was charged with ketone **1** (2.2 mmol, 1.1 equiv), aldehyde **2** (2.0 mmol, 1.0 equiv), (*S*)-proline (23 mg, 0.2 mmol, 0.1 equiv), and 60 zirconium oxide balls. Stirring was started in a grinding bowl using the ball mill with a rotation speed of 250–400 rpm (see Supporting Information for details). After an appropriate reaction time, the crude product was washed off the reaction vessel with Et_2O or CH_2Cl_2 (4×40 mL), and the combined organic fractions were filtered and concentrated in vacuo. Purification by flash chromatography on silica gel (pentane/EtOAc 100:0 → 80:20) afforded the pure aldol product **3** in the yields and enantioselectivities reported in Tables 4–7 (see main Text). The identity and purity of the product was confirmed by ^{1}H and ^{13}C NMR spectroscopic analysis. Aldol products *anti*-**3a–h**, **3i**, *anti*-**3n–r** and *anti*-**3t** are known compounds.[6,12b,27,44b] The diastereoselectivity of the reaction was determined by ^{1}H NMR spectroscopy of the crude product. The enantiomeric excess of *anti*-aldol products was determined by chiral-phase HPLC analysis. The absolute configuration of aldol products was determined by comparison with published HPLC retention times.

Reaction performed in a round-bottom flask (Method B): A 10 mL round-bottomed flask was charged with ketone **1** (2.2 mmol, 1.1 equiv), aldehyde **2** (2.0 mmol, 1.0 equiv), and (*S*)-proline (23 mg, 0.2 mmol, 0.1 equiv). Stirring was started using a conventional magnetic stirring bar. After an appropriate reaction time, the vessel was washed with Et_2O or CH_2Cl_2 (6×7 mL), and the combined organic fractions were filtered and concentrated in vacuo. The diastereoselectivity of the reaction was determined by ^{1}H NMR spectroscopy of the crude product. Purification by flash chromatography on silica gel (pentane/EtOAc 100:0 → 80:20) afforded the pure aldol product **3** in the yields and enantioselectivities reported in Tables 5–7 (see main Text). The identity and purity of the product was confirmed by ^{1}H and ^{13}C NMR spectroscopic analysis.

(2*S*,1′*R*)-2-[1′-Hydroxy-1′-(4-nitrophenyl)methyl]cyclohexan-1-one [(2*S*,1′*R*)-3a]:[27] The enantiomeric excess was determined by HPLC (Daicel Chiralpak AD, heptane/*i*PrOH 90:10, flow rate 0.5 mL min^{-1}, λ = 254 nm): t_R = 51.6 min (minor), t_R = 69.6 min (major). Data for the major isomer (2*S*,1′*R*)-**3a**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.32–1.72 (m, 4H; cyclohex-*H*), 1.80–1.88 (m, 1H; cyclohex-*H*), 2.08–2.15 (m, 1H; cyclohex-*H*), 2.32–2.41 [m, 1H; C*H*HC(O)], 2.47–2.53 [m, 1H; CH*H*C(O)], 2.55–2.62 (m, 1H; C*H*CHOH), 4.07 (brs, 1H; CHO*H*), 4.90 (d, J = 8.4 Hz, 1H; C*H*OH), 7.50–7.52 (m, 2H; Ar*H*), 8.19–8.23 ppm (m, 2H; Ar*H*); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.7 (CH_2), 27.6 (CH_2), 30.7 (CH_2), 42.6 (CH_2), 57.2 (CH), 74.0 (CH), 123.5 (CH, 2C), 127.8 (CH, 2C), 147.5 (C), 148.3 (C), 214.7 ppm (C).

(2*S*,1′*R*)-2-[1′-Hydroxy-1′-(3-nitrophenyl)methyl]cyclohexan-1-one [(2*S*,1′*R*)-3b]:[27] The enantiomeric excess was determined by HPLC (Daicel Chiralpak AD, heptane/*i*PrOH 92:8, flow rate 0.5 mL min^{-1}, λ = 210 nm): t_R = 49.3 min (major), t_R = 63.1 min (minor). Data for the major isomer (2*S*,1′*R*)-**3b**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.33–1.73 (m, 4H; cyclohex-*H*), 1.79–1.86 (m, 1H; cyclohex-*H*), 2.08–2.15 (m, 1H; cyclohex-*H*), 2.33–2.41 [m, 1H; C*H*HC(O)], 2.47–2.53 [m, 1H; CH*H*C(O)], 2.58–2.65 (m, 1H; C*H*CHOH), 4.12 (brs, 1H; CHO*H*), 4.89 (d, J = 8.5 Hz, 1H; C*H*OH), 7.52 (t, J = 7.9 Hz, 1H; Ar*H*), 7.65–7.68 (m, 1H; Ar*H*), 8.16 (ddd, J = 8.2, 2.3, 1.1 Hz, 1H; Ar*H*), 8.20–8.21 ppm (m, 1H; Ar*H*); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.6 (CH_2), 27.6 (CH_2), 30.6 (CH_2), 42.6 (CH_2), 57.0 (CH), 73.9 (CH), 121.9 (CH), 122.8 (CH), 129.2 (CH), 133.2 (CH), 143.2 (C), 148.2 (C), 214.8 ppm (C).

(2*S*,1′*R*)-2-[1′-Hydroxy-1′-(2-nitrophenyl)methyl]cyclohexan-1-one [(2*S*,1′*R*)-3c]:[27] The enantiomeric excess was determined by HPLC (Daicel Chiralcel OD-H, heptane/*i*PrOH 97:3, flow rate 0.8 mL min^{-1}, λ = 254 nm): t_R = 32.0 min (major), t_R = 38.7 min (minor). Data for the major isomer (2*S*,1′*R*)-**3c**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.55–1.87 (m, 5H; cyclohex-*H*), 2.05–2.14 (m, 1H; cyclohex-*H*), 2.28–2.39 [m, 1H; C*H*HC(O)], 2.41–2.49 [m, 1H; CH*H*C(O)], 2.71–2.80 (m, 1H; C*H*CHOH), 3.98 (brs, 1H; CHO*H*), 5.44 (d, J = 7.1 Hz, 1H; C*H*OH), 7.39–7.45 (m, 1H; Ar*H*), 7.60–7.66 (m, 1H; Ar*H*), 7.75–7.78 (m, 1H; Ar*H*), 7.83–7.86 ppm (m, 1H; Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.0 (CH_2), 27.8 (CH_2), 31.1 (CH_2), 42.8 (CH_2), 57.3 (CH), 69.7 (CH), 123.9 (CH), 128.3 (CH), 128.9 (CH), 132.9 (CH), 136.4 (C), 148.5 (C), 214.7 ppm (C).

(2*S*,1′*R*)-2-[1′-Hydroxy-1′-(4-chlorophenyl)methyl]cyclohexan-1-one [(2*S*,1′*R*)-3d]:[27] The enantiomeric excess was determined by HPLC (Daicel Chiralpak AD, heptane/*i*PrOH 90:10, flow rate 0.5 mL min^{-1}, λ = 230 nm): t_R = 29.1 min (minor), t_R = 34.2 min (major). Data for the major isomer (2*S*,1′*R*)-**3d**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.13–1.28 (m, 1H; cyclohex-*H*), 1.42–1.73 (m, 4H; cyclohex-*H*), 1.96–2.05 (m, 1H; cyclohex-*H*), 2.21–2.52 [m, 3H; CH_2C(O) + C*H*CHOH], 4.12 (d, J = 2.8 Hz, 1H; CHO*H*), 4.68 (dd, J = 6.7, 2.6 Hz, 1H; C*H*OH), 7.15–7.26 ppm (m, 4H; Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.7 (CH_2), 27.7 (CH_2), 30.8 (CH_2), 42.7 (CH_2), 57.3 (CH), 74.0 (CH), 128.2 (CH, 2C), 128.4 (CH, 2C), 133.4 (C), 139.4 (C), 215.0 ppm (C).

(2*S*,1′*R*)-2-[1′-Hydroxy-1′-(2-methoxyphenyl)methyl]cyclohexan-1-one [(2*S*,1′*R*)-3e]:[27] The enantiomeric excess was determined by HPLC (Daicel Chiralcel OD-H, heptane/*i*PrOH 95:5, flow rate 0.5 mL min^{-1}, λ = 210 nm): t_R = 28.8 min (major), t_R = 37.5 min (minor). Data for the major isomer (2*S*,1′*R*)-**3e**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.32–1.74 (m, 5H; cyclohex-*H*), 1.93–2.01 (m, 1H; cyclohex-*H*), 2.23–2.31 [m, 1H; C*H*HC(O)], 2.36–2.42 [m, 1H; CH*H*C(O)], 2.62–2.69 (m, 1H; C*H*CHOH), 3.74 (s, 3H; OCH_3), 5.19 (d, J = 8.6 Hz, 1H; C*H*OH), 6.79 (dd, J = 8.3, 0.8 Hz, 1H; Ar*H*), 6.91 (m, 1H; Ar*H*), 7.18 (ddd, J = 8.2, 7.5, 1.7 Hz, 1H; Ar*H*), 7.33 ppm (dd, J = 7.6, 1.7 Hz, 1H; Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.8 (CH_2), 28.0 (CH_2), 30.5 (CH_2), 42.6 (CH_2), 55.4 (CH_3), 57.3 (CH), 68.6 (CH), 110.4 (CH), 120.8 (CH), 127.8 (CH), 128.5 (CH), 129.5 (C), 156.6 (C), 215.3 ppm (C).

(2*S*,1′*R*)-2-(1′-Hydroxy-1′-phenylmethyl)cyclohexan-1-one [(2*S*,1′*R*)-3f]:[6] The enantiomeric excess was determined by HPLC (Daicel Chiralcel OD-H, heptane/*i*PrOH 95:5, flow rate 0.5 mL min^{-1}, λ = 210 nm): t_R = 26.3 min (major), t_R = 39.8 min (minor). Data for the major isomer (2*S*,1′*R*)-**3f**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.21–1.28 (m, 1H; cyclohex-*H*), 1.46–1.73 (m, 4H; cyclohex-*H*), 1.99–2.04 (m, 1H; cyclohex-*H*), 2.25–2.34 [m, 1H; C*H*HC(O)], 2.38–2.45 [m, 1H; CH*H*C(O)], 2.51–2.59 (m, 1H; C*H*CHOH), 3.89 (d, J = 3.0 Hz, 1H; CHO*H*), 4.72 (dd, J = 8.8, 2.7 Hz, 1H; C*H*OH), 7.20–7.30 ppm (m, 5H; Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.7 (CH_2), 26.7 (CH_2), 29.8 (CH_2), 41.6 (CH_2), 56.3 (CH), 73.6 (CH), 125.8 (CH, 2C), 126.7 (CH), 127.2 (CH, 2C), 139.7 (C), 214.2 ppm (C).

(2*S*,1′*R*)-2-[1′-Hydroxy-1′-(4-nitrophenyl)methyl]cyclopentan-1-one [(2*S*,1′*R*)-3g]:[27] The enantiomeric excess was determined by HPLC (Daicel Chiralpak AD, heptane/*i*PrOH 97:3, flow rate 0.5 mL min^{-1}, λ = 254 nm): t_R = 140.1 min (minor), t_R = 145.9 min (major). Data for the major isomer (2*S*,1′*R*)-**3g**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.45–1.73 (m, 3H; cyclopent-*H*), 1.91–2.00 (m, 1H; cyclopent-*H*), 2.16–2.44 [m, 3H; CH_2C(O) + C*H*CHOH], 4.69 (d, J = 0.9 Hz, 1H; CHO*H*), 4.78 (d, J = 9.2 Hz, 1H; C*H*OH), 7.45–7.49 (m, 2H; Ar*H*), 8.13–8.17 ppm (m, 2H; Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.4 (CH_2), 26.9 (CH_2), 38.6 (CH_2), 55.1 (CH), 74.4 (CH), 123.6 (CH, 2C), 127.2 (CH, 2C), 147.5 (C), 148.5 (C), 222.0 ppm (C).

(2*S*,1′*R*)-2-[1′-Hydroxy-1′-(3-nitrophenyl)methyl]cyclopentan-1-one [(2*S*,1′*R*)-3h]:[27] The enantiomeric excess was determined by HPLC (Daicel Chiralpak AD, heptane/*i*PrOH 96:4, flow rate 1.0 mL min^{-1}, λ = 254 nm): t_R = 43.7 min (major), t_R = 67.4 min (minor). Data for the major isomer (2*S*,1′*R*)-**3h**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.50–1.55 (m, 1H; cyclopent-*H*), 1.61–1.78 (m, 2H; cyclopent-*H*), 1.92–2.01 (m, 1H; cyclopent-*H*), 2.16–2.47 [m, 3H; CH_2C(O) + C*H*CHOH], 4.72 (s, 1H; CHO*H*), 4.77 (d, J = 9.3 Hz, 1H; C*H*OH), 7.47 (t, J = 7.9, Hz, 1H; Ar*H*), 7.62–7.65 (m, 1H; Ar*H*), 8.10 (ddd, J = 8.1, 2.3, 1.1 Hz, 1H; Ar*H*), 8.17–8.18 ppm (m, 1H; Ar*H*); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.3 (CH_2), 26.8 (CH_2), 38.6 (CH_2), 55.0 (CH), 74.3 (CH), 121.5 (CH), 122.9 (CH), 129.4 (CH), 132.6 (CH), 143.6 (C), 148.3 (C), 222.3 ppm (C).

(4*R*)-4-Hydroxy-4-nitrophenylbutan-1-one (3i):[27] The enantiomeric excess was determined by HPLC (Daicel Chiralpak AS, heptane/*i*PrOH 70:30, flow rate 0.5 mL min^{-1}, λ = 254 nm): t_R = 26.4 min (major), t_R = 35.4 min (minor). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.22 (s, 3H; CH_3), 2.84–2.86 (m, 2H; CH_2CHOH), 3.59 (s, 1H; CHO*H*), 5.26 (dd, J = 8.0, 4.3 Hz, 1H; C*H*OH), 7.52–7.55 (m, 2H; Ar*H*), 8.19–8.22 ppm (m, 2H; Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 30.7 (CH_3), 51.5 (CH_2), 68.8 (CH), 123.5 (CH, 2C), 126.3 (CH, 2C), 147.0 (C), 149.9 (C), 208.2 ppm (C).

(2*S*,4*S*,1′*R*)-4-*tert*-Butyl-2-[1′-hydroxy-1′-(4-nitrophenyl)methyl]cyclohexan-1-one [(2*S*,4*S*,1′*R*)-3j]: The enantiomeric excess was determined by HPLC (Daicel Chiralcel OD-H, heptane/*i*PrOH 92:8, flow rate 0.5 mL min^{-1}, λ = 280 nm): t_R = 53.4 min (major), t_R = 66.6 min (minor). Data for the major isomer (2*S*,4*S*,1′*R*)-**3j**, which was obtained in enantiomerically pure form after recrystallization: M.p. 184–185 °C; $[\alpha]_D^{22}$ = −11.4 (c = 1.00 in $CHCl_3$, ≥ 99 % *ee*); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.79 (s, 9H; CH_3), 1.34–1.68 (m, 4H; cyclohex-*H*), 1.94–2.00 (m, 1H; cyclohex-*H*), 2.38–2.47 (m, 1H; C*H*HC(O)), 2.51–2.57 [m, 1H; CH*H*C(O)], 2.63–2.69 (m, 1H; C*H*CHOH), 3.62 (br, 1H; CHCHO*H*), 4.97 (dd, J = 9.4, 2.9 Hz, 1H; CHC*H*OH), 7.53–7.55 (m, 2H; Ar*H*), 8.23–8.25 ppm (m, 2H; Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.3 (CH_2), 27.0 (CH_2), 27.1 (CH_3, 3C), 33.0 (C), 39.4 (CH_2), 42.5 (CH), 54.4 (CH), 74.0 (CH), 123.7 (CH, 2C), 127.7 (CH, 2C), 147.7 (C), 148.5 (C), 215.7 ppm (C); IR (KBr): $\tilde{\nu}$ = 3468, 2956, 1702, 1600, 1520, 1452, 1392, 1343, 1267, 1042, 856 cm^{-1}; MS (EI): m/z (%): 305 (2) [M^+], 287 (13) [M^+−H_2O], 154 (98), 151 (72), 139 (97), 70 (78), 57 (100); elemental analysis calcd (%) for $C_{17}H_{23}NO_4$ (305.4): C 66.86, H 7.59, N 4.59; found: C 67.12, H 7.33, N 4.59.

(2*S*,4*S*,1′*R*)-4-*tert*-Butyl-2-[1′-hydroxy-1′-(3-nitrophenyl)methyl]cyclohexan-1-one [(2*S*,4*S*,1′*R*)-3k]: The enantiomeric excess was determined by HPLC (Daicel Chiralcel OG, heptane/*i*PrOH 85:15, flow rate 0.7 mL min^{-1}, λ = 210 nm): t_R = 30.0 min (minor), t_R = 43.3 min (major). Data for the major isomer (2*S*,4*S*,1′*R*)-**3k**, which was obtained in enantiomerically pure form after recrystallization: M.p. 154–155 °C; $[\alpha]_D^{22}$ = −5.3 (c = 1.00 in $CHCl_3$, ≥ 99 % *ee*); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.79 (s, 9H; CH_3), 1.37–1.68 (m, 4H; cyclohex-*H*), 1.97–2.02 (m, 1H; cyclohex-*H*), 2.41–2.56 [m, 2H; CH_2C(O)], 2.65–2.71 (m, 1H; C*H*CHOH), 3.69 (d, J = 3.3 Hz, 1H; CHO*H*), 4.99 (dd, J = 9.3, 3.3 Hz, 1H; C*H*OH), 7.56 (t, J = 7.8 Hz, 1H; Ar*H*), 7.72 (d, J = 7.7 Hz, 1H; Ar*H*), 8.18–8.21 (m, 1H; Ar*H*), 8.24–8.26 ppm (m, 1H; Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.6 (CH_2), 27.1 (CH_3, 3C), 27.3 (CH_2), 32.9 (C), 39.4 (CH_2), 42.4 (CH), 54.7 (CH), 74.0 (CH), 121.9 (CH), 123.1 (CH), 129.5 (CH), 132.9 (CH), 143.5 (C), 148.2 (C), 215.7 ppm (C); IR (KBr): $\tilde{\nu}$ = 3328, 2962, 1702, 1526, 1444, 1345, 1218, 1060, 823 cm^{-1}; MS (EI): m/z (%): 305 (2) [M^+], 287 (13) [M^+−H_2O], 154 (99), 151 (45), 139 (100), 70 (73), 57 (67); elemental analysis calcd (%) for $C_{17}H_{23}NO_4$ (305.4): C 66.86, H 7.59, N 4.59; found: C 66.64, H 7.69, N 4.63.

(2*S*,4*S*,1′*R*)-4-*tert*-Butyl-2-[1′-hydroxy-1′-(2-nitrophenyl)methyl]cyclohexan-1-one [(2*S*,4*S*,1′*R*)-3l]: The enantiomeric excess was determined by HPLC (Daicel Chiralpak AD, heptane/*i*PrOH 85:15, flow rate 0.4 mL min^{-1}, λ = 210 nm): t_R = 22.7 min (minor), t_R = 25.8 min (major). Data for the major isomer (2*S*,4*S*,1′*R*)-**3l**: M.p. 83–84 °C; $[\alpha]_D^{22}$ = −4.5 (c = 1.00 in $CHCl_3$, 90 % *ee*); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.78 (s, 9H; CH_3), 1.50–1.70 (m, 4H; cyclohex-*H*), 1.88–1.93 (m, 1H; cyclohex-*H*), 2.37–2.46 [m, 2H; CH_2C(O)], 2.80–2.86 (m, 1H; C*H*CHOH), 3.55 (br, 1H; CHO*H*), 5.46 (d, J = 7.2 Hz, 1H; C*H*OH), 7.43 (dt, J = 7.8, 1.4 Hz, 1H; Ar*H*), 7.63 (dt, J = 8.4, 1.4 Hz, 1H; Ar*H*), 7.73 (dd, J = 8.0, 1.4 Hz, 1H; Ar*H*), 7.84 ppm (dd, J = 8.0, 1.3 Hz, 1H; Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.3 (CH_2), 27.0 (CH_3, 3C), 27.6 (CH_2), 32.8 (C), 39.7 (CH_2), 42.4 (CH), 53.7 (CH), 69.7 (CH), 124.3 (CH), 128.7 (CH), 129.1 (CH), 133.3 (CH), 136.9 (C), 148.7 (C), 216.1 ppm (C); IR (KBr): $\tilde{\nu}$ = 3455, 2870, 1702, 1527, 1446, 1353, 1093, 1032, 861 cm^{-1}; MS (EI): m/z (%): 306 (53) [(M+1)$^+$], 288 (13) [(M+1)$^+$−H_2O], 155 (100), 152 (86); elemental analysis calcd (%) for $C_{17}H_{23}NO_4$ (305.4): C 66.86, H 7.59, N 4.59; found: C 66.48, H 7.76, N 4.63.

(2*S*,4*S*,1′*R*)-4-*tert*-Butyl-2-[1′-hydroxy-1′-(4-chlorophenyl)methyl]cyclohexan-1-one [(2*S*,4*S*,1′*R*)-3m]: The enantiomeric excess was determined by HPLC (Daicel Chiralpak AD, heptane/*i*PrOH 95:5, flow rate 0.5 mL min^{-1}, λ = 230 nm): t_R = 33.3 min (minor), t_R = 63.8 min (major). Data for the major isomer (2*S*,4*S*,1′*R*)-**3m**: M.p. 150–151 °C; $[\alpha]_D^{22}$ = −6.3 (c = 1.00 in $CHCl_3$, 93 % *ee*); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.79 (s, 9H; CH_3), 1.38–1.59 (m, 4H; cyclohex-*H*), 1.96–2.02 (m, 1H; cyclohex-*H*), 2.41–2.54 [m, 2H; CH_2C(O)], 2.62 (dt, J = 9.6, 6.6 Hz, 1H; C*H*CHOH), 3.28 (br, 1H; CHO*H*), 4.86 (dd, J = 9.6, 2.8 Hz, 1H; C*H*OH), 7.27–7.36 ppm (m, 4H; Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.2 (CH_2), 27.2 (CH_3, 3C), 27.6 (CH_2), 32.9 (C), 39.3 (CH_2), 42.3 (CH), 55.2 (CH), 74.2 (CH), 128.2 (CH, 2C), 128.7 (CH, 2C), 133.9 (C), 139.8 (C), 215.7 ppm (C); IR (KBr): $\tilde{\nu}$ = 3472, 2958, 2871, 1699, 1486, 1091, 1041, 830 cm^{-1}; MS (EI): m/z (%): 294 (1) [M^+], 276 (7) [M^+−H_2O], 154 (66), 140 (32), 139 (100), 70 (51), 57 (35); elemental analysis calcd (%) for $C_{17}H_{23}O_2Cl$ (294.8): C 69.26, H 7.86; found: C 69.19, H 8.07.

(3*S*,1′*R*)-3-[1′-Hydroxy-1′-(4-nitrophenyl)methyl]tetrahydrothiopyran-4-one [(3*S*,1′*R*)-3n]:[12b,44b] The enantiomeric excess was determined by HPLC (Daicel Chiralcel OD-H, heptane/*i*PrOH 92:8, flow rate 0.5 mL min^{-1}, λ = 254 nm): t_R = 79.7 min (major), t_R = 127.2 min (minor). Data for the major isomer (3*S*,1′*R*)-**3n**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.51 [ddd, J = 13.7, 4.7, 2.2 Hz, 1H; SC*H*HCHC(O)], 2.66 [dd, J = 13.7, 11.0 Hz, 1H; SCH*H*CHC(O)], 2.74–2.83 (m, 2H; SCH_2), 2.94–3.04 [m, 3H; CH_2C(O) + C*H*CHOH], 3.64 (d, J = 4.1 Hz, 1H; CHO*H*), 5.05 (dd, J = 8.2, 3.9 Hz, 1H; C*H*OH), 7.54 (d, J = 8.8 Hz, 2H; Ar*H*), 8.23 ppm (d, J = 8.8 Hz, 2H; Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 30.8 (CH_2), 32.8 (CH_2), 44.8 (CH_2), 59.5 (CH), 73.2 (CH), 123.8 (CH, 2C), 127.8 (CH, 2C), 147.7 (C), 147.8 (C), 211.2 ppm (C).

(3*S*,1′*R*)-3-[1′-Hydroxy-1′-(3-nitrophenyl)methyl]tetrahydrothiopyran-4-one [(3*S*,1′*R*)-3o]:[44b] The enantiomeric excess was determined by HPLC (Daicel Chiralpak AD, heptane/*i*PrOH 92:8, flow rate 0.7 mL min^{-1}, λ = 254 nm): t_R = 67.9 min (major), t_R = 85.0 min (minor). Data for the major isomer (3*S*,1′*R*)-**3o**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.52 [ddd, J = 13.7, 4.7, 2.2 Hz, 1H; SC*H*HCHC(O)], 2.68 [dd, J = 13.7, 11.0 Hz, 1H; SCH*H*CHC(O)], 2.76–2.85 (m, 2H; SCH_2), 2.95–3.07 [m, 3H; CH_2C(O) + C*H*CHOH], 3.69 (d, J = 4.0 Hz, 1H; CHO*H*), 5.04 (dd, J = 8.2, 4.0 Hz, 1H; C*H*OH), 7.55 (t, J = 7.9 Hz, 1H, Ar*H*), 7.70 (d, J = 7.7 Hz, 1H, Ar*H*), 8.16–8.24 ppm (m, 2H, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 30.8 (CH_2), 32.8 (CH_2), 44.8 (CH_2), 59.4 (CH), 73.23 (CH), 122.0 (CH), 123.2 (CH), 129.6 (CH), 133.0 (CH), 142.6 (C), 148.4 (C), 211.4 ppm (C).

(3*S*,1′*R*)-3-[1′-Hydroxy-1′-(2-nitrophenyl)methyl]tetrahydrothiopyran-4-one [(3*S*,1′*R*)-3p]:[44b] The enantiomeric excess was determined by HPLC (Daicel Chiralpak AD, heptane/*i*PrOH 90:10, flow rate 0.5 mL min^{-1}, λ = 210 nm): t_R = 64.6 min (minor), t_R = 82.9 min (major). Data for the major isomer (3*S*,1′*R*)-**3p**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.61 [ddd, J = 13.6, 4.5, 2.4 Hz, 1H; SC*H*HCHC(O)], 2.73–2.84 (m, 2H; SCH_2), 2.88–3.02 [m, 3H; SCH*H*CHC(O), CH_2C(O)], 3.11–3.19 (m, 1H; C*H*CHOH), 5.54 (d, J = 6.7 Hz, 1H; C*H*OH), 7.45 (dt, J = 7.2, 1.5 Hz, 1H; Ar*H*), 7.66 (dt,

J=7.7, 1.5 Hz, 1H; Ar*H*), 7.77 (dd, J=7.9, 1.5 Hz, 1H; Ar*H*), 7.89 ppm (dd, J=8.2, 1.5 Hz, 1H; Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ=30.8 (CH_2), 33.4 (CH_2), 45.2 (CH_2), 59.6 (CH), 69.4 (CH), 124.4 (CH), 128.9 (CH), 129.0 (CH), 133.5 (CH), 136.0 (C), 148.6 (C), 211.5 ppm (C).

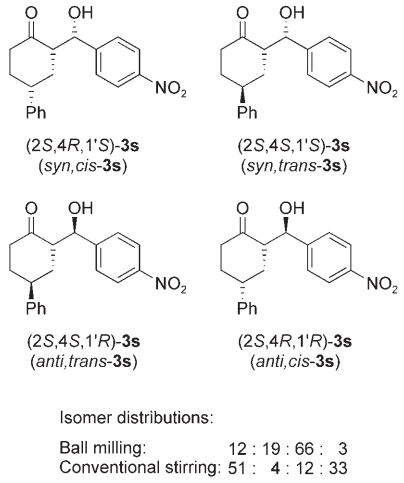
(3*S*,1′*R*)-3-[1′-Hydroxy-1′-(4-chlorophenyl)methyl]tetrahydrothiopyran-4-one [(3*S*,1′*R*)-3q]:[12b,44b] The enantiomeric excess was determined by HPLC (Daicel Chiralcel OD-H, heptane/*i*PrOH 92:8, flow rate 0.5 mL min^{-1}, λ=210 nm): t_R=35.6 min (major), t_R=53.3 min (minor). Data for the major isomer (3*S*,1′*R*)-**3q**: ^{1}H NMR (400 MHz, $CDCl_3$): δ= 2.49 [ddd, J=13.7, 4.9, 1.9 Hz, 1H; SC*H*HCHC(O)], 2.57 [dd, J=13.7, 10.1 Hz, 1H; SCH*H*CHC(O)], 2.72–2.87 (m, 2H; SCH_2), 2.91–2.99 [m, 3H; CH_2C(O) + C*H*CHOH], 3.46 (d, J=3.6 Hz, 1H; CHO*H*), 4.93 (dd, J=8.5, 3.3 Hz, 1H; C*H*OH), 7.27–7.35 ppm (m, 4H; Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ=31.0 (CH_2), 32.9 (CH_2), 44.7 (CH_2), 59.7 (CH), 73.3 (CH), 128.3 (CH, 2C), 128.8 (CH, 2C), 134.0 (C), 138.7 (C), 211.5 ppm (C).

(3*S*,1′*R*)-3-[1′-Hydroxy-1′-(4-nitrophenyl)methyl]-4-oxopiperidine-1-carboxylic acid *tert*-butyl ester [(3*S*,1′*R*)-3r]:[44b] When the reaction was performed in the ball mill, the major isomer obtained was (3*S*,1′*R*)-**3r**. The enantiomeric excess was determined by HPLC (Daicel Chiralpak AD-H, heptane/*i*PrOH 85:15, flow rate 0.5 mL min^{-1}, λ=210 nm): t_R=26.0 min (major), t_R=28.0 min (minor). Data for the isomer (3*S*,1′*R*)-**3r**: ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.40 (brs, 9H; CH_3), 2.48–2.59 (m, 2H; CH_2C(O)), 2.76 (br, 1H; C*H*CHOH), 2.93 (brt, J=11.3 Hz, 1H, piperidinyl-*H*), 3.27 (br, 1H, piperidinyl-*H*), 3.70–3.88 (m, 1H, piperidinyl-*H*), 3.88 (d, J=3.6 Hz, 1H, CHO*H*), 4.11–4.17 (m, 1H, piperidinyl-*H*), 4.99 (dd, J=8.0, 2.7 Hz, 1H; C*H*OH), 7.56 (d, J=8.9 Hz, 2H; Ar*H*), 8.24 ppm (d, J=8.9 Hz, 2H; Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ=28.3 (CH_3, 3C), 41.5 (CH_2), 42.8 (CH_2), 43.7 (CH_2), 56.4 (CH), 71.7 (CH), 81.0 (C), 123.6 (CH, 2C), 127.7 (CH, 2C), 147.1 (C), 147.6 (C), 154.2 (C), 210.0 ppm (C).

(2*S*,4*S*,1′*R*)-2-[1′-Hydroxy-1′-(4-nitrophenyl)methyl]-4-phenylcyclohexan-1-one [(2*S*,4*S*,1′*R*)-3s]: When the reaction was performed in the ball mill, the major isomer obtained was (2*S*,4*S*,1′*R*)-**3s**. The enantiomeric excess was determined by HPLC (Daicel Chiralpak AD-H, heptane/*i*PrOH 90:10, flow rate 0.5 mL min^{-1}, λ=210 nm): t_R=78.5 min (minor), t_R= 119.4 min (major). Data for the isomer (2*S*,4*S*,1′*R*)-**3s**: M.p. 142–143 °C; $[\alpha]_D^{22}$=+33.6 (c=1.00 in $CHCl_3$, 84% *ee*); ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.76–1.86 (m, 1H; cyclohex-*H*), 1.93–2.04 (m, 1H; cyclohex-*H*), 2.15–2.24 (m, 1H; cyclohex-*H*), 2.36–2.43 (m, 1H; cyclohex-*H*), 2.54–2.61 [m, 2H; CH_2C(O)], 2.75–2.83 (m, 1H; C*H*CHOH), 3.16–3.19 (m, 1H; C*H*Ph), 3.67 (d, J=3.2 Hz, 1H; CHO*H*), 5.04 (dd, J=8.7, 3.1 Hz, 1H; C*H*OH), 7.13–7.33 (m, 5H; Ar*H*), 7.53 (d, J=8.7 Hz, 2H; Ar*H*), 8.23 ppm (d, J=8.4 Hz, 2H; Ar*H*); ^{13}C NMR (75 MHz, $CDCl_3$): δ=31.2 (CH_2), 34.2 (CH_2), 36.9 (CH), 39.2 (CH_2), 54.1 (CH), 74.0 (CH), 123.7 (CH, 2C), 126.4 (CH, 2C), 126.7 (CH), 127.8 (CH, 2C), 128.8 (CH, 2C), 142.2 (C), 147.7 (C), 148.2 (C), 213.8 ppm (C); IR (KBr): $\tilde{\nu}$=3345, 2919, 2856, 1702, 1597, 1508, 1340, 1055, 851 cm^{-1}; MS (EI): m/z (%): 325 (2) [M^+], 307 (14) [M^+–H_2O], 174 (68), 151 (36), 104 (100); elemental analysis calcd (%) for $C_{19}H_{19}NO_4$ (325.4): C 70.14, H 5.89, N 4.31; found: C 69.74, H 6.27, N 4.25.

When the reaction was performed in a flask, after 8 d at 60 °C the major *anti* isomer was (2*S*,4*R*,1′*R*)-**3s**. The enantiomeric excess was determined by HPLC (Daicel Chiralpak AD-H, heptane/*i*PrOH 90:10, flow rate 0.5 mL min^{-1}, λ=210 nm): t_R=83.6 min (minor), t_R=86.6 min (major). Data for the isomer (2*S*,4*R*,1′*R*)-**3s**: ^{1}H NMR (400 MHz, $CDCl_3$): δ= 1.65–1.71 (m, 2H; cyclohex-*H*), 1.89–2.04 (m, 1H; cyclohex-*H*), 2.22–2.25 (m, 1H; cyclohex-*H*), 2.58–2.62 [m, 2H; CH_2C(O)], 2.81–2.88 (m, 1H; C*H*CHOH), 2.98–3.05 (m, 1H; C*H*Ph), 4.17 (d, J=3.0 Hz, 1H; CHO*H*), 4.96 (dd, J=8.8, 3.3 Hz, 1H; C*H*OH), 7.11–7.28 (m, 5H; Ar*H*), 7.50 (d, J=8.8 Hz, 2H; Ar*H*), 8.15 ppm (d, J=8.8 Hz, 2H; Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ=34.8 (CH_2), 37.7 (CH_2), 42.3 (CH_2), 42.9 (CH), 56.5 (CH), 73.8 (CH), 123.6 (CH, 2C), 126.5 (CH, 2C), 126.9 (CH), 127.9 (CH, 2C), 128.7 (CH, 2C), 143.6 (C), 147.5 (C), 148.0 (C), 213.8 ppm (C).

(2*S*,1′*R*)-2-[1′-Hydroxy-1′-(4-nitrophenyl)methyl]cycloheptan-1-one [(2*S*,1′*R*)-3t]:[6] The enantiomeric excess was determined by HPLC analysis of the *anti* isomer (Daicel Chiralpak AD-H, heptane/*i*PrOH 90:10, flow rate 0.5 mL min^{-1}, λ=254 nm): t_R=39.0 min (major), t_R=92.6 min (minor). Data for the *anti* isomer (2*S*,1′*R*)-**3t**: ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.25–1.42 (m, 3H; cyclohept-*H*), 1.56–1.92 (m, 5H; cyclohept-*H*), 2.43–2.58 [m, 2H; CH_2C(O)], 2.95–3.00 (m, 1H; C*H*CHOH), 3.72 (brs, 1H; CHO*H*), 4.92 (d, J=7.4 Hz, 1H; C*H*OH), 7.51–7.54 (m, 2H; Ar*H*), 8.20–8.23 ppm (m, 2H; Ar*H*); ^{13}C NMR (75 MHz, $CDCl_3$): δ=23.4 (CH_2), 28.2 (CH_2), 28.6 (CH_2), 28.7 (CH_2), 44.1 (CH_2), 57.8 (CH), 74.8 (CH), 123.6 (CH, 2C), 127.7 (CH, 2C), 147.5 (C), 149.2 (C), 216.9 ppm (C).



Acknowledgements

We are grateful to the Fonds der Chemischen Industrie and to the Deutsche Forschungsgemeinschaft (DFG) within the SPP 1179 ("Organocatalysis") for financial support. A.B. thanks DFG for a doctoral fellowship (GRK 440).

[1] For some selected examples, see: a) B. List, R. A. Lerner, C. F. Barbas III, *J. Am. Chem. Soc.* **2000**, *122*, 2395–2396; b) D. Enders, C. Grondal, *Angew. Chem.* **2005**, *117*, 1235–1238; *Angew. Chem. Int. Ed.* **2005**, *44*, 1210–1212.

[2] For some recent reviews, see: a) B. List, *Acc. Chem. Res.* **2004**, *37*, 548–557; b) A. Berkessel, H. Gröger, *Asymmetric Organocatalysis*, Wiley-VCH, Weinheim, **2005**, Chapter 6; c) B. List, *Chem. Commun.* **2006**, 819–824.

[3] For very interesting contributions on the possible role of amino acids as catalysts in the evolution of prebiotic homochirality, see: a) S. Pizzarello, A. L. Weber, *Science* **2004**, *303*, 1151; b) M. Klussmann, H. Iwamura, S. P. Mathew, D. H. Wells Jr, U. Pandya, A. Armstrong, D. G. Blackmond, *Nature* **2006**, *441*, 621–623, and references therein; c) J. Crusats, S. Veintemillas-Verdaguer, J. M. Ribó, *Chem. Eur. J.* **2006**, *12*, 7776–7781; d) see also: R. M. Kellogg, *Angew. Chem.* **2007**, *119*, 498–502; *Angew. Chem. Int. Ed.* **2007**, *46*, 494–497.

[4] For recent reviews on organic reactions in aqueous media, see: a) C.-J. Li, *Chem. Rev.* **2005**, *105*, 3095–3165; b) C.-J. Li, L. Chen, *Chem. Soc. Rev.* **2006**, *35*, 68–82; c) H. C. Hailes, *Org. Process Res. Dev.* **2007**, *11*, 114–120.

[5] a) Y. Hayashi, T. Sumiya, J. Takahashi, H. Gotoh, T. Urushima, M. Shoji, *Angew. Chem.* **2006**, *118*, 972–975; *Angew. Chem. Int. Ed.* **2006**, *45*, 958–961; b) Y. Hayashi, S. Aratake, T. Okano, J. Takahashi, T. Sumiya, M. Shoji, *Angew. Chem.* **2006**, *118*, 5653–5655; *Angew. Chem. Int. Ed.* **2006**, *45*, 5527–5529.

[6] N. Mase, Y. Nakai, N. Ohara, H. Yoda, K. Takabe, F. Tanaka, C. F. Barbas III, *J. Am. Chem. Soc.* **2006**, *128*, 734–735.

[7] Additional examples of organocatalyzed aldol reactions performed in water can be found in: a) D. Font, C. Jimeno, M. A. Pericàs, *Org. Lett.* **2006**, *8*, 4653–4655; b) Y. Wu, Y. Zhang, M. Yu, G. Zhao, S. Wang, *Org. Lett.* **2006**, *8*, 4417–4420; c) Z. Jiang, Z. Liang, X. Wu, Y. Lu, *Chem. Commun.* **2006**, 2801–2803; d) P. Dziedzic, W. Zou, J. Háfren, A. Córdova, *Org. Biomol. Chem.* **2006**, *4*, 38–40; e) S. S. Chimni, D. Mahajan, *Tetrahedron: Asymmetry* **2006**, *17*, 2108–2119; f) for other examples of aldol reactions performed in aqueous systems, see A. Córdova, W. Notz, C. F. Barbas III, *Chem. Commun.* **2002**, 3024–3025; g) Y.-Y. Peng, Q.-P. Ding, Z. Li, P. G. Wang, J.-P. Cheng, *Tetrahedron Lett.* **2003**, *44*, 3871–3875.

[8] The insolubility of organic compounds in water can also cause them to react on its surface, which implies that hydrogen-bond-type interactions are responsible for rate accelerations and greater selectivities observed in aqueous reaction media compared with organic ones. Sharpless and co-workers introduced the term "on-water" chemistry to denote the reaction between insoluble reactants suspended on water. For the descriptions of the concept, see: a) S. Narayan, J. Muldoon, M. G. Finn, V. V. Fokin, H. C. Kolb, K. B. Sharpless, *Angew. Chem.* **2005**, *117*, 3339–3343; *Angew. Chem. Int. Ed.* **2005**, *44*, 3275–3279; b) some additional details on the discussion concerning this terminology can be found in: A. P. Brogan, T. J. Dickerson, K. D. Janda, *Angew. Chem.* **2006**, *118*, 8278–8280; *Angew. Chem. Int. Ed.* **2006**, *45*, 8100–8102; c) Y. Hayashi, *Angew. Chem.* **2006**, *118*, 8281–8282; *Angew. Chem. Int. Ed.* **2006**, *45*, 8103–8104.

[9] Here, we would like to refer to these reactions as performed either in water, in the presence of water or in an aqueous environment, without participating in any controversy on that issue.

[10] For a general concept article, see M. C. Pirrung, *Chem. Eur. J.* **2006**, *12*, 1312–1317, and references therein.

[11] For a recently published application of this concept in the study of organocatalyzed ring opening of oxiranes, see: C. M. Kleiner, P. R. Schreiner, *Chem. Commun.* **2006**, 4315–4317.

[12] For an interesting study on the water-accelerated aldol reaction catalyzed by proline in DMF using a stoichiometric amount of solid ketones, see: a) A. I. Nyberg, A. Usano, P. M. Pihko, *Synlett* **2004**, 1891–1896; b) P. M. Pihko, K. M. Laurikainen, A. Usano, A. I. Nyberg, J. A. Kaavi, *Tetrahedron* **2006**, *62*, 317–328, and references therein.

[13] Some examples of metal-catalyzed reactions accelerated by the presence of water can be found in ref. [8a] and references therein. See also: M. Carril, R. SanMartin, I. Tellitu, E. Domínguez, *Org. Lett.* **2006**, *8*, 1467–1470.

[14] For an overview on solvent-free organic reactions, see: a) G. W. Cave, C. L. Raston, J. L. Scott, *Chem. Commun.* **2001**, 2159–2169; b) K. Tanaka, *Solvent-Free Organic Synthesis*, Wiley-VCH, Weinheim, **2003**.

[15] For a recent review on highly efficient organic solid-state reactions, see: a) G. Kaupp, *Top. Curr. Chem.* **2005**, *254*, 95–183; b) for information on the mechanism of solid-state reactions, see: G. Kaupp, *CrystEngComm* **2003**, *5*, 117–133.

[16] a) *Green Chemistry: Theory and Practice* (Eds.: P. T. Anastas, J. C. Warner), Oxford University Press, Oxford, **1998**; b) see also: P. A. Wender, S. T. Handy, D. L. Wright, *Chem. Ind.* **1997**, *765*, 767–769; for some recent reviews on the use of green solvents in organic synthesis, see: c) C. K. Z. Andrade, L. M. Alves, *Curr. Org. Chem.* **2005**, *9*, 195–218; d) R. A. Sheldon, *Green Chem.* **2005**, *7*, 267–278; e) M. Avalos, R. Babiano, P. Cintas, J. L. Jiménez, J. C. Palacios, *Angew. Chem.* **2006**, *118*, 4008–4012; *Angew. Chem. Int. Ed.* **2006**, *45*, 3904–3908.

[17] Some isolated examples of solvent-free organocatalytic aldol reactions can be found in ref. [5], see also: a) Y. Sekiguchi, A. Sasaoka, A. Shimomoto, S. Fujioka, H. Kotsuki, *Synlett* **2003**, 1655–1658; b) Z. Tang, Z.-H. Yang, X.-H. Chen, L.-F. Cun, A.-Q. Mi, Y.-Z. Jiang, L.-Z. Gong, *J. Am. Chem. Soc.* **2005**, *127*, 9285–9289; c) M. Jiang, S.-F. Zhu, Y. Yang, L.-Z. Gong, X.-G. Zhou, Q.-L. Zhou, *Tetrahedron: Asymmetry* **2006**, *17*, 384–387; d) Y. Hayashi, S. Aratake, T. Itoh, T. Okano, T. Sumiya, M. Shoji, *Chem. Commun.* **2007**, 957–959.

[18] Reviews: a) G. Kaupp, M. R. Naimi-Jamal, H. Ren, H. Zoz in *Advanced Technologies based on Self-Propagating and Mechanochemical Reactions for Environmental Protection* (Eds.: G. Cao, F. Delogu, R. Orrû), Research Signpost, Kerala, **2003**, pp. 83–100; b) S. Kipp, V. Sepelák, K. D. Becker, *Chem. Unserer Zeit* **2005**, *39*, 384–392.

[19] For an interesting review on waste-free, large-scale transformations using the ball-milling technique, see: G. Kaupp, *CrystEngComm* **2006**, *8*, 794–804.

[20] K. Komatsu, *Top. Curr. Chem.* **2005**, *254*, 185–206.

[21] Z. Zhang, J. Gao, J.-J. Xia, G.-W. Wang, *Org. Biomol. Chem.* **2005**, *3*, 1617–1619.

[22] a) G. Kaupp, M. R. Naimi-Jamal, V. Stepanenko, *Chem. Eur. J.* **2003**, *9*, 4156–4160; b) G. Kaupp, M. R. Naimi-Jamal, J. Schmeyers, *Tetrahedron* **2003**, *59*, 3753–3760.

[23] C. L. Raston, J. L. Scott, *Green Chem.* **2000**, *2*, 49–52.

[24] V. P. Balema, J. W. Wiench, M. Pruski, V. K. Pecharsky, *J. Am. Chem. Soc.* **2002**, *124*, 6244–6245.

[25] M. O. Rasmussen, O. Axelsson, D. Tanner, *Synth. Commun.* **1997**, *27*, 4027–4030.

[26] a) E. Tullberg, D. Peters, T. Frejd, *J. Organomet. Chem.* **2004**, *689*, 3778–3781; b) E. Tullberg, F. Schacher, D. Peters, T. Frejd, *Synthesis* **2006**, 1183–1189.

[27] B. Rodríguez, T. Rantanen, C. Bolm, *Angew. Chem.* **2006**, *118*, 7078–7080; *Angew. Chem. Int. Ed.* **2006**, *45*, 6924–6926.

[28] T. Rantanen, I. Schiffers, C. Bolm, *Org. Process Res. Dev.* ASAP; DOI: 10.1021/op6002743.

[29] When the solid aldehyde **2a** was not used as finely ground powder, only low conversion was observed and unreacted starting material was recovered as a crystalline aggregate.

[30] The prolate ellipsoid-shaped magnetic stirring bar, which adjusts to the shape of a round-bottom vessel, was employed because higher conversions were observed with this stirring bar compared to others.

[31] When the same experiment was performed using a cylindrical magnetic stirring bar, the aldol product was isolated in only 76% yield (along with 20% of recovered aldehyde), with no differences in selectivities. This experiment illustrates the importance of a suitable mixing method.

[32] Some isolated examples can be found in refs. [5a] and [6].

[33] An obvious advantage of this is that the solvent-free protocol can be more easily applied on industrial scale, where a reagent purification is difficult.

[34] Although ZrO_2 presents very good resistance to abrasion and acid treatment, it is not entirely non-abrasive. In order to ensure that the ZrO_2 is chemically inert and does not affect the reaction outcome, a comparative experiment between cyclohexanone and *p*-nitrobenzaldehyde as substrates, in the presence of one equivalent of ZrO_2 salt as additive was performed. In this experiment, freshly purified starting materials were used under inert and dry conditions. The reaction mixture was stirred for 24 h in a flask at room temperature using conventional magnetic stirring. In this case aldol product **3a** was obtained in 67% yield, with an *anti*/*syn* ratio of 80:20 and with 94% *ee* (compare with the result showed in Table 1, entry 2). The decrease in the reaction rate was not surprising, since the stirring mode was different and the addition of an inert salt resulted in a decrease in the concentration of the components in the reaction mixture.

[35] In accordance with the application and in order to prevent attrition, a few measures should be taken into account. First, overheating due to friction should be avoided. Thus, long grinding times and/or high rotational speeds should only be used in combination of pause periods. Second, depending on the sample amount an adequate number of balls should be placed in the grinding bowls. A larger number of balls will reduce the grinding time, but also cause higher abrasion, which should be avoided. In the 2 mmol scale experiments reported here 60 balls were used in order to mix and homogenize the reaction mixture.

[36] The temperature and pressure increase appeared to be higher when higher rotational speeds were programmed. Unfortunately, both parameters could not precisely be measured while performing the reaction. When the bowls were opened, the crude reaction mixture appeared like a thick slightly inhomogeneous paste.
[37] To some extend, this rate enhancement might be due to the elevated temperature in the ball-milling experiment. In proline-catalyzed Mannich reactions, a significant temperature tolerance has been observed. B. Rodríguez, C. Bolm, *J. Org. Chem.* **2006**, *71*, 2888–2891.
[38] Only traces (< 5% each) of the corresponding *cis*-isomers were formed.
[39] For the ^{13}C NMR spectroscopic data of *cis*- and *trans*-2-hydroxymethyl-4-*tert*-butylcyclohexanones, see: a) R. A. Wanat, D. B. Collum, *J. Am. Chem. Soc.* **1985**, *107*, 2078–2082. Additionally, the ^{1}H and ^{13}C NMR spectroscopic data of the major products **3j–m** correspond well with the data reported for other *trans*-4-*tert*-butylcyclohexanones substituted with a hydroxymethyl-group at C2. For examples, see in ref. [12] and in b) D. E. Ward, W.-L. Lu, *J. Am. Chem. Soc.* **1998**, *120*, 1098–1099.
[40] The signs of the specific rotations of the major products **3j–m** correspond with those reported in ref. [12].
[41] For a general concept article, see: G. Rothenberg, A. P. Downie, C. L. Raston, J. L. Scott, *J. Am. Chem. Soc.* **2001**, *123*, 8701–8708.
[42] Since the existence of an intermediate melt is requisite for the reaction to occur, these aldol reactions should not be called solid-state reactions.
[43] In some cases this intermediate melt phase rapidly solidified, and the appearance of the mixture was not completely homogeneous. However, we assume that in the case of the liquid–solid systems the melt intermediate phase (peritectic mixture) was also a requisite for the reaction to occur.
[44] For aldol reactions using solid ketones **1d**, **1e** or **1f** as donors, see: a) D. E. Ward, V. Jheengut, *Tetrahedron Lett.* **2004**, *45*, 8347–8350; b) J.-R. Chen, X.-Y. Li, X.-N. Xing, W.-J. Xiao, *J. Org. Chem.* **2006**, *71*, 8198–8202; c) P. Dinér, M. Amedjkouh, *Org. Biomol. Chem.* **2006**, *4*, 2091–2096.
[45] When the reaction was performed on a 10 g scale (40 mmol), about 150 balls were placed in the grinding bowl. The full vessel was rotated at 400 rpm (15 min milling + 5 min pause) over 6 h. An increased pressure was detected when the vessel was opened. The product was obtained quantitatively (yield determined by ^{1}H NMR) with an *anti*/*syn* ratio of 84:16 and 92% *ee* (for the *anti* isomer). After recrystallization in AcOEt/pentane, the *anti*-aldol product was isolated as white solid in 76% yield.

Received: February 2, 2007

