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# Chitosan Aerogel Beads as a Heterogeneous Organocatalyst for the Asymmetric Aldol Reaction in the Presence of Water: An Assessment of the Effect of Additives

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The catalytic properties of chitosan aerogel for the direct asymmetric aldol reaction in water assisted by various surfactants and acid co-catalysts have been evaluated by employing a range of donor and acceptor systems. A beneficial effect on both the yields and enantioselectivities was observed, and the combination of surfactants and acid co-catalysts has proven particularly useful in the case of heterocyclic ketone donors.

## Introduction

Catalytic transformations involving "organocatalysts" have attracted considerable interest in recent years.[1] The advantages, such as the ready separation of products and the reusability of catalysts, which are very important in large-scale production, has recently led to the development of strategies involving the functionalization of both inorganic and polymeric supports with organic catalysts.[2] On the other hand, the emphasis on environmentally friendly and sustainable resources and processes is leading to an increasing use of natural materials in catalysis.[3] Biopolymers, a diverse and versatile class of materials that are cheap and widely abundant in Nature,[4] have therefore attracted in recent years great interest as supports for catalysts.[5] Among polysaccharides, chitosan (Figure 1), produced by the alkaline deacetylation of chitin, the most abundant biopolymer in Nature after cellulose, is a widely used support for catalytic applications.[6] In this context, the chiral organic catalyst L-proline was recently supported on chitosan and was successful in promoting a heterogeneous asymmetric aldol reaction in various organic solvents and in the presence of water.[7]

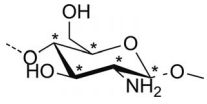


Figure 1. Chitosan monomer.

Although chitosan is a chiral polyamine, its direct use in heterogeneous organocatalysis has been the subject of only a limited number of investigations. Chitosan microspheres have been used as a green catalyst in the synthesis of monoglyceride by the addition of fatty acid to glycidol,[8,9] whereas chitosan hydrogels have found applications in aldol and Knoevenagel reactions.[10] Very recently, a comprehensive assessment has been made of the efficiency of chitosan beads as recyclable and heterogeneous organocatalysts for a variety of C–C bond-forming reactions.[11] However, no significant induction of stereoselectivity caused by the backbone chirality of the chitosan polymer was noted in any of these reports.

As a part of our current interest in organocatalysed asymmetric reactions,[12] we recently succeeded in developing the first direct asymmetric aldol reaction in the presence of water catalysed by chemically unmodified chitosan, thus demonstrating that this biopolymer-derived material is efficient not only as a heterogeneous recyclable organocatalyst, but also as a source of chirality.[13] Chitosan aerogel microspheres[14] were preferred over commercial chitosan or hydrogel chitosan. The aerogel formulation of chitosan gives a well-characterized material with a defined molecular weight distribution, (high) surface area and (high) accessibility to the amine function. This guarantees a better reproducibility compared with commercial chitosan, the molecular weight and composition of which are dependent on the natural source, and even a slightly better catalytic efficiency compared with hydrogel chitosan.[13] In

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addition, the solid, spongy morphology of the chitosan aerogel microsphere allowed for easier handling compared with its hydrogel formulation and facilitated filtration for recycling.

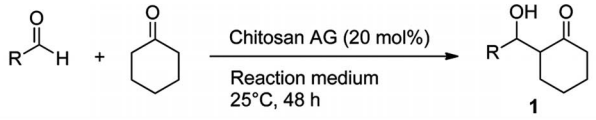
Herein, we report a thorough investigation of the role of different kinds of additives on the chemical and stereochemical outcomes of the aldol reaction catalysed by chitosan aerogel microspheres, ultimately resulting in a remarkable improvement in both reaction scope and efficiency.

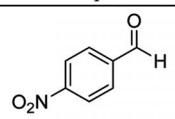
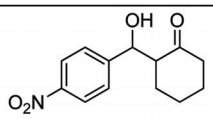
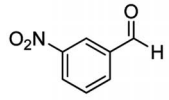
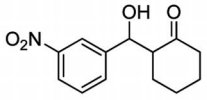
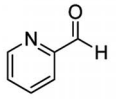
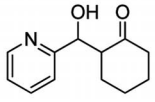
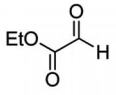
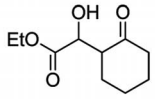
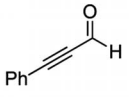
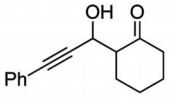
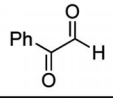
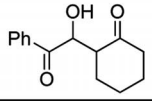
## Results and Discussion

An intriguing aspect of the use of the chitosan aerogel as an organocatalyst is related to its efficacy in the interaction of donor and acceptor systems in the absence or presence of water. This aspect being closely related to the construction of the optimal reaction medium, we performed a series of initial tests on the prototype reaction between 4-nitrobenzaldehyde as aldol acceptor and cyclohexanone as pro-nucleophile (Table 1). Several organic solvents, such as DMSO and THF, were screened, but very little or no aldol product was detected (Entries 1 and 2), and the same outcome was observed (Entry 3) when the reaction was performed in neat cyclohexanone. Conversely, the reaction performed with water as the bulk medium[15] turned out to be successful, no substantial variations being noticed on varying the amount of water within the range of 0.3 and 0.5 mL (compare Entries 4 and 5).

To expand the scope of the reaction beyond the acceptor systems previously studied,[13] a series of acceptor aldehydes were examined under the conditions optimized with cyclohexanone as the ketone donor. As shown in Table 1, not only aromatic and heteroaromatic aldehydes (Entries 5–7), but also variously structured acceptor systems (Entries 9–11) in the presence of water afforded the aldol products in fairly high yields, moderate diastereoselectivities and signifi-

Table 1. Chitosan aerogel organocatalysed asymmetric aldol reaction between aldehydes and cyclohexanone in the presence of water.[a]




| Entry | Reaction medium | Acceptor | Product | 1 | Yield [%][b] | *anti*/*syn*[c] | *ee* [%][d] |
|---|---|---|---|---|---|---|---|
| 1 | THF (0.3 mL) |  |  | **1a** | traces | n.d. | n.d. |
| 2 | DMSO (0.3 mL) | " | " | " | traces | n.d. | n.d. |
| 3 | neat | " | " | " | traces | n.d. | n.d. |
| 4 | $H_2O$ (0.3 mL) | " | " | " | 75 | 70/30 | 80 (50) |
| 5 | $H_2O$ (0.5 mL) | " | " | " | 85 | 70/30 | 84 (60) |
| 6 | " |  |  | **1b** | 70 | 69/31 | 80 (60) |
| 7 | " |  |  | **1c** | 70 | 67/33 | 70 (62)[e] |
| 8 | " |  |  | **1d** | <10 | – | – |
| 9 | " |  |  | **1e** | 90[f] | 53/47 | 5 (62)[f] |
| 10 | " |  |  | **1f** | 90 | 57/43 | 70 (77) |
| 11 | " |  |  | **1g** | 80 | 53/47 | 48 (64) |

[a] Reagents and conditions: 4.9 mg of chitosan AG, which corresponds to 20 mol-% of free amino units with respect to the aldehyde, 0.10 mmol of acceptor aldehyde, 2 mmol of cyclohexanone donor (donor/acceptor ratio = 20:1), 48 h, 25 °C. [b] Isolated yield after chromatography on silica gel. [c] Determined by $^1H$ NMR analysis of the crude mixture (n.d. = not determined). [d] Determined by chiral stationary phase HPLC analyses (results in parentheses refer to the minor diastereoisomer). [e] Determined on the crude mixture. [f] After benzoylation.

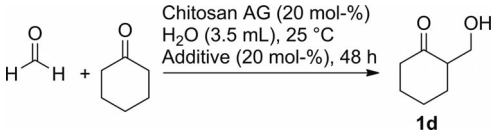
cant enantiomeric excesses. Only in the case of water-miscible formaldehyde (Entry 8) did the reaction fail, which was predictable[16] and attributed to the fact that this acceptor system in bulk water is strongly hydrated,[17] resulting in a low concentration of the reactive form.

We then turned our attention to the effect of different types of additives. Surfactants such as PEG and SDS are frequently employed when reactions are performed in aqueous media, and this strategy has also been attempted under conditions of organocatalysis.[18] Moreover, the use of acidic co-catalysts is common practice[19] in direct aldol reactions proceeding via an enamine intermediate and performed under homogeneous conditions, and chitosan is known to be a lipid binder as demonstrated by its use in pharmaceutical chemistry as an anti-lipidemic.[20] These considerations prompted us to consider that lipid moieties appended with an acidic head group might prove beneficial for catalysis in pure water, because they would simultaneously act as efficient acidic co-catalysts and assist in solubilizing the organic substrates with their lipophilic tail. It is also conceivable that the proven affinity of saturated and unsaturated fatty acids for chitosan[21] might provide an additional asset, favouring the recognition of the reagents by the catalyst.

As shown in Table 2, a general improvement in yield and enantiomeric excess was observed in the presence of anionic (SDS; Entry 2) and neutral (PEG; Entry 3) surfactants as well as acidic additives (Entries 4–7). With the acidic additives, the beneficial effect does not seem only related to their p$K_a$ values, as they are very similar [2,4-dinitrophenol (DNP): p$K_a$ = 4.11, Entry 4; acetic acid, p$K_a$ = 4.76, Entry 5; linoleic acid: p$K_a$ = 4.78,[22a] Entry 6; stearic acid: p$K_a$ = 4.7,[22b] Entry 7]. Presumably, the chain lipophilicity of the additives also affects the catalytic process. However, its efficacy under the conditions employed might be depressed by the presence of a conspicuous amount of organic phase coming from the excess (20:1) of the donor (cyclohexanone) acting as organic co-solvent.

Compared with the advantages induced by the additive in the prototype reaction, a more sizeable improvement was detected (Table 3) in the reaction with formaldehyde as the acceptor. Only by using these additives was it possible to obtain the expected aldol product **1d**, although the yields were only moderate and enantioselectivities not satisfactory. The benefits induced by additives such as SDS when using formaldehyde in the presence of water have been very recently highlighted in the aminomethylation of oxindoles by a three-component Mannich reaction.[18c]

Table 3. Effects of additives on the asymmetric direct aldol reaction between formaldehyde and cyclohexanone in the presence of water.[a]

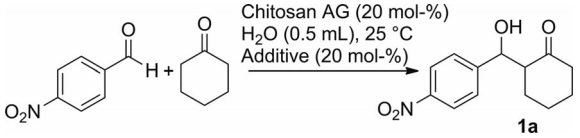



| Entry | Additive | Yield [%][b] | *ee* [%][c] |
|---|---|---|---|
| 1 | – | <10 | n.d. |
| 2 | SDS | 40 | 57 |
| 3 | PEG | 25 | 46 |
| 4 | stearic acid | 35 | 44 |
| 5 | linoleic acid | 30 | 48 |

[a] Reagents and conditions: 34.3 mg of chitosan AG, which corresponds to 20 mol-% of free amino units with respect to formaldehyde (0.70 mmol), 14 mmol of cyclohexanone donor (donor/acceptor ratio = 20:1), 25 °C. [b] Isolated yield after chromatography on silica gel. [c] Determined by chiral stationary phase HPLC analysis after benzoylation (n.d. = not determined).

Despite the large variety of aldol acceptors that can nowadays be used in direct aldol reactions, the range of donors remains quite small. Moreover, although the prototype reaction is good for establishing the potential usefulness of the new catalysts, it leads to products lacking functional-group diversity typical of drug-like building blocks. Re-

Table 2. Effect of additives on the asymmetric direct aldol reaction between 4-nitrobenzaldehyde and cyclohexanone in the presence of water.[a]




| Entry | Additive | Time [h] | Conv. [%][b] | Yield [%][c] | *anti*/*syn*[b] | *ee* [%][d] |
|---|---|---|---|---|---|---|
| 1 | – | 48 | 90 | 85 | 70:30 | 84 |
| 2 | SDS | 48 | 98 | 90 | 70:30 | 90 |
| 3 | PEG | 48 | 98 | 92 | 66:34 | 86 |
| 4 | DNP | 24 | 90 | 85 | 76:24 | 92 |
| 5 | AcOH | 48 | 95 | 90 | 66:34 | 74 |
| 6 | linoleic acid | 48 | 98 | 95 | 70:30 | 87 |
| 7 | stearic acid | 48 | 90 | 88 | 69:31 | 93 |

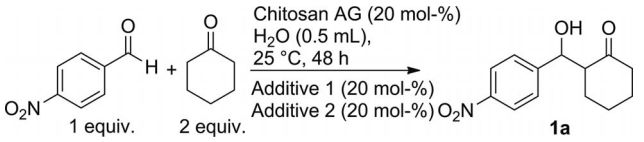
[a] Reagents and conditions: 4.9 mg of chitosan AG, which corresponds to 20 mol-% of free amino units with respect to 4-nitrobenzaldehyde (0.10 mmol), 2 mmol of cyclohexanone donor (donor/acceptor ratio = 20:1), 25 °C. [b] Determined by $^1$H NMR analysis of the crude mixture. [c] Isolated yield after chromatography on silica gel. [d] Determined by chiral stationary phase HPLC analysis, refers to the major *anti* diastereoisomer.

cently, several highly stereoselective aldol reactions of heterocyclic ketones such as tetrahydro-4*H*-thiopyran-4-one (**2**) and 1-Boc-4-piperidone (**3**) have been reported in organic media,[23] under solvent-free conditions[24] and in the presence of water,[25] thus prompting us to expand the chitosan aerogel catalysed aldol reaction beyond the prototype cyclohexanone to include these donors. However, these donors are not the cheapest. In addition, both ketones **2** and **3**, as well as the acceptor 4-nitrobenzaldehyde and the catalyst, are water-insoluble solids, making the reaction more difficult to perform due to the mixing of large amounts of solids. The use of a large excess of these ketones to push the reactions, as in our original procedure with cyclohexanone, should thus be avoided. To this end, we examined the effect of lowering the ketone/aldehyde ratio to 2:1, first for the aldol addition of cyclohexanone to 4-nitrobenzaldehyde using chitosan aerogel as the organocatalyst (Table 4).

The reaction, run for the standard time of 48 h in the absence of additives, occurs with strongly reduced yields and a sizeable erosion of the enantioselectivity (Table 4, Entry 1). On the other hand, satisfactory yields and to some extent lower but still remarkably good enantiomeric excesses as compared with the reaction performed with the previously employed 20:1 ketone/aldehyde ratio were observed (Table 4, Entries 2–6) when the reaction was performed in the presence of additives. Note, the significant quantities of the aldol elimination product formed in the absence of additives (Entry 1), or in smaller amounts in the presence of lipophilic acids (Entries 2 and 3), were almost completely suppressed (Entries 4–6) in the presence of SDS. Under these reaction conditions, the normally used strong excess of nucleophile required to shift the involved equilibria can be avoided without substantially affecting the stereochemical outcome, although, as expected, the reaction rate is normally lower.

Table 4. Effect of additives on the reference reactions performed with a reduced donor/acceptor ratio.[a]

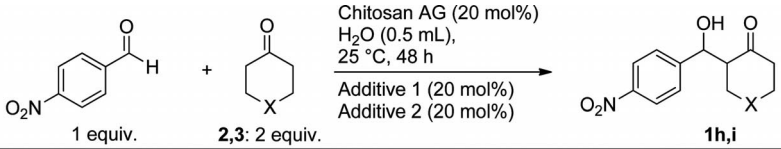


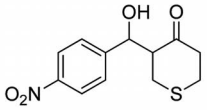
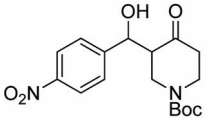

| Entry | Additive 1 | Additive 2 | Yield [%][b] | *anti*/*syn*[c] | *ee* [%][d] |
|---|---|---|---|---|---|
| 1 | – | – | 45 | 66:34 | 70 (60) |
| 2 | linoleic acid | – | 65 | 65:35 | 77 (63) |
| 3 | stearic acid | – | 68 | 67:33 | 80 (66) |
| 4 | – | SDS | 75 | 70:30 | 87 (82) |
| 5 | linoleic acid | SDS | 85 | 63:37 | 84 (35) |
| 6 | DNP | SDS | 86 | 71:29 | 90 (77) |

[a] Reagents and conditions: 4.9 mg of chitosan AG, which corresponds to 20 mol-% of free amino units with respect to 4-nitrobenzaldehyde (0.10 mmol), 0.2 mmol of cyclohexanone donor (donor/acceptor ratio = 2:1), 25 °C. [b] Isolated yield after chromatography on silica gel. [c] Determined by $^1$H NMR analysis of the crude mixture. [d] Determined by chiral stationary phase HPLC analysis (results in parentheses refer to the minor diastereoisomer).

Having established the feasibility of the benchmark direct aldol reaction under these new conditions, the reaction was extended to heterocyclic donors (Table 5). In the colloidal dispersions formed in water in the presence of SDS, the reaction of tetrahydro-4*H*-thiopyran-4-one (**2**) and 1-Boc-

Table 5. Heterocyclic ketones as donors in the aldol reactions with 4-nitrobenzaldehyde.[a]




| Entry | X | Product **1** | | Additive 1 | Additive 2 | Yield [%][b] | *anti*/*syn*[c] | *ee* [%][d] |
|---|---|---|---|---|---|---|---|---|
| 1 | S |  | **1h** | – | SDS | 10 | 60/40 | 15 (5) |
| 2 | S | " | **1h** | linoleic acid | SDS | 60 | 73/27 | 50 (50) |
| 3 | S | " | **1h** | DNP | SDS | 55 | 87/13 | 60 (60) |
| 4 | NBoc |  | **1i** | – | SDS | 25 | 82/18 | 43 (12) |
| 5 | NBoc | " | **1i** | linoleic acid | – | 58 | 60/40 | 61 (26) |
| 6 | NBoc | " | **1i** | DNP | – | 50 | 63/37 | 67 (57) |
| 7 | NBoc | " | **1i** | linoleic acid | SDS | 70 | 61/39 | 70 (5) |
| 8 | NBoc | " | **1i** | DNP | SDS | 83 | 75/25 | 85 (60) |

[a] Reagents and conditions: 4.9 mg of chitosan AG, which corresponds to 20 mol-% of free amino units with respect to aldehyde, 0.10 mmol of acceptor aldehyde, 2 mmol of heterocyclic ketone donor (donor/acceptor ratio = 2:1), 48 h, 25 °C. [b] Isolated yield after chromatography on silica gel. [c] Determined by $^1$H NMR analysis of the crude mixture. [d] Determined by chiral stationary phase HPLC analysis of the crude mixture (results in parentheses refer to the minor diastereoisomer).

4-piperidone (**3**) occurred, albeit in poor yields and enantioselectivities (Entries 1 and 4). The susceptibility to *syn*/*anti* isomerization by enolization[25a] as well as the occurrence of a retro-aldol reaction of **1h** in the presence of bases and the marked tendency of **1i** to racemize[24] account for these drawbacks in the presence of anionic surfactant. Some improvement was noted (Entries 5 and 6) by performing the reaction in the presence of acidic co-catalysts, with the lipophilic linoleic acid proving advantageous over DNP in terms of yields. Finally, the heterocyclic donors **1h** and **1i** readily reacted with 4-nitrobenzaldehyde in the presence of both SDS and acid co-catalysts leading to the aldol products **1h** and **1i**, respectively (Entries 2, 3, 7 and 8), in satisfactory to good yields with still moderate diastereoselectivities but fairly high enantioselectivities. These results for the heterogeneous organocatalysis promoted by chitosan aerogel in the aldol reactions provided further support[25] for the beneficial effect of combining anionic surfactants with acidic additives when reactions are performed in bulk water.

## Conclusions

The ability of chitosan aerogel to promote stereoselective direct aldol reactions in the presence of water represents a "green" complement to the previously described procedures and has been successfully applied to a range of acceptor and donor systems. The use of surfactants and acid co-catalysts in the chitosan-catalysed aldol reaction had a beneficial effect on the outcome of the reaction. In particular, a new protocol for this reaction that avoids the use of a large excess of the ketone donor has been developed by combining an ionic surfactant with an acidic co-catalyst. This new protocol has allowed us to broaden the scope of this reaction to heterocyclic ketone donors.

## Experimental Section

**General Methods and Materials:** Analytical grade solvents were from commercial sources. All the reagents were commercially available and used as received, except for 3-phenylpropiolaldehyde synthesized according to a literature procedure.[26] Chromatographic purifications were performed with 70–230 (chromatography) or 230–400 mesh silica gel (flash chromatography). Racemic samples were prepared by using *rac*-proline as the catalyst. Chitosan aerogel microspheres (4.06 mmol/g accessible $NH_2$ groups) were prepared as described previously.[14] $^1$H NMR spectra were recorded with Varian AS 400 or 600 spectrometers. Enantiomeric excesses (*ee*s) of products were determined by chiral stationary phase HPLC (Daicel Chiralpak AD-H, Chiralcel OJ-H, Chiralcel AS, Phenomenex Lux) using a UV detector operating at 254 nm.

**General Procedure for the Aldol Reactions:** Chitosan aerogel microspheres (4.9 mg, which corresponds to 20 mol-% of free amino units with respect to the acceptor), aldol acceptor (0.10 mmol), additive (0.020 mmol, 20 mol-%), $H_2O$ (0.5 mL) and ketone donor (2.0 or 0.2 mmol) were sequentially added to a vial. A second additive (0.020 mmol, 20 mol-%) was added as indicated. The mixture was gently stirred with a shaker at 25 °C for the stated time. EtOAc was then added, and the phases were separated. The aqueous phase, which contains the chitosan beads, was then extracted with EtOAc (3× 5 mL). The combined organic phases were concentrated, and the crude product was analysed by $^1$H NMR spectroscopy to determine the diastereomeric ratio. The aldol adducts **1** were finally obtained by chromatographic purification or as outlined below.

**2-[Hydroxy(4-nitrophenyl)methyl]cyclohexanone (1a):** According to the general procedure (2.0 mmol of donor) and performing the reaction without additives (48 h reaction time), the title compound was obtained in 85% yield as a white solid and as a mixture of diastereoisomers after chromatography on silica gel (*n*-hexane/EtOAc from 85:15 to 75:25). The diastereomeric ratio, as determined by $^1$H NMR analysis of the crude mixture, was found to be 70:30 in favour of the *anti* isomer. The enantiomeric excess of the product was determined by HPLC analysis (Daicel Chiralpak ADH column, flow 0.75 mL/min, *n*-hexane/*i*PrOH, 90:10; *anti* isomer: $t_{maj}$ = 43.9 min, $t_{min}$ = 33.1 min, 84% *ee*; *syn* isomer: $t_{maj}$ = 29.5 min, $t_{min}$ = 26.1 min, 60% *ee*). The spectral and analytical data are consistent with literature values.[27] The absolute configuration of the major *anti* diastereoisomer was assigned as (1′*R*,2*S*) by comparison of the HPLC retention times of its two enantiomers with literature values.[28]

**2-[Hydroxy(3-nitrophenyl)methyl]cyclohexanone (1b):** According to the general procedure (2.0 mmol of donor) and performing the reaction without additives (48 h reaction time), the title compound was obtained in 70% yield as a white solid and as a mixture of diastereoisomers after chromatography on silica gel (*n*-hexane/EtOAc from 85:15 to 75:25). The diastereomeric ratio, as determined by $^1$H NMR analysis of the crude mixture, was found to be 69:31 in favour of the *anti* isomer. The enantiomeric excess of the product was determined by HPLC analysis (Daicel Chiralpak ADH column, flow 1 mL/min, *n*-hexane/*i*PrOH, 90:10; *anti* isomer: $t_{maj}$ = 20.1 min, $t_{min}$ = 25.1 min, 80% *ee*; *syn* isomer: $t_{maj}$ = 17.7 min, $t_{min}$ = 16.8 min, 60% *ee*). The spectral and analytical data are consistent with literature values.[29]

**2-[Hydroxy(pyridin-2-yl)methyl]cyclohexanone (1c):** According to the general procedure (2.0 mmol of donor) and performing the reaction without additives (48 h reaction time), the title compound was obtained in 70% yield as a white solid and as a mixture of diastereoisomers after flash chromatography on silica gel (*n*-hexane/EtOAc = 70:30). The diastereomeric ratio, as determined by $^1$H NMR analysis of the crude mixture, was found to be 67:33 in favour of the *anti* isomer. The enantiomeric excess of the product was determined by HPLC analysis of the crude mixture, as significant epimerization was observed during the chromatographic purification (Daicel Chiralpak OJ-H column, flow 1 mL/min, *n*-hexane/*i*PrOH, 99:1; *anti* isomer: $t_{maj}$ = 23.7 min, $t_{min}$ = 26.0 min, 70% *ee*; *syn* isomer: $t_{maj}$ = 21.0 min, $t_{min}$ = 18.7 min, 62% *ee*). The spectral and analytical data are consistent with literature values.[29]

**2-(Hydroxymethyl)cyclohexanone (1d):** According to the general procedure on a larger scale (0.7 mmol of formaldehyde, 1.4 mmol of cyclohexanone, 3.5 mL of $H_2O$) and performing the reaction by using SDS as additive, the title compound was obtained in 40% yield after 48 h. The *ee* was determined by HPLC after benzoylation (see below). The spectral and analytical data are consistent with literature values.[16,30]

**Ethyl 2-Hydroxy-2-(2-oxocyclohexyl)acetate (1e):** According to the general procedure (2.0 mmol of donor) and performing the reaction in the absence of additives (48 h reaction time), the title compound was obtained in 90% yield as a colourless oil and as a mixture of diastereoisomers after chromatography on silica gel (*n*-hexane/EtOAc = 80:20). The diastereomeric ratio, as determined by

$^1$H NMR analysis of the crude mixture, was found to be 53:47 in favour of the *anti* isomer. The enantiomeric excess of the product was determined by HPLC analysis after benzoylation (see below). The spectral and analytical data are consistent with literature values.[31]

**2-(1-Hydroxy-3-phenylprop-2-ynyl)cyclohexanone (1f):** According to the general procedure (2.0 mmol of donor) and performing the reaction without additives (48 h reaction time), the title compound was obtained in 90% yield as a colourless oil and as a mixture of diastereoisomers after chromatography on silica gel (*n*-hexane/EtOAc from 80:20). The diastereomeric ratio, as determined by $^1$H NMR analysis of the crude mixture, was found to be 57:43 in favour of the *anti* isomer. The enantiomeric excess of the product was determined by HPLC analysis (Daicel Chiralpak OJ-H column, flow 1 mL/min, *n*-hexane/*i*PrOH, 90:10; *anti* isomer: $t_{maj}$ = 11.0 min, $t_{min}$ = 14.7 min, 70% *ee*; *syn* isomer: $t_{maj}$ = 16.5 min, $t_{min}$ = 13.0 min, 77% *ee*). The spectral and analytical data are consistent with literature values.[32]

**2-(1-Hydroxy-2-oxo-2-phenylethyl)cyclohexanone (1g):** According to the general procedure (2.0 mmol of donor) and performing the reaction without additives (48 h reaction time), the title compound was obtained in 80% yield as a colourless oil and as a mixture of diastereoisomers after flash chromatography on silica gel (*n*-hexane/EtOAc, 80:20). The diastereomeric ratio, as determined by $^1$H NMR analysis of the crude mixture, was found to be 53:47 in favour of the *anti* isomer. The enantiomeric excess of the product was determined by HPLC analysis (Daicel Chiralpak AS column, flow 1 mL/min, *n*-hexane/*i*PrOH, 90:10; *anti* isomer: $t_{maj}$ = 16.9 min, $t_{min}$ = 37.6 min, 48% *ee*; *syn* isomer: $t_{maj}$ = 56.5 min, $t_{min}$ = 26.7 min, 64% *ee*). The spectral and analytical data are consistent with literature values.[33]

**Tetrahydro-3-[hydroxy(4-nitrophenyl)methyl]thiopyran-4-one (1h):** The procedure based on a 2:1 donor/acceptor ratio was applied. By starting from 0.2 mmol of donor and with SDS and linoleic acid as additives (48 h reaction time) the title compound was obtained in 60% yield after chromatography on deactivated silica gel (1% $Et_3N$, *n*-hexane/EtOAc from 85:15 to 70:30). The diastereomeric ratio, as determined by $^1$H NMR analysis of the crude mixture, was found to be 73:27 in favour of the *anti* isomer. The enantiomeric excess of the product was determined by HPLC analysis of the crude mixture as significant epimerization was observed during the chromatographic purification (Daicel Chiralpak AD-H column, flow 1 mL/min, *n*-hexane/*i*PrOH, 80:20; *anti* isomer: $t_{maj}$ = 14.9 min, $t_{min}$ = 26.1 min, 50% *ee*; *syn* isomer: $t_{maj}$ = 29.8 min, $t_{min}$ = 18.0 min, 50% *ee*). The spectral and analytical data are consistent with literature values.[23]

***tert*-Butyl 3-[Hydroxy(4-nitrophenyl)methyl]-4-oxopiperidine-1-carboxylate (1i):** The procedure based on a 2:1 donor/acceptor ratio was applied. By starting from 0.2 mmol of donor and with SDS and DNP as additives (48 h reaction time) the title compound was obtained in 83% yield as a colourless oil and as a mixture of diastereoisomers after chromatography on deactivated silica gel (1% $Et_3N$, *n*-hexane/EtOAc from 85:15 to 70:30). The diastereomeric ratio, as determined by $^1$H NMR analysis of the crude mixture, was found to be 75:25 in favour of the *anti* isomer. The enantiomeric excess of the product was determined by HPLC analysis of the crude mixture as significant epimerization was observed during the chromatographic purification (Daicel Chiralpak AD-H column, flow 1 mL/min, *n*-hexane/*i*PrOH, 95:5; *anti* isomer: $t_{maj}$ = 41.4 min, $t_{min}$ = 46.7 min, 85% *ee*; *syn* isomer: $t_{maj}$ = 34.6 min, $t_{min}$ = 36.8 min, 60% *ee*). The spectral and analytical data are consistent with literature values.[23]

**General Procedure for the Benzoylation of Products 1d,e:** Purified aldol product **1** (1 equiv., 0.1 mmol), $CH_2Cl_2$ (0.5 mL), benzoyl chloride (2 equiv., 0.2 mmol) and pyridine (5 equiv., 0.5 mmol) were sequentially added to a vial. After stirring at room temperature for 2 h, the reaction was quenched with $H_2O$. The mixture was extracted with $CH_2Cl_2$, and the organic layer was washed with brine and dried with anhydrous $Na_2SO_4$. After filtration, the solvents were evaporated, and the residue was purified by short-column chromatography.

**(2-Oxocyclohexyl)methyl Benzoate:** After purification of the crude mixture by chromatography on silica gel (*n*-hexane/EtOAc, 90:10), the enantiomeric excess of the product was determined to be 57% by HPLC analysis (Phenomenex Lux column, flow 1 mL/min, *n*-hexane/*i*PrOH, 98:2; $t_{maj}$ = 13.0 min, $t_{min}$ = 16.2 min). The spectral and analytical data are consistent with literature values.[30]

**2-Ethoxy-2-oxo-1-(2-oxocyclohexyl)ethyl Benzoate:** After purification of the crude mixture by chromatography on silica gel (*n*-hexane/EtOAc, 90:10), the enantiomeric excess of the product was determined by HPLC analysis (Daicel Chiralpak ADH +AS column, flow 0.9 mL/min, *n*-hexane/*i*PrOH, 90:10; *anti* isomer: $t_{maj}$ = 30.0 min, $t_{min}$ = 26.9 min, 5% *ee*; *syn* isomer: $t_{maj}$ = 28.9 min, $t_{min}$ = 37.7 min, 62% *ee*). The spectral and analytical data are consistent with literature values.[31]

**Supporting Information** (see footnote on the first page of this article): $^1$H and $^{13}$C NMR spectra for compounds **1**.

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