Asymmetric Organocatalytic Aldol Reaction in Water: Mechanistic Insights and Development of a Semi-Continuously Operating Process

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Dedicated to Professor Dr. Jürgen Martens on the occasion of his 65th birthday

Abstract: A detailed study on the impact of the catalyst loading on conversion and enantioselectivity of the direct aldol reaction of an aldehyde and acetone in aqueous solvent with nonimmobilized and immobilized proline amide-based organocatalysts is described. Based on a polymer-supported catalyst, batch and semi-continuously operating processes, comprising recycling studies in the latter case, were investigated.

Key words: aldol reaction, catalysis, enantioselectivity, supported catalysis, polymers

The organocatalytic aldol reaction is commonly known as the most essential tool in synthetic organic chemistry for the production of β-hydroxy ketones.[1] In the last decade, an increasing number of catalysts for this reaction have been developed. However, only a few of them are able to catalyze an asymmetric aldol reaction of aldehydes and acetone in aqueous medium.[2] The proline amide-based catalysts of type **1** developed by the Singh group (Figure 1) appear to be among the most suitable types of organocatalysts for this reaction.[3] For example, catalyst **1a** induces high enantioselectivity and is highly active in water, thus allowing its use at a low catalyst loading of 0.5 mol%.[3b,4]

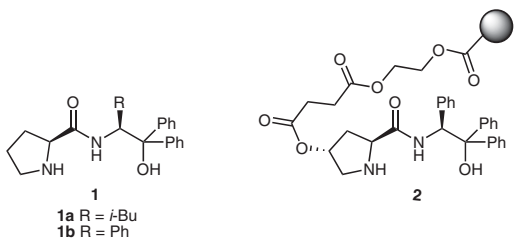

Figure 1 Proline amide-based organocatalyst **1** and polymer-supported proline-based organocatalyst **2**

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The advantages of this organocatalytic aldol reaction such as beneficial catalytic properties, the use of readily accessible substrates (without the need of protecting groups), and availability of an attractive, optimized access to the catalyst[5] encouraged us to conduct deeper kinetic and mechanistic investigations for a detailed characterization of the reaction course.

Since a range of process features of this aldol reaction already fulfill the technical requirements, we also became interested in further process development and the set-up of a semi-continuously operating process. For the latter issue we planned to use the polymer-supported organocatalyst **2**, which was developed by the Hansen group recently.[6] Furthermore, in such a study the reaction course in the presence of immobilized catalysts **2** should be compared with the one of related nonimmobilized organocatalysts **1** (Figure 1). The required immobilized catalysts of type **2** are accessible by means of a co-polymerization of styrene and divinylbenzene with the monomeric proline amide unit and already showed a promising recycling potential.[6–8]

To start with our study on a detailed characterization of the asymmetric aldol reaction in aqueous media, the 'monomeric' organocatalyst **1b** was first applied. The results with catalyst **1b** also serve as a benchmark for the experiments with the immobilized catalyst **2**, which has the same structural motif of the catalytic moiety. In accordance with previous results collected with the opposite enantiomer of catalyst **1a**,[4] a comparable reaction rate was obtained when using either 0.5 mol% of organocatalyst **1a** (confirming the previous study) or 0.5 mol% of organocatalyst **1b** in the aldol reaction of 3-chlorobenzaldehyde (**3**; 0.7 M; 0.5 mmol scale) with acetone in a saturated NaCl solution (Figure 2).

Thus, a change of the substituent at the β-amino alcohol moiety of the organocatalyst **1** (e.g., exchange of an isobutyl group by a phenyl group) does not have a significant impact on the reaction course (Figures 2 and 3). Since the reactions are kinetically controlled at 0.5 mol% catalyst loading of **1** and a reaction time of 24 hours, the enantiose-

Biographical Sketches

Giuseppe Rulli was born in Perugia, Italy, in 1984. He studied chemistry at the Friedrich Alexander University Erlangen-Nürnberg and received his diploma degree in 2010. He is currently conducting his PhD studies under the supervision of Prof. Harald Gröger in the field of asymmetric organocatalysis and chemoenzymatic syntheses.

Kim Alex Fredriksen was born in Norway in 1987. He graduated from University of Oslo in 2011 were he obtained his Bachelor and Master's degree under the supervision of Associate Professor Tore Bonge-Hansen. He is now pursuing a PhD at the same university under the supervision of Associate Professor Mohamed Amedjkouh.

Nongnaphat Duangdee was born in Surin, Thailand. She received her Bachelor's degree in chemistry from Khon Kaen University in 1996. In 1997, she joined the Department of Science Service (DSS, Thailand) where she worked as an analytical chemist until 2009. In parallel, she obtained her MSc (organic chemistry) under the supervision of Professor Manat Pohmakotr at Mahidol University, Bangkok in 2002. In 2009, she started her doctoral studies under the supervision of Professor Albrecht Berkessel at the University of Cologne (Germany) investigating 'Organocatalytic Asymmetric Aldol Reactions with Ketone Acceptors' and recently obtained her PhD in 2013.

Tore Bonge-Hansen was born in Trondheim, Norway, in 1969. He obtained his PhD from State University of New York, Buffalo under the supervision of Professor Huw M. L. Davies working on the development of catalytic asymmetric intermolecular C–H insertion reactions. He was a postdoctoral fellow in the laboratory of Professor Karl Anker Jørgensen in Århus, Denmark, working on asymmetric metal-catalyzed reactions and organocatalysis. After working in the medicinal chemistry department at H. Lundbeck A/S in Copenhagen, he started his independent research career as an Associate Professor at the University of Oslo in 2003. The research in his group is focused on carbenoid chemistry and immobilized organocatalysis.

Albrecht Berkessel was born in Saarlouis, Germany, in 1955. He obtained his Diplom in 1982 at the University of Saarbrücken. For his PhD studies, he moved to the laboratory of Professor Waldemar Adam at the University of Würzburg. After receiving his PhD in 1985, he joined the research group of Professor Ronald Breslow at Columbia University, New York. His habilitation at the University of Frankfurt/Main (associated to Professor Gerhard Quinkert) was completed in 1990. In 1992, he became Associate Professor at the University of Heidelberg. Since 1997, he is a Full Professor of Organic Chemistry at the University of Cologne. His research interests center around various aspects of catalysis research, such as mechanism and method development in metal-based catalysis and in particular organocatalysis, biomimetic and medicinal chemistry.

Harald Gröger was born in Erlangen, Germany, in 1968. He studied chemistry at the Universities of Erlangen-Nürnberg and Oldenburg and received his diploma degree in chemistry from the University of Oldenburg in 1994. He completed his doctoral thesis at the University of Oldenburg in 1997 under the supervision of Prof. Dr. Martens. After staying as a postdoctoral fellow at the University of Tokyo in the group of Prof. Dr. Shibasaki, he joined the research department Chemische Forschung of SKW Trostberg AG in 1998. After the merger with Degussa-Hüls AG to Degussa AG in 2001, he became project manager in the Project House Biotechnology of Degussa AG. From 2004 to 2006 he worked as a senior project manager at the research unit Service Center Biocatalysis of Degussa AG. From 2006 to 2011 he was W2-professor (associate professor) for organic chemistry at the University of Erlangen-Nürnberg, and since April 2011 he is a W3-professor (full professor) for Organic Chemistry at Bielefeld University. He is the recipient of several awards, including the Degussa Innovation Award 2003 (category: new products), the Degussa Innovation Award 2005 (category: new or improved processes), and the Carl-Duisberg-Memorial-Prize 2008 of the German Chemical Society (GDCh). His main research areas center on the use of biocatalysts in organic synthesis, comprising, for example, the development of industrially feasible biotransformations and the combination of bio- and chemocatalysis towards chemoenzymatic one-pot processes.

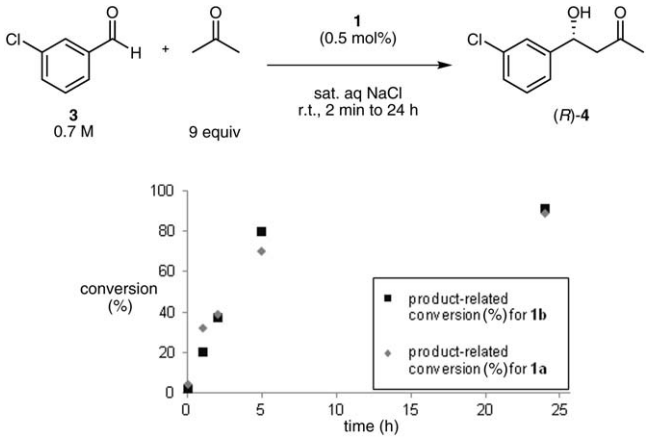


Figure 2 Dependency of the conversion of the aldol reaction on the reaction time when using organocatalysts **1a** and **1b**

lectivity remains quite constant during the reaction, reaching, for example, 98% ee at the beginning of the reaction and 96% ee after 24 hours when using **1b** (Figure 3).

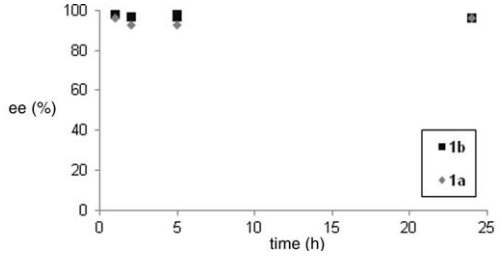


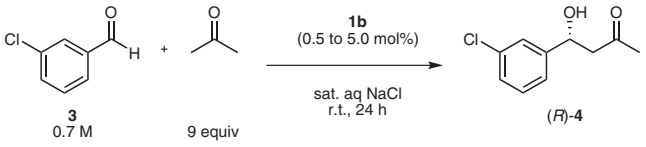
Figure 3 Dependency of the enantioselectivity of the aldol reaction on the reaction time when using 0.5 mol% of organocatalyst **1a** or **1b** (for reaction conditions, see reaction scheme in Figure 2)

Since we earlier observed that at an elevated catalytic loading of the opposite enantiomer of **1a** (e.g., at 5.0 mol%),[4] a thermodynamic control of the process was reached rapidly, a related reaction with 5.0 mol% of **1b** was conducted. As expected, an increased catalyst loading of **1b** leads to a decrease of enantioselectivity (Table 1). For example, 5.0 mol% of **1b** gives 35% ee after 24 hours at room temperature.[9]

As an explanation, we had proposed earlier (when observing similar results with the opposite enantiomer of catalyst **1a**[4]) the increasing impact of an organocatalytic retro-aldol reaction at a prolonged reaction time, thus leading to the thermodynamically favored racemate as the product in a thermodynamically controlled process.[4] To find further support for this hypothesis we became interested in evaluating the course of the ee value of product **4** after mixing enantiomerically enriched product (*R*)-**4** (89% ee) with acetone (9 equiv) in the presence of 0.5 mol% and 5.2 mol% of the organocatalyst **1a**, respectively (Scheme 1).

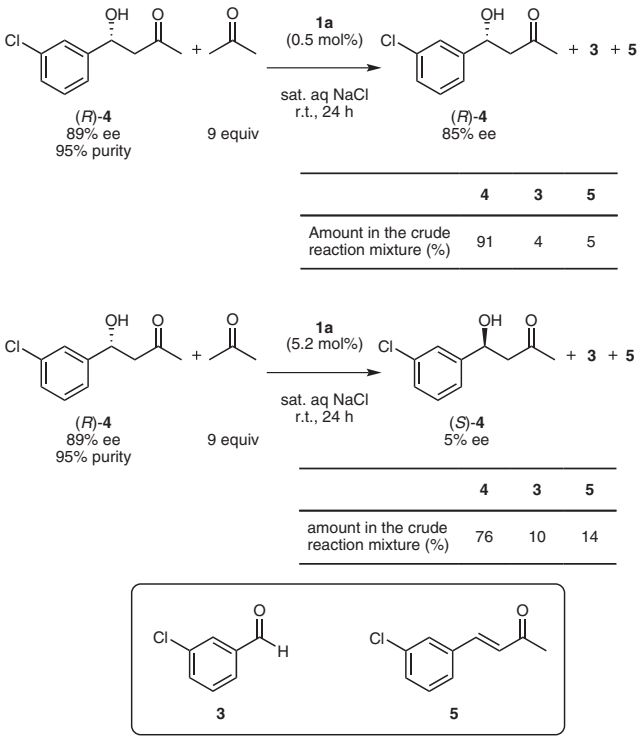
Any change in enantiomeric composition would indicate the existence of such a thermodynamic control of the aldol reaction. In fact, while the enantiomeric excess of product (*R*)-**4** decreases only slightly to 85% ee after 24 hours

Table 1 Dependency of the Course of the Aldol Reaction on the Catalytic Amount of **1b**[a]



Entry	**1b** (mol%)	Overall conv. (%)[b]	Product-related conv. (%)[c]	ee (%)
1	0.5	95	91	96
2	1.0	93	90	95
3	2.5	87	79	80
4	5.0	87	73	35

[a] Reaction time: 24 h.
[b] The overall conversion is defined as conversion according to the consumption of substrate **3**.
[c] The product-related conversion is defined as conversion related to formation of aldol product (*R*)-**4**.



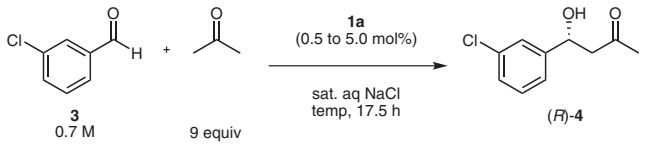
Scheme 1 Change of enantiomeric purity of (*R*)-**4** by adding different amounts of organocatalyst **1a**

when mixed with 0.5 mol% of **1a**, a tremendous decrease of the ee value of product **4** to 5% ee (with preference even for the opposite *S*-enantiomer) was found when being mixed with 5.0 mol% of **1a**. The (slight) inversion of the enantiomeric ratio of **4** in this experiment is postulated to be related to a different decomposition rate for the two

enantiomers of the aldol product **4** under formation of the undesired condensation by-product **5** in the presence of the catalyst.

Furthermore, the impact of the reaction temperature on the aldol reaction of 3-chlorobenzaldehyde (**3**) with acetone was studied in the presence of 0.5 mol% or 5.0 mol% organocatalyst **1a** (Table 2). Notably, when using a catalytic amount of 0.5 mol% within a reaction time of 17.5 hours, the enantiomeric excess of β-hydroxy ketone (*R*)-**4** turned out to be high with 96–99% ee over a broad temperature range between –20 to 25 °C, underlining the kinetic control of these reactions. In strong contrast, the use of 5.0 mol% catalyst causes a significant decrease of enantioselectivity when operating at the same reaction time. This indicates the impact of a thermodynamic control of the aldol reaction when using a catalytic amount of 5.0 mol% within a reaction time of 17.5 hours independent of the applied reaction temperature, and even at –20 °C.

Table 2 Temperature-Dependency of Enantioselectivity with Variation of the Catalytic Amount of **1a**



Entry	**1a** (mol%)	Temp (°C)	Overall conv. (%)	ee (%)
1	0.5	–20	16	99
2	0.5	0	47	97
3	0.5	10	87	98
4	0.5	25	>95	96
6	5.0	–20	90	89
7	5.0	0	92	71
8	5.0	10	90	75
9	5.0	25	95	54

A further option to find support for the proposed retro-aldol reaction (at higher catalyst loading) as an explanation for the racemization of β-hydroxy ketone **4** consists in treating a mixture of **4** and catalyst **1a** with deuterated acetone-d_6 and monitoring the reaction course via ^{1}H NMR spectroscopy (Figure 4).

In the case of operating under thermodynamic control, retro-aldol reaction proceeds, thus forming aldehyde **3** in situ. Vice versa, in a thermodynamic equilibrium of the aldol reaction the aldehyde **3** is then reconverted to **4**. Since in this experiment acetone-d_6 is used in excess (9 equiv), the probability of the aldol reaction of aldehyde **3** is higher with acetone-d_6 compared to acetone, which is formed in situ. Thus, in the case of a thermodynamic control and the presence of a retro-aldol reaction, we then should observe a decrease of nondeuterated aldol adduct **4** (used as a starting material) in the ^{1}H NMR spectrum, corresponding to

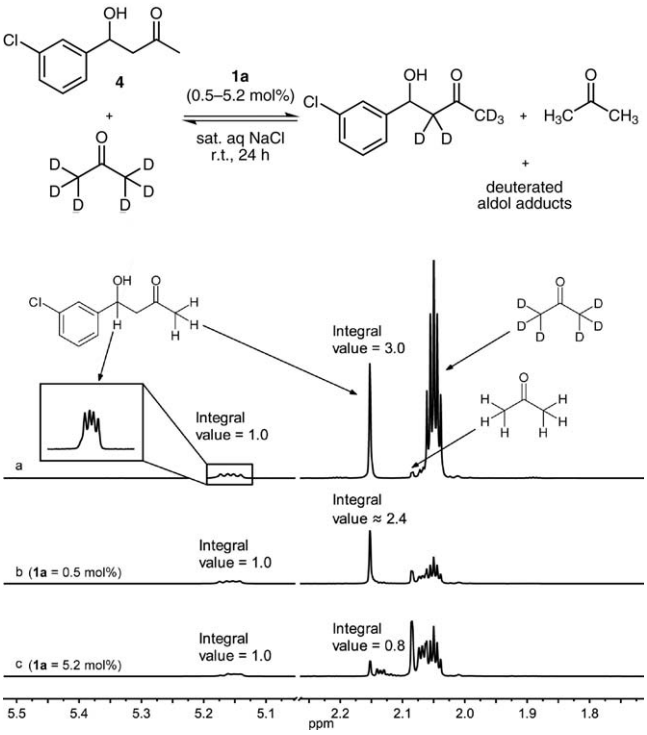


Figure 4 Reaction of **4** with deuterated acetone and varying amount of catalyst **1a** and ^{1}H NMR spectra (extracted parts) of substance **4** before and after the reaction with deuterated acetone in acetone-d_6 as a solvent: spectrum a): reference compound prior to the reaction; spectrum b): compound after reaction with 0.5 mol% organocatalyst **1a**; spectrum c): compound after reaction with 5.2 mol% organocatalyst **1a**.

the formation of a deuterated analogue of aldol product **4**. Exactly this observation was made at a high catalyst loading of 5.2 mol% after 24 hours, whereas a negligible depletion of nondeuterated product **4** was found when adding 0.5 mol% of organocatalyst **1a** (Figure 4). At the same time, the signal intensity of possibly released acetone increases at higher catalyst amount. These results indicate a significant impact of a retro-aldol reaction of aldol adduct **4** within 24 hours when operating at a catalytic amount of 5.2 mol%. Nevertheless, with these experiments alone, exchange of α-acidic protons via enamine formation and subsequent protonation as an alternative explanation for this effect cannot be excluded (although in this case at a high percentage partially deuterated products would have been expected due to statistic reasons, which, however, were not observed).

With this kinetic and mechanistic picture of the enantioselective aldol reaction with monomeric 'homogeneous' organocatalysts **1** in hand, we became interested in analogous aldol reactions with related heterogeneous organocatalysts. A particular focus was on the study of their impact on enantioselectivity and conversion of aldol products as a function of time and catalyst loading. Heterogeneous catalysts offer advantages such as easy separation from the reaction mixture and simple reuse of the catalyst. As such heterogeneous immobilized organocatalysts

polymer-supported derivatives of proline amides of type **1** attracted our attention due to their ability to catalyze highly enantioselective aldol reactions in an efficient way.[6–8,10a] According to the literature, catalyst loading of most immobilized proline amide organocatalysts does not seem to have any impact on enantioselectivity within a reaction time of up to 24–95 hours.[6,10b]

Indeed, when choosing again the aldol reaction of aldehyde **3** with acetone in aqueous medium as a model reaction, the catalytic amount of **2** can be increased up to 10.0 mol% (catalyst loading 0.65 mmol/g) without any loss of enantioselectivity of the resulting product **4** within 24 hours (Figure 5). Accordingly, the reactivity of the heterogeneous catalysts of type **2** is much lower compared to their homogeneous 'monomeric' counterparts **1**. This is also supported when comparing the conversion versus reaction time-curves. For example, the reaction course with 10.0 mol% of the heterogeneous catalyst **2** (Figure 5) is similar to the one obtained when using 0.5 mol% of the related nonimmobilized catalyst **1b** (see Figure 2). Thus, within a typical reaction time of 24 hours, the aldol reactions based on the use of the heterogeneous, immobilized organocatalyst **2** still run under kinetic control, although an elevated catalytic amount of up to 10.0 mol% was used and a high ee value of 93% ee was reached after 24 hours (Figure 5 and Table 3, entry 6).

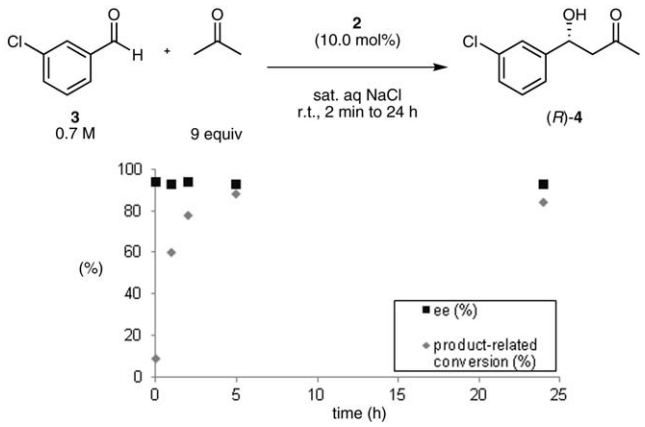
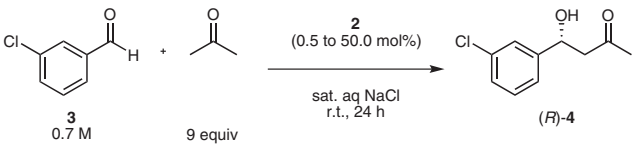


Figure 5 Dependency of the conversion and enantioselectivity of the aldol reaction on the reaction time when using 10.0 mol% of organocatalyst **2**

Next we conducted a detailed study of the impact of catalyst loading of the heterogeneous organocatalyst **2** on the enantiomeric excess of the resulting aldol adduct (*R*)-**4**, varying the catalyst loading between 0.5 mol% and 50.0 mol% (Table 3). A decrease of the enantioselectivity was only observed when using a very large amount of polymer-supported catalyst **2**. Accordingly, the use of 50.0 mol% of **2** causes a drop of the enantiomeric excess of (*R*)-**4** to 74% ee (Table 3, entry 7).[11]

Table 3 Comparison of Enantioselectivity with Variation of Catalyst **2**



Entry	**2** (mol%)	Overall conv. (%)	Product-related conv. (%)	ee (%)
1	0.5	10	10	95
2	1.0	11	11	94
3	2.5	28	27	93
4	2.5	32	30	94
5	5.0	61	58	93
6	10.0	>95	84	93
7	50.0[a]	>95	64	74

[a] Due to the high amount of polymer, the reaction takes place in a gel as a reaction medium.

Besides being used in a batch mode, the immobilized organocatalyst **2** offers an opportunity to be used for a (semi-)continuously operating process in a packed-bed reactor, which often is a technically preferred option for a reactor set-up. Although successful recycling of immobilized catalysts by simple filtration and reuse in several catalytic cycles can also be done in a batch mode,[7,12] mechanical abrasion of the immobilisate and loss of catalyst are drawbacks here. These can be often circumvented by using the immobilized catalyst in a packed-bed reactor.[13] In the following, our results based on the use of a semi-continuous flow reaction is described. In the set-up of this experiment the polymer-supported organocatalyst **2** represents the stationary phase and was inserted into a cartridge, which is connected to an adjustable pumping device (Figure 6). Since pumping the aqueous mixture of acetone and substrate **3** was considered to be disadvantageous since it represents a biphasic system, at first the catalyst was treated with water to ensure an aqueous environment of the heterogeneous catalyst **2**. Then, the reactants 3-chlorobenzaldehyde (**3**) and acetone were pumped with a constant flow of 0.5 mL/min through the packed-bed reactor and recollected in the same vessel that contains the starting materials. After 18 hours, the reaction was stopped (by interrupting the pumping) and subsequently the reaction mixture was analyzed, showing a conversion of 93% [with respect to formation of aldol product (*R*)-**4**] and an enantioselectivity of 90% ee (Table 4, entry 1). Notably, in the absence of pretreatment of catalyst **2** with water the conversion was considerably lower.[14] This underlines the importance of water as an essential component of the reaction medium for an efficient organocatalytic aldol reaction of aldehyde **3** with acetone.

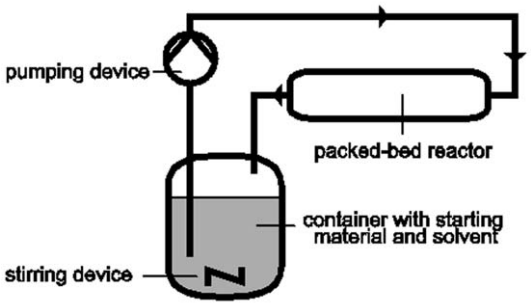
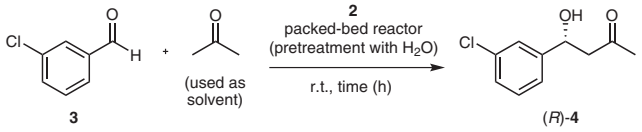


Figure 6 Sketch of the semi-continuous-flow reactor for the aldol reaction (shown in Table 4)

Table 4 Variation of Absolute Amount of Aldehyde **3** for the Aldol Reaction of Polymer-Supported Organocatalyst **2** in a Semi-Continuous Flow Reactor



Entry	**3** (mmol)	Time (h)	Product-related conv. (%)	ee (%)
1	0.5	18	93	90
2[a]	8.8	66	95	89

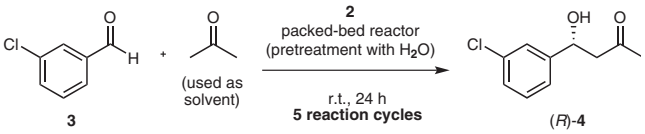
[a] Polymer-supported organocatalyst **2** was used two times (in total 36 h of previous semi-continuous use) before starting this reaction.

Furthermore, the organocatalyst **2** exhibits a promising recycling potential when being employed in the packed-bed reactor. High conversions (up to >95%) and high enantioselectivities (88–92% ee) were observed over five cycles, each lasting at least 24 hours (Table 5). It should be added that pretreatment of the stationary phase (consisting of immobilized catalyst **2**) with water was done prior to each reaction cycle.

In addition, reutilization of **2** (after 36 h of previous semi-continuous use, as shown in Table 4) in combination with an 18-fold amount of 3-chlorobenzaldehyde (**3**) and a prolonged reaction time of 66 hours leads to the formation of the desired β-hydroxy ketone (*R*)-**4** with 95% conversion and 89% ee (Table 4, entry 2).

In summary, a detailed kinetic and mechanistic study for the characterization of the reaction course of the enantioselective direct aldol reaction catalyzed by 'monomeric' proline amide-based catalysts **1** was conducted. The results indicate that an elevated catalytic amount of 5.0 mol% in combination with a reaction time of 24 hours led to a significant impact of the retro-aldol reaction and a thermodynamic control of the reaction. In contrast, excellent enantioselectivities (at high conversions) were obtained within this reaction time at a decreased catalytic amount of 0.5 mol%. However, the use of the polymer-supported organocatalyst **2** leads to a kinetically controlled reaction within a broad range of the catalytic amount of 0.5 to 10.0 mol%. This is due to a lower reactivity of the heterogeneous catalyst. Furthermore, based on the use of the immobilized catalyst **2** a proof of concept was demonstrated for a semi-continuously operating organocatalytic aldol reaction with a packed-bed reactor bearing the organocatalyst **2** as a stationary phase. When employed in such a semi-continuous flow reactor the immobilized catalyst **2** also showed a promising recycling potential, giving high conversion and enantioselectivities for the aldol product (*R*)-**4** within five reaction cycles.

Table 5 Recycling of Polymer-Supported Organocatalyst **2** in a Semi-Continuous Flow Reactor



Entry	Cycle	Product-related conv. (%)	ee (%)
1	1	94	92
2	2	93	92
3	3	93	92
4	4[a]	93	88
5	5[a]	>95	88

[a] A different pumping device was used for this reaction (see experimental section).

All reagents were purchased from commercial sources and used without further purification, unless otherwise indicated. Acetone was distilled before use. 3-Chlorobenzaldehyde (**3**) was distilled before use (if its purity was less than 97%). Organocatalysts **1a**, **1b**, and **2** were synthesized in analogy to literature-known procedures.[3a,4–7] ^{1}H NMR spectra were recorded on a Bruker Avance 400 and 300 spectrometer and the chemical shift values refer to $CDCl_3$ [δ (^{1}H), 7.24 ppm] and acetone-d_6 [δ (^{1}H), 2.05 ppm]. HPLC was carried out with a Jasco LCNet II/ADC using a UV-1575 UV/Vis Detector and Daicel Chiralpak® column AD-H. Low-temperature reactions were carried out with a JULABO typ/model FT902 Kryostat. The packed-bed reactor consists of a Chiralpak® column cartridge (Ø = 4.6 mm, length = 250 mm), with organocatalysts **2** included therein (particle size: ca. 200 μm) connected to A Shimadzu LC-10AT or alternatively to a Jasco LCNet II pumping device (see Table 5, entries 4 and 5). Conversions were determined from the ratio of the integral of product signals in the ^{1}H NMR spectra of the crude products in relation to the corresponding sum of integrals of substrate (aldehyde), product and clearly identifiable side-products (the synthesis of compound **5** as a reference is given herein, the synthesis of a second by-product is given in the Supporting Information). Enantioselectivities were determined by chiral HPLC (Chiralpak® column AD-H, hexane–*i*-PrOH, 95:5, flow 1.0 mL/min, 220 nm), after complete removal of the solvent, directly from the crude product, without further purification. The analytical data obtained for the synthesized compound **4** were in accordance with the corresponding literature-known data.[3b,4]

Organocatalytic Aldol Reaction (Figures 2 and 3); General Procedure

A mixture of 3-chlorobenzaldehyde (**3**; 59 μL, 0.5 mmol), organocatalyst **1a** (0.9 mg, 0.0025 mmol, corresponding to a catalytic amount of 0.5 mol%) or organocatalyst **1b** (1.0 mg, 0.0025, corresponding to a catalytic amount of 0.5 mol%), and acetone (329 μL, 4.5 mmol, 9 equiv) in a sat. aq solution of NaCl (0.33 mL, corresponding to about 50% v/v) was stirred at r.t. (for reaction times, see Figures 2 and 3). The reaction mixture was extracted with CH_2Cl_2 (3 × 2 mL) and after the organic layers were combined, the solvent was removed by evaporation (600 mbar, 40 °C). The resulting crude product was then analyzed with respect to conversion as well as enantiomeric excess of (*R*)-**4**.

Organocatalytic Aldol Reaction (Table 1); General Procedure

A mixture of 3-chlorobenzaldehyde (**3**; 59 μL, 0.5 mmol), organocatalyst **1b** (1.0–9.6 mg, 0.0025–0.025 mmol, corresponding to a catalytic amount of 0.5–5.0 mol%), and acetone (329 μL, 4.5 mmol, 9 equiv) in a sat. aq solution of NaCl (0.33 mL, corresponding to about 50% v/v) was stirred at r.t. for 24 h. The reaction mixture was extracted with CH_2Cl_2 (3 × 2 mL) and after the organic layers were combined, the solvent was removed by evaporation (600 mbar, 40 °C). The resulting crude product was then analyzed with respect to conversion as well as enantiomeric excess of (*R*)-**4**.

Detection of Organocatalytic Retro-Aldol Reaction (Scheme 1); General Procedure

A mixture of β-hydroxy ketone (*R*)-**4** (100 μL, 103.9 mg, 95% purity, corresponding to 0.48 mmol, 89% ee), organocatalyst **1a** (0.9–9.1 mg, 0.0025–0.025 mmol, corresponding to a catalytic amount of 0.5–5.2 mol%), and acetone (329 μL, 4.5 mmol, 9 equiv) in a sat. aq solution of NaCl (0.33 mL) was stirred at r.t. for 24 h. The reaction mixture was diluted with CH_2Cl_2 (5 mL) and the phases were separated over a phase-separating filter. After removing most of the solvent of the organic filtrate by evaporation (600 mbar, 40 °C), the amount of aldol product (*R*)-**4** or (*S*)-**4** was determined via ^{1}H NMR from the ratio of the integral of its signals in relation to the sum of integrals of aldehyde and detectable side-product **5**.

(*E*)-4-(3-Chlorophenyl)but-3-en-2-one (5, Scheme 1)

The synthesis of this reference compound **5** was carried out in analogy to a literature-known protocol;[15] yield: 22%; colorless solid; mp 36 °C; R_f = 0.53 [petroleum ether (bp 40–65 °C)–EtOAc, 5:1].

HPLC (Chiralpak AD-H-column; hexanes–*i*-PrOH, 95:5; 1.0 mL/min): t_R = 6.7 min.

IR (film): 3075, 3024, 1664, 16407, 1625, 1391, 1285, 1258, 1089, 980, 783, 686 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.50–7.30 (m, 5 H), 6.70–6.65 (d, *J* = 16.3 Hz, 1 H), 2.36 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 198.0, 141.6, 136.2, 134.9, 130.3, 130.2, 128.1, 127.9, 126.4, 27.7.

MS (EI): *m*/*z* = 180 ([M$^+$], 100%).

Anal. Calcd for $C_{10}H_9ClO$: C, 66.49; H, 5.02. Found: C, 66.69; H, 5.11.

Organocatalytic Aldol Reaction (Table 2); General Procedure

A mixture of 3-chlorobenzaldehyde (**3**; 59 μL, 0.5 mmol), organocatalyst **1a** (0.9–9.1 mg, 0.0025–0.025 mmol, corresponding to a catalytic amount of 0.5–5.0 mol%), and acetone (329 μL, 4.5 mmol, 9 equiv) in a sat. aq solution of NaCl (0.33 mL, corresponding to about 50% v/v) was stirred for 17.5 h (for reaction temp, see Table 2). The reaction mixture was diluted with CH_2Cl_2 (5 mL) and the phases were separated over a phase-separating filter. The solvent of the organic filtrate was removed by evaporation (600 mbar, 40 °C). The resulting crude product was then analyzed with respect to conversion as well as enantiomeric excess of (*R*)-**4**.

Organocatalytic Retro-Aldol Reaction (Figure 4); General Procedure

A mixture of β-hydroxy ketone **4** (100 μL, 103.9 mg, 95% purity, corresponding to 0.48 mmol), organocatalyst **1a** (0.9–9.1 mg, 0.0025–0.025 mmol, corresponding to a catalytic amount of 0.5–5.2 mol%), and acetone-d_6 (329 μL, 4.4 mmol, 9 equiv) in a sat. aq solution of NaCl (0.33 mL) was stirred at room temperature for 24 h. The organic layer was separated and analyzed via ^{1}H NMR spectroscopy.

Organocatalytic Aldol Reaction (Figure 5); General Procedure

A mixture of 3-chlorobenzaldehyde (**3**, 59 μL, 0.5 mmol), organocatalyst **2** (76.9 mg, catalyst loading 0.65 mmol/g, corresponding to a catalytic amount of 10.0 mol%), and acetone (329 μL, 4.5 mmol, 9 equiv) in a sat. aq solution of NaCl (0.33 mL, corresponding to about 50% v/v) was stirred at r.t. (for reaction times, see Figure 5). The reaction mixture was diluted with CH_2Cl_2 (5 mL) and the phases were separated over a phase-separating filter. The solvent of the organic filtrate was removed by evaporation (600 mbar, 40 °C). The resulting crude product was then analyzed with respect to conversion as well as enantiomeric excess of (*R*)-**4**.

Organocatalytic Aldol Reaction (Table 3); General Procedure

A mixture of 3-chlorobenzaldehyde (**3**; 59 μL, 0.5 mmol), organocatalyst **2** (3.9–384.6 mg, catalyst loading 0.65 mmol/g, corresponding to a catalytic amount of 0.5–50.0 mol%), and acetone (329 μL, 4.5 mmol, 9 equiv) in a sat. aq solution of NaCl (0.33 mL, corresponding to about 50% v/v) was stirred at r.t. for 24 h. The reaction mixture was diluted with CH_2Cl_2 (5 mL for entries 1–5, 20 mL for entries 6, 7) and the phases were separated over a phase-separating filter. The solvent of the organic filtrate was removed by evaporation (600 mbar, 40 °C). The resulting crude product was then analyzed with respect to conversion as well as enantiomeric excess of (*R*)-**4**.

Organocatalytic Aldol Reaction (Tables 4, 5); General Procedure

Distilled H_2O was filled into a 250 mL glass bottle and pumped with a flow of 0.5 mL/min through the packed-bed reactor filled with of organocatalyst **2** [1.32 g (Table 4) or 1.66 g (Table 5), catalyst loading 0.65 mmol/g]. Subsequently, the pump was stopped and the bottle was replaced by a 250 ml glass bottle filled with a mixture of acetone (25 mL) and 3-chlorobenzaldehyde (**3**; 59 μL–1.0 mL, 0.5–8.8 mmol). Under constant stirring, this solution was also pumped with a flow of 0.5 mL/min into the packed bed reactor and recollected into the bottle (for reaction times, see Tables 4, 5). Afterwards, the pumping was stopped and the solution was diluted with CH_2Cl_2 (25 mL) (Table 4) or extracted (Table 5) with CH_2Cl_2 (3 × 20 mL) and decanted over a phase-separation filter. The solvent of the organic filtrate was removed by evaporation (500 mbar, 40 °C). After rinsing the reactor with acetone, the system was reused for the next cycle. The resulting crude product was then analyzed with respect to conversion as well as enantiomeric excess of (*R*)-**4**.

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

References

(1) (a) *Modern Methods in Stereoselective Aldol Reactions*; Mahrwald, R., Ed.; Wiley-VCH: Weinheim, **2013**. (b) Berkessel, A.; Gröger, H. *Asymmetric Organocatalysis*; Wiley-VCH: Weinheim, **2005**. (c) Melchiorre, P.; Marigo, M.; Carlone, A.; Bartoli, G. *Angew. Chem. Int. Ed.* **2008**, *47*, 6138; *Angew. Chem.* **2008**, *120*, 6232.

(2) (a) Tang, Z.; Yang, Z.-H.; Chen, X.-H.; Cun, L.-F.; Mi, A.-Q.; Jiang, Y.-Z.; Gong, L.-Z. *J. Am. Chem. Soc.* **2005**, *127*, 9285. (b) Raj, M.; Singh, V. K. *Chem. Commun.* **2009**, 6687.

(3) (a) Raj, M.; Maya, V.; Ginotra, S. K.; Singh, V. K. *Org. Lett.* **2006**, *8*, 4097. (b) Maya, V.; Raj, M.; Singh, V. K. *Org. Lett.* **2007**, *9*, 2593. (c) Raj, M.; Maya, V.; Singh, V. K. *J. Org. Chem.* **2009**, *74*, 4289. (d) Duangdee, N.; Harnying, W.; Rulli, G.; Neudörfl, J.-M.; Gröger, H.; Berkessel, A. *J. Am. Chem. Soc.* **2012**, *134*, 11196. (e) Baer, K.; Kraußer, M.; Burda, E.; Hummel, W.; Berkessel, A.; Gröger, H. *Angew. Chem. Int. Ed.* **2009**, *48*, 9355; *Angew. Chem.* **2009**, *121*, 9519.

(4) Rulli, G.; Duangdee, N.; Baer, K.; Hummel, W.; Berkessel, A.; Gröger, H. *Angew. Chem. Int. Ed.* **2011**, *50*, 7944; *Angew. Chem.* **2011**, *123*, 8092.

(5) Berkessel, A.; Harnying, W.; Duangdee, N.; Neudörfl, J.-M.; Gröger, H. *Org. Process Res. Dev.* **2011**, *16*, 123.

(6) Kristensen, T. E.; Vestli, K.; Fredriksen, K. A.; Hansen, F. K.; Hansen, T. *Org. Lett.* **2009**, *11*, 2968.

(7) Kristensen, T. E.; Vestli, K.; Jakobsen, M. G.; Hansen, F. K.; Hansen, T. *J. Org. Chem.* **2010**, *75*, 1620.

(8) Kristensen, T. E.; Hansen, T. *Eur. J. Org. Chem.* **2010**, 3179.

(9) The overall conversions decrease slightly by applying higher catalyst loadings (e.g., 1.0 mol%: 93%; 5.0 mol%: 87%). Although no detailed explanation is as yet available, this effect might be related (at least to some extent) to an increased formation of an inactive catalyst–substrate adduct in the case of reactions conducted at higher catalyst loading (for the formation of related adducts, see ref. 3d). The differences in the product-related conversions are primarily caused by the higher impact of the side-product formation (via dehydration of aldol product **4**) in the case of the reactions conducted at higher catalyst loading.

(10) (a) Gruttadauria, M.; Giacalone, F.; Noto, R. *Chem. Soc. Rev.* **2008**, *37*, 1666. (b) Gruttadauria, M.; Giacalone, F.; Marculescu, A. M.; Noto, R. *Adv. Synth. Catal.* **2008**, *350*, 1397.

(11) Because of the large amount of catalyst, the solvent is completely absorbed by the polymer, leading to the formation of a gel.

(12) An example for the recycling of **2** in a batch reactor is given in the Supporting Information.

(13) For recent applications of immobilized organocatalysts in continuous flow systems, see: (a) Ötvös, S. B.; Mándity, I. M.; Fülöp, F. *ChemSusChem* **2012**, *5*, 266. (b) Ayats, C.; Henseler, A. H.; Pericàs, M. A. *ChemSusChem* **2012**, *5*, 320. (c) Arakawa, Y.; Wennemers, H. *ChemSusChem* **2013**, *6*, 242.

(14) (a) Rulli, G.; Gröger, H., unpublished results. (b) For further information about the role of water as an essential component for an efficient organocatalytic aldol reaction, see ref. 2b and: Gruttadauria, M.; Giacalone, F.; Noto, R. *Adv. Synth. Catal.* **2009**, *351*, 33.

(15) Li, X.; Li, L.; Tang, Y.; Zhong, L.; Cun, L.; Zhu, J.; Liao, J.; Deng, J. *J. Org. Chem.* **2010**, *75*, 2981.