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Prolinamide-Derived Ionic-Liquid-Supported Organocatalyst for Asymmetric Mono- and Bis-Aldol Reactions in the Presence of Water

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A novel recyclable prolinamide-derived ionic-liquid-supported organocatalyst of asymmetric cross-aldol reactions in aqueous medium has been developed. In its presence, aromatic aldehydes react with cyclic or linear ketones to afford chiral aldol adducts in moderate to high yields and with excellent *dr* (*anti*/*syn* up to 96:4) and *ee* (81–99 %) values that do not tend to decline over ten recycles of the catalyst. Furthermore, it allows a highly enantioselective catalytic synthesis of linear bis-aldols in aqueous medium.

Introduction

The catalytic asymmetric aldol reaction is one of the most important methods for the enantioselective formation of carbon–carbon bonds in organic compounds.[1] During the past decade, a number of metal-free organocatalytic versions of this reaction have been developed.[2] Efficient organocatalysts, such as proline derivatives, significantly widened applications and amazingly improved stereo- and enantioselectivity of the aldol reaction.[3] Moreover, particular organocatalysts bearing hydrophobic structural units were designed to allow asymmetric aldol reactions to proceed in the presence of water,[4] where similar enzymatic reactions (synthesis of carbohydrates from glycerin aldehyde phosphates and dihydroxyacetone[5]) occur in nature in the presence of aldolases, which can be considered organocatalyst prototypes.[6] α-Amino acid amides[7] and some other chiral compounds[8] are regarded as very promising catalysts of asymmetric aldol reactions in the aqueous environment. Among them, water-tolerant supported prolinamide derivatives tagged to polymers[9] or ionic groups (imidazolium cations and PF_6^- or NTf_2^- anions)[10] attract attention as promising candidates for industrial applications,[11] because these hybrid systems[12] are potentially recoverable and recyclable. Polystyrene-supported organocatalysts are nearly insoluble in two-phase reagents, where the addition of an organic cosolvent to an aqueous system is commonly needed to ensure high-molecular catalyst swelling in the reaction medium.[13] Ionic-liquid-supported prolinamide **1**, which has a much lower molecular weight than polymer-supported organocatalysts, efficiently catalyzes asymmetric aldol reactions in "pure" water.[14] However, its activity significantly drops after three regenerations because of gradual leaching of catalyst **1** into organic solution during isolation of products. Later on, more robust C_2-symmetric catalysts **2** bearing two prolinamide units modified with ionic groups were designed. They retained high performance of asymmetric catalysis in water over 15 cycles.[15] Yet, one had to pay for higher recyclability by a noticeable reduction of catalytic activity (efficient loading is 2–5 mol-% for **1** vs. 10 mol-% for **2**) in this case.

Herein we propose to address this issue by an approach based on the modification of the cation unit present in catalyst **1** with a Brønsted-acidic group (Scheme 1). Many asymmetric organocatalytic aldol reactions are known to proceed at a higher rate and with better enantioselectivity in the presence of acidic additives.[16] We expected that a remote carboxy group in catalyst **3** would act as an acidic cocatalyst and simultaneously assist in retaining the catalyst in the aqueous phase during the product extraction. Recently, we reported a favorable impact of the incorporated carboxy group on catalytic performance and recyclability of ionic-liquid-supported primary-amine-derived chiral organocatalysts in asymmetric Michael reactions.[17] To the best of our knowledge, no attempt has been made to improve catalytic performance of prolinamide-derived supported organocatalysts in asymmetric aldol reactions by the incorporation of the Brønsted-acidic group.

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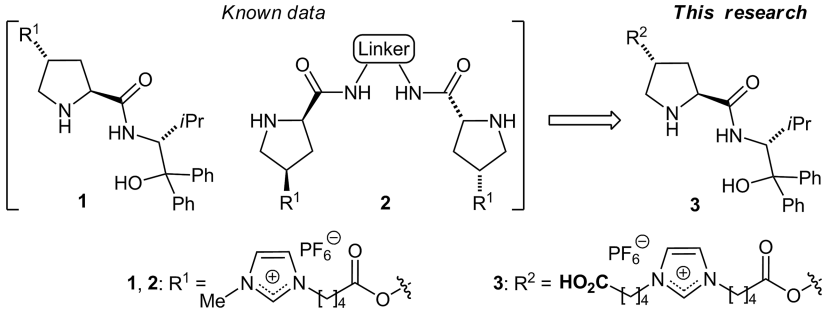


Scheme 1. Research strategy.

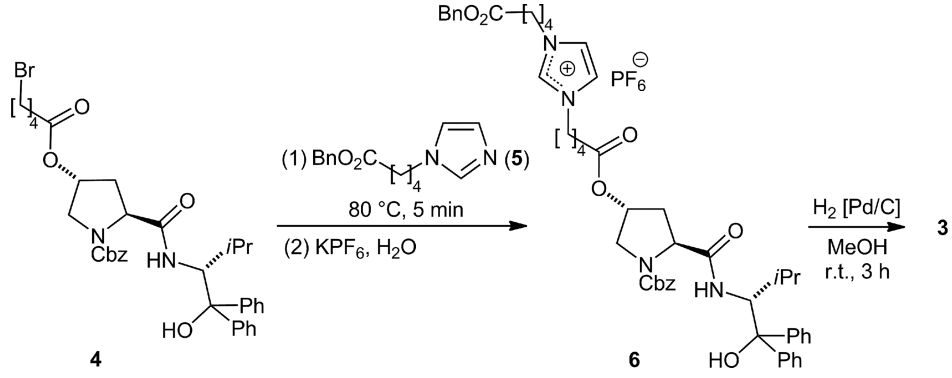
Results and Discussion

To verify this hypothesis, we prepared hybrid catalyst **3** by a synthetic scheme that included a reaction of prolinamide **4**,[14] which bears an α,α-diphenylvalinol structural unit, with benzyl 5-(1*H*-imidazol-1-yl)pentanoate **5**[18] followed by a one-pot replacement of the bromide anion for the PF_6^- anion and removal of protecting groups in hexafluorophosphate **6** by catalytic (Pd/C) hydrogenation (Scheme 2). The relatively low melting point of imidazolium salt **3** (105–107 °C) allows its categorization as a task-specific chiral ionic liquid.

The catalytic performance of amide **3** was tested in asymmetric aldol reactions of aromatic (heteroaromatic) aldehydes **7** with ketones **8a**–**h** or aldehyde donors **8i**,**j** in the presence of water under comparable conditions (catalyst loading 5 mol-%, **7**/**8** ratio 1:3, 25 equiv. of water, room temp.). The reactions were carried out over the period of time required for a full conversion of **7**, though no longer than 24 h (48 h in the case of **9g**) (Table 1).

Under the studied conditions, carbonyl compounds **7** and **8** generated corresponding aldol products **9** in moderate to high yields and with superior *dr* and *ee* values as compared with corresponding reactions catalyzed by analog **1** (Table 1, Entries 1, 5 and 8). An advantage of catalyst **3** over **1** was especially noticeable in the reaction of **7a** with acetone (**8h**) (Table 1, Entry 8) where the *ee* values of product **9h** improved from 40% to 91%, which testified to a favorable impact of the carboxy group present in catalyst **3** on the stereoinduction process. Catalyst loading reduction down to 2 mol-% did not change enantioselectivity (Table 1, Entry 9), whereas reaction temperature reduction to 2 °C improved it up to 95% *ee*, though at the expense of the product yield (Table 1, Entry 10).

Importantly, the reaction between compounds **7g** and **8h** (1:3 ratio) catalyzed by **3** afforded bis-aldol product **10a** along with expected mono-aldol product **9m** in a 19:81 ratio (^{1}H NMR spectroscopic data) (Table 1, Entry 15). A convenient enantioselective synthesis of linear bis-aldols in the presence of organometallic catalysts has been developed recently.[19] However, in asymmetric organocatalytic aldol reactions, these valuable compounds were generated in a very low yield[20] and, according to the best of our knowledge, no data on their synthesis in aqueous medium have been reported so far. To improve a poor yield of bis-aldol adduct **10a**, we studied aldolization of compounds **7g** and **8h** catalyzed by compound **3** in the presence of water (25 equiv.) at various **7g**/**8h** molar ratios. It was found that the amount of **8h** directly correlated with the **10a** yield that reached 58% in the experiment where a **7g**/**8h** molar ratio of 1:0.33 was used (Table 2, Entries 1–4). A further decrease in the amount of ketone **8h** did not noticeably enhance the yield of bis-aldol product **10a**. Under the optimal conditions, compounds **7a** and **8h** generated the corresponding bis-aldol product **10b** in 49% yield (Table 2, Entry 5). Alternatively, bis-aldol product **10a** was prepared in 51% yield by reaction of aldehyde **7g** with mono-aldol adduct **9m** catalyzed by **3** under the proposed conditions (Table 2, Entry 6).



Scheme 2. Synthesis of task-specific chiral ionic liquid **3**.

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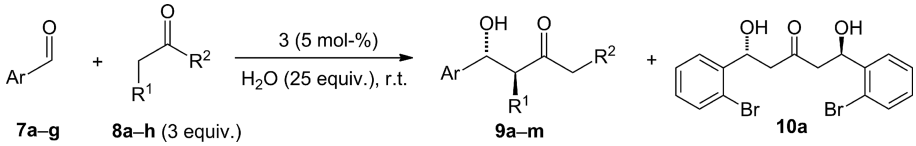
Table 1. Mono-aldol reactions of aldehydes **7** with ketones **8a**–**h** or aldehyde donors **8i**,**j** in the presence of **3**.[a]

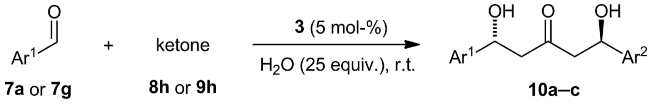


7a–g **8a–h** (3 equiv.) **9a–m** **10a**

Entry[a]	Ar	R^1, R^2	Time [h]	**9**, **10a** Yield [%][b]	*dr* (*anti*/*syn*)[c]	*ee* (**9**) [%][d]
1	4-$O_2NC_6H_4$ (**7a**)	–$(CH_2)_4$– (**8a**)	4	99 (99[e]) (**9a**)	96:4 (94:6)	92 (89[e])
2	3-$PhOC_6H_4$ (**7b**)	–$(CH_2)_4$– (**8b**)	24	47 (**9b**)	96:4	95
3	4-$O_2NC_6H_4$ (**7a**)	–CH_2–CH(Me)–$(CH_2)_2$– (**8c**)	24	99 (**9c**)	96:4	90
4	4-$O_2NC_6H_4$ (**7a**)	–CH_2–O–CH_2– (**8d**)	24	86 (**9d**)	92:8	94
5	4-$O_2NC_6H_4$ (**7a**)	H, *n*Pr (**8e**)	24 (38)	73 (95[e]) (**9e**)	–	94 (82[e])
6	4-$O_2NC_6H_4$ (**7a**)	H, *n*-hexyl (**8f**)	24	92 (**9f**)	–	92
7	4-$O_2NC_6H_4$ (**7a**)	H, –CH_2–*c*-Pr (**8g**)	48	16 (**9g**)	–	> 99
8	4-$O_2NC_6H_4$ (**7a**)	H, CH_3 (**8h**)	24	93 (85[f], 89[g], 96[h]) (**9h**)	–	91 (40[f], 50[g], 48[h])
9	4-$O_2NC_6H_4$ (**7a**)	H, CH_3 (**8h**)	24	60 (**9h**)	–	91[i]
10	4-$O_2NC_6H_4$ (**7a**)	H, CH_3 (**8h**)	24	40 (**9h**)	–	95[j]
11	2-$O_2NC_6H_4$ (**7c**)	H, CH_3 (**8h**)	24	96 (**9i**)	–	98
12	2-FC_6H_4 (**7d**)	H, CH_3 (**8h**)	24	93 (**9j**)	–	87
13	2-pyridyl (**7e**)	H, CH_3 (**8h**)	24	80 (**9k**)	–	92
14	4-BrC_6H_4 (**7f**)	H, CH_3 (**8h**)	24	85 (**9l**)	–	81
15	2-BrC_6H_4 (**7g**)	H, CH_3 (**8h**)	24	97[k] (95[k,l]) (**9m** + **10a**)	–	91[m] (91[l,m])
16	4-$O_2NC_6H_4$ (**7a**)	CH_3, H (**8i**)	24	95 (**9n**)	80:20	97
17	4-$O_2NC_6H_4$ (**7a**)	*i*Pr, H (**8j**)	24	68 (**9o**)	82:18	91

[a] Unless otherwise specified, all reactions were carried out with **3** (3.82 mg, 0.005 mmol), **7** (0.10 mmol), **8** (0.30 mmol), and water (0.045 mL). [b] Isolated yield of product **9** after column chromatography on silica gel. [c] ^{1}H NMR spectroscopic data. [d] HPLC analysis data for *anti* isomers (Chiralpak AD-H and OJ-H). [e] Reported data[14] on corresponding reactions in the presence of catalyst **1** (5 mol-%) are given in parentheses. [f] Data of this research for catalyst **1** (5 mol-%) are given in parentheses. [g] Data for **1** (5 mol-%)/AcOH (5 mol-%) catalytic system are given in parentheses. [h] Data for **1** (5 mol-%)/stearic acid (5 mol-%) catalytic system are given in parentheses. [i] The reaction was carried out in the presence of **3** (2 mol-%) at room temp. [j] The reaction was carried out in the presence of **3** (2 mol-%) at 2 °C. [k] Total yield of **9m** and **10a** (81:19 ratio) (^{1}H NMR spectroscopic data). [l] The reaction was carried out with **3** (120 mg, 0.159 mmol), **7g** (12.0 g, 64.9 mmol), **8h** (16 mL, 194 mmol), and water (15 mL). [m] *ee* of mono-aldol **9m**.

Table 2. Bis-aldol reactions of aldehydes **7** with ketones **8** or **9** in the presence of **3**.[a]



7a or **7g** **8h** or **9h** **10a–c**

Entry	Aldehyde	Ketone	Aldehyde/ketone molar ratio	Time [h]	Ar^1, Ar^2	Yield [%][b]	*ee* [%][c]
1	**7g**	**8h**	1:2	24	2-BrC_6H_4, 2-BrC_6H_4 (**10a**)	29	> 99
2	**7g**	**8h**	1:1	48	2-BrC_6H_4, 2-BrC_6H_4 (**10a**)	34	> 99
3	**7g**	**8h**	1:0.5	48	2-BrC_6H_4, 2-BrC_6H_4 (**10a**)	41	> 99
4	**7g**	**8h**	1:0.33	60	2-BrC_6H_4, 2-BrC_6H_4 (**10a**)	58	> 99
5	**7a**	**8h**	1:0.33	60	4-$O_2NC_6H_4$, 4-$O_2NC_6H_4$ (**10b**)	49	> 99
6	**7g**	**9m**	1:0.33	60	2-BrC_6H_4, 2-BrC_6H_4 (**10a**)	51[d]	> 99[d]
7	**7g**	**9h**	1:0.33	60	2-BrC_6H_4, 4-$O_2NC_6H_4$ (**10c**)	55	84

[a] Reaction conditions: organocatalyst **3** (3.82 mg, 0.005 mmol), aldehyde **7** (0.10 mmol), ketone **8h** or **9h** (0.33–2.00 mmol) and water (0.045 mL). [b] Isolated yield of product **10** after column chromatography on silica gel and recrystallization from the hexane/EtOAc (4:1) solvent system. [c] HPLC analysis data. [d] The reaction was carried out with **3** (16.0 mg, 0.02 mmol), **7g** (1.14 g, 6.2 mmol), **9m** (0.50 g, 2.05 mmol), and water (1 mL, 25 equiv.).

This method appeared to be applicable to the synthesis of bis-aldol **10c**, which bears different aldehyde units from compounds **7g** and **9h** (Table 2, Entry 7). Both mono- and bis-alolization catalytic reactions were scalable (Table 1, Entry 15 and Table 2, Entry 6). Furthermore, the 7 g scale preparation of the bromides **9m** + **10a** (81:19) efficiently proceeded in the presence of just 0.2 mol-% of catalyst **3** with no decrease of product yield or reaction selectivity (Table 1, Entry 15, see Supporting Information).

Pure enantiomers of products **10a** and **10b** (> 99% *ee*) were attained after the single crystallization of corresponding chromatographically isolated samples from the hexane/EtOAc (4:1) solvent system. Minor amounts (ca. 20%) of *meso*-**10a** or *meso*-**10b** were separated in this way from corresponding enantiomers and were not analyzed. Bis-aldol **10a** was obtained as transparent needles with a (1*R*,5*R*) absolute configuration (X-ray data) (Figure 1 and Supporting Information). The absolute (*R*) configuration was assigned

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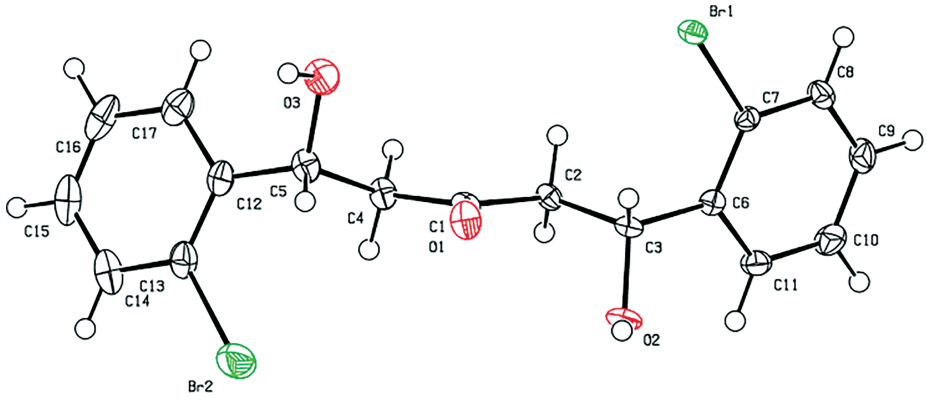
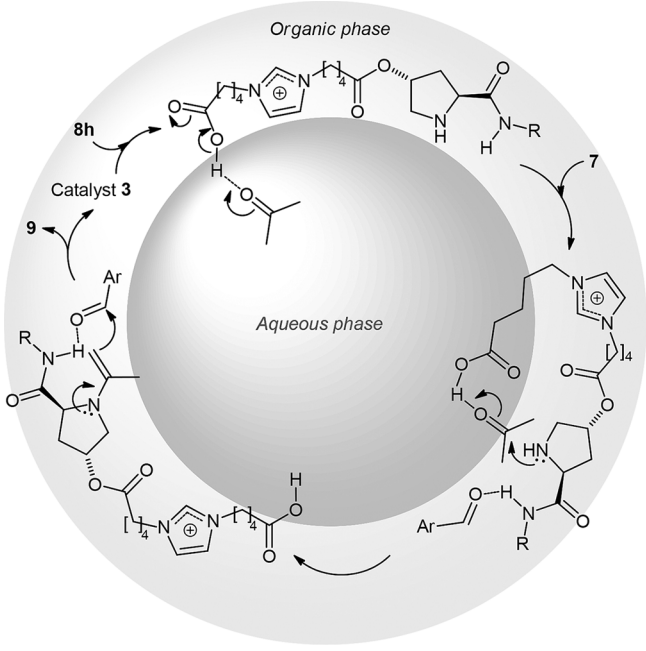


Figure 1. (1*R*,5*R*)-1,5-bis(2-bromophenyl)-1,5-dihydroxypentan-3-one (**10a**).

to mono-aldol compounds **9** based on the comparison of specific optical rotations of compounds **9h** and **9m** with reported data.[21]

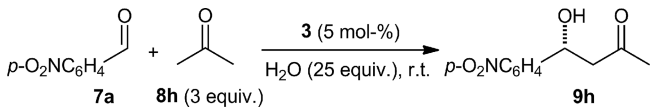
To clarify the role of the auxiliary COOH function in the catalytic aldol reactions in the aqueous environment, we carried out the reaction between aldehyde **7a** and acetone **8h** in the presence of carboxy-group-free catalyst **1** (5 mol-%) with or without acidic additive (AcOH or stearic acid, 5 mol-%) under similar conditions. In all cases, aldol **9h** was generated in high yields but with significantly lower enantioselectivity (40–50% *ee*) than in the corresponding **3**-catalysed reaction (Table 1, Entry 8). The different level of stereoinduction displayed by catalyst **3** on the one hand and the **1**/AcOH or **1**/stearic acid catalytic systems on the other hand was unexpected, because a COOH functionality was present in all these systems, and each system had similar acidic properties and hydrogen-bonding abilities. Neither hydrophilic AcOH, nor ambiphilic stearic acid[22] appeared to be an efficient cocatalyst in asymmetric aldol reactions between **7a** and **8h** in the presence of water. These results strongly support the observation that the covalent linkage between the carboxy group and the catalyst unit is essential for attaining a high level of enantioselectivity in the studied reactions. Apparently, a combination of H-bonding ability and adjacent location of the carboxy group incorporated into catalyst **3** allowed efficient transfer of hydrophilic **8h** molecules from the aqueous phase to a convenient position within the organic/water interfacial region, where the active sites (pyrrolidine rings) of **3** and hydrophobic aldehyde **7** molecules are located, and the enamine-type catalytic transformation occurs in a highly enantioselective manner (Scheme 3).

Furthermore, the presence of the auxiliary COOH moiety significantly improved recyclability of catalyst **3** as compared with catalyst **1** in the asymmetric mono-aldol reaction between compounds **7a** and **8h** (Table 3). After completion of the reaction, aldol **9h** was extracted with Et_2O, and fresh portions of the starting compounds were added to the



Scheme 3. Plausible catalytic cycle of asymmetric aldol reactions catalyzed by compound **3** between compounds **7** and **8h** in the presence of water.

Table 3. Recycling of catalyst **3** in the reaction of **7a** with **8h** in the presence of water.[a,b]



Entry	Time [h]	Conversion [%]	*ee* (**9h**) [%]
1	24	93 (85)	91 (40)
2	24	96 (82)	91 (40)
3	24	99 (64)	92 (39)
4	24	96	92
5	24	96	94
6	24	98	93
7	24	96	94
8	24	97	93
9	24	90	93
10	30	93	94

[a] Reaction conditions: organocatalyst **3** (3.82 mg, 0.005 mmol), **7a** (15.1 mg, 0.10 mmol), **8h** (17.4 mg, 0.30 mmol), and water (0.045 mL). [b] Corresponding data for catalyst **1** are given in parentheses.

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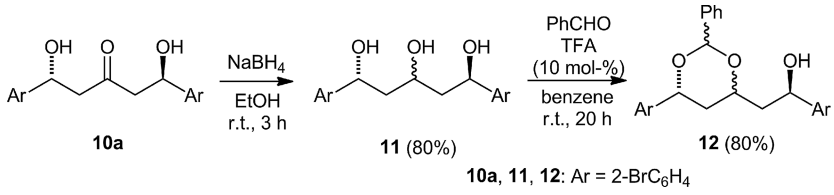

Scheme 4. Derivatization of **10**.

remaining suspension of **3** in water. In this manner, catalyst **3** was successfully recycled ten times without any reduction of the reaction rate or process enantioselectivity, whereas catalyst **1** was significantly deactivated already in the third cycle.

The possibility for further derivatization of bis-aldols adducts **10** was demonstrated through reduction of (1*R*,5*R*)-**10a** to axially symmetric 1,3,5-triol **11** with $NaBH_4$ followed by conventional treatment of **11** with benzaldehyde to afford a mixture of diastereomeric (HPLC data) ketals **12** (Scheme 4).

Conclusions

We have developed a prolinamide-derived ionic-liquid-supported recyclable organocatalyst for asymmetric aldol reactions of aromatic aldehydes with linear or cyclic ketones in the presence of water. Under the proposed conditions, corresponding aldol adducts were generated in moderate to high yields and with excellent *dr* (*anti*/*syn* up to 96:4) and *ee* (81–99%) values that did not change over ten recycles of the catalyst. Furthermore, the catalyst allowed a highly enantioselective synthesis of linear bis-aldol adducts that have not been so far prepared in aqueous medium.

Experimental Section

General: ^1H and ^{13}C NMR spectra were recorded with a Bruker AM 300 spectrometer in $CDCl_3$ and [D_6]DMSO. The chemical shifts of ^1H and ^{13}C signals were measured relative to Me_4Si or $CDCl_3$, respectively. The high-resolution mass spectra (HRMS) were measured with a Bruker microTOF II spectrometer using electrospray ionization (ESI). The measurements were taken either in the positive ion mode (interface capillary voltage 4500 V) or in the negative ion mode (3200 V) in a mass range m/z = 50–3000 Da; external or internal calibration was done with electrospray calibrant solution (Fluka). Syringe injection was used for solution in MeCN/H_2O (1:1, v/v) (flow rate 3 μL/min). Nitrogen was applied as a dry gas, and the interface temperature was set at 180 °C. Specific optical rotations $[\alpha]_D^{20}$ were measured with a Jasco DIP-360 polarimeter at 589 nm. Silica gel 0.060–0.200 μm (Acros) was used for column chromatography. Prolinamide **4**[14] and benzyl 5-(1*H*-imidazol-1-yl)pentanoate (**5**)[18] were synthesized according to known methods. Compounds **7** and **8** were purchased from Aldrich and used without purification. The solvents were purified by standard procedures. For experimental details and spectral or HPLC data see Supporting Information.

General Procedure for Mono-Aldol Reactions in the Presence of Water: A suspension of aldehyde **7** (0.10 mmol), ketone or aldehyde **8** (0.30 mmol), catalyst **3** (3.82 mg, 5 mol-%), and H_2O (0.045 mL, 25 equiv.) was stirred at ambient temperature for the time given in Table 1. The reaction mixture was extracted with Et_2O (3× 0.5 mL). The combined extracts were dried with anhydrous Na_2SO_4 and concentrated under reduced pressure (700 Pa). The conversion was determined by ^1H NMR spectroscopy of crude products. Products **9** were then purified by column chromatography on silica gel (*n*-hexane/ethyl acetate, 1:1 to 1:3).

General Procedure for Bis-Aldol Reactions in the Presence of Water: A suspension of aldehyde **7** (0.10 mmol), ketone **8h** or **9h** (0.03–0.20 mmol), catalyst **3** (3.82 mg, 5 mol-%), and H_2O (0.045 mL, 25 equiv.) was stirred at ambient temperature for 24 h. The reaction mixture was extracted with Et_2O (3× 0.5 mL). The combined extracts were dried with anhydrous Na_2SO_4 and concentrated under reduced pressure (700 Pa). The resulting raw bis-aldol products were purified by column chromatography on silica gel (*n*-hexane/ethyl acetate, 1:5 to 1:10) and crystallized from hexane/EtOAc (4:1) to afford bis-aldol products **10**. **10a**: m.p. 47–49 °C (ref.[23] n/a data), **10b**: m.p. 53–55 °C (ref.[20e] n/a data) and **10c**: m.p. 74–75 °C. For the ^1H and ^{13}C NMR spectra or HPLC data for compounds **10a**–**c**, and X-ray data for compound **10a**, see Supporting Information.

Gram-Scale Procedure for the Synthesis of 10a from 7g and 9m in the Presence of Water: A suspension of 2-bromobenzaldehyde (1.14 g, 6.2 mmol), 4-(2-bromophenyl)-4-hydroxybutan-2-one (**9m**) (0.50 g, 2.05 mmol), catalyst **3** (16 mg, 0.02 mmol), and H_2O (1 mL, 25 equiv.) was stirred at ambient temperature for 60 h. The reaction mixture was extracted with Et_2O (3× 25 mL). The combined extracts were dried with anhydrous Na_2SO_4 and concentrated under reduced pressure (700 Pa). The resulting orange viscous product was then recrystallized (hexane/EtOAc, 4:1) to afford 0.44 g (51%) of white needles, m.p. 47–49 °C.

Recycling of Catalyst 3: A suspension of aldehyde **7a** (15.1 mg, 0.10 mmol), acetone **8h** (0.30 mmol), catalyst **3** (3.82 mg, 5 mol-%), and H_2O (0.045 mL, 25 equiv.) was stirred at ambient temperature for 24 h. Aldol product **9h** was extracted with Et_2O (3× 0.5 mL). Fresh portions of reagents were added to the remaining aqueous suspension of catalyst **3**, and the reaction was performed again as described above.

Acknowledgments

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