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The Ion Tag Strategy as a Route to Highly Efficient Organocatalysts for the Direct Asymmetric Aldol Reaction

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Abstract: The installation of an imidazolium tag *via* acetate connection to the C-4 of *cis*-4-hydroxy-L-proline provides a highly efficient catalyst for the direct asymmetric aldol reaction, that works in a remarkably low catalyst loading (0.1 mol%) affording TONs up to 930 in the case of electron-poor aromatic aldehydes with *ee* up to >99%.

Keywords: asymmetric aldol reactions; catalyst recycling; ionic-tagged catalysts; organic catalysis; solvent-free conditions

Introduction

One of the most pressing challenges facing synthetic chemists is to join efficiency, traditionally determined as yield and selectivity parameters, to sustainability issues. Paraphrasing Noyori, chemists must pursue "practical elegance" in developing new synthetic protocols, where "practical" has to be read as efficient and sustainable at once.[1] A biomimetic approach to this challenge is proposed by organocatalysis,[2] which aims to mimic the action of enzymes with small organic molecules, and, possibly, perform reactions in water with comparable efficiency and stereoselectivity. At its outset, organocatalysis provided enantioselective reaction protocols that that took place in organic solvents, only. For example, the proline-catalyzed asymmetric cross-aldol reaction afforded good enantioselectivity and yield when excess acetone and aromatic aldehydes were treated with a catalytic amount of (*S*)-proline (typically 20–30 mol%) in DMSO or DMF.[3] Several other amino acid derivatives, including primary, cyclic and acyclic secondary amino acids, were screened as catalysts, while an intense catalyst design and development started resulting in an ever increasing number of new solutions reported in the literature.[4] Catalytic efficiency was the major limit of the former protocols, since TONs of 10 were hardly achieved in the literature up to 2004.

The presence of water, the solvent where class I aldolases catalyze the direct aldol reaction with excellent stereocontrol,[5] had in the original organocatalytic protocols a deleterious effect on enantioselectivity,[6] while proline in water does not work at all.[7]

In 2006 the field of enantioselective organocatalytic aldol and related reactions in water recorded an exceptional breakthrough, with the contributions reported by Barbas and co-workers,[7,8] Hayashi and co-workers,[9] and other groups.[10]

The key to success was to develop heterogeneous aqueous biphasic conditions which simulated the hydrophobic pocket where class I aldolases are supposed to promote their aldol reactions through the so called "asymmetric aminocatalysis". Process design focus on the preparation of water-insoluble catalysts which, together with an excess of donor ketone (2–5 equivalents with respect to the limiting aldehyde) and the acceptor aldehyde, form a concentrated hydrophobic medium which is in contact with the aqueous phase.

These heterogeneous systems are claimed to benefit from a catalytic effect by the water molecules at the oil-water interface, as rationalized by Jung and Marcus.[11] The best results are obtained with catalysts resulting from the installation of hydrophobic substituents on the scaffold of a reference catalyst such as proline. Following this guideline, Barbas developed (*S*)-*N*-decyl-*N*-(2-pyrrolidinylmethyl)decan-1-amine, trifluoroacetic salt ($\mathrm{TON_{max}} = 10$),[8a] Hayashi prepared 4-*tert*-butyldimethylsiloxy-L-proline and 4-decanoyloxy-L-proline ($\mathrm{TON_{max}} = 8$), the latter working with aliphatic aldehydes as donors.[9]

A slightly different approach combined partially water-soluble catalysts with salts that facilitate hydrophobic aggregation by "salting out".[12] The result was on outstanding increase of the reaction efficiency expressed as TONs. Indeed, TON = 58 was observed using 2.5–5 mol% of a L-prolinethioamide, dichloroacetic acid salt[12a], a value that increased to 170 using 0.5 mol% of amides deriving from proline and chiral 1,2-amino alcohols.[12b]

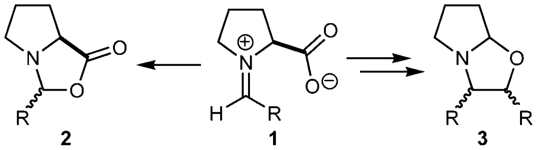
In all the foregoing cases, process design and catalyst optimization aimed at magnifying the catalyst solubility in the organic phase, where the aldol reaction must take place to ensure the best yields and stereochemical results. Recent contributions by Armstrong[13] and Pericàs[14] further implemented the value of the organocatalytic aldol reaction.

Solvent-free reactions[15] provide the most straightforward answer to the solvent problem, the most important contributor to the sheer magnitude of the waste problem in chemical manufacture.[16] Bolm and co-workers reported that the reaction time of proline-catalyzed intermolecular aldol reactions was significantly shortened when magnetic stirring was replaced by ball-milling under solvent-free conditions, affording *anti*-aldols in high *ee*s.[17] The best results were obtained using stoichiometric amounts of donor ketone and acceptor aldehyde. A few other examples of asymmetric aldol reactions were reported from Lu and Hayashi labs to occur in the absence of organic solvents, but, at a deeper insight, the excess of donor ketone used plays the role of the reaction "diluent". The excess of donor partner affects the green credentials of the process in terms of waste production, unless the recovery of the excess ketone is easily performed, as in the case of sufficiently volatile compounds that can be collected in a cold trap after evaporation under vacuum. The first example refers to the use of L-tryptophan, in the presence of 5 equivalents of water with respect to the aldehyde, which acted as an efficient catalyst (the highest TON was 17) for the aldol reaction under solvent-free conditions.[18]

Lu and Teo, independently, observed that incorporation of hydrophobic siloxy groups into threonine[19] and serine[20] resulted in effective organocatalysts capable of catalyzing the asymmetric aldol reaction under solvent-free conditions in the presence of 1 equivalent of water with TONs up to 29.[19]

Proline[21] and *trans*-siloxy-L-proline[21] were reported by Hayashi to work under solvent-free conditions, and the latter resulted in one of the most effective catalysts ever developed for the aldol reaction, affording products with excellent diastereo- and enantioselectivities under neat conditions in the presence of 3 equivalents of water. The critical effects of the amount of water in solvent-free aldol reactions had been previously demonstrated by Hayashi, who got his highest TON (96) using 1 mol% of *O*-TBDPS-4-hydroxy-L-proline, 2 equivalents of cyclohexanone, β-naphthaldehyde and 3 equivalents of water at room temperature in 42 h.[21] Analogous observations on the role of water on enantioselectivity had been also reported by Córdova and co-workers using DMSO as the solvent under homogeneous conditions.[22]

The counter-intuitive benign presence of water in the generally accepted enamine mechanism of the proline-catalyzed aldol raction was due to the inhibition of the formation of iminium ion **1** and other downstream products **2** and **3**, deriving from proline and the acceptor aldehyde (Scheme 1), as elegantly demonstrated by Blackmond and co-workers.[23] The occurrence of these off-cycle processes with respect to the generally accepted enamine-driven catalytic cycle, reduces the concentration of catalytically active species causing the reaction rate and the yield to be lower than that expected for the given initial donor and acceptor concentrations.



Scheme 1. Off-cycle side-products responsible for the low efficiency of proline in the catalytic asymmetric aldol reaction.

In this context, we approached the design of a new cross-aldolization catalyst working under solvent-free conditions in the presence of water, adopting the ion-tag strategy to modify the proline scaffold.[24] Miao and Chan first reported the use of imidazolium ion-tagged catalysts of the general structure **4** (Figure 1), where the tag is connected to the 4-OH group of *trans*-4-hydroxy-L-proline. The authors reported the use of **4a** ($X = BF_4$) as catalyst in DMSO or acetone as the solvent but the catalyst loading (30 mol%) was very high resulting in poor TONs.[25]

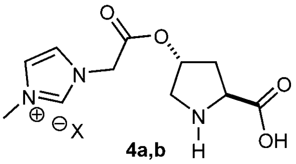
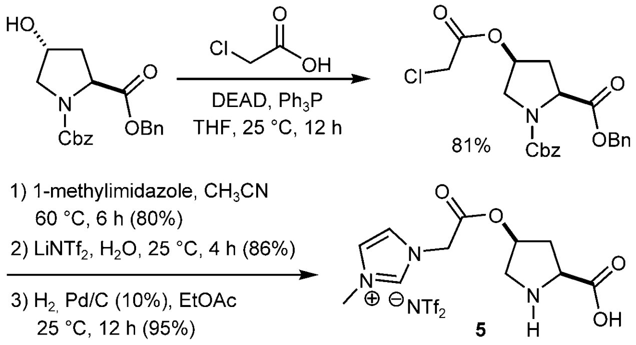


Figure 1. Ion-tagged *trans*-4-hydroxy-L-prolines. **4a**: $X = BF_4$; **4b**: $X = Tf_2N$.

A higher efficiency was achieved by working with **4b**, where the counterion was the lipophilic bis(trifluoromethylsulfonyl)imide ion ($X = Tf_2N$). In particular, TONs up to 17 were achieved in ionic liquids.[26] At last, even more efficient from a synthetic (chemical yields) and stereochemical point of view (diastereomeric ratios and *ee*s) was found in the use of **4b** under aqueous biphasic conditions.[27]



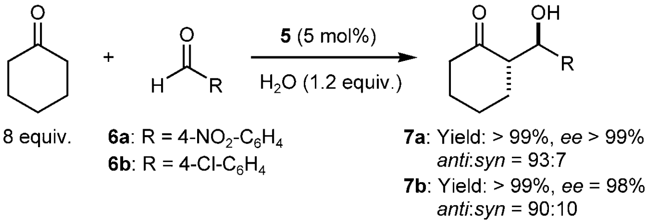
Scheme 2. Synthesis of the ionic-tagged *cis*-4-hydroxy-L-proline **5**.

Results and Discussion

On the basis of our previous experience using **4b** we planned a systematic investigation on the use of **4b** and its epimer **5** (Scheme 2) in a number of reaction protocols, with the aim to give a contribution to the TON optimization challenge without affecting the high standards achieved in the literature in terms of stereocontrol. A complete overview of all the study still in course on **4b**, **5** and analogues will be presented in an independent report; here we wish to anticipate the best results obtained with **5** under neat conditions in the presence of water. In the rational design of **5** we pursued the following considerations: rotation around the C-4–O bond can produce two effects, i) orienting the ionic tag towards the concave face of the octahydropentalene-like structure of side-products **2** and **3**, thus destabilizing them and ensuring a higher amount of available catalytically active species; ii) bringing the ionic tag and its Tf_2N^- counterion in spatial proximity to the reactive centers during the rate-determining enamine addition step. If an internal electrostatic stabilization of the transition state was in action, a reaction rate enhancement should be observed. Henceforth, we refer to this hypothesis as a "*cis* effect".

The synthesis of **5** provided no difficulties (Scheme 2, see Supporting Information) as it was smoothly met in just four operations from Cbz-protected *trans*-4-hydroxy-L-proline, benzyl ester. A standard Mitsunobu protocol applied to protected *trans*-4-hydroxy-L-proline and chloroacetic acid was followed by the installation of *N*-methylimidazole on the chloro ester moiety and anion exchange with lithium triflamide. Hydrogenolytic cleavage of the protective groups completed the synthesis of **5** in 53% overall yield from Cbz-protected *trans*-4-hydroxy-L-proline, benzyl ester.

With this new catalyst in our hands, we first checked the aqueous biphasic conditions previously applied to **4b**.[27] While stereoselectivities were comparable, yields obtained using catalyst **5** were in general less satisfactory with respect to the use of **4b**; that is, using 5 mol% of **5**, 4-nitrobenzaldehyde (**6a**) afforded the corresponding aldol **7a** in only 67% yield after 24 h at 25 °C [*anti/syn* = 96:4, *ee* (*anti*) = 97%]. In the same conditions, **4b** afforded a 97% yield [*anti/syn* = 96:4, *ee* (*anti*) = 99%].



Scheme 3. Direct asymmetric aldol reaction.

After a screening of different reaction conditions, we were delighted to observe that using 8 equivalents of cyclohexanone with respect to the limiting 4-nitrobenzaldehyde (**6a**) and 5 mol% of **5** under solvent-free conditions, in the presence of 1.2 equivalents of water, a quantitative amount of aldol **7a** could be isolated after stirring for 6 h at 25 °C, with remarkably high stereoselectivity: *anti/syn* = 93:7, *ee* (*anti*) > 99%. Under the same conditions, the less reactive 4-chlorobenzaldehyde (**6b**) was converted after 17 h to the *anti* aldol **7b** in >99% yield, *anti/syn* = 90:10, *ee* (*anti*) = 98% (Scheme 3).

Once having selected the **6a**/cyclohexanone aldol system as the benchmark reaction, we started the optimization study shown in Table 1. The work-up simply consisted of pouring the crude reaction mixture on the top of a silica gel column and eluting with cyclohexane/ethyl acetate mixtures.

Our focus was on reducing the catalyst loading without compromising the reaction times. Entry 1 demonstrated that using 5 mol% catalyst loading and 5 equivalents of donor ketone the reaction did proceed almost to completion in 20 min, corresponding to a TON of 19 and a TOF of 64 h^{-1}. The catalyst loading was then lowered to 2 mol% and after 2 h the reaction was virtually complete (entry 2, TON = 49). Under these last conditions we checked the possible reuse of **5** (entries 3–6).

The recovery of excess cyclohexanone was a facile step, just requiring to trap it in a cold-finger trap under vacuum at 25 °C (10^{-2} mmHg).[28] The aldol product was extracted from the crude residue with ether, leaving the catalyst that was reloaded with the reactants and water. Only in the fourth cycle (entry 6) did the yield decrease (20% less than in the first run), but with a remarkably constant stereoselectivity.

Furthermore, we reduced the catalyst loading to 0.5 mol%, a level that has been reached only by Maya et al., as previously discussed.[12a] We carried out a reaction over 24 h, which furnished, too, the

Table 1. Optimization studies for the reaction of cyclohexanone and 4-nitrobenzaldehyde.[a]

Entry	Catalyst, [mol%]	H_2O [equiv]	Time [h]	Yield [%][b]	*anti*/*syn*[c]	*anti ee* [%][d]	TON
1	**5**, 5	1.2	0.3	96	92:8	>99	19
2	**5**, 2	1.2	2	98	93:7	>99	49
3[e]	**5**, 2	1.2	2	97	92:8	>99	49
4[f]	**5**, 2	1.2	2	98	94:6	>99	49
5[g]	**5**, 2	1.2	2	98	92:8	>99	49
6[h]	**5**, 2	1.2	2	75	92:8	>99	38
7	**5**, 0.5	1.2	24	98	93:7	>99	196
8	**5**, 0.5	1.2	5	87	92:8	>99	174
9	**4b**, 0.5	1.2	5	37	94:6	>99	74
10[i]	**5**, 0.5	1.2	18	99	95:5	>99	198
11	**5**, 0.1	1.2	24	32	80:20	99	320
12	**5**, 0.1	0.25	24	6	73:27	97	60
13	**5**, 0.1	3.2	24	38	93:7	>99	380
14	**5**, 0.1	32	24	7	55:45	35	70

[a] Reactions are conducted at 25 °C using 5 equiv, of ketone with respect to the limiting aldehyde (1 mmol).
[b] Refers to isolated yields.
[c] Determined by ^{1}H NMR of the crude mixture.
[d] Determined by chiral HPLC (see Supporting Information).
[e] 1st run.
[f] 2nd run.
[g] 3rd run.
[h] 4th run.
[i] Reaction on 10 mmol of 4-nitrobenzaldehyde.

aldol in quantitative yield and remarkable stereoselectivity (entry 7, TON = 196). A drop in the yield was observed only when we carried out a reaction over only 5 h using 0.5 mol% of the catalyst, whereupon we obtained an 87% yield of the aldol (entry 8, TON = 174, TOF = 35 h^{-1}).

For a direct comparison, when **4b** had been subjected to these identical reaction conditions (entry 9) similar results were again obtained in terms of stereoselectivities, but the corresponding aldols were isolated in only 37% yield, *anti*/*syn* = 94:6, *ee* (*anti*) >99%.

The better performance of **5** seems to be consistent with the favorable previously quoted "*cis* effect" between the ion tag-containing substituent and the carboxyl group that drives the reaction stereoselectivity.

From a general synthetic point of view, to validate the results obtained in entries 7 and 8, we scaled up the reaction to 10 mmol of limiting 4-nitrobenzaldehyde (entry 10). After 18 h at 25 °C removal of excess cyclohexanone under vacuum and silica gel chromatography provided us 2.47 g (9.9 mmol) of product, corresponding to a 99% yield, with a slightly higher *anti*/*syn* ratio (95:5) and a virtually complete enantioselectivity (*ee* (*anti*) >99%).

As refers to the stereochemical outcome of entries 1–8, *anti*-aldols were invariably obtained in a virtually pure configuration, while diastereomeric ratios fluctuated in the 13(±2):1 range.

We were curious to attempt a reaction with just 0.1 mol% catalyst loading, a level very rarely met in organocatalysis to date. Using 1.2 equivalents of water, after 24 h we obtained a yield of 32% of the aldol but, surprisingly, there was a drop in the diastereoselectivity (entry 11). This prompted us to study the reaction with different amounts of water and the best yield of 38% was obtained using a slightly larger amount of water (entry 13, 3.2 equivalents), with the diastereoselectivity restored to its original ratio. This reaction marked a hitherto unrealized TON of 380 in asymmetric organocatalytic aldol reactions. Both activity and stereoselectivity are destroyed by higher amounts of water (entry 14). The last entries demonstrate that, in an optimization study of these catalytic processes, catalyst loading, amount of water, reaction time, plus excess of donor which was arbitrarily set at 5 equivalents in this work, have to be carefully investigated.

The next task was to explore the scope of the catalyst. A careful optimization will be presented in due time, while we present here a simple extension of the conditions reported in Table 1 to a number of acceptor aldehydes in the reaction with cyclohexanone first (Table 2), then to a few different donors in the reaction with 4-nitrobenzaldehyde (Table 3). As Table 2 (entries 1–20) depicts, reactions were carried out with 2, 0.5, and 0.1 mol% catalyst loading, depending on the reactivity of the acceptor aldehyde. Outstanding yields were obtained in the case of all the reactive aldehydes, and, regardless of the electronic nature of the aromatic aldehydes, excellent enantioselectivities

Table 2. Asymmetric aldol reactions of cyclohexanone with aldehydes, catalyzed by the *cis*-ionic-tagged proline **5** under solvent-free conditions in the presence of water.[a]

Entry	R in RCHO	**5** [mol%]	Time [h]	Yield [%][b]	*anti*/*syn*[c]	*anti ee* [%][d]	TON
1	4-CN-C_6H_4	2	6	>99	92:8	>99	>50
2	4-CN-C_6H_4	0.5	6	86	92:8	>99	172
3	2-NO_2-C_6H_4	2	6	95	92:8	>99	48
4	4-Cl-C_6H_4	2	18	97	92:8	> 99	49
5	4-Br-C_6H_4	2	15	95	95:5	>99	48
6	4-Br-C_6H_4	0.5	30	88	95:5	>99	176
7	4-MeO-C_6H_4	2	60	50	80:20	97	25
8	4-MeO-C_6H_4	5	60	60	75:25	97	12
9	Ph	2	19	86	92:8	>99	43
10	2-naphthyl	2	24	90	88:12	98	45
11	2-naphthyl	0.5	42	44	85:15	98	88
12	C_6F_5	0.5	4	>99	99:1	>99	>198
13	C_6F_5	0.1	24	93	99:1	>99	930
14	3-pyridyl	0.5	24	96	85:15	99	192
15[e]	3-pyridyl	0.1	24	46	84:16	98	460
16	4-pyridyl	0.5	24	94	85:15	98	188
17[e]	4-pyridyl	0.1	24	62	80:20	36	620
18[f]	4-pyridyl	0.1	24	68	86:14	70	680
19	*i*-Pr	10	72	72	>99:1	99	7
20	*c*-C_6H_{11}	10	72	68	>99:1	99	7

[a] Reactions are conducted at 25 °C using 5 equiv, of donor, 0.5 mmol of acceptor aldehyde and 1.2 equiv, of water.
[b] Refers to isolated yields.
[c] Determined by ^{1}H NMR of the crude reaction mixture.
[d] Determined by HPLC using chiral columns (see Supporting Information).
[e] 2.2 equiv. of water were used.
[f] 6.6 equiv. of water were used.

Table 3. Asymmetric aldol reactions of different donors with *p*-nitro-benzaldehyde, catalyzed by the *cis*-ionic-tagged proline **5** under solvent-free conditions in the presence of water.[a]

Entry	Ketone	**5** [mol%]	Time [h]	Yield [%][b]	*anti*/*syn*[c]	*anti ee* [%][d]	TON
1	cyclopentanone	1	3.5	97	70:30	98	97
2	cycloheptanone	5	60	45	71:29	>99	9
3	acetone	2	24	87	–	70	44

[a] Reactions are conducted at 25 °C using 5 equiv. of ketone with respect to the limiting aldehyde.
[b] Refers to isolated yields.
[c] Determined by ^{1}H NMR of the crude mixture.
[d] Determined by chiral HPLC (see Supporting Information).

were obtained. In particular, stereoselectivity was not affected by changing the reaction conditions, unless the catalyst loading limit of 0.1 mol% was used. In the last case a careful optimization of the water content is necessary. Astonishing are the TONs recorded with 4- and 3-pyridinecarboxaldehyde (entries 14–18) with a top TON value of 930 reached by pentafluorobenzaldehyde (entry 13).

Unfortunately, aliphatic aldehydes were the poorest substrates for this solvent-less reaction protocol. To force them to provide acceptable yields of aldols, 10 mol% of catalyst was necessary, even though an almost 99% enantiomerically pure *anti*-aldol was obtained in these reactions as the single product (entries 19 and 20).

Results collected in Table 3 point out the great difference in terms of reactivity between cyclopentanone and cycloheptanone (entries 1 and 2), the latter often displaying disappointing results in the organocatalysed aldol reaction.[8a,17a] Acetone displayed a reactivity intermediate between cyclopentanone and cycloheptanone, and a lower enantioselectivity with respect to cycloalkanones.

Conclusions

In conclusion, stereochemical considerations applied to the ion-tagging strategy led us to develop a new highly active and selective proline-based organocatalyst for the asymmetric aldol reaction. As mentioned earlier, the best performances were exhibited in a reaction protocol which did not use organic solvents in the reaction stage but 1.2 equivalents of water and a 5 molar excess of a liquid ketone as aldol donor which ensured the reaction to occur under homogeneous conditions with no mass transfer problems. Exceptionally high values of TON for the organocatalytic aldol condensation were achieved with the most reactive aromatic aldehydes.

Being a salt, the catalyst was not soluble in slightly aprotic polar solvents, and this allowed us to develop an easy separation procedure of the product from the catalyst, which could eventually be recycled. Indeed, once having eliminated the excess ketone under vacuum, the aldol is easily extracted with ether and the catalyst can be directly reused for another cycle. Stereocontrol was maintained at an identical level for four cycles, while the limited drop in recovered aldol in the 4th cycle should be reduced by a technical implementation of the separation step.

The process presented here was optimized for the benchmark reaction of cyclohexanone and 4-nitrobenzaldehyde and under these conditions many substrates afforded "enzymatic-like" levels of *ee*s. Work is in course to widen the scope and optimize the efficiency of **5** and other closely related catalysts.

Experimental Section

Typical Procedure (Table 1, entry 8)

Cyclohexanone (0.52 mL, 5 mmol) and water (0.022 mL, 1.2 mmol) were added to the catalyst **5** (2.7 mg, 0.005 mmol) and the mixture was allowed to stir for 20 min at room temperature, whereupon complete catalyst dissolution was observed. 4-Nitrobenzaldehyde (0.151 g, 1 mmol) was then added to the reaction mixture and allowed to stir. At the beginning 4-nitrobenzaldehyde, cyclohexanone and water do not form a homogenous mixture, but as soon as the conversion proceeds, the solution turns clear and homogeneous. The faster the reaction mixture turns homogeneous, the faster is the reaction. After 5 h stirring at room temperature, the reaction mixture was charged directly onto a silica gel column and the pure aldol was obtained upon eluting with cyclohexane/ethyl acetate (7:3) in 87% yield. The *ee* was determined by chiral HPLC using a CHIRALPAK AD column (hexane/2-propanol = 85:15, flow rate: 1.0 mL min^{-1}, $\lambda = 254$ nm); t_R *syn* = 11.1 min, t_R *syn* = 13.6 min, t_R *anti* (minor) = 14.6 min, t_R *anti* (major) = 18.8 min.

Recycling Procedure (Table 1, entries 3–6)

Cyclohexanone (0.26 mL, 2.5 mmol) and water (0.011 mL, 0.6 mmol) were added to the catalyst **5** (1.3 mg, 0.0025 mmol) and the mixture was allowed to stir for 20 min at room temperature, whereupon complete catalyst dissolution was observed. 4-Nitrobenzaldehyde (75 mg, 0.5 mmol) was then added to the reaction mixture and allowed to stir for 2 h at room temperature. The excess of cyclohexanone was removed under reduced pressure (~1 mmHg) and the reaction mixture was further dried under vacuum for 45 min. The aldol product was then extracted with Et_2O (2 mL × 5) following which, the reaction flask was again dried under vacuum for 1 h. It was then charged with the reactants and water in identical amounts and fashion as above. The aldol product was purified by evaporation of the combined organic extracts and subjecting the residue to silica gel column chromatography.

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