A modular approach to catalyst hydrophobicity for an asymmetric aldol reaction in a biphasic aqueous environment†

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Catalyst **5**, an ion pair consisting of a hydrophilic cation and a lipophilic anion, fulfils the solubility requirements needed to couple efficiency (enantioselectivities and *anti*-diastereoselectivities up to ≥99%) and catalyst recyclability in asymmetric aldol reactions under aqueous biphasic conditions.

Introduction

A milestone in the field of organocatalysis is represented by the proline-catalyzed direct asymmetric intermolecular aldol reaction, developed by List *et al.* in 2000.[1] The reaction of excess acetone with aromatic and α-branched aldehydes was found to proceed in the presence of a catalytic amount of proline (typically 20–30 mol%) in DMSO to provide the corresponding acetone aldols with good yields and enantioselectivities. Primary α-amino acids, too, have been screened as catalysts and have turned out to efficiently catalyze the reaction of cycloalkanones[2] as well as of protected hydroxyacetone and dihydroxyacetone[3] as the carbonyl donors.

Several efforts have recently been devoted to the design of more efficient catalysts for the direct asymmetric aldol reactions.[1a,4] From a practical point of view there is a strong commitment toward both optimizing catalyst activity (loading, selectivity, *etc.*) and operational protocols (excess of donor, the solvent issue, *etc.*) as well as designing recoverable and reusable catalysts, one of the major goals of organocatalysis. In the last two years, some of the most outstanding achievements in terms of catalytic efficiency have been those involving aqueous biphasic conditions. In particular we refer to reactions carried out under heterogeneous conditions, wherein, however, all the reacting components, inclusive of the catalyst, are present in the organic phase at the outset of the reaction.

In the above context, since 2006, most of the best achievements have been reported for catalysts consisting of chiral amines[5] or amides[6] deriving from L-proline, and for *O*-modified *trans*-4-hydroxy-L-proline derivatives.[7] The general strategy adopted was to install hydrophobic substituents on the proline structure, resulting in the abatement of the original hydrophilicity of the reference amino acid.

Thus, the hydrophobic catalyst does not dissolve appreciably in water, and forms with the donor–acceptor pair an organic phase. Even though the catalytic cycle takes place in the water saturated concentrated hydrophobic phase (or in the organic–water boundary layer), the presence of the aqueous phase is essential to ensure optimum results.[8]

A recent contribution by Jung and Marcus provides an interesting theoretical basis to the effect of water in heterogeneous reactions.[9]

A confirmation that formation of a such a biphasic system, with all the reacting components exclusively confined in the organic phase, is a necessary condition to get good results is demonstrated by the fact that water miscible ketones afforded moderate yield and stereoselectivity in water.[5,7a] This was further verified by Maya *et al.* who reported exceptional stereochemical results using acetone as a donor in an aqueous environment consisting of brine, necessary to decrease the water solubility of acetone by salting out.[6a]

If maximizing catalyst hydrophobicity is the key to success in the organocatalysed aldol reaction under liquid–liquid biphasic aqueous conditions, this property, however, does not provide a practical recycling procedure, since at the extraction stage catalyst and products will be extracted into the same solvent.

The strategy we suggest to design a catalyst that joins efficiency and recyclability under liquid–liquid biphasic aqueous conditions, is to confer on it the correct amphiphilicity profile. That would allow the catalyst to move from water, where it might be present dissolved at the outset, to the organic phase consisting of the donor–acceptor pair. Secondly, in the work-up stage, it would allow the catalyst to move from the organic solvent used to separate the aldol products back into water. Such a delicate balance of solubility properties is much easier to address by using the ionic tagging strategy in catalyst design.[10] A catalytically active molecular frame is tagged with a side chain containing a charged group, *e.g.* an onium group. This approach allows us to tune the partition coefficient of the catalyst in biphasic systems by a suitable choice of ion pair structure.

Ionic liquid-supported catalysts of general structure **1** (Fig. 1), where the charged tag is connected to the 4-OH group of *trans*-4-hydroxy-L-proline, have been reported in recent literature to ensure good catalytic and stereochemical performances in the asymmetric cross-aldol reaction.

Miao and Chan first reported the use of **1a** as an efficient aldolization catalyst in DMSO or acetone as the solvent.[11] We demonstrated that catalytic performances of **1b** are substantially improved by the coulombic environment created by an ionic liquid (IL) used as the solvent.[12] Catalyst **1c** was used in an analogous way in ILs by Zhou and Wang.[13] Finally, catalyst **1d** was recently reported to work under aqueous biphasic conditions allowing an easy recycling of the catalyst.[14] Even though long lipophilic chains are installed on **1d**, the outstanding role of the anion in

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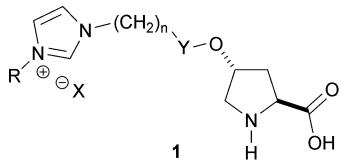


1a: Y = CO, n = 1, X = BF_4, R = CH_3
1b: Y = CO, n = 1, X = Tf_2N, R = CH_3
1c: Y = CH_2, n = 1, X = BF_4, R = CH_3
1d: Y = CO, n = 4, X = PF_6, R = n-$C_{12}H_{25}$

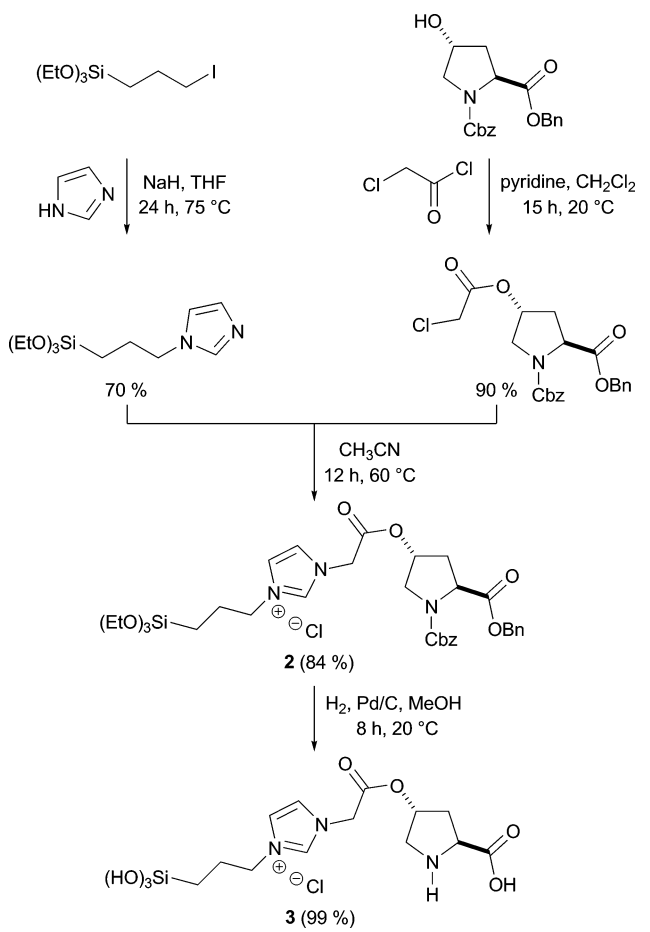
Fig. 1 General structure of ion-tagged prolines **1**.

determining the catalyst partitioning is witnessed. Indeed, the use of BF_4^- as the counterion instead of lipophilic PF_6^- abated the catalyst activity under aqueous heterogeneous conditions.

Results and discussion

Installation of the (3-(3-trihydroxysilylpropyl)-imidazolium-1-yl)-acetate tag on the 4-position of 4-hydroxy-L-proline

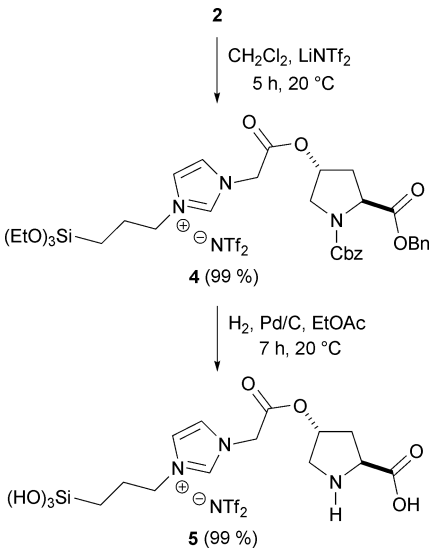
En route to structures like **1**, we synthesized the intermediate **3** containing a trialkoxysilyl group on the R appendage, according to the reaction sequence shown in Scheme 1.



Scheme 1 The synthesis of ionic-tagged proline **3**.

At the outset, the aim of this study was the preparation of hybrid 'organic–inorganic' mesoporous silicas using soft chemistry. With **2** in our hands, we investigated whether the hydrolysis of **2** to the trihydroxysilyl species **3** was followed by polycondensation in a kind of self-directed assembly of particles,[15] which, in turn, could be candidates as catalysts for the asymmetric aldol reaction. Complete hydrolysis occurred when **2** was subjected to hydrogenolytic conditions in MeOH. The proline derivative **3** was perfectly soluble in water, and even in the presence of trace amounts of HCl, no trace of aggregation into nanoparticles was observed by dynamic light scattering measurements. When **3**, in water, was tested as a catalyst in the aldol reaction of cyclohexanone and *p*-nitrobenzaldehyde, no reaction occurred at rt after 72 h.

Since the lipophilicity/hydrophilicity profile of an ionic liquid is strongly reshaped by passing from halides to the hydrophobic bis(trifluoromethylsulfonyl)imide ion (Tf_2N^-), we first subjected **2** to a Cl^-–Tf_2N^- metathesis reaction to obtain **4**, which was then exposed to Pd/C catalyzed hydrogenolysis conditions in wet EtOAc (Scheme 2). Quantitative deprotection was again accompanied by complete hydrolysis of the triethoxy moiety, releasing **5** which was still soluble in water. Herein too, no evidence of spontaneous polycondensation resulted from dynamic light scattering measures.



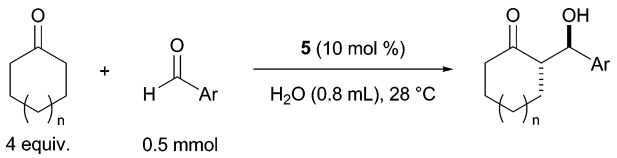
Scheme 2 The synthesis of ionic-tagged proline **3**.

The use of ionic-tagged proline 5 as a catalyst for the direct asymmetric aldol reaction

With compound **5** in our hands, we checked it as a catalyst in the benchmark reaction of cyclohexanone and *p*-nitrobenzaldehyde. The experiment was conducted under neat conditions in the absence of water. After stirring 5 equivalents of cyclohexanone and *p*-nitrobenzaldehyde (the limiting reagent) for 16 h at 28 °C in the presence of 10 mol% of **5**, the aldol **6** was isolated in 80% chemical yield, with an *anti* diastereoselectivity = 80 : 20, the *anti*-aldol being produced in 85% ee. This preliminary result prompted us to explore different reaction conditions in order to identify a more efficient catalytic protocol. The reaction in the presence of water was checked at first, according to the chemical evidence on the sometimes conflicting role of water on the outcome of the

aldol reaction.[9,16] If, indeed, the commonly accepted mechanism for the organocatalysed aldol reaction,[1] as well as for the action of class I aldolases,[17] involves the intermediate formation of an enamine, a few equivalents of water are necessary, too, to speed up the catalytic cycle. On the other hand, a massive presence of water is supposed to favor the hydrolysis of the enamine, unless the reaction takes place in an organic compartment (a hydrophobic pocket in the case of the enzyme) separated from the aqueous phase.

When the amount of water was progressively increased, both yield and stereochemical outcome improved, up to a top value of 92% yield, accompanied by an excellent diastereoselectivity (*anti–syn* = 96 : 4) and a remarkable enantioselectivity (*anti*-**6** was produced in 99% ee) after stirring for 24 h at 28 °C using the amount of water and the conditions shown in Scheme 3. Doubling the amount of water did not produce any change both in terms of chemical and stereochemical results.



Scheme 3 Conditions adopted for the aldol reaction protocol.

This preliminary result, achieved under liquid–liquid biphasic conditions, meant that **5** possessed the optimum partitioning coefficient to be extracted by cyclohexanone into the organic layer of the water–cyclohexanone biphasic system.[18] The reaction was carried out under efficient stirring to ensure formation of an emulsion in which the surface area between the two phases was maximized, as well as the transport of **5** into the organic phase. Conversely, using proline derivatives with hydrophobic substituents, it is reported that efficient stirring is less significant, owing to the complete insolubility of the catalyst in water.[7a]

An outstanding stability of the stereochemical performance both in terms of dr and ee was also observed when catalyst loading was varied. When the mol% of catalyst was decreased from 10% to 5%, 2.5% and 1%, it reflected only on reduced chemical yields, which after 24 h passed from 92% to 80%, 65% and 30%, respectively. We then explored the scope of the reaction using different substrates and the results are summarized in Table 1.

Setting the reaction time at 24 h and using 4-nitrobenzaldehyde, we first compared the reactivity of cycloalkanones (runs 1–3). The excellent *anti–syn* ratios displayed by cyclohexanone (run 2) is not shared by cyclopentanone and cycloheptanone (runs 1 and 3), the latter being the least reactive aldol donor. Correspondingly, an outstanding enantioselectivity was recorded both with cyclohexanone and cyclopentanone, cycloheptanone (run 3) being the only exception.

Table 1 Asymmetric aldol reactions catalysed by **5**

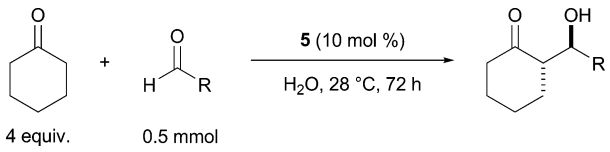
Run	Ar	*n*	*t*/h	**6**, Yield (%)	*anti–syn*[b]	*anti* ee (%)[c]
1	4-NO_2-C_6H_4	0	24	**6a**, 98	70 : 30	97
2	4-NO_2-C_6H_4	1	24	**6b**, 92	96 : 4	99
3	4-NO_2-C_6H_4	2	24	**6c**, 25	73 : 27	82
4	2-NO_2-C_6H_4	1	24	**6d**, 60	>99 : 1	>99
5	4-CN-C_6H_4	1	24	**6e**, 87	96 : 4	>99
6	C_6F_5	1	24	**6f**, 93	99 : 1	>99
7	4-Br-C_6H_4	1	72	**6g**, 81	96 : 4	>99
8	4-Cl-C_6H_4	1	70	**6h**, 78	96 : 4	>99
9	2-Naphthyl	1	72	**6i**, 78	95 : 5	96
10	Ph	1	72	**6j**, 60	95 : 5	99

[a] Yields refer to isolated products. [b] Determined by ^{1}H NMR of the products. [c] Determined by chiral HPLC (see ESI).

Electron withdrawing groups favor the aldol reaction (runs 4–6) while halobenzaldehydes (runs 7,8) and unsubstituted aldehydes (runs 9,10) require a longer time to reach good yields. In 6 examples out of ten, enantioselectivities were ≥99%, and in all the examples involving cyclohexanone, diastereomeric *anti–syn* ratios were ≥95 : 5.

Unfortunately, the foregoing reaction protocol suffered for the main limitation of being not applicable to aliphatic aldehydes. To widen the scope of the cross-aldol reaction to aliphatic aldehydes, *i.e.* isobutyraldehyde and cyclohexane carboxaldehyde as acceptors, we started re-examining other reaction conditions. Again, the amount of water was revealed to be a critical factor, as shown by the results collected in Table 2.

Table 2 Direct aldol reaction of aliphatic aldehydes and cyclohexanone with organocatalyst **5**



Run	R	H_2O (mL)	**6**, Yield (%)[a]	*anti–syn*[b]	*anti* ee (%)[c]
1	*i*-Pr	0.8	**6k**, 9	>99 : 1	99
2	*c*-C_6H_{11}	0.8	**6l**, 7	>99 : 1	99
3	*i*-Pr	0.012	**6k**, 58	>99 : 1	99
4	*c*-C_6H_{11}	0.012	**6l**, 50	>99 : 1	99

[a] Refers to isolated yields. [b] Determined by ^{1}H NMR of the products. [c] Determined by chiral HPLC (see ESI†).

Recycling experiments

Thus, having exploited the partitioning properties of **5** in a profitable reaction protocol, we addressed the second important goal mentioned earlier, that is, the recyclability of the catalyst. The complete insolubility of **5** in ether and its corresponding solubility in water formed the basis of an efficient separation of **5** from the product and of a simple catalyst recycling procedure.

The reaction work-up by a direct extraction with ether of the reaction mixture was not efficient since part of the catalyst was extracted in the cyclohexanone containing organic phase. We modified the work-up procedure by preliminarily removing both ketone and water under reduced pressure (~0.1 mmHg, rt). The solid residue was eventually partitioned between water and ether. During the elimination of the excess of ketone and water, all the enamine present in solution was hydrolysed delivering a residue which consisted of free **5** and the aldol product, only. Separation of the product did occur very efficiently with no loss of catalyst into the ether phase, while the catalyst remained in the aqueous phase ready to be reused.

Table 3 Recycling experiments under the same conditions reported for Table 1, run 2

Cycle	**6a**, Yield (%)[a]	*anti–syn*[b]	*anti* ee (%)[c]
1	93	96 : 4	99
2	94	95 : 5	98
3	88	95 : 5	97
4	76	96 : 4	98
5	51	94 : 6	87

[a] Refers to isolated yields. [b] Determined by ^{1}H NMR of the products. [c] Determined by chiral HPLC (see ESI†).

Indeed, the catalyst containing aqueous phase was directly charged with the aldol reaction partners and the reaction was run for a few cycles. Results of 5 cycles under the same conditions reported in Table 1 run 2, are collected in Table 3.

Recovered yields in the first three runs were essentially stable, and only in the fourth cycle a 20% drop in chemical yield was recorded, while a decrease of the enantioselectivity by a factor of 12% was observed only in the fifth cycle. A partial catalyst epimerization in the long run can occur, likely as the consequence of the formation of iminium ions between the proline group and the aldehyde. It is indeed known that heating proline in the presence of a catalytic amount of an aldehyde provides an efficient racemization protocol.[19]

Conclusions

We have demonstrated that a water soluble organocatalyst can be designed to function in a highly efficient and stereoselective fashion in the asymmetric cross-aldol reaction under aqueous biphasic conditions by a modulation of its partition coefficients in different aqueous biphasic environments. The cationic frame of the new proline derivative **5** contains three hydrophilic portions that render it very soluble in water. On the other hand, coupling the hydrophilic cation of **5** to the highly hydrophobic Tf_2N^- ion gives rise to an optimized favourable partitioning of the new catalyst **5** not just during the reaction stage but also during the work-up. Indeed, in the reaction stage, **5** is transported to the organic phase of the biphasic ketone–water system where the aldol reaction takes place in high yields and remarkable stereocontrol. In particular, using cyclohexanone as a donor, *anti–syn* ratios were ≥95 : 5 and ee's were up to ≥99%. In the work-up stage, on the other hand, aldol products and **5** were efficiently separated by partitioning them between ether and water, **5** being soluble in water but not in ether. This offers the opportunity to recycle **5**, which was used for 4 runs without loss of its original stereochemical performances.

Experimental

General and materials

^{1}H and ^{13}C NMR spectra were recorded on Varian Inova 300 and Varian Gemini 200 spectrometers; chemical shifts (δ) are reported in ppm relative to TMS. Gas chromatographic analyses were performed with an Agilent 6850 instrument coupled to an Agilent 5975 quadrupole mass detector (50 °C, 2 min → 280 °C, 10 °C/min → 280 °C, 10 min). Chiral HPLC studies were carried out on a Hewlett-Packard series 1090 instrument. Reactions were monitored by TLC and GC-MS. Flash-chromatography was carried out using Merck silica gel 60 (230–400 mesh particle size). All reagents were commercially available and were used without further purification, unless otherwise stated.

3-Iodopropyltriethoxy silane. A solution of 3-chloropropyltriethoxy silane (12.04 mL, 50 mmol) and NaI (7.49 g, 50 mmol) in anhydrous acetone (40 mL) was stirred under reflux for 24 h. The reaction was monitored using GC-MS. The solvent was then evaporated under reduced pressure, the residue was filtered over celite and washed with ether (15 mL). The ether was then removed *in vacuo* and the crude residue was distilled to obtain the pure 3-iodopropyltriethoxy silane (13.85 g, 83%). GC-MS: $t_R = 14.3$ min; $m/z = 332$. ^{1}H NMR (200 MHz, $CDCl_3$): 0.63–0.77 (m, 2 H), 1.19 (t, $J = 7.0$ Hz, 9 H), 1.75–2.00 (m, 2 H), 3.19 (t, $J = 7.1$ Hz, 2 H), 3.79 (q, $J = 7.0$ Hz, 6 H). ^{13}C NMR (50 MHz, $CDCl_3$): 10.5, 12.2, 18.2, 27.5, 58.3. Anal. Calcd for $C_9H_{21}IO_3Si$ (332.25): C, 32.53; H, 6.37. Found: C, 32.46; H, 6.35%.

***N*-(3-Triethoxysilyl)propyl imidazole.** To a suspension of NaH (0.792 g, 33 mmol) in anhydrous THF (55 mL) at 0 °C was added imidazole (2.25 g, 33 mmol) and it was allowed to stir for 30 min. 3-Iodopropyltriethoxy silane (9.97 g, 30 mmol) was then added to the reaction mixture at 0 °C. The reaction was allowed to warm to room temperature and stirred under reflux for a further 24 h. The conversion was monitored using GC-MS. The reaction was cooled to room temperature, filtered over celite and washed with ether. The filtrate was concentrated *in vacuo* and the crude product was purified by distillation under vacuum using a Kugel-Rohr apparatus; 5.68 g, 70%. GC-MS: $t_R = 18.1$ min; $m/z = 272$. ^{1}H NMR (200 MHz, $CDCl_3$): 0.56 (dd, $J = 9.0$, 7.1 Hz, 2 H), 1.21 (t, $J = 7.0$ Hz, 9 H), 1.78–1.98 (m, 2 H), 3.80 (q, $J = 7.0$ Hz, 6 H), 3.93 (t, $J = 7.0$ Hz, 2 H), 6.91 (s, 1 H), 7.04 (s, 1 H), 7.47 (s, 1 H). ^{13}C NMR (50 MHz, $CDCl_3$): 7.2, 18.1, 24.7, 49.0, 58.2, 58.3, 118.6, 129.0, 137.0. Anal. Calcd for $C_{12}H_{24}N_2O_3Si$ (272.42): C, 52.91; H, 8.88; N, 10.28. Found: C, 53.08; H, 8.86; N, 10.27%.

***N*-Benzyloxycarbonyl-(2*S*,4*R*)-4-(2-chloroacetyl)proline benzyl ester.** To an ice-cold solution of *N*-benzyloxycarbonyl-(2*S*,4*R*)-4-hydroxyproline benzyl ester (5.34 g, 15 mmol) and 2-chloroacetyl chloride (1.88 g, 16.5 mmol) in CH_2Cl_2 (20 mL) was slowly added pyridine (1.31 g, 16.5 mmol). The reaction mixture was allowed to warm to room temperature and stirred for a further 12 h. The precipitate was removed by filtration and the filtrate was washed with water (20 mL), 10% aq. $NaHCO_3$, then dilute HCl (2 M) and finally water (20 mL). The solution was dried over Na_2SO_4, concentrated under vacuum and the crude residue was purified by silica-gel column chromatography (cyclohexane–ethyl acetate, 70 : 30) to give the title compound as a thick oil (5.13 g, 79% yield). $[\alpha]_D^{20} = -42.0$ (*c* 1.0, $CHCl_3$); ^{1}H-NMR (200 MHz, $CDCl_3$; 2 conformational isomers): 2.16–2.37 (m, 1 H), 2.39–2.59 (m, 1 H), 3.66–3.93 (m, 2 H), 4.00–4.10 (m, 2 H), 4.43–4.66 (m, 1 H), 5.04 (d, $J = 10.3$ Hz, 2 H), 5.14–5.27 (m, 2 H), 5.38 (br. s., 1 H), 7.17–7.47 (m, 10 H); ^{13}C-NMR (75 MHz, $CDCl_3$; 2 conformational isomers): 35.4 and 36.4, 40.6, 51.9 and 52.4, 57.6 and 57.9, 67.1 and 67.2, 67.4, 73.7 and 74.4, 127.9, 128.1, 128.2, 128.3, 128.4, 128.5, 128.6, 135.1 and 135.3, 136.1 and 136.2, 154.1 and 154.6, 166.7 and 166.8, 171.5 and 171.8. Anal. Calcd for $C_{22}H_{22}ClNO_6$ (431.87): C, 61.18; H, 5.13; N, 3.24. Found: C, 60.97; H, 5.11; N, 3.22%.

***N*-(3-Triethoxysilyl)propyl imidazolium chloride-tagged *N*-Cbz-proline benzyl ester (2).** To a solution of *N*-benzyloxycarbonyl-(2*S*,4*R*)-4-(2-chloroacetyl)proline benzyl ester (5.94 g, 13.75 mmol) in CH_3CN (10 mL) was added *N*-(3-triethoxysilyl)propyl imidazole (3.97 g, 14.58 mmol) and the reaction mixture was heated at 60 °C for 12 h. The CH_3CN was then removed under reduced pressure. The crude product was washed with anhydrous ether (5 mL × 4) and vacuum dried to obtain the quarternised compound **2** as a hygroscopic solid (8.14 g, 84% yield). $[\alpha]_D^{20} = -11.2$ (*c* 0.86, $CHCl_3$); ^{1}H-NMR (300 MHz, $CDCl_3$): 0.59 (t, $J = 7.2$ Hz, 2 H), 1.21 (td, $J = 7.0$, 2.2 Hz, 9 H), 1.98 (dq, $J = 7.7$, 7.5 Hz, 2 H), 2.14–2.32 (m, 1 H), 2.48–2.70 (m, 1 H), 3.70–3.90 (m, 7 H), 4.24 (t, $J = 7.0$ Hz, 2 H), 4.46–4.59 (m, 1 H), 5.01 (dd, $J = 11.2$, 1.7 Hz, 2 H), 5.09–5.20 (m, 2 H), 5.28–5.42 (m, 2 H), 5.53–5.75 (m, 1 H), 5.92 (d, $J = 17.8$ Hz, 1 H), 7.15–7.42 (m, 11 H), 7.59 (s, 1 H), 10.53 (s, 1 H); ^{13}C-NMR (75 MHz, $CDCl_3$; 2 conformational isomers): 6.1, 17.4, 23.3, 34.4 and 35.3, 49.2, 50.9 and 51.3, 56.6 and 57.1, 57.2, 57.6, 65.9, 66.2 and 66.3, 73.7 and 73.9, 120.4, 123.6, 126.7, 126.8, 127.0, 127.1, 127.3, 127.4, 127.5, 127.58, 127.60, 134.3, 134.5, 135.2, 135.3, 137.0, 153.1 and 153.6, 165.3, 170.8, 171.0. Anal. Calcd for $C_{34}H_{46}ClN_3O_9Si$ (704.28): C, 57.98; H, 6.58; N, 5.97. Found: C, 57.78; H, 6.60; N, 5.94%.

***N*-(3-Trihydroxysilyl)propyl imidazolium chloride-tagged proline (3).** To a solution of **2** (3.52 g, 5 mmol) in MeOH (15 mL) was added palladium on charcoal (10%, 530 mg, 0.5 mmol). The mixture was stirred under hydrogen at room temperature under atmospheric pressure for 8 h. The reaction mixture was filtered over celite and washed with CH_3CN (15 mL). The filtrate was concentrated *in vacuo* to obtain **3** as a pale brown very hygroscopic solid (1.96 g, 99% yield). $[\alpha]_D^{20} = -10.3$ (*c* 1.1, CH_3OH); ^{1}H-NMR (200 MHz, CD_3OD): 0.55–0.81 (m, 2 H), 1.93–2.16 (m, 2 H), 2.31–2.49 (m, 1 H), 2.56–2.75 (m, 1 H), 3.35 (s, 2 H), 3.50–3.59 (m, 1 H), 3.62–3.70 (m, 1 H), 3.81–3.87 (m, 1 H), 4.22–4.47 (m, 1 H), 5.18–5.39 (m, 2 H), 5.47–5.62 (m, 1 H), 7.74 (br. s., 1 H), 9.24 (br. s., 1 H). ^{13}C-NMR (50 MHz, CD_3OD): 25.2, 30.1, 36.2, 51.8, 53.2, 60.9, 71.2, 77.1, 123.6, 125.5, 139.0, 167.8, 172.2. Anal. Calcd for $C_{13}H_{22}ClN_3O_7Si$ (395.87): C, 39.44; H, 5.60; N, 10.61. Found: C, 39.49; H, 5.65; N, 10.56%.

***N*-(3-Triethoxysilyl)propyl imidazolium trifluoromethane-sulfonimide-tagged *N*-Cbz-proline benzyl ester (4).** A solution of **2** (8 g, 11 mmol) and *N*-lithiotrifluoromethane-sulfonimide (3.32 g, 11.55 mmol) in CH_2Cl_2 (10 mL) was stirred at room temperature for 5 h. The reaction mixture was then washed with H_2O (3 mL) and dried over Na_2SO_4. Concentration of the organic layer under vacuum afforded **4** as a brown hygroscopic solid (10.3 g, 99% yield) that was used without further purification for the debenzylation step. $[\alpha]_D^{20} = -5.7$ (*c* 0.58, $CHCl_3$); ^{1}H-NMR (200 MHz, $CDCl_3$): 0.52–0.68 (m, 2 H), 1.12–1.36 (m, 9 H), 1.84–2.09 (m, 2 H), 2.15–2.37 (m, 1 H), 2.41–2.65 (m, 1 H), 3.64–3.94 (m, 8 H), 4.06–4.32 (m, 2 H), 4.43–4.62 (m, 1 H), 4.92–5.26 (m, 6 H), 5.38 (br. s., 1 H), 7.15–7.48 (m, 12 H), 8.88 (s, 1 H); ^{13}C-NMR (75 MHz, $CDCl_3$; 2 conformational isomers): 6.2, 6.6, 17.88, 17.93, 23.9, 35.0, 35.8, 49.5, 50.3, 51.8, 57.8, 58.35, 66.8, 67.16, 67.23, 117.4, 121.6, 123.9, 127.3, 127.4, 127.7, 127.8, 127.9, 128.16, 128.22, 128.27, 128.32, 134.9, 135.7, 136.6, 154.1, 154.6, 165.4, 171.6, 171.7. Anal. Calcd for $C_{36}H_{46}F_6N_4O_{13}S_2Si$ (948.98): C, 45.56; H, 4.89; N, 5.90. Found: C, 45.62; H, 4.87; N, 5.88%.

***N*-(3-Trihydroxysilyl)propyl imidazolium trifluoro methanesulfonimide-tagged proline (5).** To a solution of **4** (4.75 g, 5 mmol) in EtOAc (15 mL) was added palladium on charcoal (10%, 530 mg, 0.5 mmol). The mixture was stirred under hydrogen at room temperature under atmospheric pressure for 7 h. The reaction mixture was filtered over celite and washed with CH_3CN (15 mL). The filtrate was concentrated *in vacuo* to obtain the catalyst **5** as a pale brown low-melting solid (3.17 g, 99% yield). $[\alpha]_D^{20} = -11.4$ (*c* 1.1, MeOH); ^{1}H-NMR (200 MHz, CD_3OD): 0.47–0.79 (m, 2 H), 1.89–2.16 (m, 2 H), 2.25–2.47 (m, 1 H), 2.51–2.71 (m, 1 H), 3.45–3.61 (m, 2 H), 4.12–4.39 (m, 3 H), 5.16–5.24 (m, 2 H), 5.46–5.64 (m, 1 H), 7.66 (s, 2 H), 9.00 (s, 1 H). ^{13}C-NMR (75 MHz, CD_3OD): 25.3, 36.2, 39.4, 50.9, 53.9, 54.7, 61.3, 71.4, 119.2, 123.4, 125.5, 127.7, 138.7, 168.7, 174.5. Anal. Calcd for $C_{15}H_{22}F_6N_4O_{11}S_2Si$ (640.56): C, 28.13; H, 3.46; N, 8.75. Found: C, 28.04; H, 3.44; N, 8.78%.

Typical experimental procedure for the cross-aldol condensation. Catalyst **5** (16 mg, 0.025 mmol) was stirred in water (0.8 mL) until a clear solution was obtained. Cyclohexanone (0.259 mL, 2.5 mmol) was then added and stirred for a further 20 min, whereupon the reaction mixture was an emulsion. *p*-Nitrobenzaldehyde (75.5 mg, 0.5 mmol) was added to the reaction mixture and stirred at room temperature for the appropriate time; the nature of the reaction mixture remained an emulsion over the time period. The cyclohexanone and water were then removed under reduced pressure, water (0.8 mL) was added to the residue and it was extracted with Et_2O (3 mL × 4). The combined organic extracts were dried over Na_2SO_4, concentrated *in vacuo* and purified by silica-gel column chromatography (cyclohexane–ethyl acetate, 7 : 3) to obtain the pure aldol adducts.

Typical experimental procedure for recycling studies. The recycling studies were performed using the typical experimental procedure for the cross-aldol condensation on a 1 mmol scale of the aldehyde. After completion of the Et_2O extraction, the reaction flask was dried under vacuum (~0.1 mmHg, rt) for 1 h and recharged with the starting substrates.

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