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Protonated arginine and lysine as catalysts for the direct asymmetric aldol reaction in ionic liquids

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ABSTRACT

Side chain protonation of basic α-amino acids with Brønsted acids provides new effective catalysts for the direct asymmetric aldol reaction of cyclic ketones with aromatic aldehydes in ionic liquids and DMSO. Increased yields are obtained in *N*-butyl *N*-methyl pyrrolidinium triflate ([bmpy][TfO]) with respect to DMSO using argininium tosylate (Arg·PTSA) as a 1.3 M aq solution in 10% molar amount with respect to the limiting aldehyde.

1. Introduction

Asymmetric enamine organocatalysis, the α-electrophilic substitution of carbonyl compounds catalysed by primary and secondary chiral amines via enamine intermediates, is a prime milestone in the field of organocatalysis.[1] In particular, the organocatalysed direct asymmetric aldol reaction has witnessed over the last eight years an astonishing growth. This transformation has its roots in the intramolecular asymmetric version of the aldol reaction, the Hajos–Parrish–Eder–Sauer–Wiechert reaction discovered in the early 70s.[2] However, it was the seminal work by List, Lerner and Barbas III in 2000, disclosing the potential of proline as catalyst for the direct asymmetric intermolecular aldol reaction,[3] that sparked its revival. Since then, efforts directed to the design of new catalysts, new experimental protocols, synthetic applications and theoretical investigations have progressed at a tremendous pace.[1,4] Most of the recent contributions on organocatalyst design for the aldol reaction focused on proline based structures, such as *O*-protected 4-hydroxy-L-proline[5] and proline amides.[6]

Amongst unmodified natural α-amino acids, proline was the catalyst of choice for the asymmetric aldol reaction of acetone with aldehydes.[1,3,4] The reaction of excess acetone with aromatic or 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 aldols after 24–48 h with good yields and enantioselectivities.

Córdova et al. reported the application of simple acyclic α-amino acids as catalysts for the direct asymmetric aldol reaction.[7a–c] Various simple primary amino acids were investigated for the aldol reaction of cyclohexanone with *p*-nitrobenzaldehyde and, as in the case of proline, reactions were performed at ambient temperature using 30 mol % of catalyst in a variety of polar solvents (DMSO the best) for 25–92 h, depending on the amino acid. The reaction afforded good levels of *anti* diastereoselectivity while the best enantioselectivities are reported for Ala, Val,[7d] Ile and Thr (ees in the 90–99% range). Interestingly, the basic α-amino acid Arg was observed as the worst catalyst, providing neither diastereo- nor enantioselectivity, while two other basic α-amino acids, His and Lys, afforded no or low diastereoselectivity and 71 and 84% ee for the *anti*-aldol adduct, respectively. Tryptophan was also reported as an efficient organocatalyst in the presence of water,[8] while Phe, His and Trp work in an aqueous environment in the form of salts obtained by reaction with Lewis bases.[9]

Simple acyclic α-amino acids, i.e., (*S*)-Ser, (*S*)-Thr, (*S*)-Trp, as well as *O*-*t*-Bu-(*S*)-Thr and *O*-*t*-Bu-(*S*)-Tyr were explored by Barbas III et al. in the aldol addition of hydroxyacetone and dihydroxyacetone to aldehydes in *N*-methyl pyrrolidone. They observed a reversed *syn*-diastereopreference with these carbonyl donors, together with high levels of enantioselectivity.[10] Analogously, *O*-silylated threonines performed as good catalysts for the *anti*-selective aldolisation of cyclohexanone with benzaldehyde in aqueous biphasic conditions.[11]

Independent of the important achievements reported over the last five years in terms of efficiency, particularly with respect to activity and selectivity optimisation, the search for new organocatalytic processes, which address economy, simplicity and recyclability issues is still an urgent task in catalysis.[12] In an attempt to address all the above aspects, we present here an alternative to the organocatalytic asymmetric cross aldol reaction, which is based on the use of basic natural α-amino acids. It is worth noting that, among primary α-amino acids, basic ones have been reported to give the worst results, so far.[7a–c]

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2. Results and discussion

Among the basic α-amino acids, we focused our attention on (*S*)-Arg, which possesses the highest side chain basicity (pK_a=12.48) due to its guanidine group,[13] and (*S*)-Lys (side chain pK_a=10.53).

In terms of relative molar costs, the basic amino acids examined in this work plus proline, included as the reference catalyst, are in the following rough ratio: 3.7 (Pro), 3.3 (Lys), 1 (Arg). Although there is no comparison between the costs of natural amino acids and their sophisticated derivatives reported in the literature,[8–11] Arg is almost four times less expensive than routinely utilised Pro.

To exploit Arg and Lys as catalysts, a very simple solution was devised, which consisted of the use of the side chain protonated form of the corresponding amino acid. The two amino acids were used as aqueous solutions in the presence of a stoichiometric amount of a Brønsted acid. Two possible effects of the acid additive could be anticipated. (i) The first is a rate enhancement of a few steps of the catalytic cycle such as enamine formation and hydrolysis of the iminium ion resulting from the nucleophilic addition step (Fig. 1). (ii) The second beneficial effect is the suppression of interfering general base-catalysed mechanisms, which should result in poor enantioselectivities.

The latter anticipation was confirmed by comparing the Arg and arginine *p*-toluenesulfonic acid salt (Arg·PTSA) in the benchmark reaction shown in Scheme 1, using DMSO as the solvent, under the same experimental conditions.

The complete lack of diastereo- and enantioselectivity when Arg is used can be accounted for by a general base aldolisation mechanism. Once this preliminary result was established, the next issue tackled in this study was the possibility to further improve the catalytic process by using ionic liquids (ILs), instead of DMSO, as solvents. ILs are entering the R&D activities in catalysis by offering an opportunity to develop liquid/liquid biphasic conditions very useful for catalyst recovery and reuse.[14]

Within this field, Toma et al.,[15] and Loh et al.,[16] independently, tested proline in ILs, e.g., 1-butyl-3-methyl imidazolium hexafluoro phosphate ([bmim][PF_6]), in the asymmetric aldol addition of acetone to aromatic aldehydes. Yields, enantioselectivity and TONs were found to be similar to those obtained using DMSO, but the advantage of using the IL was the easy separation of the aldol product from the proline containing IL phase, which could then be recycled up to four times without loss of catalytic activity and selectivity.[15,16] The same catalytic system, proline in [bmim][PF_6], was also found by Córdova to be an excellent solution for the cross aldolisation of enolisable aldehydes.[17]

Recently we reported that *trans*-4-hydroxy-L-proline suitably tagged on the hydroxyl group with an ammonium **1a** or imidazolium **1b** ion (Fig. 2),[18] catalyses the asymmetric intermolecular aldol reaction in ILs with a significant improvement both in terms of reaction rate and enantioselectivity with respect to the use of proline.

In an analogous study, Zhou and Wang obtained ees in 65–92% range in the aldol reaction of acetone and aromatic aldehydes catalysed by 1-(2-((3*R*,5*S*)-5-carboxypyrrolidin-3-yloxy)-2-ethyl)-3-methyl-1*H*-imidazolium bromide in [bmim][BF_4].[19] The concept at the basis of the authors' reasoning was that the installation of a charged tag on the structure of the catalytically active species should secure a stronger Coulombic interaction between the catalyst and all the charged intermediates of the catalytic cycle with the IL molecules, with consequences both in terms of catalytic activity and selectivity.[20] A second point is that a charged catalyst/IL system has better chances to be separated from the reaction products and to be reused.

Basic α-amino acids present a straightforward opportunity to incorporate a charged tag onto their side chain via the simplest of operational techniques, namely protonation by means of a suitable Brønsted acid. Thus, the resulting protonated catalysts were evaluated in the aldol reaction of cyclohexanone (**1a**) with *p*-nitrobenzaldehyde (**2a**) shown in Scheme 1. A preliminary set of experiments was carried out to compare Arg·PTSA and Lys·PTSA in a few ILs, in DMSO, the most frequently used solvent in organocatalysed aldol reactions, and under solvent-free conditions. Since it had been demonstrated that the presence of water in amino acid-catalysed aldol reactions in DMSO is essential to ensure good results,[7,21] the catalyst was used in the form of a ~1.3 M aq solution. To start with, the aforementioned reaction was investigated with 10% molar amount of either Arg·PTSA or Lys·PTSA in six different media, four ionic liquids, DMSO and under neat conditions (Table 1, runs 1–9).

anti-Aldol products were obtained preferentially with high enantioselectivites in most cases along with good diastereocontrol and in good yields, in analogy with the results obtained with primary α-amino acids.[7] In all the experiments involving an IL, the aqueous solution of catalyst was poured in the IL and equilibrated for 10 min. In this time interval anion exchange between catalyst and solvent molecules can occur. We did not investigate the extent to which anion scrambling takes place. Ion mobility, strictly related to ionic conductivity, depends on viscosity, on the number of

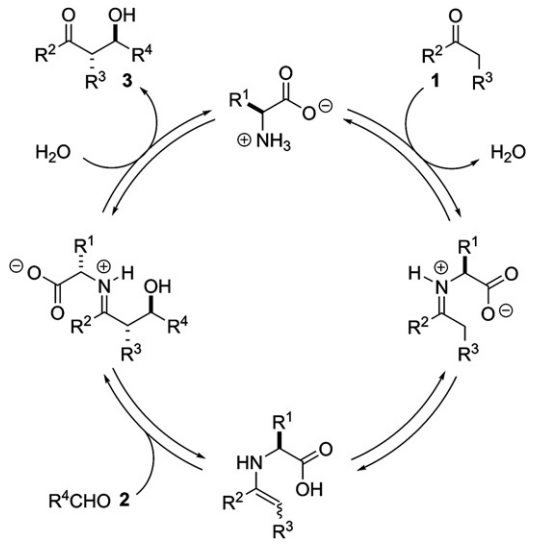
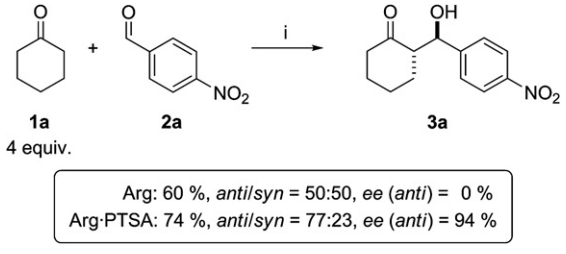


Figure 1. The enamine catalysis mechanism.



Scheme 1. Reagents and conditions. (i) Catalyst (10 mol %), DMSO/H_2O (20:1), 24 h, 25 °C.

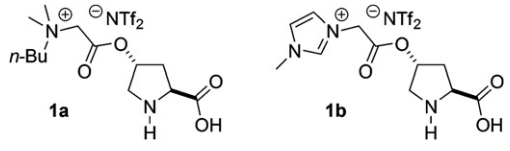


Figure 2. Structures of ionic-tagged 4-hydroxy-L-prolines.

Table 1
Comparison of the catalytic activity of Arg·PTSA and Lys·PTSA in the asymmetric aldol reaction of **1a** and **2a** in different reaction media[a]

Run	Solvent	Catalyst	Yield[b] (%)	*anti*/*syn*[c]	*anti* ee[d] (%)
1	[bmim][$N(CN)_2$]	Arg·PTSA	57	90:10	86
2	[bmim][TfO]	Arg·PTSA	60	72:28	90
3	[bmpy][Tf_2N]	Arg·PTSA	20	71:29	82
4	[bmpy][TfO]	Arg·PTSA	95	70:30	94
5	DMSO	Arg·PTSA	74	77:23	94
6	Neat	Arg·PTSA	0	—	—
7	[bmim][$N(CN)_2$]	Lys·PTSA	76	90:10	82
8	[bmpy][TfO]	Lys·PTSA	80	82:18	94
9	DMSO	Lys·PTSA	78	88:12	86
10	[bmpy][TfO]	Arg·TfOH	84	72:28	94
11	[bmpy][TfO]	Arg·TFA	88	75:25	92
12	[bmpy][TfO]	Arg·HCl	30	74:26	80

[a] Limiting aldehyde **2a** (1 mmol) and 75 μL of the 1.33 M aqueous solution of Arg·PTSA or Lys·PTSA (~10 mol %) in 1 mL of solvent were used. Reactions were performed at 23–26 °C for 24 h.
[b] Yields refer to pure products isolated by flash chromatography on silica gel.
[c] Determined by ^{1}H NMR spectroscopy.
[d] Determined by HPLC analysis on a chiral stationary phase: Daicel Chiralpak AD, *n*-hexane/*i*-PrOH (85:15), 1.0 mL min^{-1}, 14.5 min (*anti*, minor), 19.3 min (*anti*, major).

charge carriers (i.e., molecular weight), on density and on ion sizes. Any ion association will cause a decrease in the ionic conductivity through decreasing the number of available diffusible ions. Ion association is limited, however, with more delocalised charges, and fewer ion–ion interactions mean higher mobility.[22] Anions with delocalised charges were used also for this reason. Anyway, aware of the lack of information about the true anion exchange inside the solvent/catalyst system, we operationally adopted a standard pre-equilibration time of 10 min at room temperature. Then **1a** was added and again equilibrated for 30 min, followed by the addition of the limiting aldehyde **2a**. The performance of the catalyst displayed a strong dependence on the IL hydrophilicity, which was, in turn, related to the physico-chemical properties of the anion. The lowest reaction rate was recorded in *N*-butyl-*N*-methyl pyrrolidinium bis(trifluoromethane)sulfonimide ([bmpy][Tf_2N]) (run 3), which presents a hydrophobic anion, while both Arg·PTSA and Lys·PTSA gave their best results in [bmpy][TfO], containing the hydrophilic triflate ion (runs 4, 8).

If [bmpy][TfO] was the best solvent in terms of yield and enantiomeric excess (ee) of the major *anti*-aldol (run 4, 8), the best *anti*/*syn* diastereomeric ratio (dr) was achieved in [bmim][$N(CN)_2$], containing the highly hydrophilic dicyanamide ion (runs 1, 7).

DMSO (runs 5, 9) was confirmed as an excellent molecular solvent in terms of stereocontrol giving the same ee as [bmpy][TfO] and a slightly superior *anti*/*syn* ratio, but in the case of Arg·PTSA, passing from DMSO to [bmpy][TfO] the yield was lower by 20% (run 5).[20]

The total lack of activity under solvent-free conditions, the most frequently used procedure with the last generation of proline-derived catalysts, was surprising.[5,6] When the standard amount of 1.33 M solution of Arg·PTSA in water was added to a heterogeneous mixture of **1a** and **2a**, after 24 h at room temperature no trace of product was detectable by TLC. The poor solubility of the aldehyde **2a** in **1a** did not improve after the addition of the catalyst aqueous solution, and heterogeneity is likely to be responsible for this failure.

A few experiments were eventually set up to assess the possible effect of different Brønsted acids used in the preparation of the catalyst aqueous solution. Thus Arg salts with trifluoromethane sulphonic acid (TfOH), trifluoroacetic acid (TFA) and hydrochloric acid were used in [bmpy][TfO] as solvent (runs 10–12), under the same conditions reported in run 4. A significant drop of chemical yield and enantioselectivity was observed using Arg·HCl (run 12), while the other salts afforded comparable results both in terms of yields and stereoselectivity parameters with respect to Arg·PTSA (run 4).

With Arg·PTSA/[bmpy][TfO] identified as the reference catalytic system, the scope of the reaction was explored on different ketones and aromatic aldehydes (Table 2). All aldols, with the exception of **3f** and **3i**, were characterised upon comparison with the literature data.[23]

We did not optimise reaction times for the highest conversions, but for a better and direct comparison, all reactions were quenched after 24 h. Runs 1–8 of Table 2 allow us to link yields and stereochemical results to structural changes on the aldehyde moiety. The highest chemical yields were recorded with aldehydes possessing electron-withdrawing substituents. Electron-deficient aldehydes and halobenzaldehydes gave the best results in terms of ees (>90%). Correspondingly, runs 9–11 compare the reactivity of different donors towards **2a**. Cyclopentanone and acetonide protected dihydroxyacetone were slightly less reactive and selective than cyclohexanone, however, yields could be improved to 85 and 75%, respectively, by increasing the reaction time to 72 h. Acetone

Table 2
Direct asymmetric aldol reactions catalysed by Arg·PTSA in [bmpy][TfO][a]

Run	Ketone	Aldehyde	**3**, yield[b] (%)	*anti*/*syn*[c]	*anti* ee[d] (%)
1	Cyclohexanone (**1a**)	4-Chlorobenzaldehyde (**2b**)	**3b**, 63	70:30	94
2	Cyclohexanone (**1a**)	4-Bromobenzaldehyde (**2c**)	**3c**, 60	77:23	93
3	Cyclohexanone (**1a**)	4-Cyanobenzaldehyde (**2d**)	**3d**, 89	76:24	92
4	Cyclohexanone (**1a**)	2-Naphthaldehyde (**2e**)	**3e**, 50	93:07	88
5	Cyclohexanone (**1a**)	Pentafluorobenzaldehyde (**2f**)	**3f**, 81	91:09	76[e]
6	Cyclohexanone (**1a**)	2-Nitrobenzaldehyde (**2g**)	**3g**, 72	80:20	95
7	Cyclohexanone (**1a**)	Benzaldehyde (**2h**)	**3h**, 50	78:22	85
8	Cyclohexanone (**1a**)	3-Pyridinecarboxaldehyde (**2i**)	**3i**, 38	81:19	89[f]
9	Cyclopentanone (**1b**)	4-Nitrobenzaldehyde (**2a**)	**3j**, 68	67:33	78
10	Dihydroxyacetone dimethyl acetal (**1c**)	4-Nitrobenzaldehyde (**2a**)	**3k**, 56	77:23	84
11	Acetone (**1d**)	4-Nitrobenzaldehyde (**2a**)	**3l**, 20	—	52

[a] Reactions were conducted on a 1 mmol scale of the limiting aldehyde **2a–i**, with 75 μL of the 1.33 M aqueous solution of Arg·PTSA (~10 mol %) in 1 mL of solvent for 24 h in 23–26 °C range.
[b] Yields refer to pure products isolated by flash chromatography on silica gel.
[c] Determined by ^{1}H NMR spectroscopy.
[d] Determined by HPLC analysis on a chiral stationary phase, as reported by Barbas III et al.[24]
[e] Determined by HPLC analysis on a chiral stationary phase: Daicel Chiralcel OJ column, *n*-hexane/2-propanol (99:01), 1.0 mL min^{-1}, 8.15 min (*anti*, major), 9.82 min (*anti*, minor).
[f] Determined by HPLC analysis on a chiral stationary phase: Daicel Chiralcel OJ column, *n*-hexane/2-propanol (90:10), 0.5 mL min^{-1}, 23.81 min (*anti*, major), 26.37 min (*anti*, minor).

confirmed its reluctance to react in the presence of amino acids other than Pro, giving a disappointing conversion after 24 h and a modest ee (run 11). Ionic-tagged proline **1** in ILs is presently one of the best catalytic systems for the aldol reactions using acetone as donor.[18]

The last aspect considered was the possibility to recycle the catalyst. While this operation is a difficult task in DMSO, the IL phase offers a simple separation of the aldol product from the catalyst sequestering IL phase.[14] The protocol adopted consisted of an extraction of the aldol product with ether, then the ether dissolved in the IL phase was removed under vacuum and, eventually, reactants **2** and **3** were recharged on the IL phase entrapping the catalyst. The reaction (Table 1, run 4) was replicated four times by recycling the same solution of Arg·PTSA in [bmpy][TfO]. Results from the four cycles are reported in Table 3.

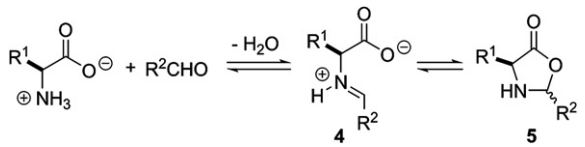
Table 3
Recycling experiments of Arg·PTSA in [bmpy][TfO] in the reaction of **1a** and **2a** (Scheme 1)

Run	Yield[a] (%)	*anti*/*syn*[b]	*anti* ee[c] (%)
1	95	72:28	95
2	86	72:28	91
3	77	71:29	90
4	55	70:30	75

[a] Yields refer to pure products isolated by flash chromatography on silica gel.
[b] Determined by ^{1}H NMR spectroscopy.
[c] Determined by HPLC analysis on a chiral stationary phase: Daicel Chiralpak AD, *n*-hexane/*i*-PrOH (85:15), 1.0 mL min^{-1}, 14.5 min (*anti*, minor), 19.3 min (*anti*, major).

The first three runs were characterised by a mean drop of yields of about 10% on each cycle, while diastereoselectivities remained unaltered and enantioselectivities were affected by modest decreases. In the fourth cycle, unfortunately, the yield almost halved with respect to the first run, with a 20% decrease of enantioselectivity with respect to the same cycle.

We believe that the slow but progressive catalyst deactivation can be accounted for by an off-catalytic cycle reaction between the α-amino acid and the acceptor aldehyde, resulting in the formation of the iminium ion **4**. In turn, **4** has been reported to undergo cyclisation to oxazolidinone **5** (Scheme 2).[21a]



Scheme 2. Off-cycle side reactions between the α-amino acid and the acceptor aldehyde.

Moving on to subsequent recycling runs, formation of **4** is a negative aspect in the long term for two reasons: (i) it removes part of the catalyst decreasing its actual loading and, hence, reducing the yield, (ii) it slowly impairs the enantiomeric purity of the catalyst, resulting in decreased ee. It is known, indeed, that a way to racemise proline is to boil it with catalytic aldehyde, the reaction proceeding via formation of **4**.[24] Luckily, at room temperature, formation of **4** is slow, but in the long run (four runs correspond to about >100 h of contact with the aldehyde), it starts to show its consequence on enantioselectivity.

3. Conclusions

As a general trend in organocatalysis, more and more efforts are devoted to the design of even more sophisticated and expensive catalysts. Our study moves in the opposite direction, showing how Arg and Lys, so far neglected for their very poor performances in asymmetric cross aldol reactions, can be recovered as useful species in catalyst and process design. A very simple trick was the key to success, the use of the protonated forms of basic α-amino acids.

There are three points of note within the system described:

(i) The catalysts are cheaper than proline itself.
(ii) The reaction protocol is very simple, consisting in a pre-equilibration of an aqueous solution of the amino acid salt with the solvent, when solvent is [bmpy][TfO], followed by addition of the ketone (4 equiv) and, after 30 min, the limiting aldehyde. Compared to earlier reports on the direct use of α-amino acids as catalysts, this reaction protocol makes use of a four-fold higher concentration of reactants while the catalyst loading is reduced from 30 to 10 mol %. From a direct comparison, it turned out that yields in [bmpy][TfO] are higher than those obtained in DMSO. Aldols are obtained in good diastereomeric ratios and good to excellent enantioselectivity. The striking effect of protonation on the reactivity of Arg is apparent comparing data reported in Scheme 1 and previous reports,[5a,c] where general base catalysis by the strongly basic guanidine functionality is likely responsible for the complete lack of stereocontrol.
(iii) Finally, catalyst recycling is possible for a few runs by simply exploiting a liquid/liquid phase separation. The process cannot be extended to many cycles because of an unavoidable limitation, i.e., the formation of **4** and **5**, which in the long run irreversibly remove the catalyst from the system.

4. Experimental

4.1. General methods

α-L-Amino acids in the (*S*)-configuration were purchased from Fluka. The hydrochlorides of arginine and lysine as well as *p*-toluenesulfonic acid, trifluoroacetic acid and trifluoromethanesulfonic acid were all purchased from the Aldrich Chemical Co. Silica gel Merck grade 9385, 60 Å from Sigma–Aldrich was used for the flash chromatographic purification of all the compounds. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Gemini 200; chemical shifts (δ) are reported in parts per million relative to TMS. Gas chromatographic analyses were performed with a HP5890 II instrument at 70 eV coupled to a HP5971 quadrupole mass detector and using a HP-5MS cross-linked 5% phenyl-methyl silicone glass capillary column, 0.25-μm film thickness. LC-electron spray ionisation (ESI$^+$) mass spectra were obtained either with an AGILENT Technologies MSD 1100 single-quadrupole mass spectrometer or with a Waters Micromass® ZQ™ 4000 (ESI$^+$) mass spectrometer. Chiral HPLC studies were carried out on a Hewlett–Packard series 1090 instrument.

With the exception of **3f** and **3i**, the products were characterised upon comparison of spectral data with the literature data.[23]

4.2. Typical experimental procedure for the preparation of the catalyst

An approximately 1.3 M aqueous solution of Arg·PTSA was prepared as follows: H_2O (0.7 mL) and PTSA (0.190 g, 1 mmol) were added to arginine (0.174 g, 1 mmol) and stirred for 2 h at room temperature. The same molar amounts were used to prepare aqueous solutions of amino acid triflates and trifluoroacetates. The salt thus prepared was used as such for the aldol reactions.

4.3. Typical experimental procedure for aldol reaction

A mixture of Arg·PTSA (75 μL of a 1.33 M aq solution, 0.1 mmol) and solvent ([bmpy][TfO] or DMSO) (1 mL) was pre-equilibrated for

10 min, then cyclohexanone was added (0.415 mL, 4.0 mmol). After stirring for 30 min at room temperature, *p*-nitrobenzaldehyde (0.151 g, 1.0 mmol) was added and the reaction mixture was stirred for a further 24 h at room temperature. The crude reaction mixture was directly charged on the top of a silica gel column and the product was purified by chromatography using cyclohexane/ethyl acetate (4:1) as eluent.

4.4. (*S*)-2-((*R*)-Hydroxy(perfluorophenyl)methyl)-cyclohexanone (3f) (Table 2, run 5)

IR (neat): 3520.6, 2974.8, 2940.2, 2927.6, 2863.9, 1705.8, 1522.6, 1498.5, 1449.3, 1400.1, 1345.2, 1296.0, 1241.0, 1122.4, 1103.1, 1032.7, 988.4, 964.3, 879.4 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 1.21–1.43 (m, 1H), 1.54–1.78 (m, 3H), 1.80–1.94 (m, 1H), 2.07–2.22 (m, 1H), 2.30–2.46 (m, 1H), 2.47–2.59 (m, 1H), 2.92–3.09 (m, 1H), 3.94 (dd, J=3.2/1.0 Hz, 1H), 5.32 (dd, J=9.5/2.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 24.5, 27.5, 30.1, 42.3, 54.2, 66.0, 113.4–114.0 (m), 135.6–136.2 (m), 138.9–139.5 (m), 142.2–142.8 (m), 143.4–143.8 (m), 146.7–147.2 (m), 214.0; GC–MS (70 eV): m/z (%): 55 (26), 67 (10), 70 (36), 83 (31), 97 (22), 98 (100), 99 (24), 117 (16), 149 (10), 167 (20), 168 (11), 169 (13), 181 (33), 187 (17), 194 (20), 195 (51), 196 (20), 197 (75), 207 (17), 248 (17), 276 (72), 277 (10); HPLC analysis: Daicel Chiralcel OJ column, *n*-hexane/2-propanol=99:01, flow rate: 1.0 mL min^{-1}, λ=220 nm, t_R (*anti*, major)=8.15 min, t_R (*anti*, minor)=9.82 min. Anal. Calcd for $C_{13}H_{11}F_5O_2$: C, 53.23; H, 3.77. Found: C, 53.07; H, 3.76.

4.5. (*S*)-2-((*R*)-Hydroxy(pyridin-3-yl)methyl)cyclohexanone (3i) (Table 2, run 8)

IR (neat): 3331.6, 2936.2, 2861.0, 1706.8, 1594.9, 1576.6, 1448.4, 1425.2, 1128.2, 1089.6, 1065.5, 1043.4, 1027.9, 983.6, 953.7, 891.0 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 1.20–1.41 (m, 1H), 1.52–1.92 (m, 4H), 1.99–2.18 (m, 1H), 2.29–2.55 (m, 1H), 2.57–2.78 (m, 1H), 4.67 (br s, 1H), 4.92 (d, J=8.1 Hz, 1H), 7.22–7.36 (m, 1H), 7.73 (d, J=7.3 Hz, 1H), 8.40–8.59 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 24.1, 27.4, 30.1, 42.1, 56.9, 71.5, 123.1, 134.4, 136.8, 148.2, 148.5, 213.8; ESI-MS: positive ion, 206 $[M+H]^+$; HPLC analysis: Daicel Chiralcel OJ column, *n*-hexane/2-propanol=90:10, flow rate: 0.5 mL min^{-1}, 28 °C, λ=254 nm, t_R (*anti*, major)=23.81 min, t_R (*anti*, minor)=26.37 min. Anal. Calcd for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37. Found: C, 70.43; H, 7.38.

4.6. Typical experimental procedure for the recycling experiment

To a pre-equilibrated mixture of Arg·PTSA (75 μL of a 1.33 M aq solution, 0.1 mmol) and [bmpy][TfO] (1 mL) was added cyclohexanone (0.415 mL, 4.0 mmol). The mixture was stirred for 30 min, then *p*-nitrobenzaldehyde (0.151 g, 1.0 mmol) was added and the reaction mixture was stirred for a further 24 h at room temperature. The aldol product was extracted with Et_2O (2 mL×3); the heterogeneous mixture was centrifuged to have the cleanest phase separation, the ether layer was separated and eventually the collected ether phase was concentrated and the products were purified by column chromatography.

The IL phase was freed from ether dissolved in it under vacuum, then the catalyst containing IL phase was charged again with the reactants. Upon completion of the last cycle, the crude mixture was directly poured on the top of a silica gel column and the product was chromatographed as usual.

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