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An Improved Protocol for the Direct Asymmetric Aldol Reaction in Ionic Liquids, Catalysed by Onium Ion-Tagged Prolines

Marco Lombardo,[a,b,*] Filippo Pasi,[a] Srinivasan Easwar,[a] and Claudio Trombini[a,b,*]

[a] Dipartimento di Chimica "G. Ciamician", Università degli Studi di Bologna, via Selmi 2, 40126 Bologna, Italy
Fax: (+39)-051-2099-456; e-mail: marco.lombardo@unibo.it or claudio.trombini@unibo.it
[b] Consorzio Interuniversitario Nazionale "La Chimica per l'Ambiente", via delle Industrie 21/8, 30175 Marghera (VE), Italy

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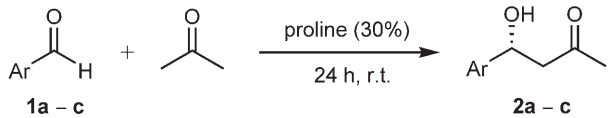
Abstract: Two onium ion-tagged prolines, imidazolium bis(trifluoromethylsulfonyl)imide-substituted proline **6** and butyldimethylammonium bis(trifluoromethylsulfonyl)imide-substituted proline **7**, were synthesised and their catalytic activity in the direct asymmetric aldol condensation was studied in ionic liquids. For the reaction of acetone with various aldehydes, using 5% of the catalyst, the yields of the aldols varied between 50–85% while the *ee* values were in the 80–85% range. Other ketones were studied too, the yields obtained in those cases being in the 35–78% range while the enantioselectivities varied between 75–94%.

Keywords: aldol reaction; ionic liquids; organocatalysis; proline-derived catalysis

Introduction

In 2000, three decades after the discovery of the proline-catalysed asymmetric intramolecular aldol reaction,[1] it was found that proline[2] as well as proline derivatives and other α-amino acids[3] are also able to catalyse the intermolecular version of the direct asymmetric aldol reaction.[4] These studies gave impetus to the extraordinary development of organocatalysis. An analogous dramatic growth has been witnessed over the last 7 years in the use of ionic liquids as new reaction media.[5] However, the exceptional research efforts in the synthesis of room temperature ionic liquids (ILs) and in their use as reaction media were not accompanied by a parallel growth in the understanding of their structure and properties, a fact that impairs the rational design of the ideal solvent for the desired reaction on the basis of a consistent structure-reactivity framework.

Despite the parallel exponential profile of the growth of organocatalysis on one hand and of the ionic liquid investigations on the other in the chemical literature, only rarely do the two fields cross each other. Focusing attention on the proline-catalysed direct aldol addition of acetone to aromatic aldehydes (Scheme 1), to the best of our knowledge, very few examples are known where the classical solvents, namely acetone itself and dimethyl sulfoxide (DMSO), have been replaced by ILs. In 2002, Toma and co-workers[6] and Loh and co-workers,[7] independently studied the use of [bmim][PF_6] as solvent in the proline-catalysed reaction of acetone with aromatic aldehydes. Their results, reported side-by-side in Scheme 1, were based on the use of 30% of catalyst along with 7–30 equivalents of acetone and reaction times of 24 h (Scheme 1). Interestingly, when only 5% of proline was used, it was observed that the chemical yield of the aldol dropped to 43% over 48 h.[7] A direct comparison with the results of the original protocol developed by List et al.,[2] also presented in Scheme 1, revealed that chemical yields, enantioselectivities and turnover numbers (TONs) in [bmim][PF_6] ranged in the same levels as recorded in DMSO. Two advantages are associated to the use of the IL: (i) the catalytic process takes place under homogeneous conditions, and (ii) thanks to the tuneble miscibility of an IL with molecular solvents, heterogeneous conditions can be found allowing the products to be extracted from the catalyst-containing IL, which



1a – c **2a – c**

1a: Ar = Ph
1b: Ar = *p*-NO_2-C_6H_4
1c: Ar = 2-naphthyl

Ref.	Solvent	Yield [%]	*ee* [%]
[2a,b]	DMSO	54 – 62	60 – 77
[6,7]	[bmim][PF_6]	43 – 68	65 – 76

Scheme 1.

can be reused for a few runs. In related, proline-catalysed direct asymmetric Mannich reactions of *N*-PMP protected α-iminoethyl glyoxylate with various carbonyl compounds in ILs, beside a facile product isolation and catalyst recycling, significantly improved reaction rates compared to molecular solvents were also enjoyed.[8]

The recently developed strategy based on the use of solid-supported ionic liquid phases (SILP)[9] was applied to the proline-catalysed reaction shown in Scheme 1 by Gruttadauria and co-workers; a monolayer of an ionic liquid covalently attached to the silica gel surface hosted proline acting as the reaction medium for the aldol reaction of acetone with the aldehyde.[10] Yields and *ee*s were comparable with those obtained in DMSO, the best improvement of SILP being its regeneration and recyclability up to 10 times.

An alternative approach to the use of ILs as solvents or of SILP as catalyst is offered by the use of catalysts containing a quaternary ammonium ion on a side chain. Such a strategy was applied by Miao and Chan to an asymmetric aldol reaction catalysed by *trans* 4-hydroxy-L-proline derivative **3** (Figure 1) using either DMSO or acetone as the solvent. The onium ion-tagged catalyst dissolves in the polar molecular solvent where the aldol reaction takes place under homogeneous conditions, then the catalyst can be recovered by extracting the product in a less polar solvent, where the catalyst is not soluble.[11] In the reported reaction conditions (30% catalyst, 25 h), the TON was close to 2, with *ee*s in the 48–72% range for **1a** and in the 71–85% range for **1b**.[12]

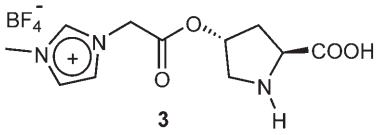


Figure 1.

Attracted by the structure of **3**, we anticipated that a quaternary ammonium-tagged proline like **3** should interact much better with an ionic liquid used as solvent, thus combining the advantages of a homogeneous phase with the opportunity of exploiting solubility differences in the work-up step. More importantly, the enamine route to the asymmetric cross-aldol reaction could enjoy rate acceleration in ILs, since charged transition states leading from uncharged reactants to iminium ion intermediates could be stabilised by the coulombic environment of the reaction medium.[5]

Results and Discussion

Herein, we report our results on the asymmetric cross-aldol addition of acetone to aromatic aldehydes,

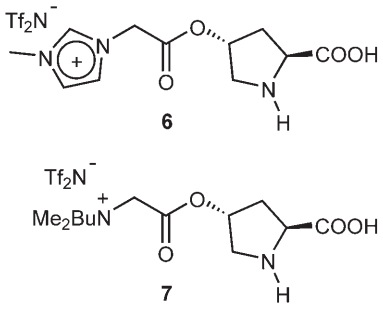
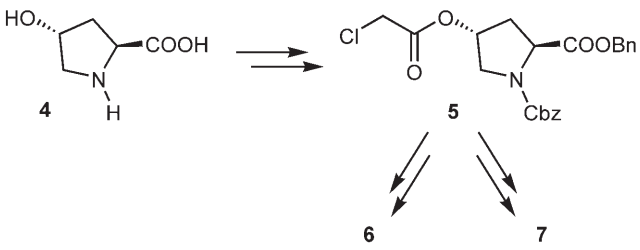


Figure 2.



Scheme 2.

promoted by organocatalysts **6** and **7** (Figure 2), in different ILs. Both **6** and **7** are derived from *trans* 4-hydroxy-L-proline **4** *via* the common intermediate **5**, as shown in Scheme 2.

Chloroacetate **5** is interesting, for it offers the opportunity to generate diversity upon reaction with a library of tertiary amines. The choice of the bis(trifluoromethylsulfonyl)imide (Tf_2N^-) anion was dictated by the very low hydrophilicity conferred to the quaternary salt by this counterion.

We studied the aldol reaction of acetone with the *p*-nitrobenzaldehyde (**1b**) under various conditions so as to determine the optimum reaction parameters. Table 1 collects a selection of experiments. Reactions are run at room temperature in various ILs, keeping the aldehyde concentration at ~1 M. We chose [bmim][TfO] and [bmim][Tf_2N] as imidazolium-based ILs, and butylmethylpyrrolidinium (bmpy) as saturated cyclic quaternary ammonium ion in the form of [bmpy][TfO] and [bmpy][Tf_2N] (runs 11 and 12).

Carrying out a reaction with catalyst **7** in [bmim]-[Tf_2N] using the molar ratios adopted for proline/DMSO[2a] resulted in near quantitave yield of the aldol in 24 h (Table 1, run 1) with improved enantioselectivity (see Scheme 1). In another experiment (Table 1, run 2) using the same catalyst loading (30%), in just 3 h we recovered 83% of the aldol with an almost 30% increase in *ee* with respect to the use of proline in [bmim][PF_6][7] (see Scheme 1). These results clearly indicate that the cross-aldol condensation enjoys a significant rate acceleration and an enhanced stereoselectivity using the onium-tagged pro-

Table 1. Asymmetric catalytic cross-aldol reactions of acetone (10 equivs.) and *p*-nitrobenzaldehyde **1b**.

Run	Solvent	Catalyst, [%]	*t* [h]	**2b**, Yield [%][a]	**2b**, *ee* [%][b]	TON
1[c]	[bmim][Tf_2N]	**7**, 30%	24	95	82	3.1
2	[bmim][Tf_2N]	**7**, 30%	3	83	83	2.7
3	[bmim][Tf_2N]	**7**, 15%	18	78	80	5.2
5	[bmim][Tf_2N]	**7**, 5%	13	62	85	12.4
6	[bmim][Tf_2N]	**7**, 5%	24	75	85	15.0
7	[bmim][Tf_2N]	**7**, 1%	48	25	83	25.0
8	[bmim][Tf_2N]	**6**, 5%	24	79	84	15.8
9	[bmim][TfO]	**7**, 5%	15	68	84	13.6
10	[bmim][TfO]	**7**, 5%	24	85	82	17.0
11	[bmpy][Tf_2N]	**6**, 5%	24	72	82	14.4
12	[bmpy][TfO]	**6**, 5%	24	70	80	14.0

[a] Isolated yields after purification by flash chromatography on silica.
[b] Determined by chiral HPLC on crude reaction mixture.
[c] 30 equivalents of acetone were used.

line/IL system. The neat kinetic benefit arising from the use of the IL with **6** or **7** is confirmed by runs 3–8, where catalyst loading was progressively decreased. Finally, we selected the acetone/**1b**/catalyst molar ratio = 10:1:0.05 as the most promising for further studies.

The 5-fold or even higher improvement in terms of catalytic efficiency can be appreciated by comparing TON values of the results discussed in Scheme 1, which ranged from 2 to 8, with the ones reported in Table 1 (TONs up to 17).

Noteworthy is the increase in the enantioselectivity recorded, corresponding to a 10–20% improvement with respect to the use of proline in DMSO[2a,b] and [bmim][PF_6][6,7] (Scheme 1). We are not in a position to correlate the stereochemical results with a different structural organisation of proline and of the onium-ion tagged catalysts **6** and **7** in the ionic liquid, nor we have evidence about the different environment tested by **3** in acetone and by its analogous **6** in ILs. Nevertheless, a high affinity of ion pairs **6** and **7** for ILs could be hypothesised, resulting in a more organised association of the catalyst to the IL within the structured domains of the solvent.[13] If the consequence was a tighter transition state in the rate-determining step of the catalytic cycle, a higher enantioselectivity could follow.

The only drawback of this procedure was represented by the difficult recovery and reuse of the catalyst at the concentration level used. Indeed, a recycling experiment showed that the catalyst could be efficiently recovered once (entry 2, Table 2), but at the third cycle, a significant drop in catalytic activity was observed (entry 3, Table 2).

Having carried out the above studies with **1b**, we then performed the aldol reaction using the aldehydes

Table 2. Recycling experiments using acetone (10 equivs), catalyst **7** (5%) and *p*-nitrobenzaldehyde **1b** in [bmim][Tf_2N] for 24 h at room temperature.

Run	**2b**, Yield [%][a]	**2b**, *ee* [%][b]	TON
1	75	85	15.0
2	65	82	13.0
3	30	80	6.0

[a] Isolated yields after purification by flash chromatography on silica.
[b] Determined by chiral HPLC on crude reaction mixture.

1a, **1c** and *p*-chlorobenzaldehyde (**1d**) under what we had chosen as routine reaction conditions; the results are presented in Table 3.

With these results in hand, we performed a few other experiments that provided us a definite indication of the advantages in using onium-tagged prolines as catalysts in ILs. Thus, upon performing a reaction under solventless conditions using the same parameters of run 6 in Table 1, the chemical yield of the aldol diminished by 50% and the *ee* by 10% with respect to our optimised conditions. We then decided to check the performance of 5% proline in [bmim]-[Tf_2N] to compare more precisely the proline performance with that of its onium-tagged analogues **6** and **7**, under identical experimental conditions. These results are presented in Table 4. Experiments carried

Table 3. Asymmetric catalytic cross aldol reactions of acetone (10 equivs.) and aromatic aldehydes in [bmim][Tf_2N] for 24 h at room temperature.

Run	ArCHO	Catalyst, [%]	**2**, Yield [%][a]	**2**, *ee* [%][b]	TON
1	**1a**	**6**, 5%	50	80	10.0
2	**1c**	**7**, 5%	57	84	11.4
3	**1d**	**7**, 5%	80	84	16.0

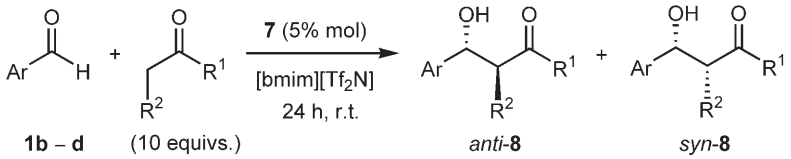
[a] Isolated yields after purification by flash chromatography on silica.
[b] Determined by chiral HPLC on crude reaction mixture.

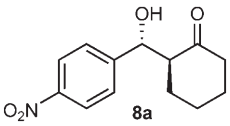
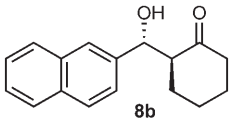
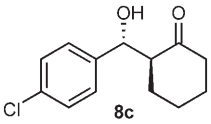
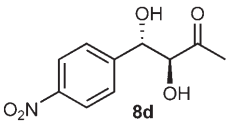
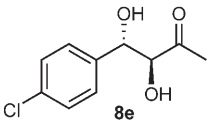
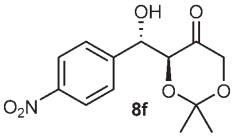
Table 4. Results of the cross-aldol reaction using 5% proline in [bmim][Tf_2N].

Run	ArCHO	*t* [h]	**2**, Yield [%][a]	**2**, *ee* [%][b]	TON
1	**1b**	24	50	72	10.0
2	**1d**	24	45	70	9.0
3[c]	**1d**	24	20	68	4.0

[a] Isolated yields after purification by flash chromatography on silica.
[b] Determined by chiral HPLC on crude reaction mixture.
[c] 2nd cycle.

Table 5. Asymmetric cross-aldol reactions explored for other ketones catalysed by **7** (5 mol%) in [bmim][Tf_2N] for 24 h at room temperature.



Run	ArCHO	Major product	**8**, Yield [%]	**8**, *anti*:*syn*[a]	*anti*-**8** (*syn*-**8**), *ee* [%][b]
1	**1b**	 **8a**	78[c]	70:30	94 (80)
2	**1c**	 **8b**	36[c]	80:20	90 (70)
3	**1d**	 **8c**	38[c]	85:15	80 (63)
4	**1b**	 **8d**	75[d]	67:33	91 (48)
5	**1d**	 **8e**	35[d]	70:30	86 (34)
6[e]	**1b**	 **8f**	72[d]	70:30	75 (56)

[a] Determined by ^{1}H NMR on crude reaction mixture.
[b] Determined by chiral HPLC on crude reaction mixture.
[c] Isolated yields after purification by flash chromatography on silica.
[d] Estimated yields by ^{1}H NMR.
[e] Reaction time was increased to 72 h.

out with aldehydes **1b** and **1d** resulted in a decrease of 30% in yield and 15% in *ee* as compared to our conditions. In attempting to recycle the catalyst, we were not able to obtain an acceptable chemical yield in the 2nd cycle (run 3); in particular this last result was clearly poorer than that obtained in the first recycle with the onium-tagged analogue (Table 2, run 2).

To confirm the excellent performance of onium ion-tagged catalysts in ILs, we selected **7** in [bmim]-[Tf_2N] as model system for the reaction of three different ketones with **1b–d**. These new experiments are shown in Table 5.

The chemical yield and diastereoselectivity obtained for the reaction of cyclohexanone with **1b** (run 1) are comparable with respect to the use of proline[14] but the *ee* was considerably higher with the onium tagged catalysts. A 50% increase in *ee* for the *anti* aldol (94% *vs.* 63%) and more than 100% increase for the *syn* aldol (80% *vs.* 36%) was obtained. High *ee*s were obtained in the reaction of **8a** with other aldehydes too, although low chemical yields after 24 h are obtained with **1c** and **1d** (runs 2 and 3). A similar behaviour was displayed by hydroxyacetone (runs 4 and 5). With the less reactive ketone derived from dihydroxyacetone (run 6),[15] the reaction had to be carried out over 72 h at room temperature under our catalytic protocol to furnish the corresponding aldol with a good chemical yield.

Conclusions

In summary, the onium ion-tagged proline catalysts in ILs proved to be an excellent catalytic system for the direct asymmetric aldol reaction. The catalytic protocol we developed makes use of a 6-fold lower amount of catalyst with respect to the preceding reports[2,6,7,12] and affords greater chemical yields and higher enantioselectivity.

In the recycling studies reported in literature,[7,12] four cycles were carried out without appreciable loss of activity of catalyst using 30 mol% loading. It must be considered that four cycles require four extensive work-up procedures with the corresponding waste generation, and requires more than 100 h to complete the series (reaction time plus time required to recover the catalyst between two cycles).

A direct comparison of the efficiency of our protocol with respect to the previously reported procedures is possible when *p*-nitrobenzaldehyde (**1b**) and benzaldehyde (**1a**) are used. The former aldehyde (Table 1, run 6) using the same molar amount of catalyst as in ref.[11] generates up to 70% more of the aldol product in overall 26 h with respect to four cycles in acetone as solvent and using 30% of **3**.[12] Similarly, an analogous comparison of run 1 of Table 3 shows that our protocol applied to **1a** affords up to 37% more of the aldol with respect to four cycles using 30% of proline in [bmim][PF_6].[7]

Further applications of **6**, **7** and congeners will be published in due course.

Experimental Section

Typical Experimental Procedure for the Cross-Aldol Condensation

Acetone (0.367 mL, 5 mmol) was added to a suspension of **7** (0.014 g, 0.025 mmol) in [bmim][Tf_2N] (0.5 mL) and the mixture was stirred for 10 min at room temperature. The aldehyde (0.5 mmol) was added and the reaction mixture was stirred for a further 24 h at room temperature. The crude reaction mixture was then directly subjected to silica gel column chromatography eluting with cyclohexane/ethyl acetate mixtures to furnish the pure aldol products.

Typical Experimental Procedure for the Recycling Experiment (Table 2, runs 2 and 3)

Acetone (0.74 mL, 10 mmol) was added to a suspension of **7** (0.028 g, 0.05 mmol) in [bmim][Tf_2N] (1.0 mL) and the mixture was stirred for 10 min at room temperature. *p*-Nitrobenzaldehyde (**1b**, 0.15 g, 1.0 mmol) was then added and the reaction mixture was stirred for a further 24 h at room temperature. Acetone was removed under reduced pressure and the reaction mixture was extracted with ether (2 mL × 4). The reaction mixture was then vacuum-dried before the second loading of the reacting components. The ether extract was concentrated under vacuum and the residue was purified by silica gel column chromatography (cyclohexane/ethyl acetate, 7:3) to obtain the pure aldol.

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