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Chiral Room Temperature Ionic Liquids as Enantioselective Promoters for the Asymmetric Aldol Reaction

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Chiral ionic liquids derived from natural amino acids are shown to be green and efficient media for direct asymmetric aldol reactions at room temperature catalyzed by (*S*)-proline. The corresponding aldol products were obtained with moderate to good enantioselectivities. A transfer of chirality from the chiral reaction media has been observed as well as the participation of match/mismatch interactions of the chiral medium with both enantiomers of proline. Moreover, these catalytic systems were easily recovered by simple filtration, and studies on their reuse have demonstrated that recycling is possible for at least four runs with only a slight reduction in activity.

Introduction

In recent years, organocatalysis has become a very attractive approach for the stereocontrolled preparation of chiral products, being an efficient alternative to the well-established asymmetric transformations based on metal-containing catalysts.[1] This is true even considering that organic molecules have been used as catalysts from the early stages of synthetic chemistry.[2] The aldol reaction is one of the most important carbon–carbon bond-forming reactions in organic synthesis for the production of enantiomerically enriched β-hydroxy ketones,[3] which are important building blocks for the synthesis of polyfunctional compounds and natural products.[4] Indeed, the β-hydroxy ketone structural motif is found in several biologically active compounds, such as macrolide antibiotics and anticancer drugs.

Since List and Barbas III reported the direct aldol reaction catalyzed by (*S*)-proline,[5] the use of small organic molecules as catalysts has received increasing attention.[6] From the toolbox of organocatalysts, proline is by far one of the most popular because it is inexpensive, readily available in both enantiomeric forms, and can be used for a wide range of synthetic transformations, including aldol reactions. However, the organic solvents employed in this reaction, dimethyl sulfoxide (DMSO) and *N*,*N*-dimethylformamide (DMF), are not environmentally friendly and make recycling of the catalyst difficult.

Over the last decade, room temperature ionic liquids (RTILs) have attracted considerable attention as environmentally benign reaction media for "green" synthetic procedures.[7] Most applications of ILs in catalysis emphasize recyclability, allowing efficient recovery of the catalyst, which usually maintains its activity for several cycles. This observation was reported independently by Toma and Loh in their pioneering studies of organocatalyzed aldol reactions using ILs in 2002.[8] More recently, the design and the use of chiral ionic liquids (CILs) as reaction media or as a catalyst has emerged as a hot research topic in asymmetric synthesis.[9] Moreover, the use of different types of additives have been reported to accelerate the aldol reaction rate and to increase its diastereo- and enantioselectivity,[10] although the ability of the additives to induce chirality have rarely been reported.[11]

Our group has recently studied the influence of the nature of several chiral imidazole derivatives as additives for the aldol reaction catalyzed by (*S*)-proline.[12] These additives seem to form supramolecular complexes with the catalyst through the formation of H-bonds, leading to significant improvement in both the reaction rates and the selectivity of the reaction.

Considering the excellent results shown with amino amides **1** in catalytic asymmetric reactions,[13] we decided to integrate this structure with imidazolium subunits to develop new families of CILs. Initial studies with this family of CILs made it possible to observe by ^{1}H NMR spectroscopy how 3-benzyl-1-[(1*S*)-1-(butylcarbamoyl)-2-phenylethyl]-1*H*-imidazol-3-ium triflamide (**2**) and other derivatives could efficiently act as chiral shift agents for the enatiodiscrimination of racemic mandelate and other chiral

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carboxylate salts.[14] Herein, as a continuation of our work with CILs, we report the application of several imidazolium salts as solvents (cosolvents) or chiral additives for asymmetric proline-catalyzed aldol reactions. The catalytic systems could be easily reused with only a slight decrease in activity.

Results and Discussion

The chiral α-amino amides **1** derived from (*S*)-valine, (*S*)-phenylalanine, and (*S*)-leucine were used as precursors for the synthesis of CILs **2**–**4** (Figure 1). Compound **1** was synthesized by following the general synthetic methodology described by our group for the preparation of related amino amides.[15] The imidazole ring was then formed by reacting **1** with formaldehyde, ammonium acetate, and glyoxal. After alkylation with butyl chloride, the imidazolium salts were converted into the corresponding bistriflamide CILs **2**–**4** by anion exchange using $LiNTf_2$. These compounds were liquid at room temperature with a melting point of –20, –12, and –19 °C for CILs **2**, **3**, and **4**, respectively.[14]

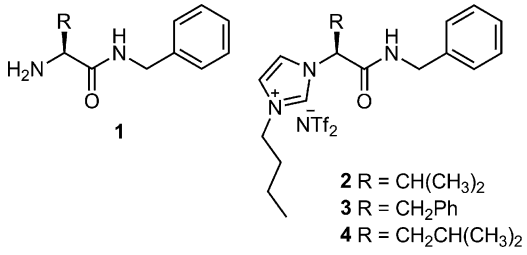
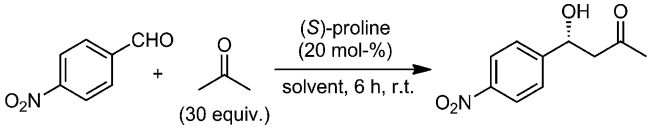


Figure 1. Structure of α-amino amide **1** and chiral ionic liquids **2**–**4**.

For the studies on catalysis, the aldol reaction of *p*-nitrobenzaldehyde with acetone (1:30 molar ratio) at room temperature was selected as the benchmark reaction, using (*S*)-proline as the organocatalyst. Originally, a screening of different solvents was undertaken to compare results using the same experimental conditions, a 20% catalyst and a volume of solvent equal to that of acetone (used in excess). Thus, the reaction was carried out in toluene, DMSO, water, MeOH, and CH_2Cl_2 (Table 1) as well as under solvent-free conditions (entry 3). The use of an excess of acetone allowed acetone to act as both reagent and solvent for the second component (aldehyde). After 6 h, conversions of up to 95%, with selectivities ranging from 89 to 99% and enantioselectivities of around 70% for the (*R*)-product were obtained when nonprotic solvents were used (entries 1–4), similar to reported results.[5] For comparison, when the experiment was conducted with the well-known nonchiral ionic liquid BMIM NTf_2 as solvent, the conversion and selectivity were both more than 99% and the *ee* was 62%; lower yields and similar *ee* values were reported for reactions using different ILs as solvent.[8] Finally, the reaction was carried out with the chiral ionic liquid (CIL **2**) as the solvent. In this case, 80% conversion and 99% selectivity were obtained and an increase of enantioselectivity was observed (77%; entry 8).

Table 1. Aldol reaction between acetone and *p*-nitrobenzaldehyde using (*S*)-proline as catalyst with different solvents.[a]

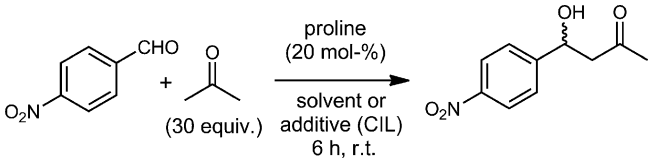


Entry	Solvent	Conversion [%][b]	Selectivity [%][c]	*ee* [%][d]
1	toluene	99	89	71
2	DMSO	99	90	71
3	–	95	97	71
4	CH_2Cl_2	98	99	67
5	H_2O	0	–	–
6	MeOH	98	90	9
7	BMIM NTf_2	99	99	62
8	CIL **2**	80	99	77

[a] Reaction conditions: RCHO/acetone/cat. = 1:30:0.2, solvent/acetone = 1:1 v/v, r.t., 6 h. [b] Conversion [%]: determined by ^1H NMR spectroscopic analysis of the crude reaction mixture. [c] Selectivity [%]: determined by ^1H NMR spectroscopic analysis of the crude reaction mixture. Selectivity refers to the ratio between aldol products and dehydration products or formed through side reactions. [d] Enantiomeric excess calculated by HPLC analysis for the enantiomer *R* (major peak) {*ee* = [peak area(*R*) – peak area (*S*)] × 100/total area (*R* + *S*)}.

To understand this process in more detail, a range of exploratory experiments were performed. Thus, we studied the effect of using variable quantities of CIL **2** in the reaction media. Given the nature of the reaction conditions, CIL **2** was used either as a solvent or as an additive under solvent-free conditions (Table 2). In all cases, selectivities were in the order of 99%. When CIL **2** was used as solvent [CIL: (*S*)-proline, equiv. ratio ca. 30] the conversion was 80%, and the *ee* was 77% (entry 5). Using a moderate excess of CIL **2** over the catalyst afforded excellent conversions and selectivities without affecting the enantioselectivity (entries 3 and 4). However, reducing the amount

Table 2. Aldol reaction between acetone and *p*-nitrobenzaldehyde using proline as catalyst and CIL **2** as solvent or additive.[a]



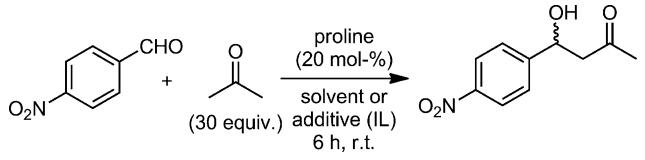
Entry	CIL **2**/Pro [equiv.]	(*S*)-Proline Conversion [%][b]	*ee* [%][c]	(*R*)-Proline Conversion [%][b]	*ee* [%][c]
1	0.4	90	72 (*R*)	92	71 (*S*)
2	1	92	74 (*R*)	95	72 (*S*)
3	3	97	78 (*R*)	94	66 (*S*)
4	8	99	76 (*R*)	97	67 (*S*)
5	30	80	77 (*R*)	78	70 (*S*)

[a] Reaction conditions: RCHO/acetone/cat. 1:30:0.2, r.t., 6 h. In all cases, selectivities were higher than 98%. [b] Conversion [%]: determined by ^1H NMR spectroscopic analysis of the crude reaction mixture. [c] Enantiomeric excess was calculated based on HPLC analysis of enantiomer *R* (major peak) {*ee* = [peak area(*R*) – peak area (*S*)] × 100/total area (*R* + *S*)}.

of CIL **2** to equimolar or lower quantities (entries 1 and 2) was accompanied by a slight decrease in both the yield and the *ee* values. It must be pointed out that when CIL **2** was used as additive, it also acted as a cosolvent and was essential for the solubilization of the catalyst. For example, for a 3:1 ratio of CIL **2**/proline (entry 3), the composition of the mixture is 23 mg proline, 188 mg CIL **2**, 106 mg benzaldehyde, and 1.7 g acetone.

Similar experiments were carried out by using the analogous nonchiral IL BMIM (Table 3). In this case, conversions initially increased with the amount of IL used, reaching 99% for a IL/(*S*)-proline, equiv. ratio of 30, and then decreased when more than 100 equiv. was used. The enantioselectivity increased from 68 to 76% when more than 60 equiv. IL was used.[8] These results suggest the formation of supramolecular species with (*S*)-proline, with its nature being important for the enantioselectivity of the reaction.[16] The formation of IL-proline supramolecular species in which the functional group of proline interacts in a specific way with the cation and/or anion of the IL can modify both the catalytic activity of proline and the nature and structure of the corresponding transition states (TSs). This interaction can involve not only proline but also the whole supramolecular species, and may lead to changes in both the activity and the enantioselectivity of the system.

Table 3. Aldol reaction between acetone and *p*-nitrobenzaldehyde using proline as catalyst in the presence of variable amounts of BMIM NTf_2.[a]

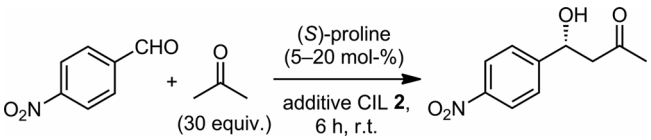


Entry	[BMIM] NTf_2/Pro [equiv.]	(*S*)-Proline Conversion [%][b]	*ee* [%][c]	(*R*)-Proline Conversion [%][b]	*ee* [%][c]
1	0	95	71 (*R*)	90	70 (*S*)
2	0.4	90	68 (*R*)	82	69 (*S*)
3	1	94	67 (*R*)	90	68 (*S*)
4	3	94	62 (*R*)	92	65 (*S*)
5	10	98	61 (*R*)	93	64 (*S*)
6	30	99	62 (*R*)	95	64 (*S*)
7	60	99	76 (*R*)	95	76 (*S*)
9	100	80	76 (*R*)	87	77 (*S*)

[a] Reaction conditions: RCHO/acetone/cat. 1:30:0.2, r.t., 6 h. In all cases, selectivities were higher than 99%. [b] Conversion [%]: determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture. [c] Enantiomeric excess calculated based on HPLC analysis. For enantiomer *R* (major peak) {*ee* = [peak area (*R*) – peak area (*S*)] × 100/total area (*R* + *S*)}; for enantiomer *S* (major peak) {*ee* = [peak area (*S*) – peak area (*R*)] × 100/total area (*R* + *S*)}.

The effect of the amount of catalyst was also investigated using CIL **2** as an additive [CIL **2**/(*S*)-proline, equiv. ratio 3:1]. As shown in Table 4, no activity was found in the absence of (*S*)-proline, confirming that proline was the active catalyst. The amount of proline could be reduced from 20 to 10 mol-% with only a slight decrease in the conversion (from 97 to 94%), but a further decrease to 5% caused a strong reduction in conversion, although the enantioselectivity remained unchanged. Finally, the effect of the reaction temperature was investigated. When the reaction temperature was reduced to –25 °C, the conversion decreased dramatically to 16% after 6 h, without an increase in the enantiomeric excess (entry 6). This indicated that the yield of the aldol product was dependent on the temperature but that the enantioselectivity was essentially insensitive to this parameter.[17]

Table 4. Aldol reaction between acetone and *p*-nitrobenzaldehyde with different loadings of (*S*)-proline as the catalyst.[a]



Entry	(*S*)-Proline [mol-%]	Conversion [%][b]	Selectivity [%][b]	*ee* [%][c]
1	–	–	–	–
2	20	97	99	78
3	15	97	99	76
4	10	94	99	77
5	5	69	99	77
6[d]	20	16	97	76

[a] Reaction conditions: RCHO/acetone = 1:30, CIL **2**/(*S*)-proline 3:1, r.t., 6 h. [b] Conversion and selectivity [%]: determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture. [c] Enantiomeric excess calculated based on HPLC analysis of enantiomer *R* (major peak) {*ee* = [peak area (*R*) – peak area (*S*)] × 100/total area (*R* + *S*)}. [d] Performed at –25 °C.

In summary, according to the initial results detailed here, a (*S*)-proline catalyst loading of 20 mol-% in conjunction with a 3:1 ratio of CIL **2**/Pro were selected as the standard conditions for further experiments.

To investigate the activity of the supramolecular complex that can be formed between the catalyst and the CIL, the reaction was carried out in the presence of the non-natural amino acid (*R*)-proline. The trends observed were different to those obtained by using the natural amino acid as the organocatalyst (see columns on the right in Table 2 and 3). In general, conversions increased when the amount of CIL increased until a maximum value, after which conversions started to decrease. With the use of (*R*)-proline, slightly lower *ee* values (for the opposite enantiomer) were obtained in the presence of CIL **2**, and the enantioselectivities observed did not increase with increased amount of CIL **2** as with (*S*)-proline (Table 2). Moreover, in this case, similar enantioselectivities were observed when a nonchiral IL was used as cosolvent (Tables 2 and 3). Thus, for example, when (*S*)-proline was used in conjunction with CIL **2** (3 equiv.) an increase in *ee* was observed relative to the use of the nonchiral IL (77 vs. 62%), but this phenomenon was not observed (66 against 65%) when (*R*)-proline was used (compare entries 3 and 4 for Tables 2 and 3, respectively). These results suggest the presence of a match/mismatch effect between the configuration of the proline and that of CIL **2**.

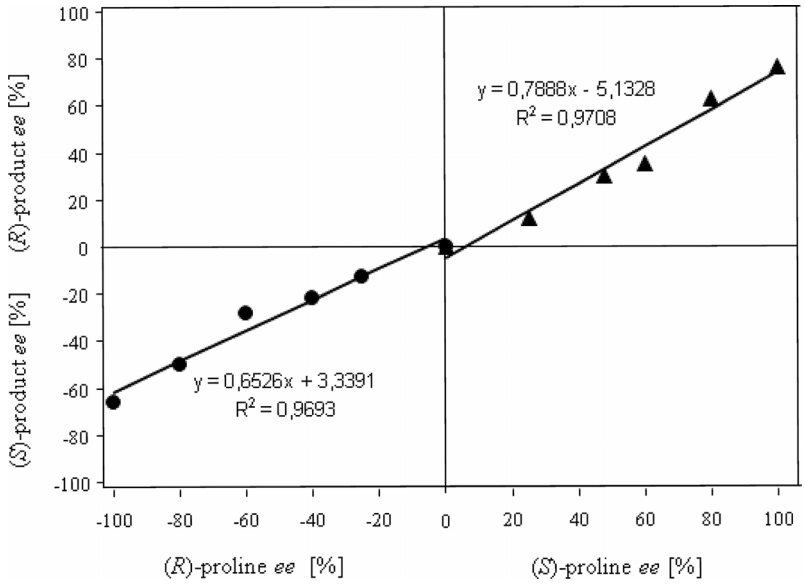


Figure 2. Linear effects observed for the aldol reaction between acetone and *p*-nitrobenzaldehyde using CIL **2** and mixtures of (*S*)- and (*R*)-proline.

To further investigate this possible match/mismatch effect, the aldol reaction was carried out by using mixtures of enantiomerically enriched (*S*)- and (*R*)-proline. The correlation between the *ee* of the catalyst and that of the aldol product showed a linear correlation for both proline enantiomers (Figure 2, see also Table S1 and Table S2 of the Supporting Information). However, the slopes for both enantiomers were clearly different. For a given level of enantiomeric enrichment in the catalyst, the observed *ee* was always higher for the mixtures enriched in (*S*)-proline. Thus, for instance, for 80% enriched (*S*)- and (*R*)-proline, the observed *ee* values were 63 and 50%, respectively, for the corresponding aldol products (opposite enantiomers).

The kinetic analysis of the reaction catalyzed by (*S*)-proline using CIL **2** (CIL **2**/Pro equiv. ratio 3:1, Figure 3, see Table S3 of the Supporting Information), showed that the reaction was essentially complete after 2 h. However, more than 6 h were needed for the (*R*)-proline catalyzed reaction to reach completion (Figure 3, see Table S4 of the Supporting Information). Therefore, this catalyzed aldol reaction goes through a transition state that is lower in energy when the CIL **2**/(*S*)-proline catalytic system is used. Interestingly, the observed enantiomeric excess decreased dramatically in the presence of (*S*)-proline for long reaction times (from the initial 79 to 57%*ee* after 24 h) whereas for the (*R*)-proline only a slight decrease was observed (from 74 to 70%*ee*). Surprisingly, no decrease in the enantioselectivity was observed when same reaction was tested at –25 °C after 24 h. This reduction in the observed *ee* values for long reaction times was smaller when (*S*)-proline was studied in the absence of CIL **2** (from 71%*ee* at 6 h to 66%*ee* after 24 h at room temperature). These results suggest that the matched CIL **2**/(*S*)-proline combination not only activates the preferential formation of the (*R*)-aldol product but also the preferential retroaldol process from this enantiomer. The kinetics for the formation of the (*S*)-aldol product and, particularly, for the corresponding retroaldol process should be much lower. On the other hand, these results also indicate that the CIL **2**/(*R*)-proline combination provides a less active catalytic system. The formation of different supramolecular catalytic complexes between CIL **2** and proline enantiomers, in which the one formed between CIL **2** and (*R*)-proline is more stable and, as a consequence, less active, could be the origin of these observations. Moreover, when the reaction was carried out using (*S*)-proline and 3 equiv. CIL **2** in the presence of 20% benzoic acid, which should contribute to destroy the CIL **2**/(*S*)-proline supramolecular complexes, the results were similar to those observed in the

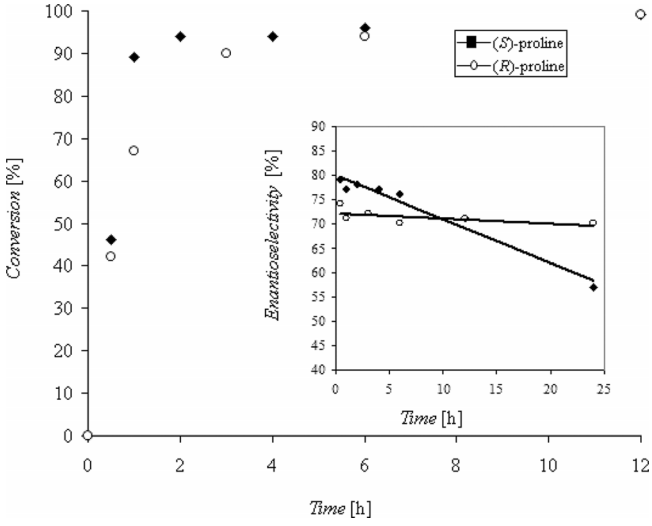
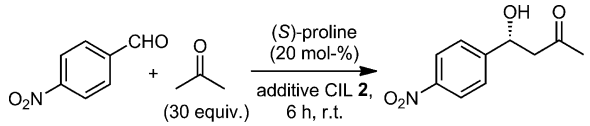


Figure 3. Kinetic curves for the aldol reaction catalyzed by (*S*)- and (*R*)-proline using CIL **2** as additive. Inset: Evolution with time of the *ee* for the aldol product. In all cases, selectivities were more than 97%.

absence of CIL **2**, showing an *ee* of 72% after 6 h reaction, which decreases to 67% after 24 h.

After completion of the aldol reaction of *p*-nitrobenzaldehyde with acetone at room temperature using CIL **2**/(*S*)-proline (3:1 ratio), the catalytic complex could be reused. After extraction of the aldol products (after vacuum evaporation of the excess acetone) with diethyl ether, the remaining residue containing the catalytic complex CIL **2**/(*S*)-proline was reused again for three successive runs with essentially no significant decrease in activity, stereoselectivity or enantioselectivity being observed (Table 5).

Table 5. Catalyst complex reuse for the aldol reaction between acetone and *p*-nitrobenzaldehyde.[a]

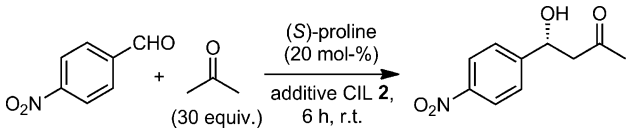


Entry	Cycle	Conversion [%][b]	Selectivity [%][b]	*ee* [%][c]
1	1st	97	99	78
2	2nd	90	94	77
3	3rd	85	95	75
4	4th	84	93	76

[a] Reaction conditions: RCHO/acetone/cat. 1:30:0.2, CIL **2**/(*S*)-proline 3:1, r.t., 6 h. [b] Conversion and selectivity [%]: determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture. [c] Enantiomeric excess calculated based on HPLC analysis for enantiomer *R* (major peak) {*ee* = [peak area (*R*) – peak area (*S*)] × 100/total area (*R* + *S*)}.

The recyclability of the chiral IL was also tested. When the solid residue obtained after evaporation of the excess of acetone was washed with water to extract the proline, chromatographic purification of the mixture containing the aldol products and the additive, allowed the recovery of CIL **2**, which could be reused as the additive for four successive runs. Until the third run, no decrease in activity or enantioselectivity was observed (Table 6). In the fourth run, however, a slight decrease in activity and a larger decrease in enantioselectivity was observed (Table 6, entry 4).

Table 6. CIL **2** reuse for the aldol reaction between acetone and *p*-nitrobenzaldehyde.[a]



Entry	Cycle	Conversion [%][b]	Selectivity [%][b]	*ee* [%][c]
1	1st	97	99	78
2	2nd	98	95	73
3	3rd	99	98	77
4	4th	90	94	61

[a] Reaction conditions: RCHO/acetone/cat. 1:30:0.2, CIL **2**/(*S*)-proline 3:1, r.t., 6 h. [b] Conversion and selectivity [%]: determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture. [c] Enantiomeric excess calculated based on HPLC analysis for enantiomer *R* (major peak) {*ee* = [peak area (*R*) – peak area (*S*)] × 100/total area (*R* + *S*)}.

Additional information on the nature of the CIL **2**/proline complex was obtained from ^{1}H NMR and ATR-FTIR experiments. ^{1}H NMR spectroscopic data showed that after the addition of proline, the signals for the N-H and C2-H protons of CIL **2** underwent a downfield shift, which indicates their involvement in hydrogen-bond interactions with the added species (Figure 4). Interestingly, the observed shifts are larger for (*R*)-proline than for (*S*)-proline, which is consistent with stronger hydrogen-bonding interactions involving these protons between CIL-**2** and (*R*)-proline.

Additionally, ATR-FTIR experiments confirmed the hydrogen bond interaction between both species. In the

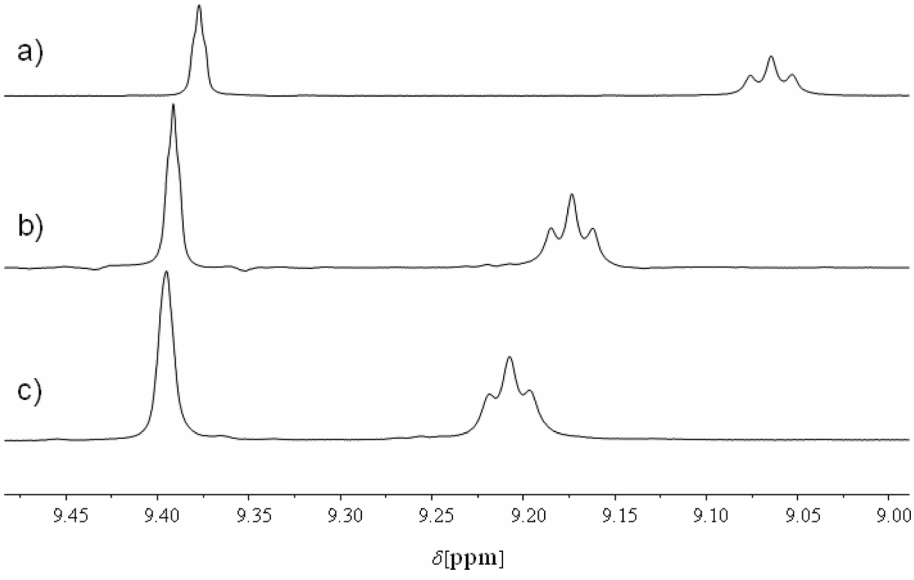


Figure 4. ^{1}H NMR spectra in [D$_6$]DMSO of (a) CIL **2**, (b) CIL **2** after (*S*)-proline addition, and (c) CIL **2** after (*R*)-proline addition. 3:1 CIL **2**/proline ratio in b and c. [CIL **2**] = 6 mM.

FTIR spectra for a solid mixture of CIL **2**/(*S*)-proline (3:1), the C2–H, C=O, and S=O stretching bands for CIL **2** moved slightly to lower wavenumbers in the presence of proline (i.e., 3068 against 3074 cm^{-1} and 1679 against 1684 cm^{-1} for C2–H and C=O, respectively), indicating the participation of these groups in hydrogen-bond interactions (Figure 5). Interestingly, in the solid state, no variation was observed for the amide N–H stretching bands. In accordance with the formation of different diastereomeric supramolecular complexes for both enantiomers of proline with CIL **2**, slight differences were observed in the aromatic C–H stretching bands for the two complexes formed between CIL **2** and (*R*)- or (*S*)-proline [i.e., for the (*R*)-proline complex, the C2–H stretching band increases in intensity and appears at slight lower wavenumbers; see Figure S1 in the Supporting Information].

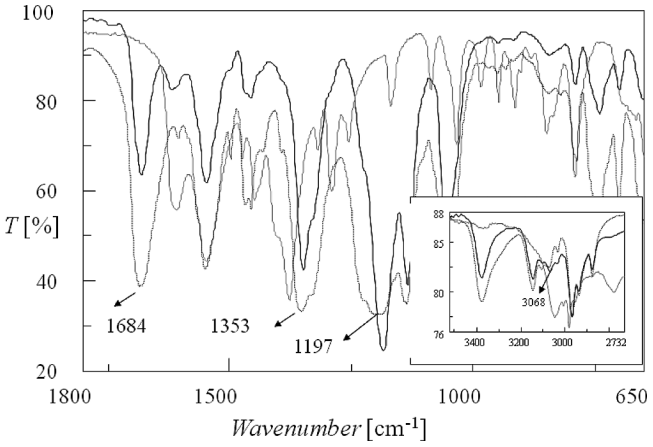
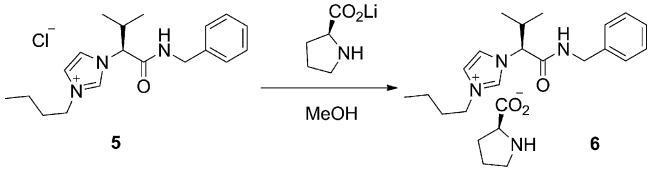


Figure 5. Partial FTIR spectra of (*R*)-proline (grey line). Partial FTIR spectra for CIL **2** in the absence (dotted line) and presence of 0.3 equiv. (*R*)-proline (black line).

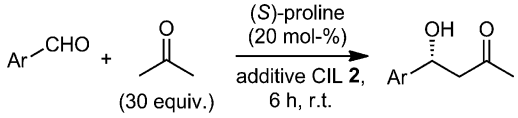
For comparison, complex **6** was synthesized by anion interchange between CIL **5** and lithium (*S*)-prolinate (Scheme 1) and evaluated for the same aldol reaction (room temperature, 20% catalyst loading, 6 h). Good conversions and selectivities were obtained but a low enantioselectivity (27%) was observed. Thus, our previous results cannot be attributed to partial formation of the corresponding salts. Indeed, when the aldol reaction was run in the presence of an acid additive (20% benzoic acid), the conversion decreased to 21% and the *ee* increased to 67%. When the reaction with **5** was carried out in the presence of catalytic amounts of the organic base 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), the enantioselectivity decreased further to 5%. Thus, the prolinate species seem to be much less enantioselective than those associated with the proline supramolecular complexes (see Table S5 in the Supporting Information). These results are consistent with the mechanism proposed by Seebach–Eschenmoser for the Michael reaction when (*S*)-proline or (*S*)-prolinate were used as catalysts.[18]



Scheme 1. Synthesis of complex **6**.

To investigate the generality of the current organocatalytic process, the aldol reaction using several aldehydes was also studied using CIL **2** as the additive under optimal conditions. As shown in Table 7, the results followed the expected trends for proline-catalyzed aldol reactions.[5a,5c] For a 6 h reaction time, conversions decreased significantly for less electrophilic aldehydes, being lower than 10% for *p*-methoxybenzaldehyde and *p*-hydroxybenzaldehyde. Selectivities were, in general, excellent (96–99%) except for benzaldehyde itself (85%), whereas enantioselectivities ranged from good to moderate (88–41%ee). As can be observed in Table 5, reactions carried out in the presence of CIL **2** provided better conversions and, in most cases, better enantioselectivities than when no additive was used. It must be noted that the increase in conversion is most likely associated with an improvement in solubility of proline in the reaction medium in the presence of CIL **2**.

Table 7. Aldol reaction between acetone and different aldehydes using (*S*)-proline as catalyst and CIL **2** as additive.[a]



Entry	Ar	Additive CIL **2** Conversion [%][b]	*ee* [%][c]	No additive Conversion [%][b]	*ee* [%][c]
1	Ph	46[d]	88	23	68
2	4-NO_2Ph	97	78	95	71
3	4-ClPh	66	41	44	65
4	3-ClPh	77	82	68	80
5	4-CH_3OPh	10	–	trace	–
6	4-OHPh	5	–	0	–

[a] Reaction conditions: RCHO/acetone/cat. 1:30:0.2, CIL **2**/(*S*)-proline 3:1, r.t., 6 h. In all cases, selectivities were higher than 96%. [b] Conversion [%]: determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture. [c] Enantiomeric excess calculated based on HPLC analysis for enantiomer *R* (major peak) {*ee* = [peak area (*R*) – peak area (*S*)] × 100/total area (*R* + *S*)}. [d] Selectivity 85%.

The feasibility of using other ketones as aldol donors using CIL **2** as additive was also investigated. The aldol reaction between cyclohexanone and *p*-nitrobenzaldehyde using 20% (*S*)-proline as catalyst in the presence of CIL **2** [CIL **2**/(*S*)-proline, 3:1] provided good conversion (76%) after 6 h reaction, moderate diastereoselectivity (79:21, *anti*/*syn*), and good *ee* values for both enantiomers (77 and 86%, respectively). It must be pointed out that the observed diastereoselectivity was significantly higher than that reported for the use of (*S*)-proline under the same solvent-free experimental conditions (50:50, *anti*/*syn*)[12] or using DMSO as solvent (63:37, *anti*/*syn*).[5c] A considerable increase in the diastereoselectivity and *ee* has been reported

with the use of chiral or no chiral additives for this aldol reaction.[10i,10l,12]

Finally, the influence of the steric bulk of the amino acid residue present in CIL on the catalytic results was investigated under the optimized reaction conditions between acetone and *p*-nitrobenzaldehyde. As reported by other authors, the steric bulk around the chiral carbon atom or the nitrogen atom in chiral ligands derived from amino acids generally enhances the enantioselectivity of the process.[19] Thus, CILs derived from (*S*)-valine, (*S*)-phenylalanine, and (*S*)-leucine were used in the model reaction;[14] however, no significant differences were detected in the enantioselectivity (Table S6 in the Supporting Information). This observation suggests that the nature of the amino acid side chain has a minor influence in the enantioselectivity of the final product.

Conclusions

We have found that chiral room temperature ionic liquids derived from amino acids can be efficiently used as solvents or additives for direct enantioselective aldol reactions. These additives seem to form supramolecular complexes with the catalyst, leading to an improvement in the enantioselectivity of the aldol reaction between *p*-nitrobenzaldehyde and acetone (78 against 62% using CIL **2** or BMIM NTf_2 as additives, respectively). Up to four catalytic cycles were performed without any significant decrease in activity or selectivity, using the same conditions, with the same CIL **2**/(*S*)-proline complex, recovered after a simple workup. A match/mismatch effect between the configuration of CIL **2** and that of proline, has been observed, with the enantioselectivity observed being higher for the (*S*)-proline/CIL **2** complex. Thus, our results provide an attractive alternative method for the efficient enantioselective synthesis of β-hydroxy ketones. The observed transfer of chirality from the chiral media is encouraging for the development of other chiral ionic liquids, designed to provide specific interactions with the corresponding organocatalysts.

Experimental Section

General: All reagents were purchased from commercial suppliers and used as received. Chiral α-amino amides were synthesized as described previously;[13] all the N-protected amino acids were commercially available. The synthesis of chiral room temperature ionic liquids has been described.[14] The NMR spectroscopic experiments were carried out at 500 or 125 MHz for ^{1}H and ^{13}C NMR, respectively. The chemical shifts are reported using trimethylsilane as the internal standard. FTIR spectra were acquired with a MIRacle single-reflection ATR diamond/ZnSe accessory.

Synthesis of Catalyst 6: A solution of LiOH (7.68 mg, 0.3 mmol) and (*S*)-proline (0.037 g, 0.3 mmol) in anhydrous MeOH (5 mL) was stirred for 2 h at room temperature. A solution of CIL **5** (0.122 g, 0.3 mmol; synthesized by following the general synthetic methodology described by our group for the preparation of related imidazolium salts[14]) in anhydrous MeOH (5 mL), was added. The reaction mixture was stirred for 1 h at 0 °C and 20 h at room temperature. After filtration to remove LiCl, the solvent was evaporated and catalyst **6** (0.12 g, 98%) was obtained as a yellow oil. $[\alpha]_D^{25} = -14.3$. ^{1}H NMR (500 MHz, CD_3OD): δ = 7.81 (s, 1 H), 7.77 (s, 1 H), 7.40–7.32 (m, 5 H), 4.67 (d, *J* = 9.8 Hz, 1 H), 4.52 (d, *J* = 14.7 Hz, 1 H), 4.42 (d, *J* = 14.6 Hz, 1 H), 4.33 (t, *J* = 7.3 Hz, 2 H), 3.68–3.62 (m, 1 H), 3.25–3.19 (m, 1 H), 2.91 (dt, *J* = 10.8, 7.1 Hz, 1 H), 2.58–2.49 (m, 1 H), 2.21 (dd, *J* = 12.7, 7.7 Hz, 1 H), 1.98–1.91 (m, 3 H), 1.84 (dt, *J* = 13.2, 6.6 Hz, 2 H), 1.41 (m, *J* = 14.8, 7.4 Hz, 2 H), 1.10 (d, *J* = 6.6 Hz, 3 H), 1.05 (t, *J* = 7.4 Hz, 3 H), 0.92 (d, *J* = 6.7 Hz, 3 H) ppm. ^{13}C NMR (126 MHz, CD_3OD): δ = 168.7, 139.2, 129.6, 129.0, 128.6, 123.7, 123.4, 70.1, 62.8, 50.9, 48.8, 47.2, 44.5, 33.2, 33.0, 31.0, 25.7, 20.4, 19.2, 18.7, 13.7 ppm. MS (ESI^+): *m*/*z* (%) = 314.0 (100) [M^+]. MS (ESI^-): *m*/*z* (%) = 114.0 (100) [M^-]. $C_{24}H_{36}N_4O_3$ (428.57): calcd. C 67.26, H 8.47, N 13.07; found C 66.88, H 8.88, N 12.92.

General Procedure for the Aldol Reactions: (*S*)-Proline (20 mol-%) and the corresponding CIL were mixed in either acetone or cyclohexanone (30 mmol). After stirring for 10 min, aromatic aldehyde (1 mmol) was added and the reaction mixture was stirred at room temperature (25 °C) for 6 h, following the reaction by TLC (EtOAc/hexane, 33%). After this time, the acetone was evaporated and the residue was extracted with diethyl ether (3 × 3 mL). The remaining CIL/proline complex was dried under vacuum at 40 °C for 5 h for use in the next cycle. The collected solvent was evaporated and the crude material was analyzed to determine conversion and selectivity, and then purified by chromatography on a silica gel column (EtOAc/hexane, 33%) to give the aldol product. The *ee* was determined by HPLC analysis, using Chiralpak AD (benzaldehyde, 3-chlorobenzadehyde, 4-chlorobenzaldehyde, 4-nitrobenzaldhyde: cyclohexanone products) or Chiralcel OJ (4-nitrobenzaldehyde product) columns.

4-Hydroxy-4-(4-nitrophenyl)butan-2-one:[12] Yield 94% (0.19 g). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.21 (d, *J* = 8.4 Hz, 2 H), 7.54 (d, *J* = 8.4 Hz, 2 H), 5.26 (dd, *J* = 8.0, 4.0 Hz, 1 H), 2.85 (d, *J* = 7.7 Hz, 2 H), 2.22 (s, 3 H) ppm. The enantioselectivity of the reaction was determined by HPLC (Chiralcel OJ column; Hex/IPA (90:10); flow: 0.75 mL min^{-1}; *T*: 30 °C; λ: 254 nm): t_R = 36.2 (*R*), 41.0 (*S*) min.

2-[Hydroxy(4-nitrophenyl)methyl]cyclohexan-1-one:[12] Yield 55% (0.14 g); *anti* isomer. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.13 (d, *J* = 8.5 Hz, 1 H), 7.44 (d, *J* = 8.5 Hz, 2 H), 5.41 (s, 1 H, CH, *syn*), 4.83 (d, *J* = 8.3 Hz, 1 H, CH, *anti*), 2.26–2.53 (m, 4 H), 1.32–1.78 (m, 5 H) ppm. The enantioselectivity of the reaction was determined by HPLC (Chiralpak AD column; Hex/IPA (90:10); flow: 1 mL min^{-1}; *T*: 30 °C; λ: 254 nm): t_R = 18.2 and 23.1 (*syn*) min; 24.7 (2*S*,1′*R*) and 33.6 (2*R*,1′*S*) (*anti*) min.

4-Hydroxy-4-phenylbutan-2-one:[5c] Yield 34% (55 mg). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.38–7.27 (m, 5 H), 5.16 (dd, *J* = 9.1, 3.2 Hz, 1 H), 2.88 (dd, *J* = 25.6, 16.5 Hz, 2 H), 2.20 (s, 3 H) ppm. The enantioselectivity of the reaction was determined by HPLC (Chiralpak AD column; Hex/IPA (95:5); flow: 0.75 mL min^{-1}; *T*: 30 °C; λ: 210 nm): t_R = 17.3 (*R*), 19.0 (*S*) min.

4-Hydroxy-4-(4-chlorophenyl)butan-2-one:[20] Yield 60% (0.12 g). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.29 (m, 4 H), 3.63 (s, 1 H), 5.06 (dd, *J* = 8.4, 3.9 Hz, 1 H), 2.80–2.68 (m, 2 H), 2.12 (s, 3 H) ppm. The enantioselectivity of the reaction was determined by HPLC (Chiralpak AD column; Hex/IPA (95:5); flow: 0.75 mL min^{-1}; *T*: 30 °C; λ: 210 nm): t_R = 17.0 (*R*), 18.9 (*S*) min.

4-Hydroxy-4-(3-chlorophenyl)butan-2-one:[21] Yield 70% (0.14 g). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.38–7.18 (m, 4 H), 5.07 (dd, *J* = 8.4, 3.9 Hz, 1 H), 2.77–2.75 (m, 2 H), 2.13 (s, 3 H) ppm. The enantioselectivity of the reaction was determined by HPLC (Chi-

ralpak AD column; Hex/IPA (95:5); flow: 0.75 mL min^{-1}; *T*: 30 °C; λ: 210 nm): t_R = 20.8 (*R*), 23.2 (*S*) min.

Supporting Information (see footnote on the first page of this article): ^{1}H and ^{13}C NMR spectra for catalyst **6**, and chiral HPLC chromatograms.

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