Organic LETTERS

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Improving the Catalytic Performance of (*S*)-Proline as Organocatalyst in Asymmetric Aldol Reactions in the Presence of Solvate Ionic Liquids: Involvement of a Supramolecular Aggregate

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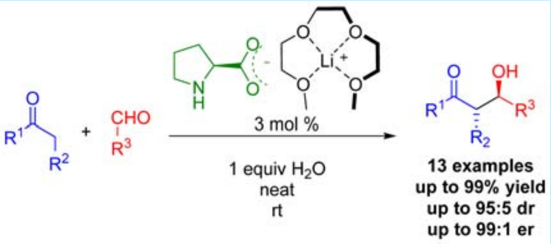
Supporting Information

ABSTRACT: For the first time, a highly efficient and stereoselective asymmetric aldol reaction employing (*S*)-proline in the presence of solvate ionic liquids is reported. The reaction seems to proceed via a supramolecular aggregate of (*S*)-proline, the solvate ionic liquid, and water, affording high yields and excellent stereoselectivities with low catalyst loadings.



Since its application in the asymmetric aldol reaction, (*S*)-proline has been widely used as a chiral organocatalyst and has become a salient successful example in the field of asymmetric organocatalysis, being a natural, simple, and inexpensive molecule.[1] Nevertheless, (*S*)-proline presents several limitations associated with its poor solubility in most organic solvents. In order to overcome this drawback, one strategy utilizes cocatalysts or additives to improve the efficiency of (*S*)-proline.[2]

In this context, ionic liquids, which are organic salts with melting points below 100 °C, have also been used as an alternative solvent in (*S*)-proline organocatalyzed reactions, including the asymmetric aldol reaction, in order to facilitate the dissolution and recovery of the catalyst.[3]

A novel type of ionic liquid corresponds to *solvate ionic liquids* (SILs), which consist of equimolar mixtures of alkaline metal salts and glymes, which give rise to complexes presenting strong coordination of the alkaline cation, usually lithium, by the glyme.[4] In particular, Watanabe et al. developed several SILs and used them mainly as electrolytes for batteries. SILs exhibit the advantage of being easily prepared by simple dissolution of the metal salt in the glyme of choice.[5]

Very recently, a report by Henderson and co-workers described the use of SILs as solvent for electrocyclic organic reactions,[6] opening the field to the application of these molecules in organic transformations. Inspired by this work, we decided to explore the use of SILs as cocatalysts in the asymmetric aldol reaction catalyzed by (*S*)-proline.

Accordingly, four lithium SILs were prepared by mixing equimolar amounts of lithium perchlorate ($LiClO_4$) or lithium bis(trifluoromethanesulfonimide) ($LiNTf_2$) and triglyme (G3) or tetraglyme (G4). In this manner SILs $G3NTf_2$, $G3ClO_4$, $G4NTf_2$, and $G4ClO_4$ were obtained and evaluated in the present study (Figure 1).

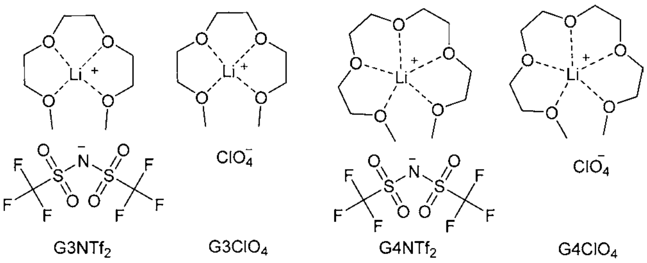


Figure 1. Structure of the solvate ionic liquids employed in this work.

An equimolar mixture of SIL $G3NTf_2$ and (*S*)-proline was tested in the asymmetric aldol reaction between cyclohexanone and *p*-nitrobenzaldehyde. Initial experiments examined the effect of water as an additive, demonstrating that the use of 1 equiv of water led to the highest yields and stereoselectivities (Table 1, entry 3), while larger amounts of water caused the reaction to become sluggish (Table 1, entries 4−6).

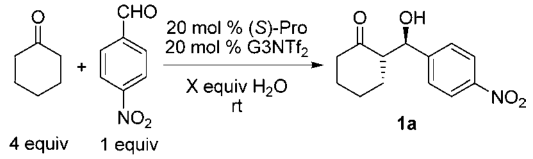
If a 1:1 ratio of (*S*)-proline and SIL $G3NTf_2$ is maintained, the efficiency of the catalytic system was preserved down to 3 mol % (entry 5 in Table 2).

On the other hand, it was observed that SILs with perchlorate anions ($G3ClO_4$ and $G4ClO_4$) afforded lower yields of the aldol products relative to their NTf_2 analogs (compare entries 1 and 3 with entries 2 and 4 in Table 3). Relative to ClO_4^-, Tf_2N^- is a weaker coordinating anion toward Li^+,[7] which apparently facilitates an effective interaction of Tf_2N^- and the Li+·glyme cation with (*S*)-proline. Yet, SILs derived from tetraglyme gave lower stereoselectivities when

Received: January 14, 2017
Published: February 15, 2017

DOI: 10.1021/acs.orglett.7b00129

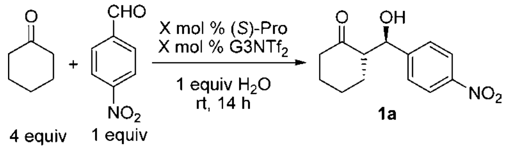
Table 1. Determination of the Optimum Amount of Water As Additive in the Model Aldol Reaction



entry	H_2O equiv	time (h)	yield (%)[a]	dr (*anti*/*syn*)[b]	er (*anti*)[c]
1	0.5	16	97	89:11	97:3
2	0.7	16	92	91:9	98:2
3	1	16	92	93:7	98:2
4	2	72	90	85:15	97:3
5	4	72	89	82:18	97:3
6	8	72	80	90:10	97:3

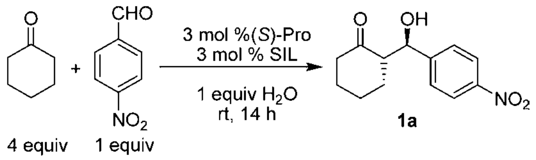
[a]Determined after purification by flash chromatography. [b]Determined by ^1H NMR from the crude reaction. [c]Determined by HPLC with chiral stationary phase.

Table 2. Optimization of the Amount of (*S*)-Proline and SIL in the Asymmetric Aldol Reaction



entry	mol % of (*S*)-proline and SIL	yield (%)	dr (*anti*/*syn*)	er (*anti*)
1	30	92	93:7	98:2
2	20	92	93:7	98:2
3	10	95	93:7	97:3
4	5	90	94:6	98:2
5	3	92	94:6	98:2
6	1.5	64	89:11	95:5

Table 3. Evaluation of Various SILs and Blanks in the Model Aldol Reaction



entry	SIL	yield (%)[a]	dr (*anti*/*syn*)[b]	er (*anti*)[c]
1	$G3NTf_2$	94	94:6	98:2
2	$G3ClO_4$	84	93:7	98:2
3	$G4NTf_2$	96	90:10	96:4
4	$G4ClO_4$	87	89:11	94:6
5[d]	–	18	64:36	88:12
6	–	67	82:18	92:8

[a]Determined after purification by flash chromatography. [b]Determined by ^1H NMR from the crude reaction. [c]Determined by HPLC with chiral stationary phase. [d]No water was added, 24 h of reaction.

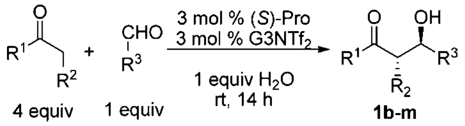
compared with SILs obtained from triglyme (compare entries 3 and 4 with entries 1 and 2, respectively, in Table 3).

To confirm the essential role of the SIL and water in the reaction, the model reaction was run in their absence (Table 3, entry 5). The obtained low yield and stereoselectivity are comparable to those obtained by Barbas and co-workers in their pioneering work with (*S*)-proline in water solvent.[8] By the same token, when the reaction was carried out in the presence of water but in the absence of SIL (Table 3, entry 6), a lower yield and lower stereoselectivity were observed (compared with entry 1, Table 3).

We then examined the efficiency of the catalytic system when conducting the reaction at 3 °C instead of ambient temperature. It was found that the dr increased to 98:2, to be compared with dr = 94:6 observed at ambient temperature. However, the reaction time had to be increased to 48 h. Nevertheless, the stereochemical integrity of the aldol adducts is not eroded in longer, 2−3 days reactions.[9]

Finally, different ketones and aldehydes were screened (Table 4). As it can be appreciated, in terms of yield and stereoselectivity, the catalytic performance was excellent in most cases where cyclohexanone was used as a carbonyl substrate (Table 4, entries 1−10). However, in the case of cyclopentanone the diastereoselectivity was rather low (entry 11, Table 4). With acetone as the substrate, only moderate enantioselectivity was achieved (entry 12, Table 4).

Table 4. Screening of Substrates To Evaluate the Scope of the Reaction with Aromatic Aldehydes



entry	R^1	R^2	R^3	yield (%)	dr (*anti*/*syn*)	er (*anti*)
1	$-(CH_2)_4-$		4-CN-Ph	94	94:6	99:1
2	$-(CH_2)_4-$		3-NO_2-Ph	89	96:4	99:1
3	$-(CH_2)_4-$		2-Cl-Ph	70	96:4	96:4
4	$-(CH_2)_4-$		4-Br-Ph	73	93:7	98:2
5	$-(CH_2)_4-$		2-CF_3Ph	30	94:6	95:5
6	$-(CH_2)_4-$		2-MeO-Ph	49	92:8	97:3
7	$-(CH_2)_4-$		Ph	36	92:8	97:3
8	$-(CH_2)_4-$		4-Me-Ph	12	84:16	96:4
9	$-(CH_2)_4-$		1-Naph	61	94:6	98:2
10	$-(CH_2)_4-$		4-Ph-Ph	36	90:10	97:3
11	$-(CH_2)_3-$		4-NO_2-Ph	92	44:56	92:8
12	Me	H	4-NO_2-Ph	84	–	74:26

We then sought to obtain information about the lithium's environment in the course of the reaction. This was achieved through the acquisition of ^7Li NMR spectra under solvent-free conditions (Figure S1, Supporting Information). It was observed that while pure SIL showed an intense signal at 1.468 ppm (Figure S1a, Supporting Information), addition of an equimolar amount of (*S*)-proline gave rise to two signals at +0.443 and +0.281 ppm (Figure S1b, Supporting Information). The appearance of these signals suggests the formation of two distinct (perhaps diastereomeric, see below) coordination species between the SIL and (*S*)-proline. When water was added to this last mixture, also in an equimolar ratio, only the downfield signal (+0.443 ppm) was observed (Figure S1c, Supporting Information). When 1 equiv of cyclohexanone was added, the signal sharpened but did not suffer changes in its displacement (Figure S1d, Supporting Information), which suggests that the formation of the expected enamine does not affect the apparent coordination between proline and SIL. Finally, the ^7Li NMR signal did not change after addition of benzaldehyde suggesting that interaction between the carboxylate group of the (*S*)-proline and the lithium of the SIL is maintained during the course of the reaction.

DOI: 10.1021/acs.orglett.7b00129
Org. Lett. 2017, 19, 1108−1111

Seeking support for this hypothesis, infrared spectra were acquired and analyzed. (*S*)-Proline alone shows three intense bands in the region between 1700 to 1300 cm^{-1} (Figure S2a, Supporting Information). A peak at 1612 cm^{-1} corresponds to the stretching of the carbonyl group, while one at 1548 cm^{-1} is assigned to stretching of the ammonium group in proline,[10] and the third peak at 1374 cm^{-1} corresponds to the OH in-plane deformation coupled to the C−O stretching vibration.[10] When the SIL is mixed with (*S*)-proline, the IR spectrum shows a reduction in intensity of the band at 1548 cm^{-1}, possibly as a consequence of a hydrogen bond interaction. On the other hand, the band at 1374 cm^{-1} disappears and a new intense band at 1350 cm^{-1} appears (Figure S2b, Supporting Information), which may be associated with the S=O stretching of the Tf_2N^- anion.[10] These changes indicate that an interaction takes place between (*S*)-proline and the SIL, which is in line with the ^{7}Li NMR spectra (see Figure S1b, Supporting Information). When 1 equiv of water was added, the band at 1548 cm^{-1} disappeared and the carbonyl band moved to 1633 cm^{-1} (Figure S2c, Supporting Information). The disappearance of the N−H signal supports the hypothesis that this group is involved in the formation of diastereomeric complexes, originated from coordination to either diastereotopic N−H, and giving rise to complexes between the ammonium group in protonated proline and the sulfonyl groups in the bis(trifluoromethanesulfonimide) anion. Finally, 1 equiv of concentrated hydrochloric acid was added resulting in the disappearance of the band at 1633 cm^{-1}, while a new band at 1731 cm^{-1} is formed (Figure S2d, Supporting Information). This implies that the carboxylate group is protonated as anticipated. Thus, both IR and ^{7}Li NMR spectra seem to support the existence of an interaction between the carboxylate group of proline and the coordinated lithium in the SIL, giving rise to a supramolecular aggregate.

To determine the structural arrangement of the reactive catalytic aggregate, Auxiliary Density Functional Theory (ADFT) calculations were carried out using the deMon2k software,[11] with PBE as the functional, DZVP as the base, and GEN-A2 as the auxiliary function. According to the calculations, the carboxylate group of the (*S*)-proline coordinates electrostatically with the lithium cation of the SIL, in apparent agreement with the ^{7}Li NMR experiments (see above), while the bis(trifluoromethanesulfonimide) anion (Tf_2N^-) interacts with the ammonium group of the pyrrolidine via hydrogen bonding (Figure 2), which is in line with the observation recorded from the IR spectrum in Figure S2b (Supporting Information).

The transition state of the reaction was also modeled, with the finding that water acts as a bridge between the carboxylate group of proline and the carbonyl group of the aldehyde in the transition state (Figure S3, Supporting Information). It is then apparent that the supramolecular ensemble works as a cooperative system, leading to the enantioselective aldol reaction by addition to the *Re* enantiotopic face of the carbonyl group.

These computational results are in agreement with the experimentally observed major aldol product and are in line with the calculations performed by Houk and List for the parent proline-catalyzed aldol reaction.[12] Indeed, rotation of the aldehyde so that enamine addition would take place on the *Si* rather than the *Re* face of the aromatic aldehyde, to afford the *syn* diastereoisomeric product, would result in severe steric hindrance with the SIL segment.

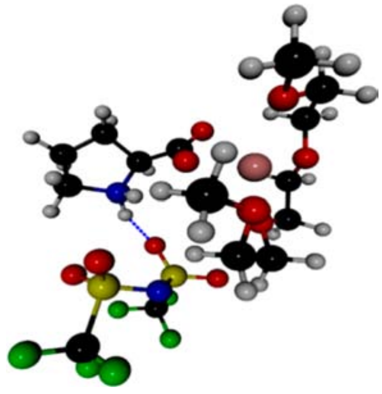
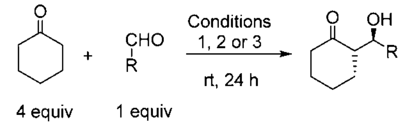


Figure 2. Optimized structure of the (*S*)-proline-G3NTf$_2$ catalyst by ADFT, showing the supramolecular aggregate.

In order to corroborate the generality of the observed improvement of the aldol reaction through the assistance of the SIL, a screening of the reaction of cyclohexanone with aldehydes of different reactivity was carried out. Three reaction conditions were employed: (1) reaction catalyzed by (*S*)-proline (3 mol %) under neat conditions; (2) reaction catalyzed by (*S*)-proline (3 mol %) together with a traditional ionic liquid 1-butyl-3-methylimidazolium hexafluorophosphate (3 mol %); (3) reaction catalyzed by equimolar amounts of (*S*)-proline and SIL G3NTf$_2$ (3 mol %) and water (1 equiv) additive (Table 5). It was found that reactions 1 and 2 afforded similarly moderate yields and diastereoselectivities. By contrast, substantially

Table 5. Aldol Reactions Carried out with Several Aldehydes of Different Reactivity and under Three Reaction Conditions



Cond. 1: (*S*)-proline 3 mol % neat
Cond. 2: (*S*)-proline and BMImPF$_6$ 3 mol %
Cond. 3: (*S*)-proline and G3NTf$_2$ 3 mol %, 1 equiv H_2O

group	R	cond.	yield (%)[a]	dr (*anti*/*syn*)[b]	er (*anti*)[c]
EWG	4-NO$_2$-Ph	1	18	64:36	88:12
	4-NO$_2$-Ph	2	27	58:42	93:7
	4-NO$_2$-Ph	3	94	94:6	98:2
	4-CN-Ph	1	20	50:50	68:32
	4-CN-Ph	2	11	50:50	85:15
	4-CN-Ph	3	94	94:6	98:2
Neutral	Ph	1	43	72:28	75:25
	Ph	2	30	69:31	58:42
	Ph	3	36	92:8	97:3
	1-Naph	1	17	71:29	76:24
	1-Naph	2	14	68:32	81:19
	1-Naph	3	61	94:6	98:2
EDG	4-Ph-Ph	1	19	66:34	78:22
	4-Ph-Ph	2	22	59:41	96:4
	4-Ph-Ph	3	36	90:10	97:3
	2-MeO-Ph	1	29	58:42	82:18
	2-MeO-Ph	2	20	52:48	91:9
	2-MeO-Ph	3	49	94:6	97:3

[a]Determined after purification by flash chromatography. [b]Determined by ^{1}HNMR from the crude reaction. [c]Determined by HPLC with chiral stationary phase.

DOI: 10.1021/acs.orglett.7b00129
Org. Lett. 2017, 19, 1108−1111

improved results, especially in terms of stereoselectivity, were found in the presence of the SIL (conditions 3). Thus, the experimental observations show that the SIL is working through a different mechanism than the imidazolium ionic liquid. This improvement in stereoselectivity can be explained in terms of the calculated transition state presented in Figure S3 (Supporting Information).

One referee suggested the possibility that the high activity and selectivity observed in the reactions has to do with the carboxylic acid moiety of proline becoming more acidic by coordination with the Li center, thus favoring the formation of the enamine of cyclohexanone.[13] In apparent agreement with this reasoning, a reaction with the (*S*)-proline-Li-SIL complex (prepared by dissolving the lithium carboxylate of (*S*)-proline in the glyme afforded an essentially racemic product. Nevertheless, our spectroscopic evidence, in particular the IR spectra, suggest that proline is present in the form of carboxylate throughout the reaction. Thus, according to this observation and our theoretical calculations the models proposed in Figures 2 and S3 (Supporting Information) seem to be more adequate.

In conclusion, we have demonstrated that the effectiveness of (*S*)-proline in the asymmetric aldol reaction, in terms of both reactivity and selectivity, can be significantly improved with the aid of solvate ionic liquids (SILs) and water as the additive. This effect seems to operate through the involvement of a supramolecular ensemble of these three molecules, held together by electrostatic interaction between the carboxylate group and the glyme-coordinated lithium, and with one molecule of water acting as a bridge to the carbonyl group of the aldehyde substrate.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b00129.

Experimental procedures, NMR spectra, IR spectra and chromatograms, Figures S1, S2, and S3 (PDF)

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

Financial support from CONACYT, via grant 220945, is gratefully acknowledged. A.O.-Z. thanks CONACYT for PhD scholarship 283367. We also thank R. Delgado-Venegas (CINVESTAV) for his assistance in the theoretical calculations. Useful suggestions by Editor W. D. Lubell (Université de Montréal) are gratefully acknowledged.

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