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Small organic molecule catalyzed enantioselective direct aldol reaction in water

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Abstract—Protonated pyrrolidine based small organic molecules have been designed and evaluated for the asymmetric direct aldol reaction in water. The designed organocatalysts are multifunctional in nature and exploit the combined effect of hydrogen bonding and hydrophobic interactions for enantioselective catalysis in water. As a result a unique direct asymmetric aldol reaction in water catalyzed by a small organic molecule having an amide linkage has been developed. The developed catalyst affords chiral β-hydroxyketones in good yields (93%) and enantioselectivities (upto 62%) in water.

1. Introduction

Organic synthesis in water is a rapidly growing area of research since it holds great promise for the future in terms of the cheaper and less hazardous production of chemicals.[1] The use of water as solvent in asymmetric reactions has not been appreciated earlier due to the fact that water tends to inhibit the catalyst's activity or alter the enantioselectivity by interrupting ionic interactions and hydrogen bonds, which are critical for stabilizing the transition state of the reaction. Furthermore, the non-polar organic compounds are less soluble in water. However, water due to its small size, high polarity and the three-dimensional hydrogen bonded network system of bulk water, provides some unique properties, which include large cohesive energy density, a high surface tension and hydrophobic effect.[2] The pioneering studies of Breslow et al.[3] and Grieco[4] on Diels–Alder reaction in early 1980s have shown that reactions in water proceed with much higher rates as well as unprecedented regioselectivities than in organic solvents. The accelerating effect of water has been ascribed to a number of factors, including the hydrophobic effect as well as hydrogen bonding between water molecules and reactants. These unique properties of water can be exploited in organocatalyzed direct asymmetric aldol reactions.

In the organocatalytic direct aldol reaction, water, in a small amount has been found to enhance the rate of the proline catalyzed direct aldol reaction in organic media but the use of excess water results in the formation of racemic aldol addition product.[5] Janda et al.[6] based on theoretical studies, have proposed the active involvement of a water molecule in proton transfer in the nornicotine catalyzed aldol reaction. Thus water seems to exert an important influence on the organocatalyzed aldol reaction. The development of efficient, direct asymmetric organocatalyzed aldol reaction in water may result in the development of synthetic methodology having the dual benefits offered by metal free organocatalyst and water as reaction media, favouring green synthesis.

2. Results and discussion

We seek to design metal free small organic molecules with structural diversity for catalyzing enantioselective organic transformations in water or under physiological medium.[7,9] Water has been found to accelerate the pyrrolidine catalyzed direct aldol reaction of different ketones with a range of aromatic aldehydes. The amine catalysis of an aldol reaction has been shown to proceed through an enamine intermediate rather than involving a competing general base catalysis.[7]

The asymmetric version of the pyrrolidine catalyzed aldol reaction in water can be achieved by designing pyrrolidine

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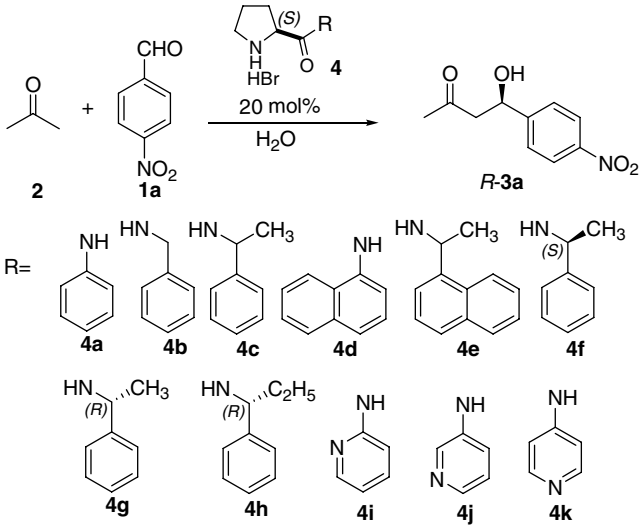
based catalysts capable of inducing asymmetry in the products. We envisaged that the introduction of an asymmetric centre and a suitable hydrophobic unit may provide pyrrolidine based asymmetric organocatalysts useful for direct aldol reaction in water. Furthermore, it has been observed by Spencer et al.[8] that nucleophilic catalysis in water can be enhanced by decreasing the effective base strength of the amine catalysts, which can be done through protonation of the amine.[9]

Herein we report the evaluation of protonated chiral prolinamide derivatives as asymmetric organocatalysts for the direct enantioselective aldol reaction in water. The direct organocatalytic aldol reaction of 4-nitrobenzaldehyde **1a** (2 mmol), and acetone **2** (40 mmol) in water (3 mL) using (*S*)-2-(phenylcarbamoyl)pyrrolidinium bromide **4a** (20 mol %) as a catalyst at ambient temperature 27 ± 1 °C on continuous stirring for 36 h, affords 4-hydroxy-4-(4′-nitrophenyl)butan-2-one **3a**[10] as a yellow crystalline solid, mp: 59–61 °C in 87% yield and 15% ee.

Similarly the direct aldol reaction catalyzed by other organocatalysts (Scheme 1) have been performed and are presented in Table 1. Organocatalyst **4b** derived from L-proline and benzylamine shows high activity with a reaction time of 7 h affording **3a** in 88% yield and 8% ee (Table 1, entry 2). The catalyst **4a** catalyzes the same reaction in 36 h (Table 1, entry 1). This difference in reaction time can be ascribed to the small structural difference in the two catalysts. The catalyst **4b** has a $-CH_2-$ spacer between the amide nitrogen and the phenyl ring, which imparts flexibility whereas catalyst **4a** has a comparatively rigid structure.

Catalyst **4a** may be considered to have two structures **A** and **B** (Fig. 1) having *cis* amide and the other having *trans* amide linkage, respectively. In the *cis* structure **A**, the phenyl ring covers the catalytic nitrogen of the pyrrolidine ring thus inhibiting the reaction, whereas in *trans* structure **B** the catalytic nitrogen of pyrrolidine is not hindered. Both



Scheme 1.

Table 1. Direct asymmetric aldol reaction of acetone **2** and 4-nitrobenzaldehyde **1a** catalyzed by organocatalysts **4**

Entry	Catalyst **4**	Time	**3a** Yield[a] (%)	ee (*R*/*S*)
1	**a**	36 h	87	15 (*R*)
2	**b**	7 h	88	8 (*R*)
3	**c**	8 h	92	33 (*R*)
4	**d**	32 h	83	3 (*S*)
5	**e**	8.5 h	86	24 (*R*)
6	**f**	6 h	87	39 (*R*)
7	**g**	26 h	88	45 (*R*)
8	**h**	8 h	83	46 (*R*)
9	**i**	10 days	nd	nd
10	**j**	10 days	52	31 (*R*)
11	**k**	10 days	Traces	nd

[a] Isolated yields after column chromatography.

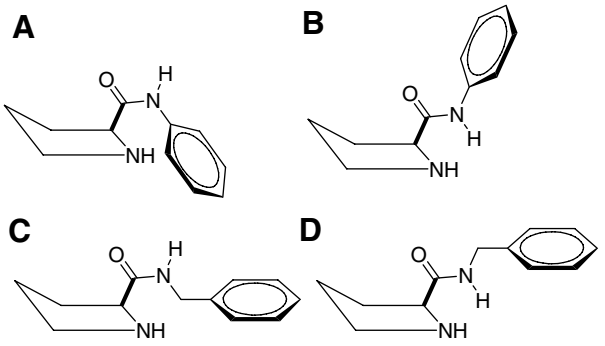


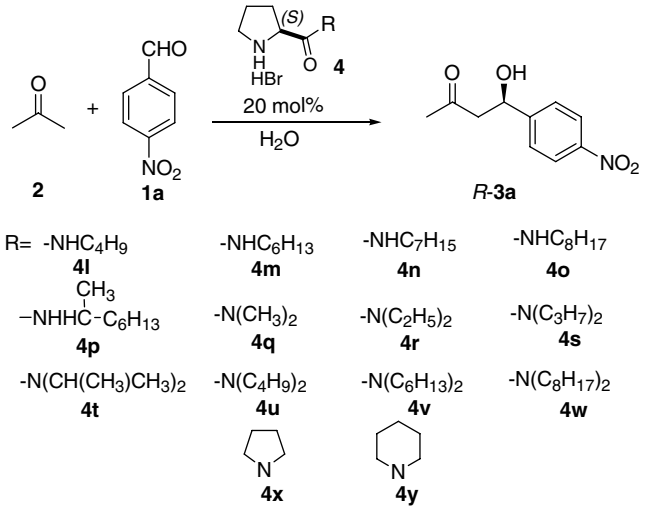
Figure 1.

the *trans* and *cis* structures of catalyst **4b** (**C** and **D**) are flexible due to the presence of $-CH_2-$ spacer between nitrogen and phenyl ring and hence provide unhindered access of the reactants to the catalytic site. Similar difference in the reaction rate is also observed in catalysts **4d** and **4e** having naphthyl groups (Table 1, entries 4 and 5). Organocatalyst **4c** derived from L-proline and (±)-1-phenylethylamine (entry 3) leads to a considerable increase in the enantioselectivity and affords (*R*)-**3a** in 92% yield and 33% ee. Organocatalyst **4d** with a naphthyl group afforded (*S*)-**3a** with 3% ee (entry 4). Where as organocatalyst (2*S*,1′*R*/*S*)-**4e** afforded (*R*)-**3a** in 24% ee. Out of these organocatalysts, only **4c**, which is a diastereomeric mixture of (2*S*,1′*R*) and (2*S*,1′*S*) diastereomers gave higher enantioselectivities (entry 3). To study the enantioselective catalytic effect of diastereomeric catalysts **4c**, the pure diastereomers **4g** and **4f** were synthesized. The aldol reaction with (2*S*,1′*R*)-**4g** and (2*S*,1′*S*)-**4f** gave (*R*)-**3a** with ee of 45% (26 h) and 39% (6 h), respectively (entries 6 and 7). Diastereomer (2*S*,1′*S*)-**4f** catalyzes the reaction faster than diastereomer (2*S*,1′*R*)-**4g**. Catalyst (2*S*,1′*R*)-**4h** with an ethyl group in place of the methyl, as in (2*S*,1′*R*)-**4g**, gave (*R*)-**3a** in 83% yield in 8 h with 46% ee (entry 8). The catalysis of the enantioselective aldol reaction by (2*S*,1′*R*)-**4h** is faster than that catalyzed by (2*S*,1′*R*)-**4g** while the enantioselectivity is comparable. This indicates that the diastereomeric catalysts **4g** and **4h** with mismatched configurations at the two stereogenic centres are better than catalyst **4f** with a matched configuration. Additionally catalysts **4i**, **4j** and **4k** prepared from L-proline and

2-, 3- and 4-aminopyridine,[11] respectively, were screened to determine the effect of a heteroaromatic ring. The aldol reactions with these catalysts were run for 10 days. Catalyst **4j** gave the aldol product in 52% yield and 31% ee, while **4i** was not an effective catalyst and **4k** gave traces of aldol product (*R*)-**3a**.

Thus, from the above results of screening it can be concluded that catalysts **4g** and **4h** are potential organocatalysts for the direct asymmetric aldol reaction in water with high activity and moderate enantioselectivity whereas other organocatalysts derived from L-proline and aromatic amines have been found to be less efficient catalysts.

Hydrophobic effects have been invoked to explain the unusual reactivity of organic reactions in water. The importance of hydrophobicity in the direct aldol reaction catalyzed by organocatalysts in water has been further elucidated by studying the reactivity and selectivity of the organocatalysts prepared from L-proline and alkyl amines (Scheme 2). The screening of the catalysts having butyl, hexyl, heptyl and octyl groups revealed that enantioselectivity increases with an increase in the chain length. Catalyst **4o** having a linear octyl chain affords an ee of 36% (Table 2, entry 4) whereas the catalyst (2*S*,1′*R*/*S*)-**4p** having a branched heptyl chain affords (*R*)-**3a** with an ee of 39% (entry 5). The catalysts with smaller chain lengths afforded (*R*)-**3a** with lower enantiomeric excess, thus indicating the importance of hydrophobic effects in the enantioselective catalysis. The hydrophobic nature of the catalysts can be further enhanced by dialkyl groups. Catalysts **4q–w** synthesized by using dimethylamine, diethylamine, dipropylamine, dibutylamine, dihexylamine, dioctylamine and diisopropylamine, respectively, catalyzed the aldol reaction of acetone **2** and 4-nitrobenzaldehyde **1a** to afford (*R*)-**3a** with ees ranging from 2% to 39%. Clearly, the same trend follows and there is slight enhancement in enantioselectivity due to the introduction of two alkyl chains in the catalysts. The comparison of catalyst **4l** and catalyst **4u** having an *N*-butyl group and an *N*,*N*-dibutyl group, respectively, shows an increase in enantioselectivity from 29% to 31%.



Scheme 2.

Table 2. Direct asymmetric aldol reaction of acetone **2** and 4-nitrobenzaldehyde (**1a**) in water catalyzed by organocatalysts **4**

Entry	Catalyst	Time	Conversion[a] (%)	Yield[b] (%)	ee (*R*)
1	**4l**	4 h	100	92.7	29
2	**4m**	30 min	100	93	30
3	**4n**	90 min	95	87	35
4	**4o**	150 min	97	89	36
5	**4p**	4 h	100	92	39
6	**4q**	10 h	92	89	2
7	**4r**	10 h	—	90	10
8	**4s**	10 days	37	36	22
9	**4t**	5 h	100	92	24
10	**4u**	5 h	90.4	84	31
11	**4v**	12 h	100	90	35
12	**4w**	5 h	98	89	39
13	**4x**	18 h	87	78	13
14	**4y**	8 h	93	87	9

[a] Conversion based on ^{1}H NMR.
[b] Isolated yields after column chromatography.

A similar comparison of catalyst **4o** (R = NHC_8H_{17}) and catalyst **4w** (R = $N(C_8H_{17})_2$) also showed an enhancement in enantioselectivity from ee 36% (Table 2, entry 4) to ee 39% (Table 2, entry 12). The comparison of an *N*,*N*-diisopropyl group (catalyst **4t**) and an *N*,*N*-dipropyl group (catalyst **4s**) shows that the catalyst with a branched alkyl chain **4t** afforded (*R*)-**3a** with higher ee of 24% ee whereas catalyst **4s** affords (*R*)-**3a** with an ee of 22% (Table 2, entries 8 and 9). Further, catalysts **4x** and **4y** having pyrrolidine and piperidine groups were found to be inferior affording ees of 13% and 9%, respectively (Table 2, entries 13 and 14).

Thus the study reveals that the presence of linear hydrophobic groups on L-prolinamide based catalysts enhances the enantiomeric excess in the direct aldol reaction in water. The reaction catalyzed by the catalysts having a monoalkyl chain (Fig. 2A) occurs at a faster rate than the reaction catalyzed by catalysts having dialkyl chains (Fig. 2B). This difference in reactivity indicates the involvement of amide NH in the transition state of aldol reaction.

As is clear from Tables 1 and 2 in all the cases, the (*R*)-isomer is predominant in the aldol product irrespective of the catalyst used (except catalyst **4d**, Table 1, entry 4). Similar results were obtained, when employing **4f**, **4g** or **4h** as the organocatalysts irrespective of the stereocentre present at the α-carbon of the amine (Table 1, entries 6, 7 and 8). It should be noted that a similar stereochemical outcome [(*R*)-isomer] can be found in proline's enamine catalysis in organic media.[12] It may be concluded that the stereocentre at the pyrrolidine ring is directing the stereochemistry of the process. Hence, we envisioned a transition state favouring *re*-facial attacks similar to enamine catalysis of proline for the aldol reaction. The enantioselectivity and reactivity of the direct aldol reaction of acetone **2** and 4-nitrobenzaldehyde **1a** catalyzed by L-prolinamide hydrobromide catalysts can be accounted for by invoking the transition state as shown in Figure 2, involving a proton mediated six-

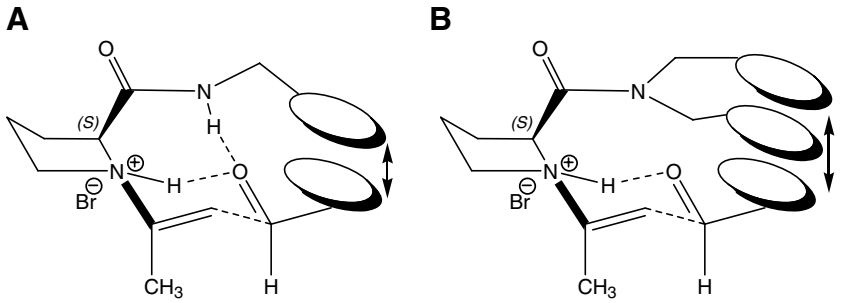
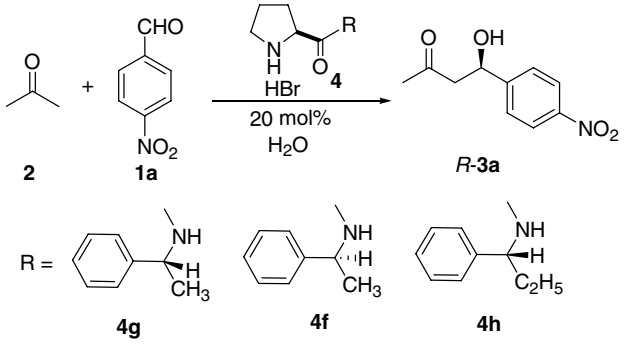


Figure 2.

membered cyclic transition state with additional activation and orientation of the aldehyde by the amide proton. The favourable hydrophobic interaction of the aryl/alkyl groups of the catalyst and the aldehydes enforces an asymmetric environment. In the absence of activation of aldehyde by amide NH, the reaction is slower but enantioselectivity is not affected. Thus, the enantioselectivity of the process is mainly controlled by the hydrophobic interactions between the hydrophobic groups of aldehyde and the catalysts. An increase in the hydrophobicity of the catalyst results in an increase in the enantioselectivity of the aldol process.

The importance of hydrophobic interactions in determining the enantioselectivity of the aldol reaction has been known for class I aldolase enzymes[13] and aldolase catalytic antibodies[14] that use enamine mechanisms for catalyzing enantioselective aldol reaction in water. During the writing of this work, similar observations were reported by Takabe et al.[15] using a diamine catalyst bearing hydrophobic alkyl chains in the presence of an acid additive.

The role of water was examined in the organocatalyzed direct aldol reaction (Scheme 3). The direct aldol reaction of acetone **2** and 4-nitrobenzaldehyde **1a** in dry acetone using catalyst (2*S*,1′*R*)-**4g** and (2*S*,1′*S*)-**4f** gave aldol products in traces even after 5 days (Table 3, entries 7 and 10). But same reaction in water affords (*R*)-**3a** in 45% ee and 89% yield. The use of water in smaller amounts led to an increase in enantioselectivity to 50% (Table 3, entries 2 and 3) using catalyst (2*S*,1′*R*)-**4g**. The same reaction when performed at lower temperature 0–4 °C using (2*S*,1′*R*)-**4g** as catalyst afforded (*R*)-**3a** in 56% ee in a reaction time of 60 h (Table 3, entry 5). The lower concentration of water leads to longer reaction time in the case of catalyst (2*S*,1′*S*)-**4f** and (2*S*,1′*R*)-**4h** (Table 3, entries 9 and 12), but the effect was not observed in the case of (2*S*,1′*R*)-**4g** (Table 3, entries 1–3). The aldol reaction catalyzed by (2*S*,1′*R*)-**4g** performed using a lesser volume of both acetone (1.5 mL) and water (1.5 mL) results in a decrease in the yield and enantioselectivity (39%) of (*R*)-**3a** (entry 6).



2 **1a** **4** *R*-**3a** **4g** **4f** **4h**

Scheme 3.

Additives are known to alter the reactivity and selectivity of organic reactions, so it was planned to study the effect of co-solvents on the aldol reaction using catalyst (2*S*,1′*R*)-**4g** and (2*S*,1′*S*)-**4h**. The results are presented in Table 4. The results show that in the case of catalyst (2*S*,1′*R*)-**4g**, the addition of THF improves the enantioselectivity in comparison to the reactions performed without a co-solvent and when DMSO or DMF are used as a co-solvent (Table 4, entries 2–4). In the case of catalyst (2*S*,1′*S*)-**4f**, DMF as co-solvent affords higher enantioselectivity of (*R*)-**3a** (Table 4, entry 5) as compared to DMSO or THF (entries 6 and 7). The enantioselectivity is similar to that obtained with catalyst (2*S*,1′*R*)-**4g** in the absence of any co-solvent (entry 1). Thus the co-solvent does not seem to offer any distinct advantage.

The role of Bronsted acids in enhancing the catalytic ability of pyrrolidine-based organocatalysts has been reported.[16] Since in the present investigations, L-prolinamide hydrobromide derivatives have been found to be excellent catalysts, it was planned to investigate the role of a counter ion in the direct asymmetric aldol reaction in water. For this purpose organocatalysts **4g**, **6** and **7** were prepared. The direct asymmetric aldol reaction of acetone **2** and 4-nitrobenzaldehyde **1a** catalyzed by these catalysts has been studied (Scheme 4) and the results are presented in Table 5. The catalyst having counterion Br^-, Cl^- and CF_3COO^- gave comparable enantiomeric excess for (*R*)-**3a**, but the effect on the rate of reaction is tremendous. Catalyst **6** gave a fast reaction with 100% conversion in 30 h, but the aldol reaction catalyzed by catalysts **7** gave 63% conversion in 50 h. The fastest but the least selective was the amine catalyst **5**, which affords (*R*)-**3a** in 3 h with 16% ee and 87% conversion.

The lower enantioselectivity for the amine catalyst can be ascribed to the competing general base catalysis. The higher enantioselectivity as shown by catalysts **4g**, **6** and **7** can be ascribed to the lower basic strength of the catalysts, which inhibits the competing general base catalyzed reac-

Table 3. Effect of amount of water on the direct asymmetric aldol reaction

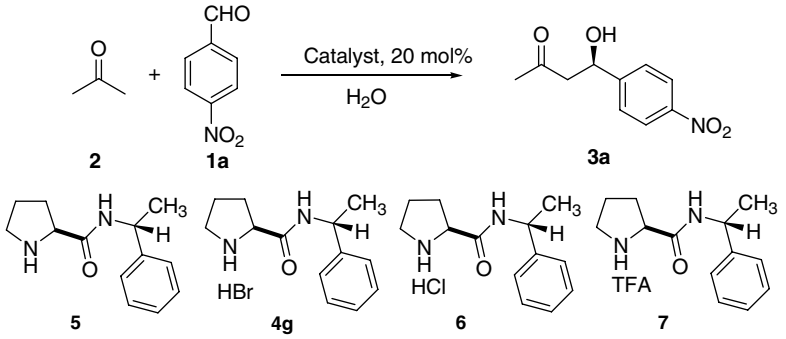
Entry	Catalyst (mol %)	Acetone (mL)	Water (mL)	Solvent Acetone/water	Time	Yield (%) **3a**	ee (%) (*R*)
1	**4g** (20)	3	3	1:1	40 h	89	45
2	**4g** (20)	3	1.5	2:1	40 h	89	48
3	**4g** (20)	3	0.735	4:1	40 h	86	50
4	**4g** (5)	3	0.735	4:1	72 h	88	49
5	**4g** (20)	3	0.735	4:1	60 h	60	56[a]
6	**4g** (20)	1.5	1.5	1:1	40 h	69	39
7	**4g** (20)	3	0	0	5 days	Traces	nd
8	**4f** (20)	3	3	1:1	6 h	87	39
9	**4f** (20)	3	0.735	4:1	24 h	78	38
10	**4f** (20)	3	0	0	5 days	Traces	nd
11	**4h** (20)	3	3	1:1	8 h	83	46
12	**4h** (20)	3	0.735	4:1	19 h	83	49
13	Proline (20)	3	3	1:1	3 h	78	3

[a] Reaction performed at 0–4 °C.

Table 4. Effect of co-solvent on the aldol reaction between acetone **2** and 4-nitrobenzaldehyde **1a** catalyzed by **4g** and **4f**

Entry	Catalyst	Acetone (mL)	Water (mL)	Solvent (1.5 mL)	Time (h)	Yield[a] (%) **3a**	ee (*R*)
1	**4g**	1.5	1.5	—	40	69	39
2	**4g**	1.5	1.5	DMSO	24	80	40
3	**4g**	1.5	1.5	THF	48	78	48
4	**4g**	1.5	1.5	DMF	24	69	39
5	**4f**	1.5	1.5	DMF	7	71	40
6	**4f**	1.5	1.5	DMSO	20	85	26
7	**4f**	1.5	1.5	THF	16	85	27
8	**4f**	1.5	1.5	PEG	10	60	32

[a] Isolated yields after column chromatography.



Scheme 4.

Table 5. The effect of a counter ion on organocatalyzed direct asymmetric aldol reaction of acetone **2** with 4-nitrobenzaldehyde **1a** in water

Entry	Catalyst	Counter ion	Time (h)	Conversion (^{1}H NMR)	ee (%) (*R*)
1	**5**	—	3	87	16
2	**4g**	Br^-	40	95	45
3	**6**	Cl^-	30	100	43
4	**7**	CF_3COO^-	50	63	45

tion and favours the enantioselective nucleophilic catalysis as observed by Spencer et al.[8]

The X-ray crystal structure determination of **4g** and **7** indicates that the CF_3COO^- anion is closely held by pyrrolidinium cation as compared to the Br^- ion (Figs. 3 and 4). Since, the hydrogen bonds in case of **4g** between the two N–H hydrogens and Br^- ion are shown to be at a distance of 2.62 and 2.43 Å, the two N–H hydrogens bond with different bromide ions. The hydrogen bond in case of **7** between the N–H hydrogen of pyrrolidinium cation and the carboxylate oxygen of trifluoroacetate shows a distance of 2.101 and 1.88 Å and the two N–H hydrogens bond to different trifluoroacetate anions. Thus, the experimental results and the X-ray structure determination suggest that the

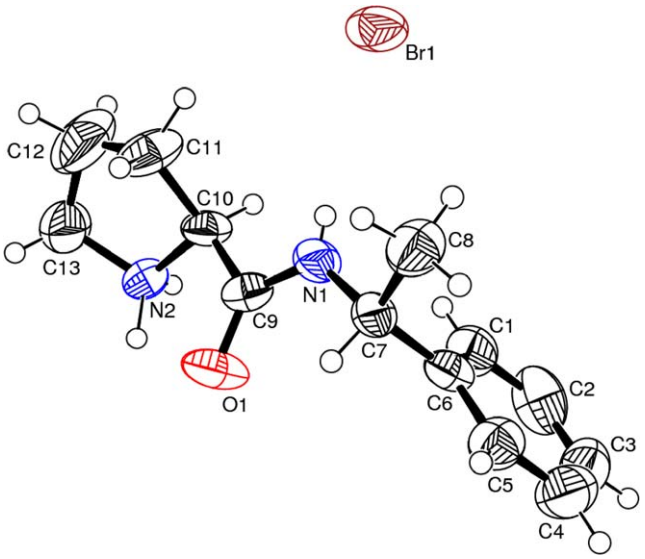


Figure 3. X-ray structure of **4g**.

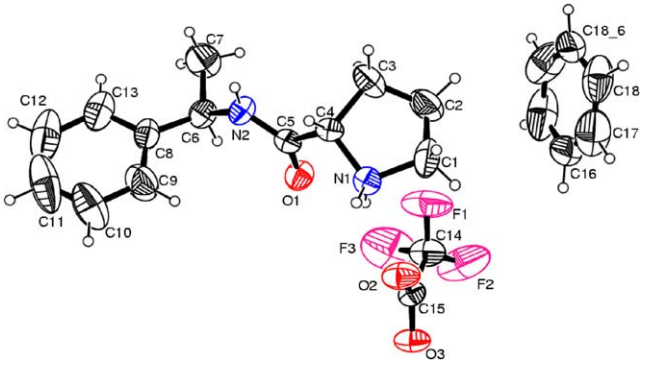


Figure 4. X-ray structure of **7** with benzene trapped in interstitial site.

anion has a detrimental effect on the catalytic activity, but has no effect on the enantioselectivity of the catalyst.

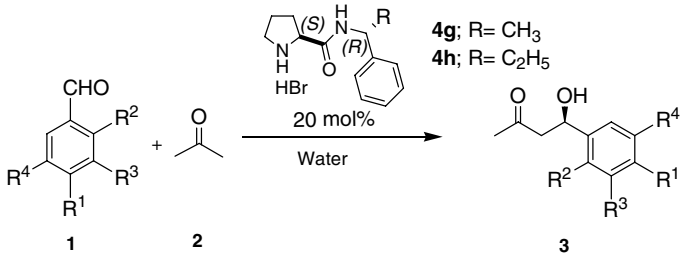
In order to explore the general scope of this methodology, the aldol reaction of acetone and other aromatic aldehydes was performed using catalysts **4g** and **4h** (Scheme 5). The results of this investigation are presented in Table 6. In general, it was observed that catalyst (2*S*,1′*R*)-**4h**, catalyzes the direct aldol reaction at a faster rate and affords aldol addition product **3** in higher enantioselectivity than catalyst (2*S*,1′*R*)-**4g**. The position and nature of the substituents of the aromatic ring affects the reactivity and selectivity of the aldol reaction.[7]

Aldehydes with electron withdrawing substituents show high reactivity. The aldol reaction of *ortho*-substituted aldehydes shows higher selectivity than the aldol reaction of *para*-substituted aldehydes (Table 6, entries 1, 2 and 9,

Table 6. Direct aldol reaction of acetone **2** with different aromatic aldehydes **1** in water, catalyzed by **4g** and **4h**[a]

Entry	Aldehyde	Catalyst	Rxn time	Conversion (^{1}H NMR)	Yield[c]	ee (*R*)
1	**1a**	**4g**	40	95	89	45
2	**1a**	**4h**	8	92	83	46
3	**1c**	**4g**	24	87	82	24
4	**1c**	**4g**	118[b]	29	25	47
5	**1c**	**4h**	10	94	90	41
6	**1c**	**4h**	72[b]	70	68	47
7	**1b**	**4g**	18	100	90	48
8	**1b**	**4g**	118[b]	67	63	55
9	**1b**	**4h**	10	100	93	60
10	**1b**	**4h**	30	100	93	62
11	**1k**	**4g**	72	No reaction	—	—
12	**1k**	**4h**	72	No reaction	—	—
13	**1d**	**4g**	96	31	28	25
14	**1d**	**4h**	72	33	30	36
15	**1e**	**4g**	96	22	19	22
16	**1e**	**4h**	72	84	80	41
17	**1j**	**4g**	20	34	30	37
18	**1j**	**4h**	72	17	—	36
19	**1i**	**4g**	24	100	93	21
20	**1i**	**4h**	18	100	92	36
21	**1l**	**4g**	72	Traces	—	nd
22	**1h**	**4h**	24	26	23	37

[a] Aldehyde (**1**, 2 mmol), acetone (**2**, 40 mmol), 3 mL water and 20 mol % of the catalyst stirrer at 27 ± 1 °C.
[b] Ratio of acetone to water is 4:1 (0.735 mL of water).
[c] Isolated yield after column chromatography.



1 **2** **3**

a: $R^1 = NO_2$; $R^2 = R^3 = R^4 = H$
b: $R^1 = H$; $R^2 = NO_2$; $R^3 = R^4 = H$
c: $R^1 = R^2 = H$; $R^3 = NO_2$; $R^4 = H$
d: $R^1 = Cl$; $R^2 = R^3 = R^4 = H$
e: $R^1 = H$; $R^2 = Cl$; $R^3 = R^4 = H$
h: $R^1 = F$; $R^2 = R^3 = R^4 = H$
i: $R^1 = CN$; $R^2 = R^3 = R^4 = H$
j: $R^1 = R^2 = R^3 = R^4 = H$
k: $R^1 = OCH_3$; $R^2 = R^3 = R^4 = H$
l: $R^1 = H$; $R^2 R^3 = C_4H_4$; $R^4 = H$

Scheme 5.

10), thus indicating that reaction occurs through a sterically hindered transition state. 1-Naphthaldehyde **1l** affords the aldol product in traces (Table 6, entry 21) whereas benzaldehyde **1h** gave aldol (*R*)-**3** in low yield and low enantiomeric excess (Table 6, entries 17 and 18). Thus the catalysts (2*S*,1′*R*)-**4g** and (2*S*,1′*R*)-**4h** catalyze the direct asymmetric aldol reaction of acetone and substituted aromatic aldehydes, although the nature of the substituents of the aromatic aldehyde controls the overall success of the reaction.

3. Conclusion

In conclusion, we have demonstrated a unique direct asymmetric aldol reaction in water catalyzed by a small organic molecule having a simple amide linkage for procuring chiral β-hydroxyketones in good yields and good to moderate enantioselectivities without any major side product. The study reveals an interesting area of aqueous asymmetric organocatalysis. The designed catalysts are multifunctional in nature and exploit the combined effect of hydrogen bonding and hydrophobic interactions for the enantioselective catalysis in water. Moreover, this simple amide based organocatalysis in water provides an insight into the peptide and enzyme catalysis under physiological conditions, which may further help in the rational design of the simple yet highly evolved organocatalysts and enzyme mimics. Our studies indicate that small organic molecules as catalysts have the ability to achieve the level of stereoselectivity that is shown by peptide catalysts under ambient conditions.[17] A broad mechanistic view is being generated and the scope of these organocatalysts for other carbon–carbon bond formation reactions is being pursued.

4. Experimental

4.1. General

NMR spectra were obtained at 200 MHz (Bruker AC 200E) or 300 MHz (Jeol AL-300) for ^{1}H and at 50 MHz or 75 MHz for ^{13}C NMR using either $CDCl_3$ or D_2O as solvents with Me_4Si in $CDCl_3$ as internal standard. Chemical shifts are reported in δ values relative to TMS and coupling constants (*J*) are expressed in hertz. Spectral patterns are designated as *s* = singlet; d = doublet; dd = doublet of doublets; *q* = quartet; *t* = triplet; br = broad; *m* = multiplet. When necessary, assignments were aided by DEPT-135 and decoupling experiments. IR spectra were obtained with Nicolet Avatar 320 FTIR and are reported in wavenumbers (cm^{-1}). Mass spectra were recorded on GCMS-QP-2000 mass spectrometer or Jeol SX-102 (FAB) spectrophotometer. Analytical thin-layer chromatography (TLC) was performed on either (i) aluminum sheets pre-coated with silica gel $60F_{254}$ (Merck, India) or (ii) glass plates (7.5 × 2.5 cm) coated with silica gel GF-254 (Spectrochem India) containing 13% calcium sulfate as binder and various combinations of ethyl acetate and hexane were used as eluents. Visualization of the spots was accomplished by exposure to UV light or iodine vapours. Column chromatography was performed on silica gel (100–200 mesh) using 1–5% methanol in chloroform as eluent. Organic substrates, aryl and alkyl amines were obtained from Aldrich and L-proline and Boc-L-proline were procured from Spectrochem, India and used as received. Dicyclohexylcarbodiimide and benzylchloroformate (CbzCl) as 50% solution in toluene were also procured from Spectrochem, India and used directly.

4.2. Synthesis of (*S*)-2-(alkyl/arylcarbamoyl)pyrrolidinium bromide 4

To an ice cold stirred solution of (*S*)-*N*-(benzyloxycarbonyl)proline[18a] (1 g, 3.4 mmol), alkyl/aryl amine (3.4 mmol) in dichloromethane (15 mL), a solution of dicyclohexylcarbodiimide (0.88 g, 3.8 mmol) in dichloromethane was added dropwise. The resulting mixture was stirred and the temperature of the reaction mixture was allowed to rise to room temperature. The progress of the reaction was monitored by TLC (R_f 0.4, ethyl acetate/hexane, 2:3). After completion of the reaction, the reaction mixture was filtered and evaporated to obtain the crude product, which on column chromatography gave (*S*)-2-(alkyl/arylcarbamoyl)-*N*-(benzyloxycarbonyl)prolinamide as a white solid in 65–90% yield. A mixture of (*S*)-2-(alkyl/arylcarbamoyl)-*N*-(benzyloxycarbonyl)prolinamide (1 g) and 33% solution of HBr in acetic acid (3 mL) was then stirred for 3 h.[18b] The reaction was stopped by distillation of acetic acid under reduced pressure and the crude product was obtained as thick liquid, which on column chromatography (60–120 mesh silica) using ethyl acetate followed by mixture of chloroform with increasing concentration of methanol (1–5%) as eluent gave the (*S*)-2-(alkyl/arylcarbamoyl)pyrrolidinium bromide as a pure product.

4.2.1. (*S*)-2-(Phenylcarbamoyl)pyrrolidinium bromide 4a. Yield, 64%; white solid, mp: 170–172 °C; R_f 0.3 (methanol/chloroform, 1:99); MS (*m*/*z*) FAB: 191 (M^+); $[\alpha]_D^{20} = -18.0$ (*c* 0.38, MeOH); ^{1}H NMR (D_2O): δ 2.09–2.29 (m, 3H, CH_2), 2.51–2.63 (m, 1H, CH_2), 3.41–3.56 (m, 2H, CH_2), 4.54 (t, 1H, *J* = 7.6 Hz, CH), 7.27–7.33 (m, 1H, ArH), 7.43–7.50 (m, 4H, ArH); ^{13}C DEPT NMR ($CDCl_3$ + DMSO-d_6): 22.9 (−ve), 29.2 (−ve), 45.1 (−ve), 58.9 (+ve), 118.7 (+ve), 123.2 (+ve), 127.6 (+ve), 136.9, 165.4.

4.2.2. (*S*)-2-(Benzylcarbamoyl)pyrrolidinium bromide 4b. Yield, 79%; brown liquid; R_f 0.3 (methanol/chloroform, 1:99); MS (*m*/*z*) FAB: 205 (M^+); $[\alpha]_D^{20} = -29.0$ (*c* 0.61, MeOH); IR (neat): 1230, 1520, 1690, 2410, 2920, 3060 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.87–1.99 (m, 3H, CH_2), 2.48–2.53 (m, 1H, CH_2), 3.27–3.40 (m, 2H, CH_2), 4.34 (dd, 1H, *J* = 15.3 and 5.7 Hz, CH_2), 4.44 (dd, 1H, *J* = 15.3 and 6.0 Hz, CH_2), 4.78–4.82 (m, 1H, CH_2), 7.20–7.29 (m, 5H, ArH), 8.64 (t, 1H, *J* = 6.0 Hz, NH); ^{13}C DEPT NMR ($CDCl_3$ + DMSO-d_6): δ 23.7 (−ve), 29.9 (−ve), 42.9 (−ve), 46.0 (−ve), 59.2 (+ve), 126.8 (+ve), 127.1 (+ve), 128.0 (+ve), 137.4, 167.8.

4.2.3. (2*S*,1′*R*/*S*)-2-(1′-Phenylethylcarbamoyl)pyrrolidinium bromide 4c. Yield, 57%; pale yellow liquid as a mixture of two diastereomers (2*S*,1′*R*) and (2*S*,1′*S*); R_f 0.2 (methanol/chloroform, 1:99); MS (*m*/*z*) FAB: 219 (M^+); $[\alpha]_D^{20} = -28.5$

(*c* 0.56, MeOH); IR (neat): 1680, 2400, 2750, 3020 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.51 (d, 3H, $J = 6.9$ Hz, CH_3), 1.81–2.03 (m, 4H, CH_2 and NH), 2.53–2.58 (m, 1H, CH_2), 3.16–3.47 (m, 4H, CH_2), 4.76–4.84 (m, 1H, CH), 4.89–5.01 (m, 1H, CH), 7.19–7.41 (m, 5H, ArH), 8.71 (t, 1H, $J = 3.4$ Hz, NH); ^{13}C DEPT NMR ($CDCl_3$): δ 22.4 (+ve), 23.9 (+ve), 30.3 (+ve), 30.6 (+ve), 46.6 (−ve), 46.7 (−ve), 49.9 (+ve), 50.0 (+ve), 59.4 (+ve), 59.5 (+ve), 125.5 (+ve), 125.9 (+ve), 126.8 (+ve), 126.9 (+ve), 128.3 (+ve), 128.7 (+ve), 143.0, 143.3, 167.5, 167.7.

4.2.4. (*S*)-2-(Naphth-1′-ylcarbamoyl)pyrrolidinium bromide 4d. Yield, 65%; white solid; mp: 213–215 °C; R_f 0.2 (methanol/chloroform, 1:99); MS (*m*/*z*) FAB: 241 (M^+); $[\alpha]_D^{20} = -16.0$ (*c* 0.54, MeOH); IR (KBr): 1679, 2892, 3013, 3149, 3249 cm^{-1}; ^1H NMR ($CDCl_3$ + DMSO-d_6): δ 2.08–2.69 (m, 4H, CH_2), 3.39–3.45 (m, 1H, CH_2), 3.49–3.55 (m, 1H, CH_2), 5.01 (t, 1H, $J = 7.5$ Hz, CH), 7.43–7.55 (m, 3H, NapH), 7.18 (d, 1H, $J = 8.1$ Hz, NapH), 7.78–7.86 (m, 2H, NapH), 8.11 (d, 1H, $J = 8.1$ Hz, NapH), 10.43 (br s, 1H, NH); ^{13}C DEPT NMR ($CDCl_3$ + DMSO-d_6): 23.6 (−ve), 30.2 (−ve), 45.8 (−ve), 59.5 (+ve), 121.4 (+ve), 122.0 (+ve), 124.9 (+ve), 125.7 (+ve), 127.4, 127.8 (+ve), 131.7, 133.5, 167.5.

4.2.5. (2*S*,1′*R*/*S*)-2-(1′-Naphth-1″-yl-ethylcarbamoyl)-pyrrolidinium bromide 4e. Yield 62%; as a mixture of two diastereomers, 2*S*,1′*R* and 2*S*,1′*S*; white solid; mp: 180–182 °C; R_f 0.2 (methanol/chloroform, 1:99); MS (*m*/*z*) FAB: 269 (M^+); $[\alpha]_D^{20} = -17.5$ (*c* 0.89, MeOH); ^1H NMR ($CDCl_3$): δ 1.54–1.92 (m, 4H, CH_2 and NH), 1.62 (d, 3H, $J = 6.9$ Hz, CH_3), 2.29–2.42 (m, 0.5H, diastereomeric H of CH_2), 2.43–2.57 (m, 0.5H, diastereomeric H of CH_2), 2.90–3.23 (m, 2H, CH_2), 4.78 (q, 1H, $J = 8.4$ Hz, CH), 5.75 (sep, 1H, $J = 6.9$ Hz, CH), 7.37–7.55 (m, 3H, NapH), 7.66–7.74 (m, 3H, NapH), 7.80–7.86 (m, 1H, NapH), 7.98–8.03 (m, 1H, NapH), 8.73 (d, 1H, $J = 7.5$ Hz, NH of one diastereomer), 8.89 (d, 0.5H, $J = 7.8$ Hz, NH of one diastereomer); ^{13}C DEPT NMR ($CDCl_3$ + DMSO-d_6): δ 13.4 (+ve), 20.7 (+ve), 20.8 (+ve), 23.3 (−ve), 29.8 (−ve), 44.8 (+ve), 44.9 (+ve), 45.6 (−ve), 58.7 (+ve), 59.5 (−ve), 121.7 (+ve), 122.0 (+ve), 122.1 (+ve), 122.4 (+ve), 124.7 (+ve), 124.9 (+ve), 125.4 (+ve), 125.6 (+ve), 126.9 (+ve), 127.0 (+ve), 128.0 (+ve), 128.1 (+ve), 129.7, 129.8, 132.8, 132.9, 138.4, 166.4, 166.7.

4.2.6. (2*S*,1′*S*)-2-(1′-Phenylethylcarbamoyl)pyrrolidinium bromide 4f. Yield, 65%; low melting yellow solid; R_f 0.2 (methanol/chloroform, 1:99); MS (*m*/*z*) FAB: 219 (M^+); $[\alpha]_D^{20} = -114.8$ (*c* 0.25, MeOH); ^1H NMR ($CDCl_3$): δ 1.54 (d, 3H, $J = 6.9$ Hz, CH_3), 1.88–2.04 (m, 4H, CH_2, and NH), 2.62–2.68 (m, 1H, CH_2), 3.25–3.33 (m, 1H, CH_2), 3.43–3.49 (m, 1H, CH_2), 4.88–4.92 (m, 1H, CH), 4.90–5.02 (m, 1H, CH), 7.20–7.32 (m, 5H, ArH), 8.77 (d, 1H, $J = 5.4$ Hz, NH); ^{13}C DEPT NMR ($CDCl_3$): δ 22.6 (+ve), 24.2 (−ve), 30.6 (−ve), 46.8 (−ve), 50.2 (+ve), 59.6 (+ve), 125.6 (+ve), 126.9 (+ve), 127.1 (+ve), 128.4 (+ve), 128.8 (+ve), 143.4, 167.5.

4.2.7. (2*S*,1′*R*)-2-(1′-Phenylethylcarbamoyl)pyrrolidinium bromide 4g. Yield, 52%; white crystalline solid; mp: 108–110 °C; R_f 0.2 (methanol/chloroform, 1:99); MS (*m*/*z*) FAB: 219 (M^+); $[\alpha]_D^{20} = +39.0$ (*c* 0.34, MeOH); IR (KBr): 1672, 2979, 3071, 3274 cm^{-1}; ^1H NMR (D_2O): δ 1.37 (d, 3H, $J = 6.9$ Hz, CH_3), 1.86–2.05 (m, 3H, CH_2), 2.34–2.41 (m, 1H, CH_2), 3.24–3.35 (m, 2H, CH_2), 4.22–4.27 (m, 1H, CH), 4.84 (q, 1H, $J = 6.9$ Hz, CH); ^1H NMR ($CDCl_3$): δ 1.51 (d, 3H, $J = 6.9$ Hz, CH_3), 1.90–1.98 (m, 4H, CH_2 and NH), 2.49–2.57 (m, 1H, CH_2), 3.18–3.25 (m, 1H, CH_2), 3.29–3.35 (m, 1H, CH_2), 4.73–4.77 (m, 1H, CH), 4.86 (t, 1H, $J = 7.2$ Hz, CH), 7.21–7.38 (m, 5H, ArH), 8.63 (d, 1H, $J = 7.2$ Hz, NH); ^{13}C DEPT NMR ($CDCl_3$): δ 22.5 (+ve), 24.2 (−ve), 30.8 (−ve), 46.8 (−ve), 50.3 (+ve), 59.7 (+ve), 126.3 (+ve), 127.2 (+ve), 128.4 (+ve), 128.9 (+ve), 143.2, 167.8.

4.2.7.1. X-ray analysis of compound 4g. The diffraction data were obtained with graphite-monochromated Mo Kα radiation on Nonius MACH3 diffractometer at 293(2) K. Standard reflection for each data set showed no significant decrease in intensity through the acquisition. The structure was solved by direct method and refined by full matrix least square on F. The crystallographic calculations were performed using Argus (Nonius, MACH3 software) for data collection, and cell refinement, and Maxus (Nonius software) for data reduction. SHELXS-97 software was used for structure solution and refinement. Crystal data: $C_{13}H_{19}BrN_2O$ $M = 299.21$, orthorhombic, $P\ 2_1\ 2_1\ 2_1$, $a = 5.3300(7)$ Å, $b = 11.2870(9)$ Å, $c = 23.603(2)$ Å, $\beta = 90.00°$, $V = 1419.9(3)$ $Å^3$, $T = 293(2)$ K, μ(Mo Kα) = 2.883 cm^{-1}, $R = 0.0597$, $R_w = 0.1388$, GOF = 1.073, 1490 unique reflections with $[I > 2\sigma(I)]$. The details of the crystal data have been deposited with Cambridge Crystallographic Data Centre as supplementary publication No. CCDC-616021.

4.2.8. (2*S*,1′*R*)-2-(1′-Phenylpropylcarbamoyl)pyrrolidinium bromide 4h. Yield, 55%; low melting yellow solid; R_f 0.2 (methanol/chloroform, 1:99); MS (*m*/*z*) FAB: 233 (M^+); $[\alpha]_D^{20} = +42.0$ (*c* 0.39, MeOH); IR (neat) 1675, 2967, 3062, 3208 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.89 (t, 3H, $J = 7.2$ Hz, CH_3), 1.75–2.00 (m, 6H, CH_2 and NH), 2.54–2.58 (m, 1H, CH_2), 3.16–3.22 (m, 1H, CH_2), 3.28–3.34 (m, 1H, CH_2), 4.62 (q, 1H, $J = 7.2$ Hz, CH), 4.79–4.82 (m, 1H, CH), 7.18–7.38 (m, 5H, ArH), 8.75 (d, 1H, $J = 8.1$ Hz, NH); ^{13}C DEPT NMR ($CDCl_3$): 11.0 (+ve), 24.3 (−ve), 29.6 (−ve), 31.1 (−ve), 46.9 (−ve), 56.5 (+ve), 59.8 (+ve), 126.9 (+ve), 127.0 (+ve), 128.3 (+ve), 142.2, 168.1.

4.2.9. (*S*)-2-(Pyridinium-2′-ylcarbamoyl)pyrrolidinium dibromide 4i. Yield, 60%; brown liquid; R_f 0.2 (methanol/chloroform, 1:99); MS (*m*/*z*) FAB: 192 (M^+); $[\alpha]_D^{20} = +1.5$ (*c* 0.80, MeOH); IR (neat): 1640, 1745, 3418 cm^{-1}; IR (neat): ^1H NMR (D_2O): δ 2.00–2.17 (m, 3H, CH_2), 2.37–2.42 (m, 1H, CH_2), 3.34–3.46 (m, 2H, CH_2), 4.31 (t, 2H, $J = 7.8$ Hz, CH), 6.90 (t, 1H, $J = 6.9$ Hz, PyH), 7.02 (d, 1H, $J = 8.1$ Hz, PyH), 7.78 (d, 2H, $J = 6.9$ Hz, PyH), 7.90 (t, 1H, $J = 8.1$ Hz, PyH); ^{13}C DEPT NMR ($CDCl_3$ + DMSO-d_6): δ 22.3 (−ve), 27.3 (−ve), 44.7 (−ve), 58.2 (+ve), 111.0 (+ve), 112.9 (+ve), 133.7 (+ve), 142.4 (+ve), 153.1, 169.4.

4.2.10. (*S*)-2-(Pyridinium-3′-ylcarbamoyl)pyrrolidinium dibromide 4j. Yield, 62%; sticky solid; R_f 0.2 (methanol/

chloroform, 1:99); MS (*m/z*) FAB: 192 (M^+); $[\alpha]_D^{20} = +4.0$ (*c* 0.70, MeOH); IR (neat): 1530, 1650, 2410, 2990, 3010 cm^{-1}; ^1H NMR (D_2O): δ 2.12–2.30 (m, 3H, CH_2), 2.57–2.62 (m, 1H, CH_2), 3.46–3.57 (m, 2H, CH_2), 4.66 (dd, 1H, $J = 9.0$ and 6.6 Hz, CH), 8.03–8.08 (dd, 1H, $J = 8.5$ and 6.3 Hz, PyH), 8.51–8.55 (d, 2H, $J = 8.5$ Hz, PyH), 8.57–8.60 (m, 1H, PyH), 9.27 (diffused d, 1H, $J = 2.4$ Hz, PyH); ^{13}C DEPT NMR ($CDCl_3$ + DMSO-d_6): δ 23.6 (−ve), 29.7 (−ve), 55.1 (−ve), 59.8 (+ve), 127.9 (+ve), 132.2 (+ve), 135.0 (+ve), 137.5 (+ve), 137.6, 168.0.

4.2.11. (*S*)-2-(Pyridinium-4′-ylcarbamoyl)pyrrolidinium dibromide 4k. Yield, 60%; brown liquid; R_f 0.2 (methanol/chloroform, 1:99); MS (*m/z*) FAB: 192 (M^+); $[\alpha]_D^{20} = +2.5$ (*c* 0.65, MeOH); ^1H NMR (D_2O): δ 2.00–2.30 (m, 3H, CH_2), 2.56–2.64 (m, 1H, CH_2), 3.41–3.57 (m, 2H, CH_2), 4.64–4.81 (m, 1H, CH), 8.08 (d, 2H, $J = 7.2$ Hz, PyH), 8.61 (d, 2H, $J = 7.2$ Hz, PyH); ^{13}C DEPT NMR ($CDCl_3$ + DMSO-d_6): δ 23.1 (−ve), 29.3 (−ve), 45.6 (−ve), 59.7 (+ve), 114.4 (+ve), 135.0 (+ve), 143.5 (+ve), 150.3, 170.4.

4.2.12. (*S*)-2-(Butylcarbamoyl)pyrrolidinium bromide 4l. Yield, 65%; pale yellow liquid; R_f 0.4 (methanol/chloroform, 1:99); MS (*m/z*) FAB: 171 (M^+); $[\alpha]_D^{20} = -14.5$ (*c* 0.29, MeOH); IR (neat): 1667, 2931, 3221, 3406 cm^{-1}; ^1H NMR (D_2O): δ 0.87–0.95 (diffused t, $J = 7.5$ Hz, 3H, CH_3), 1.26–1.43 (m, 2H, CH_2), 1.59–1.81 (m, 2H, CH_2), 1.98–2.09 (m, 3H, CH_2), 2.39–2.50 (m, 1H, CH_2), 3.16–3.33 (m, 2H, CH_2), 3.38–3.55 (m, 2H, CH_2), 4.32–4.36 (m, 1H, CH); ^{13}C DEPT NMR ($CDCl_3$): δ 13.5 (+ve), 19.6 (−ve), 24.6 (−ve), 27.5 (−ve), 28.5 (−ve), 40.3 (−ve), 47.1 (−ve), 59.7 (+ve), 168.3.

4.2.13. (*S*)-2-(Hexylcarbamoyl)pyrrolidinium bromide 4m. Yield, 65%; brown liquid; R_f 0.4 (methanol/chloroform, 1:99); MS (*m/z*) FAB: 199 (M^+); $[\alpha]_D^{20} = -21.0$ (*c* 0.27, MeOH); IR (neat): 1675, 2930, 3223 cm^{-1}; ^1H NMR (D_2O): δ 0.87 (diffused t, 3H, $J = 6.6$ Hz, CH_3), 1.26–1.34 (m, 6H, CH_2), 1.40–1.60 (m, 2H, CH_2), 1.99–2.06 (m, 3H, CH_2), 2.38–2.44 (m, 1H, CH_2), 3.15–3.40 (m, 2H, CH_2), 3.33–3.43 (m, 2H, CH_2), 4.24–4.29 (m, 1H, CH); ^{13}C DEPT NMR ($CDCl_3$): δ 13.9 (+ve), 22.4 (−ve), 24.5 (−ve), 26.5 (−ve), 29.0 (−ve), 30.8 (−ve), 31.3 (−ve), 39.9 (−ve), 46.9 (−ve), 59.8 (+ve), 169.1.

4.2.14. (*S*)-2-(Heptylcarbamoyl)pyrrolidinium bromide 4n. Yield, 65%; yellow solid, mp: 90–92 °C; R_f 0.4 (methanol/chloroform, 1:99); MS (*m/z*) FAB: 213 (M^+); $[\alpha]_D^{20} = -29.0$ (*c* 1.43, MeOH); IR (neat): 1672, 2930, 3214 cm^{-1}; ^1H NMR (D_2O): δ 0.84–0.89 (diffuse t, 3H, CH_3), 1.15–1.38 (m, 8H, CH_2), 1.44–1.62 (m, 2H, CH_2), 1.90–2.10 (m, 3H, CH_2), 2.37–2.48 (m, 1H, CH_2), 3.16–3.34 (m, 2H, CH_2), 3.51–3.65 (m, 2H, CH_2), 4.27–4.34 (m, 1H, CH); ^{13}C DEPT NMR ($CDCl_3$): δ 13.9 (+ve), 22.4 (−ve), 24.7 (−ve), 26.8 (−ve), 28.8 (−ve), 30.9 (−ve), 31.6 (−ve), 32.3 (−ve), 40.1 (−ve), 46.9 (−ve), 59.7 (+ve), 168.2.

4.2.15. (*S*)-2-(Octylcarbamoyl)pyrrolidinium bromide 4o. Yield, 59%; pale yellow liquid; R_f 0.3 (methanol/chloroform, 1:99); MS (*m/z*) FAB: 227 (M^+); $[\alpha]_D^{20} = -19.0$ (*c* 0.52, MeOH); IR (neat): 1675, 2927, 3222 cm^{-1}; ^1H NMR (D_2O): δ 0.84–0.88 (diffuse t, 3H, CH_3), 1.25–1.32 (m, 10H, CH_2), 1.48–1.57 (m, 2H, CH_2), 2.01–2.10 (m, 3H, CH_2), 2.40–2.48 (m, 1H, CH_2), 3.14–3.34 (m, 2H, CH_2), 3.35–3.47 (m, 2H, CH_2), 4.31–4.36 (m 1H, CH); ^{13}C DEPT NMR ($CDCl_3$): δ 13.9 (+ve), 22.5 (−ve), 24.4 (−ve), 26.8 (−ve), 29.0 (−ve), 29.1 (−ve), 30.9 (−ve), 31.7 (−ve), 40.1 (−ve), 46.9 (−ve), 59.7 (+ve), 168.4.

4.2.16. (*S*)-2-(1′-Methylheptylcarbamoyl)pyrrolidinium bromide 4p. Yield, 61%; yellow solid, mp: 118–120 °C; R_f 0.4 (methanol/chloroform, 1:99); MS (*m/z*) FAB: 227 (M^+); $[\alpha]_D^{20} = -15.5$ (*c* 0.62, MeOH); IR (neat): 1670, 2933, 3216, 3412 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.16–1.43 (m, 7H, CH_2 and CH_3), 1.56–1.91 (m, 4H, CH_2 and CH_3), 2.01–2.15 (m, 3H, CH_2), 2.64–2.70 (m, 1H, CH_2), 3.43–3.46 (m, 1H, CH_2), 3.56–3.59 (m, 1H, CH_2), 3.60–3.78 (m, 1H, CH), 4.77–4.83 (m, 1H, CH), 8.09 (d, 1H, $J = 7.8$ Hz, NH); ^{13}C DEPT NMR ($CDCl_3$): δ 24.3, 24.4, 24.7, 24.8, 25.2, 30.7, 31.1, 32.3, 32.4, 47.1, 49.6, 59.7, 167.5.

4.2.17. (*S*)-2-(*N*,*N*-Dimethylcarbamoyl)pyrrolidinium bromide 4q. Yield, 55%; brown liquid; R_f 0.4 (methanol/chloroform, 1:99); MS (*m/z*) FAB: 143 (M^+); $[\alpha]_D^{20} = -41.0$ (*c* 0.44, MeOH); IR (neat): 1660, 2400, 2995, 3015, 3130 cm^{-1}; ^1H NMR ($CDCl_3$ + DMSO-d_6): δ 1.61–1.94 (m, 4H, CH_2 and NH), 2.85–2.95 (m, 2H, CH_2), 2.98 (s, 3H, CH_3), 3.03 (s, 3H, CH_3), 3.06–3.22 (m, 1H, CH_2), 4.00 (t, 1H, $J = 6.3$ Hz, CH); ^{13}C DEPT NMR ($CDCl_3$): δ 24.7 (+ve), 29.3 (+ve), 36.1 (−ve), 36.8 (−ve), 46.5 (−ve), 58.0 (−ve), 168.5.

4.2.18. (*S*)-2-(*N*,*N*-Diethylcarbamoyl)pyrrolidinium bromide 4r. Yield, 55%; brown liquid; R_f 0.4 (methanol/chloroform, 1:99); $[\alpha]_D^{20} = -41.6$ (*c* 0.31, MeOH); ^1H NMR ($CDCl_3$): δ 1.15 (t, 3H, $J = 7.2$ Hz, CH_3), 1.28 (t, 3H, $J = 7.2$ Hz, CH_3), 1.77 (br s, 1H, NH), 1.84–1.96 (m, 1H, CH_2), 2.02–2.13 (m, 1H, CH_2), 2.20–2.92 (m, 1H, CH_2), 2.53–2.60 (m, 1H, CH_2), 3.30–3.53 (m, 5H, CH_2), 3.58–3.75 (m, 1H, CH_2), 4.81 (br t, 1H, CH); ^{13}C DEPT NMR ($CDCl_3$): δ 12.6 (+ve), 14.0 (+ve), 25.0 (−ve), 30.1 (−ve), 40.7 (−ve), 41.7 (−ve), 46.7 (−ve), 58.3 (+ve), 167.2.

4.2.19. (*S*)-2-(*N*,*N*-Dipropylcarbamoyl)pyrrolidinium bromide 4s. Yield, 60%; pale yellow liquid; R_f 0.4 (methanol/chloroform, 1:99); MS (*m/z*) FAB: 199 (M^+); $[\alpha]_D^{20} = -40.0$ (*c* 0.33, MeOH); IR (neat): 1625, 2400, 2980, 3420, 3460 cm^{-1}; ^1H NMR (D_2O): δ 0.67–0.76 (m, 6H, CH_3), 1.39–1.52 (m, 4H, CH_2), 1.76–1.94 (m, 3H, CH_2), 2.37–2.45 (m, 1H, CH_2), 2.97–3.35 (m, 6H, CH_2), 4.53 (t, 1H, $J = 8.1$ Hz, CH); ^{13}C DEPT NMR ($CDCl_3$): δ 11.2 (+ve), 20.5 (−ve), 21.8 (−ve), 25.1 (−ve), 30.2 (−ve), 46.7 (−ve), 47.8 (−ve), 49.0 (−ve), 58.2 (+ve), 167.6.

4.2.20. (*S*)-2-(*N*,*N*-diisopropylcarbamoyl)pyrrolidinium bromide 4t. Yield, 65%; sticky yellow solid; R_f 0.4 (methanol/chloroform, 1:99); MS (*m/z*) FAB: 198 (M^+); $[\alpha]_D^{20} = -18.0$ (*c* 1.19, MeOH); IR (neat): 1671, 2933, 3215 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.12–1.39 (m, 6H, CH_3), 1.56–1.98 (m,

7H, CH_3 and NH), 1.98–2.22 (m, 3H, CH_2), 2.64–2.72 (m, 1H, CH_2), 3.20–3.35 (m, 1H, CH), 3.40–3.48 (m, 1H, CH_2), 3.50–3.61 (m, 1H, CH_2), 3.62–3.78 (m, 1H, CH), 4.81–4.88 (m, 1H, CH); ^{13}C DEPT NMR ($CDCl_3$): δ 24.2 (+ve), 24.5 (+ve), 24.7 (+ve), 25.1 (+ve), 30.6 (+ve), 31.0 (+ve), 32.3 (+ve), 47.1 (−ve), 49.5 (−ve), 59.6 (−ve), 167.4.

4.2.21. (*S*)-2-(*N*,*N*-Dibutylcarbamoyl)pyrrolidinium bromide 4u. Yield, 60%; pale yellow liquid; R_f 0.4 (methanol/chloroform, 1:99); MS (*m*/*z*) FAB: 227 (M^+); $[\alpha]_D^{20} = -38.0$ (*c* 0.33, MeOH); IR (neat): 1650, 2926, 3403 cm^{-1}; ^{1}H NMR (D_2O): δ 0.70–0.77 (m, 6H, CH_3), 1.10–1.19 (m, 4H, CH_2), 1.31–1.47 (m, 4H, CH_2), 1.77–1.93 (m, 3H, CH_2), 2.30–2.42 (m, 1H, CH_2), 3.05–334 (m, 6H, CH_2), 4.84 (t, 1H, $J = 8.4$ Hz, CH); ^{13}C DEPT NMR ($CDCl_3$): δ 12.6 (+ve), 18.5 (−ve), 18.6 (−ve), 18.7 (−ve), 23.3 (−ve), 28.0 (−ve), 28.7 (−ve), 29.3 (−ve), 44.5 (−ve), 45.6 (−ve), 46.0 (−ve), 57.0 (+ve), 166.7.

4.2.22. (*S*)-2-(*N*,*N*-Dihexylcarbamoyl)pyrrolidinium bromide 4v. Yield, 58%; yellow sticky solid; R_f 0.4 (methanol/chloroform, 1:99); MS (*m*/*z*) FAB: 283 (M^+); $[\alpha]_D^{20} = -17.5$ (*c* 0.68, MeOH); IR (neat): 1671, 2857, 2934, 3214 cm^{-1}; ^{1}H NMR (D_2O): δ 0.98–1.21 (m, 11H, CH_3 and CH_2), 1.38–1.72 (m, 10H, CH_2), 1.82–1.92 (m, 6H, CH_2), 2.20–2.29 (m, 1H, CH_2), 2.90–3.50 (m, 4H, CH_2), 4.09–4.14 (m, 1H, CH); ^{13}C DEPT NMR ($CDCl_3$): δ 24.2 (−ve), 24.3 (−ve), 24.4 (−ve), 24.6 (−ve), 24.7 (−ve), 25.1 (−ve), 30.6 (−ve), 31.0 (−ve), 32.1 (−ve), 32.2 (−ve), 47.2 (−ve), 49.4 (+ve), 51.0 (+ve), 59.6 (+ve), 167.5.

4.2.23. (*S*)-2-(*N*,*N*-Dioctylcarbamoyl)pyrrolidinium bromide 4w. Yield, 68%; yellow solid, mp: 110–114 °C; R_f 0.4 (methanol/chloroform, 1:99); MS (*m*/*z*) FAB: 339 (M^+); $[\alpha]_D^{20} = -26.0$ (*c* 0.49, MeOH); IR (neat): 1670, 2932, 3214 cm^{-1}; ^{1}H NMR (D_2O): δ 0.84–1.25 (m, 15H, CH_3 and CH_2), 1.36–1.73 (m, 12H, CH_2), 1.76–1.94 (m, 7H, CH_2), 2.19–2.28 (m, 1H, CH_2), 2.90–3.10 (m, 1H, CH_2), 3.18–3.31 (m, 2H, CH_2), 3.40–3.50 (m, 1H, CH_2), 4.09–4.14 (m, 1H, CH); ^{13}C DEPT NMR ($CDCl_3$): δ 23.6 (−ve), 23.8 (−ve), 24.3 (−ve), 24.8 (−ve), 30.1 (−ve), 30.2 (−ve), 31.9 (−ve), 38.9 (−ve), 39.2 (−ve), 39.5 (−ve), 39.7 (−ve), 40.0 (−ve), 45.8 (−ve), 48.4 (+ve), 49.9 (+ve), 58.9 (+ve), 166.6.

4.2.24. (*S*)-2-(Pyrrolidine-1′-carbonyl)pyrrolidinium bromide 4x. Yield, 50%; brown liquid; R_f 0.4 (methanol/chloroform, 1:99); MS (*m*/*z*) FAB: 169 (M^+); $[\alpha]_D^{20} = -55.5$ (*c* 0.80, MeOH); IR (neat): 1649, 2940, 3406 cm^{-1}; ^{1}H NMR δ (D_2O) 1.88–2.12 (m, 7H, CH_2), 2.51–2.58 (m, 1H, CH_2), 3.35–3.60 (m, 6H, CH_2), 4.57 (t, 1H, $J = 6.9$ Hz, CH); ^{13}C DEPT NMR ($CDCl_3$): δ 23.6 (−ve), 24.1 (−ve), 25.5 (−ve), 28.5 (−ve), 46.3 (−ve), 46.4 (−ve), 46.5 (−ve), 58.9 (+ve), 166.2.

4.2.25. (S)-2-(Piperidine-1′-carbonyl)pyrrolidinium bromide 4y. Yield, 55%; brown liquid; R_f 0.4 (methanol/chloroform, 1:99); MS (*m*/*z*) FAB: 183 (M^+); $[\alpha]_D^{20} = -53.0$ (*c* 0.54, MeOH); IR (neat): 1645, 2939, 3424 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.56–1.76 (m, 6H), 1.87–1.93 (m, 1H, CH_2), 2.01–2.12 (m, 1H, CH_2), 2.14–2.25 (m, 1H, CH_2), 2.50–2.62 (m, 1H, CH_2), 3.43–3.62 (m, 6H, CH_2), 4.91 (t, 1H, $J = 6.6$ Hz, CH); ^{13}C DEPT NMR ($CDCl_3$): δ 21.0 (−ve), 22.9 (−ve), 23.3 (−ve), 24.2 (−ve), 24.9 (−ve), 28.5 (−ve), 42.7 (−ve), 45.5 (−ve), 45.7 (−ve), 57.4 (+ve), 165.3.

4.3. Synthesis of (2*S*,1′*R*)-2-(1′-Phenylethylcarbamoyl)-pyrrolidinium chloride 6

To a mixture of **4g** (1 g, 3.3 mmol) in ether (15 mL), triethyl amine (0.37 g, 3.6 mmol) was added and stirred for 3 h. The reaction mixture was filtered and evaporated to obtain the crude product. Column chromatography (60–120 mesh silica) of the crude product using ethyl acetate yielded an acid free amide as a yellow thick liquid (78% yield). The ether solution of acid free amide was stirred with concentrated HCl (5.0 mmol of 37% HCl) for 3 h. The evaporation of the solvent under reduced pressure gave the crude product, which on column chromatography (60–120 mesh silica) using increasing concentration of methanol in dichloromethane (1–5%) as eluent gave (2*S*,1′*R*)-2-(1′-phenylethylcarbamoyl)pyrrolidinium chloride as pure product (0.56 g).

4.3.1. (2*S*,1′*R*)-2-(1′-Phenylethylcarbamoyl)pyrrolidinium chloride 6d. Yield, 65%; yellow thick liquid; R_f 0.3 (methanol/chloroform, 1:99); MS (*m*/*z*) FAB: 219 (M^+); $[\alpha]_D^{20} = -37.0$ (*c* 0.32, MeOH); ^{1}H NMR (D_2O): δ 1.49 (d, 3H, $J = 7.2$ Hz, CH_3), 2.04–2.17 (m, 3H, CH_2), 2.45–2.2.53 (m, 1H, CH_2), 3.36–3.47 (m, 2H, CH_2), 4.45 (t, 1H, $J = 7.5$ Hz, CH), 4.92 (q, 1H, $J = 6.6$ Hz, CH), 7.18–7.30 (m, 5H, ArH), 8.52 (d, 1H, $J = 7.5$ Hz, NH); ^{13}C DEPT NMR ($CDCl_3$): δ 22.5 (+ve), 24.2 (−ve), 30.7 (−ve), 46.1 (−ve), 50.1 (+ve), 59.7 (+ve), 126.3 (+ve), 127.0 (+ve), 128.5 (+ve), 143.3, 167.9.

4.4. Synthesis of (2*S*,1′*R*)-2-(1′-phenylethylcarbamoyl)-pyrrolidinium trifluoroacetate 7

To an ice cold stirred solution of Boc-proline (1 g, 4.6 mmol), and (*R*)-1-phenylethylamine (4.6 mmol) in dichloromethane (15 mL), a solution of dicyclohexylcarbodiimide (4.6 mmol) in dichloromethane was added dropwise followed by the addition of a catalytic amount of DMAP. The resulting mixture was stirred and the temperature of the reaction mixture was allowed to rise to room temperature. The progress of the reaction was monitored by TLC (R_f 0.4, ethyl acetate/hexane, 2:3). After completion of the reaction, the reaction mixture was filtered and evaporated to obtain crude product, which on column chromatography gave (2*S*,1′*R*)-2-(1′-phenylethylcarbamoyl)-*N*-(*tert*-butyl ester)prolinamide (1.3 g). To a mixture of (2*S*,1′*R*)-2-(1′-phenylethylcarbamoyl)-*N*-(*tert*-butyl ester)prolinamide (1.3 g, 4.03 mmol) and dichloromethane (15 mL), trifluoroacetic acid (0.48 g, 4.03 mmol) was added and stirred for 6 h. The reaction was stopped the solvent removed under reduced pressure to obtain the crude product as a thick liquid. The column chromatography (60–120 mesh silica) of the crude using ethyl acetate followed by a mixture of chloroform with increasing concentration of methanol (1–5%) as eluent gave the (2*S*,1′*R*)-2-(1′-phenylethylcarbamoyl)pyrrolidinium trifluoroacetate as pure product (0.71 g).

4.4.1. (2*S*,1′*R*)-2-(1′-Phenylethylcarbamoyl)pyrrolidinium trifluoroacetate 7. Yield, 65%; white crystalline solid; mp: 118–120 °C; R_f 0.3 (methanol/chloroform, 1:99); MS (*m*/*z*) FAB: 219 (M^+); $[\alpha]_D^{20} = +29.5$ (*c* 0.15, MeOH); ^{1}H NMR ($CDCl_3$): δ 1.44 (d, 3H, $J = 6.9$ Hz, CH_3), 1.80–1.88 (m, 4H, CH_2 and NH), 2.00–2.30 (m, 1H, CH_2), 3.16–3.24 (m, 2H, CH_2), 4.34–4.39 (m, 1H, CH), 4.95 (q, 1H, $J = 6.6$ Hz, CH), 7.35–7.50 (m, 5H, ArH); ^{13}C DEPT NMR ($CDCl_3$): δ 21.8 (+ve), 24.2 (−ve), 29.8 (−ve), 46.1 (−ve), 50.0 (+ve), 59.5 (+ve), 126.0 (+ve), 127.3 (+ve), 128.6 (+ve), 142.9, 167.5.

4.4.1.1. X-ray analysis of compound 7. The diffraction data were obtained with graphite-monochromated Mo Kα radiation on CrysAlis RED, Oxford CCD diffractometer at 293(2) K. Standard reflection for each data set showed no significant decrease in intensity through the acquisition. The structure was solved by direct method and refined by full matrix least square on F. The crystallographic calculations were performed using CrysAlis CCD for data collection, CrysAlis RED for cell refinement and data reduction. SHELXS-97 software was used for structure solution and refinement. The structure shows the entrapment of the solvent benzene. Crystal data: $C_{15}H_{19}F_3N_2O_2$ $M = 332.32$, tetragonal, *P* 4(1)2(1)2, $a = 9.454(2)$ Å, $b = 9.474(3)$ Å, $c = 42.490(13)$ Å, $\beta = 89.74(2)°$, $V = 3805.7(19)$ Å^3, $T = 293(2)$ K, μ(Mo Kα) = 0.108 cm^{-1}, $R = 0.0664$, $R_w = 0.1722$, GOF = 0.752, 21565 unique reflections with $[I > 2\sigma(I)]$. The details of the crystal data have been deposited with Cambridge Crystallographic Data Centre as supplementary publication No. CCDC-616022.

4.5. General procedure for the organocatalyzed direct asymmetric aldol reaction of acetone 2 with 4-nitrobenzaldehyde 1a in water

To a stirring mixture of **1a** (302 mg, 2 mmol), **2** (20 mmol) and water (3 mL), the respective organocatalyst (20 mole%) was added. The reaction was monitored by TLC and quenched with saturated ammonium chloride solution (15 mL) on completion and extracted with CH_2Cl_2 (2 × 25 mL). The organic layer was dried over anhydrous Na_2SO_4 and distilled to obtain crude product. Column chromatography of the crude on silica gel (60–120 mesh) using mixture of ethyl acetate and hexane in varying proportions as eluent, gave pure product **3a**. The enantiomeric excess of **3a** was determined on HPLC using a Chiralpak AS-H column and mixture of IPA and hexane in ratio of 15:85 as eluents.

4.5.1. (*R*)-4-Hydroxy-4-(4′-nitrophenyl)butan-2-one 3a.[10] Yield, 83%; $[\alpha]_D^{25} = +30.0$ (*c* 1.24, CH_2Cl_2); enantiomeric excess: 46%, determined by HPLC (Diacel Chiralpak AS-H, *i*-PrOH/hexane 15:85), UV 254 nm, flow rate 1.0 mL/min. *R*-isomer, t_R 13.7 min and *S*-isomer, t_R 19.4 min.

4.5.2. (*R*)-4-Hydroxy-4-(2′-nitrophenyl)butan-2-one 3b.[10] Yield, 93%; $[\alpha]_D^{25} = -89.0$ (*c* 0.34, CH_2Cl_2); enantiomeric excess: 62%, determined by HPLC (Diacel Chiralpak AS-H, *i*-PrOH/hexane 30:80), UV 254 nm, flow rate 1.0 mL/min. *R*-isomer, t_R 7.8 min and *S*-isomer, t_R 6.7 min.

4.5.3. (*R*)-4-Hydroxy-4-(3′-nitrophenyl)butan-2-one 3c.[10] Yield, 68%; $[\alpha]_D^{25} = +35.0$ (*c* 1.14, CH_2Cl_2); enantiomeric excess: 47%, determined by HPLC (Diacel Chiralpak AS-H, *i*-PrOH/hexane 30:70), UV 254 nm, flow rate 1.0 mL/min. *R*-isomer, t_R 14.1 min and *S*-isomer, t_R 17.6 min.

4.5.4. (*R*)-4-Hydroxy-4-(4′-chlorophenyl)butan-2-one 3d.[10] Yield, 30%; $[\alpha]_D^{25} = +24.4$ (*c* 0.94, CH_2Cl_2); enantiomeric excess: 36%, determined by HPLC (Diacel Chiralpak AS-H, *i*-PrOH/hexane 15:85), UV 254 nm, flow rate 1.0 mL/min. *R*-isomer, t_R 11.1 min and *S*-isomer, t_R 13.9 min.

4.5.5. (*R*)-4-Hydroxy-4-(2′-chlorophenyl)butan-2-one 3e.[10] Yield, 80%; $[\alpha]_D^{25} = +50.0$ (*c* 1.07, CH_2Cl_2); enantiomeric excess: 41%, determined by HPLC (Diacel Chiralpak AS-H, *i*-PrOH/hexane 15:85), UV 262 nm, flow rate 1.0 mL/min. *R*-isomer, t_R 8.7 min and *S*-isomer, t_R 9.3 min.

4.5.6. (*R*)-4-Hydroxy-4-(4′-fluorophenyl)butan-2-one 3h.[10] Yield, 23%; $[\alpha]_D^{25} = +25.9$ (*c* 1.24, CH_2Cl_2); enantiomeric excess: 37%, determined by HPLC (Diacel Chiralpak AS-H, *i*-PrOH/hexane 15:85), UV 257 nm, flow rate 1.0 mL/min. *R*-isomer, t_R 6.5 min and *S*-isomer, t_R 7.6 min.

4.5.7. (*R*)-4-Hydroxy-4-(4′-cyanophenyl)butan-2-one 3i.[10] Yield, 92%; $[\alpha]_D^{25} = +27.0$ (*c* 0.94, CH_2Cl_2); enantiomeric excess: 36%, determined by HPLC (Diacel Chiralpak AS-H, *i*-PrOH/hexane 15:85), UV 254 nm, flow rate 1.0 mL/min. *R*-isomer, t_R 8.4 min and *S*-isomer, t_R 15.1 min.

4.5.8. (*R*)-4-Hydroxy-4-phenylbutan-2-one 3j.[10] Yield, 30%; $[\alpha]_D^{25} = +26.5$ (*c* 0.40, CH_2Cl_2); enantiomeric excess: 37%, determined by HPLC (Diacel Chiralpak AS-H, *i*-PrOH/hexane 20:80), UV 257 nm, flow rate 1.0 mL/min. *R*-isomer, t_R 8.4 min and *S*-isomer, t_R 9.9 min.

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References

1. (a) Li, C.-J. *Chem. Rev.* **2005**, *105*, 3095–3165; (b) Lindstrom, U. M. *Chem. Soc. Rev.* **2002**, *102*, 2751–2772; (c) Li, C.-J.; Chan, T.-H. *Organic Reactions in Aqueous Media*; John Wiley & Sons: New York, 1997; (d) Sinou, D. *Adv. Synth. Catal.* **2002**, *344*, 221–237.
2. (a) Li, C.-J.; Chen, L. *Chem. Soc. Rev.* **2006**, *35*, 68–82; (b) Lindstrom, U. M.; Andersson, F. *Angew. Chem., Int. Ed.* **2006**, *44*, 548–551; (c) Otto, S.; Engberts, J. B. F. N. *Org. Biomol. Chem.* **2003**, *1*, 2809–2820; (d) Chandler, D. *Nature* **2002**, *417*, 491.
3. (a) Breslow, R. *Acc. Chem. Res.* **1991**, *24*, 159–164; (b) Breslow, R.; Rideout, D. *J. Am. Chem. Soc.* **1980**, *102*, 7816–7817.

4. *Organic Synthesis in Water*; Grieco, P. S., Ed.; Blackie Academic and Professional: London, 1998.
5. (a) Nyberg, A. I.; Usano, A.; Pihko, P. M. *Synlett* **2004**, 1891–1896; (b) Torii, H.; Nakadai, M.; Ishihara, K.; Saito, S.; Yamamoto, H. *Angew. Chem., Int. Ed.* **2004**, *43*, 1983–1986.
6. (a) Dickerson, T. J.; Lovell, T.; Meijler, M. M.; Noodleman, L.; Janda, K. D. *J. Org. Chem.* **2004**, *69*, 6603–6609; (b) Roger, C. J.; Dickerson, T. J.; Janda, K. D. *Tetrahedron* **2006**, *62*, 352–356.
7. Chimni, S. S.; Mahajan, D. *Tetrahedron* **2005**, *61*, 5019–5025.
8. Robert, R. D.; Ferran, H. E.; Gula, J. M.; Spencer, T. A. *J. Am. Chem. Soc.* **1980**, *102*, 7054–7058.
9. Chimni, S. S.; Mahajan, D.; Babu, V. V. S. *Tetrahedron Lett.* **2005**, *46*, 5617–5619.
10. Tang, Z.; Jiang, F.; Cui, X.; Gong, L.-G.; Mi, A.-Q.; Jiang, Y.-Z.; Wu, Y.-D. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5755–5760.
11. The catalysts **4i**, **4j** and **4k** were obtained as their dibromide salt and used as such.
12. (a) List, B.; Lerner, R. A.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2000**, *122*, 2395–2396; (b) List, B.; Notz, W. *J. Am. Chem. Soc.* **2000**, *122*, 7386–7387; (c) Northrup, A. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 6798–6799; (d) Sakthivel, K.; Notz, W.; Bui, T.; Zhong, G.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2001**, *123*, 5260–5267.
13. (a) Machajewski, T. D.; Wong, C.-H. *Angew. Chem., Int. Ed.* **2000**, *39*, 1352–1374, and references cited therein; (b) Gijsen, H. J. M.; Qiao, L.; Fitz, W.; Wong, C.-H. *Chem. Rev.* **1996**, *96*, 443–473; (c) Wong, C.-H.; Whitesides, G. M. *Enzymes in Synthetic Organic Chemistry*; Pergamon: Oxford, 1994.
14. (a) Zhong, G.; Lerner, R. A.; Barbas, C. F., III. *Angew. Chem., Int. Ed.* **1999**, *38*, 3738–3741; (b) Hoffmann, T.; Zhong, G.; List, B.; Shabat, D.; Anderson, J.; Gramatikova, S.; Lerner, R. A.; Barbas, C. F., III. *J. Am. Chem. Soc.* **1998**, *120*, 2768–2779.
15. Mass, N.; Yusuke, N.; Ohara, N.; Yoda, H.; Takabe, K.; Tanaka, F.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2006**, *128*, 734–735.
16. (a) Mase, N.; Tanaka, F.; Barbas, C. F., III. *Org. Lett.* **2003**, *5*, 4369–4372; (b) Ji, C.; Peng, Y.; Huang, C.; Wang, N.; Jiang, Y. *Synlett* **2005**, *6*, 986–990; For protonated chiral diamines see: (c) Nakadai, M.; Saito, S.; Yamamoto, H. *Tetrahedron* **2002**, *58*, 8167–8177; (d) Nakadai, M.; Saito, S.; Yamamoto, H. *Synlett* **2001**, 1245–1248; (e) Saito, S.; Yamamoto, H. *Acc. Chem. Res.* **2004**, *37*, 570; For an excellent review on protonated chiral catalysts see: Bolm, C.; Rantanen, T.; Schiffers, I.; Zani, L. *Angew. Chem., Int. Ed.* **2005**, *44*, 1758–1763.
17. (a) Martin, H.; List, B. *Synlett* **2003**, 1901–1902; (b) Kofoed, J.; Nielsen, J.; Reymond, J.-L. *Biorg. Med. Chem. Lett.* **2003**, *13*, 2445–2447; (c) Tsogoeva, S. B.; Wei, S. *Tetrahedron: Asymmetry* **2005**, *16*, 1947–1951.
18. (a) Asami, M.; Ohno, H.; Kobayashi, S.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1978**, *51*, 1869–1873; (b) Mukaiyama, T.; Soai, K.; Saito, T.; Shimizu, H.; Suzuki, K. *J. Am. Chem. Soc.* **1979**, *101*, 1455–1460.