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Probing the Synergistic Catalytic Model: A Rationally Designed Urea-Tagged Proline Catalyst for the Direct Asymmetric Aldol Reaction

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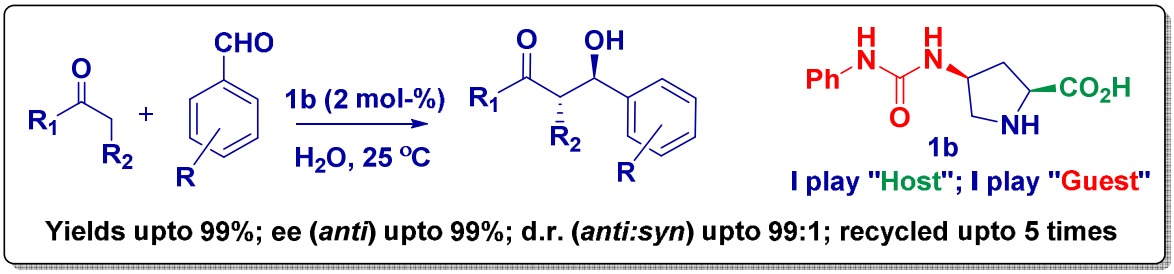


Abstract:

A urea tag was incorporated at the C-4 position of proline, *cis* to its COOH group, in order to explore the prospect of a synergistic effect between the two functional groups in the transition state of the enamine route to the asymmetric aldol reaction. The catalyst proved to be an excellent performer, delivering aldols in high yields and with excellent enantio- and diastereoselectivities using just 2 mol-% loading in the presence of water; it also exhibited good levels of recyclability under aqueous conditions. The favourable results reveal the interesting possibility of an intramolecular host-guest interaction between the urea and the amino acid moieties, exerting a beneficial effect on the catalysis. The concept could certainly offer a new direction toward more efficient catalyst design.

Introduction

The discovery of the proline catalysed direct asymmetric aldol reaction by List, Lerner and Barbas in 2000 would certainly go down as one of the landmark achievements of the century.[1] More than a decade and a half later, proline still reigns supreme as the organocatalytic model of choice for this quintessential C-C bond forming reaction, as is evident from the numerous proline-derived organocatalysts that populate the available asymmetric protocols.[2] Of late, asymmetric synthesis is witnessing the rapid rise of modularly designed organocatalysts (MDO's) and self-assembled supramolecular catalytic assemblies to leverage a synergistic effect of two individual catalytic moieties.[3] Cooperative catalysis, as this concept is termed, has also made its mark in the classic enamine route to the aldol reaction; a host of co-catalysts that include (thio)ureas,[4] BINOL,[5] guanidinium salts[6] and Bronsted acids[7,8] have been employed in combination with an amino acid – proline in most cases – to achieve a spike in the catalytic performance. On a parallel note, over the last few years amine-

thioureas and related compounds have undoubtedly had a huge impact in the field of asymmetric bifunctional catalysis, and their proficiency in promoting Michael addition reactions through a combination of enamine and hydrogen-bonding activation has been well established.[9] Therefore, amongst the co-catalysts mentioned above, the use of thioureas as a cooperative additive in the enamine route to the aldol reaction is particularly interesting.[4a-f] Demir & co-workers were the pioneers in this regard, utilizing a proline-thiourea combination for the first time in an asymmetric aldol reaction; the superior performance of their dual catalytic assembly in comparison to the parent amino acid provided an excellent illustration of synergistic catalysis. The authors proposed a specific host-guest interaction between the proline and the thiourea that operated favourably in the transition state to afford enhanced stereoselectivity even in an unconventional non-polar reaction medium.[4a,e] In a more recent study, they also showed that the model could be made to work efficiently in the presence of water by using a calixerane-linked thiourea as a hydrophobic co-catalyst.[4f] The inspirational work of Demir & co-workers entailed other reports of a similar kind, employing various thioureas as co-catalysts for the enamine mediated asymmetric aldol reaction, and also sparked mechanistic studies toward understanding and rationalizing the cooperative role of the thiourea additive.[10]

Excited by the dual catalytic host-guest complex theory and aspiring to extend our interest in proline based catalysis,[11] we pondered the design of a bifunctional catalyst that would have both the afore-mentioned features of host and guest implanted into a single molecular entity. Specifically, the idea was to construct a modular catalyst bearing a free amino acid moiety and a urea/thiourea functionality in optimal proximity, which we imagined could replicate the synergistic collaboration exhibited by two distinct molecular entities in the earlier reports. A more organized transition state might be anticipated for the asymmetric aldol reaction as a result of this intramolecular interaction, and enhanced activity and greater stereocontrol ought to ensue. Such a catalyst may be envisaged simply by incorporation of a urea/thiourea tag onto the 4-position of proline as depicted by **1** (**Figure 1**). The relative '*cis*' orientation of the cooperative moiety and the COOH group in **1** was perceived as vital for the interaction to take effect. In fact, favourable effects of appending influential groups – such as an ion-tag – *cis* to the reaction site of a proline derived catalyst for the asymmetric aldol reaction have been demonstrated and rationalized by Trombini & Lombardo and co-workers[12] and, more recently, by our group.[11a] The proposed '*cis*' urea/thiourea-tagged proline **1** presents itself therefore as a rational model to probe the idea of an inherent host-guest complex. Ureas/thioureas have previously been incoporated at the 4-position as a linker to attach the proline unit to a mesoporous support[13] or a cyclodextrin.[14] However, the focus of these reports, and the performance of these systems themselves, revolved around the heterogeneous appendage rather than the linker. It would thus be interesting to study the asymmetric aldol reaction catalysed by **1a**/**1b** in terms of any favourable effect as an upshot of a cooperative intramolecular interaction between the two distinct functional parts of the catalyst in the transition state. We herein present our efforts and the results obtained in this direction.

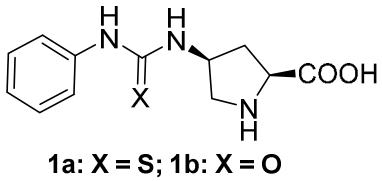
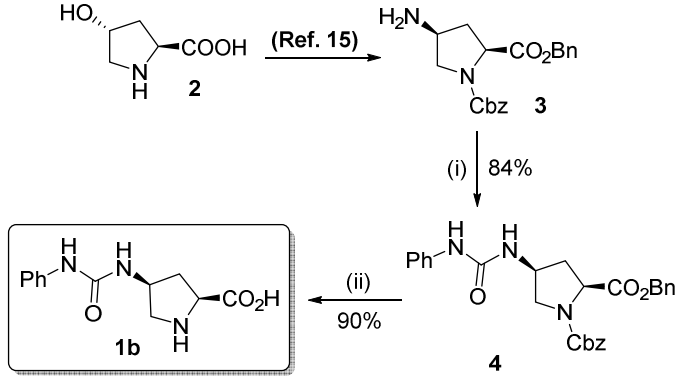


Figure 1. Proposed "*cis*" urea/thiourea tagged proline

Results and Discussion

Our endeavours started with a straightforward synthesis of the proposed proline-urea catalyst **1b**, illustrated in **Scheme 1**. Following a literature protocol,[15] *trans*-4-hydroxy-L-proline (**2**) was converted into the primary amine **3**, having the NH_2 and COOH groups *cis* to each other. Treating amine **3** with phenyl isocyanate in CH_2Cl_2 at room temperature afforded the catalyst precursor **4** bearing the desired urea substituent at the 4-position of proline. Finally, hydrogenolysis of **4** under the standard conditions exposed the amino acid and delivered the '*cis*' urea-tagged proline **1b**.

Scheme 1. Synthesis of the '*cis*' urea-tagged proline catalyst **1b**

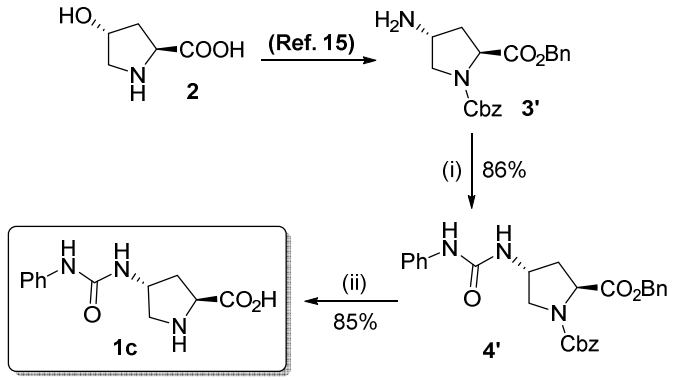


Reagents and conditions: (i) PhNCO, CH_2Cl_2 (84%); (ii) H_2, Pd/C (10%), MeOH, room temp., 4 h (90%).

The initial results obtained with the catalyst **1b** in the direct asymmetric aldol reaction of cyclohexanone (**5**) and *p*-nitrobenzaldehyde (**6a**) were quite promising. By employing just 5 mol-% of **1b** in the presence of 50 μL (ca. 1.2 equiv.) of water, a high yield of the aldol was obtained in only 6 h with very good diastereoselectivity and excellent enantioselectivity for the *anti* diastereomer (Table 1, entry 1). While the superiority of **1b** to proline itself is evident here, the result is also a significant improvement over the use of the proline-thiourea dual catalytic system, where a higher loading of the individual catalysts and a longer duration were required to achieve a similar level of performance, albeit under different reaction conditions.[4a] We were certainly delighted with the outcome since it lent weight to our assumption of an intramolecular host-guest interaction entailing a cooperative beneficial effect on the catalysis. On a further pleasing note, it was observed that the efficiency and selectivity of the catalyst remained largely undiminished even with just a 2 mol-% loading (entry 2). The result compares favourably with the use of proline based ion-tagged organocatalysts, which have come to be renowned for their exceptional performance in the direct asymmetric aldol reaction over

the past decade.[11a,12a,16] A more detailed comparative study was needed at this stage to corroborate the presence of the proposed intramolecular interaction and place our results in better perspective. A simple way to further substantiate our theory would be to compare the performance of **1b** with the corresponding '*trans*' urea-tagged proline catalyst, in which the proposed intramolecular interaction would be sterically complicated. This diastereomeric catalyst **1c** was synthesized by gaining access to the required *trans*-amine **3'** using a literature protocol, followed by a replication of the steps used for the conversion of **3** to catalyst **1b** (**Scheme 2**). The aldol reaction carried out using the '*trans*' catalyst **1c** was quite revealing; with a 2 mol-% loading and under identical conditions employed with **1b**, only a 45% yield of the aldol could be obtained, albeit accompanied by comparable stereoselectivity values (Table 1, entry 3). The steep drop (~50%) in the yield while using the '*trans*' urea-tagged proline **1c** provides a clear indication of a favourable intramolecular interaction between the amino acid and urea moieties in the diastereomer **1b**, where the *cis* relation between the two functional groups orients them proximal in space for the interaction to take effect. Furthermore, to gain a better perspective of the catalytic efficiency of **1b**, comparative studies under identical reaction conditions were taken up with proline as well as with the Demir-Rios proline-thiourea dual catalytic system,[4a,b] using two different thioureas – the unsubstituted 1,3-diphenyl thiourea (**I**) and (3,5-bistrifluoromethylphenyl)thiourea **II**. The use of proline resulted in only a 9% conversion (Table 1, entry 4); the combination of proline with **I** / **II** did not prove effective in mediating the aldol reaction either (Table 1, entries 5 & 6). This could perhaps be due to the minimal interaction of the principal catalyst – the highly hydrophilic amino acid – with the substrates in the presence of water, leaving no role for the secondary catalysts **I** / **II**. We therefore conducted additional experiments with these systems in the absence of water. As expected, the conversion shot up several notches, but yet did not match up to the efficiency of **1b**, while there was also a dip in the stereochemical performance (Table 1, entries 7 & 8). The results provide further evidence of the proposed synergistic host-guest interaction in operation in **1b**; they also place added emphasis on the design of suitably derivatised prolines such as **1b** to achieve optimum results for the asymmetric aldol reaction in the presence of water. It is perhaps pertinent to add here that thiourea-tagged catalyst **1a** (**Figure 1**) could not be accessed by an analogous synthetic route; the

Scheme 2. Synthesis of the '*trans*' urea-tagged proline catalyst **1c**.

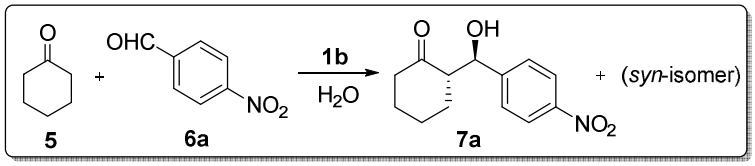


Reagents and conditions: (i) PhNCO, CH_2Cl_2 (86%); (ii) H_2, Pd/C (10%), MeOH, room temp., 4 h (85%).

Pd-catalysed deprotection at the last step met with failure, presumably due to the presence of the sulphur. Fortunately, the oxy-analog has proven quite proficient toward exploring our hypothesis. Nonetheless, we have taken up the synthesis of **1a** by an alternative route – involving a Boc- rather than Cbz-protected proline. This is currently in progress in our laboratory and the results in this regard shall be communicated in due course.

Satisfied with the comparative study, we proceeded to optimize the asymmetric aldol addition using **1b**. The critical and often intriguing role of water in organocatalysed asymmetric transformations[17] was once again exemplified by a reaction in its absence, which resulted in a drop in both efficiency and selectivity of the catalyst (Table 1, entry 9). Further optimization showed the ideal amount of added water to be 25 or 50 μL (ca. 1.2 or 2.4 eq. respectively) for the reaction on a 0.5 mmol scale (entries 10-13). Organocatalytic reactions in/on/in the presence of water have entailed interesting discussions and mechanistic investigations.[18,19] The studies carried out by Blackmond and co-workers[19a] to comprehend the advantages of the addition of "micro" quantities of water in enamine catalysis are particularly pertinent here; while, the efforts of Jung and Marcus[19b]

Table 1. Comparative and optimisation studies for the reaction of cyclohexanone and *p*-nitrobenzaldehyde[a]



Entry	Catalyst [mol-%]	H_2O [μL]	Time [h]	Yield [%][b]	d.r. [*anti*/*syn*][c]	*anti* ee [%][d]
1	**1b** [5]	50	6	95	96:4	99
2	**1b** [2]	50	8	92	98:2	99
3	**1c** [2]	50	8	45	96:4	95
4	L-Pro [2]	50	8	9[e]	n.d.	n.d.
5	L-Pro [2] + **I**[f] [2]	50	8	7[e]	n.d.	n.d.
6	L-Pro [2] + **II**[f] [2]	50	8	5[e]	n.d.	n.d.
7	L-Pro [2] + **I** [2]	0	8	58	85:15	88
8	L-Pro [2] + **II** [2]	0	8	62	87:13	95
9	**1b** [2]	0	8	78	91:9	89
10	**1b** [2]	25	8	93	96:4	97
11	**1b** [2]	100	8	62	93:7	99
12	**1b** [2]	250	24	85	96:4	98
13	**1b** [2]	500	24	91	95:5	99
14	**1b** [1]	50	8	75	97:3	98
15	**1b** [0.3]	50	24	7[e]	n.d.	n.d.
16	**1b** [0.3]	10	24	12[e]	n.d.	n.d.

[a] Reactions were carried out at 25 °C on 0.5 mmol of *p*-nitrobenzaldehyde using 5 eq. of cyclohexanone. [b] Refers to isolated yields. [c] Determined by ^{1}H NMR of the crude reaction mixture. [d] Determined by HPLC on a chiral stationary phase (see Supporting Information). [e] Refers to % conversion determined by 1H NMR analysis. n.d. = not determined. [f] **I**: 1,3-diphenyl thiourea; **II**: 1,3-bis(3,5-bis(trifluoromethyl)phenyl) thiourea.

that sought to rationalize the beneficial effects of "on water" reactions employing heterogeneous aqueous biphasic conditions must also be acknowledged. A noteworthy outcome of this study was the admirable ability of **1b** to exhibit near identical stereoselectivity even when a large quantity of water was employed – "bulk" water conditions as it is termed – albeit with a lowered efficiency. Lastly, a reaction was attempted with just 1 mol-% of the catalyst was also found to work reasonably well – a 75% yield of the aldol was obtained in 8 h with 98% *ee*, impressive for a proline derived catalyst in the direct asymmetric aldol reaction (entry 14). An interesting study carried out by Rulli et al[20] on kinetic versus thermodynamic control in organocatalysed asymmetric aldol additions in aqueous medium offered considerable insight with regards to the above results obtained using **1b**. In a series of experiments, the authors observed a significant drop in the optical purity of the aldol with increased catalyst loading over a range of 0.5 to 10 mol%, which was attributed to a switch from kinetic to thermodynamic control for the enamine mediated reaction. Pertinently on the basis of the above report, the admirable *ee*'s obtained with just a 2 mol% loading of **1b** in the present case may presumably be the outcome of a predominantly kinetically controlled reaction, giving rise to enhanced stereocontrol.

Catalyst recyclability is often considered an important aspect in the organocatalysis domain, as the research community strives towards ever more sustainable protocols.[21] Curious to examine **1b** on this platform, we tested it in the standard reaction between **5** and **6a** employing two different work-up methods – one involving a direct extraction of the product from the reaction mixture, and the other involving removal of excess cyclohexanone under reduced pressure prior to extraction of the product. The variation did not seem to affect the performance, as the catalyst remained admirably efficient up to 5 cycles in both cases. It is worth noting though that consistently excellent levels of diastereoselectivity and enantioselectivity were maintained through all the recycling runs using both methods (**Table 2**).

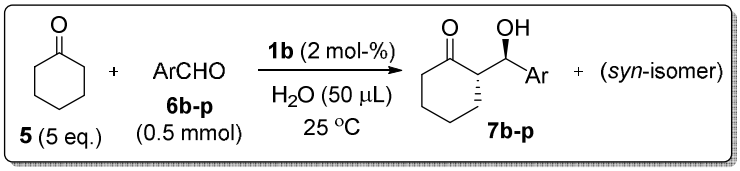
Table 2. Recycling studies for the reaction of cyclohexanone (**5**) with *p*-nitrobenzaldehyde (**6a**) catalysed by **1b**.[a]

Method A[b]				**Method B**[f]			
Run	**Yield [%]**[c]	***anti/syn***[d]	***anti* ee [%]**[e]	**Run**	**Yield [%]**[c]	***anti/syn***[d]	***anti* ee [%]**[e]
1	95	96:4	98	1	96	96:4	98
2	91	96:4	98	2	93	95:5	97
3	93	96:4	98	3	93	96:4	97
4	90	96:4	98	4	91	96:4	97
5	85	96:4	97	5	87	96:4	96
6	66	93:7	97	6	65	96:4	96
7	29	91:9	97	7	45	94:6	95
				8	20	*n.d.*	90

[a] Recycling studies were carried out on 0.5 mmol scale of the aldehyde using 5 mol-% of **1b**, 5 eq. of **5** and 50 μL of water. [b] Involved removal of excess cyclohexanone from the reaction mixture prior to work-up (for details, see Experimental Section). [c] Refers to isolated yields. [d] Determined by ^{1}H NMR of the crude reaction mixture. [e] Determined by HPLC on a chiral stationary phase (see Supporting Information). [f] Excess cyclohexanone was not removed prior to the work-up (for details, see Experimental Section).

Pleased with the recyclability results, we then explored the scope of the reaction with cyclohexanone as the donor using a number of acceptor aldehydes (**Table 3**) and with a couple of donor ketones using *p*-nitrobenzaldehyde as the electrophile (**Table 4**). Reactions were carried out using the optimized conditions – using a 2 mol-% loading of the catalyst, 50 μL of water and 5 eq. of the donor ketone. Electron deficient aldehydes resulted in excellent yields as expected, along with very good enantio- and diastereoselectivities (Table 3, entries 1-8). A swift reaction was observed with pentafluorobenzaldehyde, delivering a near quantitative yield of the aldol with an excellent *ee* and exceptionally high diastereomeric ratio (entry 5). The heteroaromatic nicotine and iso-nicotine aldehydes (entries 6 & 7) also participated with high efficiency, although the *ee* was marginally compromised in an especially rapid reaction with the latter. The other aldehydes employed in the study, including the electron neutral benzaldehyde and *β*-naphthaldehyde, delivered the corresponding aldols in moderate to good yields, accompanied by consistently high levels of stereoselectivity (entries 9-14). Only the strongly electron donating *p*-anisaldehyde resulted in a poor yield of

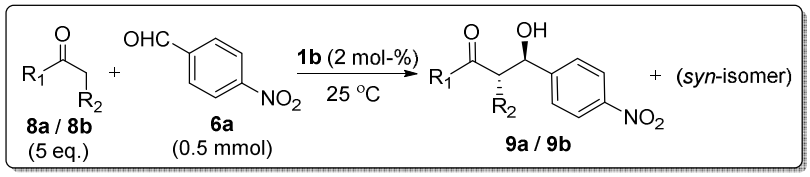
Table 3. Asymmetric aldol reactions of cyclohexanone (**5**) with various aldehydes catalysed by **1b** in the presence of water



Entry	Ar	Time [h]	Yield [%][a]	*anti*/*syn*[b]	*anti* ee [%][c]
1	2-NO_2-C_6H_4 (**7b**)	12	94	96:4	96
2	3-NO_2-C_6H_4 (**7c**)	12	90	97:3	97
3	4-CN-C_6H_4 (**7d**)	12	95	96:4	97
4	4-CF_3-C_6H_4 (**7e**)	15	93	98:2	97
5	C_6F_5 (**7f**)	5	99	>99:1	98
6[d]	3-pyridyl (**7g**)	5	90	96:4	97
7[d]	4-pyridyl (**7h**)	3	95	94:6	90
8	4-Cl-3-NO_2-C_6H_3 (**7i**)	12	95	97:3	99
9[d]	4-Cl-C_6H_4 (**7j**)	24	67	94:6	92
10	3-Cl-C_6H_4 (**7k**)	24	55	94:6	94
11[d]	4-Br-C_6H_4 (**7l**)	48	81	93:7	91
12[e]	C_6H_5 (**7m**)	30	52	95:5	96
13	2-Napthyl (**7n**)	30	54	92:8	94
14	3-C_6H_5-O-C_6H_4 (**7o**)	30	60	93:7	95
15[e]	4-OMe-C_6H_4 (**7p**)	120	35	81:19	95

[a] Refers to isolated yields. [b] Determined by ^{1}H NMR of the crude reaction mixture. [c] Determined by HPLC on a chiral stationary phase (see Supporting Information). [d] 25 μL H2O was used. [e] 5 mol-% catalyst was used.

Table 4. Asymmetric aldol reactions of different donors with *p*-nitrobenzaldehyde (**6a**) catalysed by **1b** in the presence of water



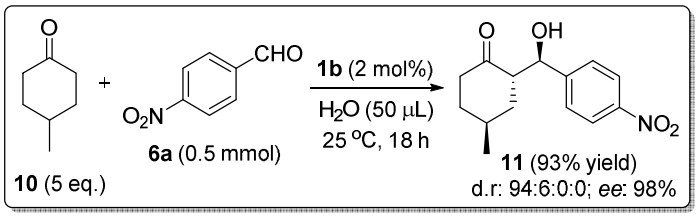
Entry	R_1, R_2	H_2O [μL]	Time [h]	Yield [%][a]	*anti*/ *syn*[b]	*anti* ee [%][c]
1	-$(CH_2)_3$- (**9a**)	50	7	99	77:23	90
2	CH_3, H (**9b**)	50	8	80	-	8
3	CH_3, H (**9b**)	-	8	51	-	59

[a] Refers to isolated yields. [b] Determined by ^{1}H NMR of the crude reaction mixture. [c] Determined by HPLC on a chiral stationary phase (see Supporting Information).

the aldol, nevertheless with high enantiomeric purity (entry 15). Varying the donor ketone in reactions with *p*-nitrobenzaldehyde worked excellently in the case of cyclopentanone, affording near quantitative yield of the aldol with 90% *ee* in just 7 h (Table 4, entry 1). The reaction with the water-miscible acetone as the donor was interesting; when the reaction was attempted without water, a 51% of the aldol was obtained in 8 h, with 59 % *ee* (entry 3). However, in stark contrast, the reaction of acetone under the standard conditions that employed 50 μL of water afforded the aldol with just 8% *ee*, albeit in 80% yield (entry 2). If one were to attempt to rationalize these results, the higher efficiency in the latter case is presumably a consequence of the enhanced homogeneity of the reaction provided by the more hydrophilic acetone. Unfortunately however, this would also imply a dominant interfering presence of water in the transition state, which apparently has a detrimental effect on the steroselectivity. On the other hand, in the reaction without water, the absence of the interfering water molecules in the transition state evidently spikes up the stereoselectivity but simultaneously compromises the ease of interaction of the amino acid catalyst with the substrate ketone, resulting in the observed poor conversion. This is in complete contrast to the use of more lipophilic donors such as cyclohexanone, where the presence of water has a beneficial effect on the catalyst performance.[11a,12a,17,19] The example once again offers a glimpse into the intriguing role that water many a time plays in organocatalytic reactions, especially so in the enamine-mediated asymmetric aldol addition.

Lastly, we also attempted an enantioselective and diastereoselective desymmetrisation of 4-methyl cyclohexanone (**10**) by the **1b**-mediated aldol addition to 4-nitrobenzaldehyde (**6a**). Rios and co-workers had earlier utlized the proline-thiourea dual catalytic system to carry out this challenging reaction, which gives rise to 4 possible diastereomeric product pairs, with excellent levels of stereoselectivity.[4b] We were very pleased to find that using just 2 mol-% of **1b**, the reaction of **10** with **6a** proceeded to deliver the corresponding aldol **11** in 93% yield accompanied by excellent levels of both diastereo- and enantioselectivity (**Scheme 3**).

Scheme 3. Desymmetrisation of 4-methyl cyclohexanone by an aldol addition mediated by **1b**



Turning to the mechanism, we pondered a transition state illustrated by **C** in **Figure 2** for the reaction using **1b**, based on our hypothesis and the observed results. As is typical of proline catalysed aldol additions, the transition state may be expected to involve concomitant development of partial iminium and carboxylate ions on the proline moiety and H-bonding activation of the aldehyde. Of further significance, an intramolecular interaction between the –COOH group and the *cis* urea moiety is envisioned to be in operation in the **1b**-mediated reaction – similar to the supramolecular assembly proposed by Demir & co-workers in the transition state of the reaction mediated by the proline-thiourea dual catalytic system – depicted by **B** in **Figure 2**.[4a,e] The proposed interaction might be expected to have a stabilising effect, leading to a more organized and "tighter" transition state, and eventuates in considerably enhanced activity and greater stereocontrol of **1b**. Admittedly, such an interaction is still a conjecture at this stage; various other factors might be at play, e.g. the presence of water. Nevertheless, the results obtained in this study using **1b** and **1c** have certainly provided a favourable indication of the possibility, and further probing – possibly with the help of computational studies – might help shed more light on this aspect.

In summary, a urea moiety tagged onto the 4-position of proline, *cis* to the –COOH group, proved to be a favourable factor in the direct asymmetric aldol reaction in the presence of water. The catalyst was quite proficient, delivering high yields of the aldol adducts with just 2 mol-% loading, along with excellent levels of enantio- and diastereoselectivity. To our knowledge, the performance of the urea-tagged proline is on par with

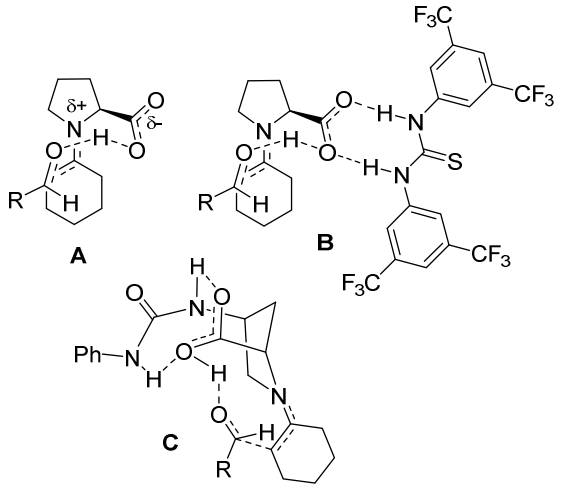


Figure 2. A: The List-Houk model of the transition state of the proline catalysed aldol reaction. **B**: Demir & co-workers' proline-thiourea host-guest complex model of the transition state. **C**: The proposed intramolecular host-guest interaction in the transition state of the aldol reaction catalysed by urea-tagged proline **1b**.

some of the best reported catalytic systems for the asymmetric aldol reaction under aqueous conditions, particularly the popular ion-tagged proline derivatives; it also surpassed the deeds of conceptually similar predecessors such as the dual catalytic supramolecular proline-thiourea model. Further of note was the exceptional ability of **1b** to afford identical levels of stereoselectivity in both a micro aqueous environment as well as under aqueous biphasic "bulk water" conditions. Lastly, it was also pleasing to observe that the catalyst could be recycled with a good degree of success. Mechanistically, the study alludes to a non-covalent role of the urea moiety, possibly in the genesis of an intramolecular synergistic interaction that stabilises the transition state. Computational studies are currently being strategized in our group to gain a better understanding of the favourable influence of the urea tag. Presently though, we believe that the commendable results achieved by tagging a urea moiety onto proline could open up a new avenue in the design of proline derived bifunctional catalysts that can be employed for mediating asymmetric transformations in the presence of water.

Experimental Section

General: Chemicals and solvents were purchased from commercial suppliers or purified by standard techniques. Merck 60 F_{254} pre-coated silica gel plates were used for thin layer chromatography (TLC) and compounds were visualised by irradiation with UV light and/or by treatment with a solution of $KMnO_4$ followed by heating. Column chromatography was performed using silica gel of mesh 60-120 / 100-200, procured from Merck. ^1H and ^{13}C NMR spectra were recorded on a Brucker Avance 500 MHz NMR spectrometer. Mass spectra were obtained using HRMS-ESI-Q-Time of Flight LC-MS (Synapt G2, Waters). Chiral HPLC studies were carried out on a Shimadzu LC-2010CHT HPLC system. Cyclohexanone, acetone, benzaldehyde, pyridine-3-/pyridine-4-carboxaldehyde were distilled before use. Commercial samples of all the other substrates were used without any purification.

Synthesis of dibenzyl (2*S*,4*S*)-4-(3-phenylureido)pyrrolidine-1,2-dicarboxylate (4): To a solution of *cis*-N-cbz-4-aminoproline benzyl ester **3** (1.01 g, 2.85 mmol) in CH_2Cl_2 (5 mL), phenyl isocyanate (0.34 mL, 3.13 mmol) was added drop-wise and the reaction mixture was stirred for 2 h at room temperature. The solvent was removed under vacuum and the residue was purified by column chromatography (petroleum ether / ethyl acetate 3:2) to give **4** as a colourless hygroscopic solid (1.13 g, 84%). $[\alpha]_D^{20}$ = -42.33 (*c* = 1.5, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$, two conformational isomers): δ 1.96-2.22 (m, 1 H), 2.23-2.60 (m, 1 H), 3.47-3.68 (m, 1 H), 3.69-3.89 (m, 1 H), 4.35-4.53 (m, 1 H), 4.55-4.65 (m, 1 H), 4.93-5.25 (m, 4 H), 5.27-5.34 (& 5.61-5.69) (m, 1 H), 6.39 (& 6.67) (bs, 1 H), 7.00-7.12 (m, 1 H), 7.20-7.45 (& 7.46-7.72) (m, 14 H); ^{13}C NMR (125 MHz, $CDCl_3$, two conformational isomers): δ 36.2 (& 37.2), 48.8 (& 49.7), 53.6 (& 53.8), 57.8 (& 58.3), 67.3 (& 67.4), 67.5 (& 67.6), 120.0 (& 120.3), 123.3 (& 123.5), 127.6 (& 127.9), 128.0 (& 128.1), 128.2 (& 128.3), 128.5 (& 128.6), 128.63 (& 128.7), 129.1 (& 129.13), 132.0 (& 132.1), 135.0 (& 135.2), 136.0 (& 136.1), 138.6 (& 138.4), 154.2 (& 154.6), 155.0 (& 155.4), 173.8 (& 173.9); HRMS (ESI-TOF): *m/z* $[M + H]^+$ calculated for $C_{27}H_{28}N_3O_5$: 474.2023; found: 474.2024.

Synthesis of the '*cis*' urea-tagged proline catalyst [(2*S*,4*S*)-4-(3-phenylureido)pyrrolidine-2-carboxylic acid (1b)]: To a solution of **4** (500 mg, 1.05 mmol) in MeOH (15 mL) was added 5% palladium on carbon (50 mg). The mixture was stirred for 2 h under hydrogen at room temperature and atmospheric pressure. The reaction mixture was then filtered and washed with methanol (5 mL × 5). The combined organic layer was concentrated in vacuo to afford the proline derivative **1b** as a white hygroscopic solid (235 mg, 90%). $[\alpha]_D^{20}$ = -103.57 (*c* = 2.8, MeOH); ^{1}H NMR (500 MHz, D_2O): δ 1.96-2.05 (m, 1 H), 2.51-2.61 (m, 1 H), 3.28 (dd, *J* = 5 & 12.5 Hz, 1 H), 3.45 (dd, *J* = 6.5 & 12.5 Hz, 1 H), 4.08 (dt, *J* = 1.4 & 8 Hz, 1 H), 4.26-4.35 (m, 1 H), 7.02 (t, *J* = 7.5 Hz, 1 H), 7.16 (d, *J* = 7.8 Hz, 2 H), 7.24 (t, *J* = 7.8 Hz, 2 H); ^{13}C NMR (125 MHz, D_2O): δ 34.5, 49.2, 50.2, 60.0, 121.3, 124.2, 129.2, 137.7, 157.5, 173.9; HRMS (ESI-TOF): *m/z* $[M + H]^+$ calculated for $C_{12}H_{16}N_3O_3$: 250.1186; found: 250.1187.

Synthesis of dibenzyl (2*S*,4*R*)-4-(3-phenylureido)pyrrolidine-1,2-dicarboxylate (4'): Prepared from *trans*-N-Cbz-4-aminoproline benzyl ester **3'** (800 mg, 2.26 mmol) following the same procedure as described for **4** above; colourless hygroscopic solid (920 mg, 86%). $[\alpha]_D^{20}$ = -36.66 (*c* = 3, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, two conformational isomers): δ 2.11-2.23 (m, 1 H), 2.24-2.31 (& 2.34-2.43) (m, 1 H), 3.44 (& 3.54) (dd, *J* = 3 & 11.5 Hz, 1 H), 3.81 (dd, *J* = 6 & 11 Hz, 1 H), 4.38-4.53 (m, 2 H), 4.90-5.20 (m, 4 H), 5.26 (& 5.30) (d, *J* = 7 Hz, 1 H), 6.73 (& 6.74) (bs, 1 H), 7.04-7.11 (m, 1 H), 7.20-7.38 (m, 14 H); ^{13}C NMR (125 MHz, $CDCl_3$, two conformational isomers): δ 36.2 (& 37.4), 48.9 (& 49.5), 52.5 (& 52.8), 57.7 (& 58.1), 67.1 (& 67.3), 67.6, 120.3 (& 120.4), 123.7, 127.6 (& 127.7), 128.15, 128.2, 128.45, 128.5 (& 128.56), 128.6, 129.2, 135.3, 135.9 (& 136.0), 138.4, 154.6 (& 154.9), 155.0 (& 155.4), 171.6 (& 171.8); HRMS (ESI-TOF): *m/z* $[M + Na]^+$ calculated for $C_{27}H_{27}N_3O_5Na$: 496.1843; found: 496.1843.

Synthesis of the '*trans*' urea-tagged proline catalyst [(2*S*,4*R*)-4-(3-phenylureido)pyrrolidine-2-carboxylic acid (1c)]: Prepared from **4'** following the same procedure as described for **1b** above; white hygroscopic solid (158 mg, 85%). $[\alpha]_D^{20}$ = -8.62 (*c* = 5.1, H_2O); ^{1}H NMR (500 MHz, D_2O): δ 2.21-2.33 (m, 2 H), 3.23 (dd, *J* = 4.5 & 12 Hz, 1 H), 3.54 (dd, *J* = 6 & 12 Hz, 1 H), 4.18 (t, *J* = 8.5 Hz, 1 H), 4.29 (quintet, *J* = 5.5 Hz, 1 H), 7.03 (t, *J* = 7.5 Hz, 1 H), 7.17 (d, *J* = 8 Hz, 2 H), 7.24 (t, *J* = 8 Hz, 2 H); ^{13}C NMR (125 MHz, D_2O): δ 34.5, 49.6, 50.6, 60.0, 121.5, 124.2, 129.1, 137.6, 157.7, 173.6; HRMS (ESI-TOF): *m/z* $[M + H]^+$ calculated for $C_{12}H_{16}N_3O_3$: 250.1186; found: 250.1174.

Typical Catalysis Procedure (Table 1, Entry 2):

Cyclohexanone (**5**, 0.26 mL, 2.5 mmol) and water (50 µL, 2.8 mmol) were added to the catalyst **1b** (2.5 mg, 0.01 mmol) and the mixture was allowed to stir for 10 min at room temperature. 4-Nitrobenzaldehyde (**6a**, 75.5 mg, 0.5 mmol) was then added and the reaction mixture was allowed to stir at room temperature. After 8 h of stirring, the reaction mixture was charged directly onto a silica gel column and eluted with petroleum ether /

ethyl acetate (~7:3) to isolate the pure aldol product **7a** (114.5 mg, 92%). The *ee* was determined by chiral HPLC using a Daicel Chiralpak AD-H column (hexane / 2-propanol = 87.5:12.5, flow rate: 0.8 mL min^{-1}, λ = 254 nm); t_R *syn* = 15.7 min, t_R *syn* = 18.8 min, t_R *anti* (minor) = 20.5 min, t_R *anti* (major) = 27.1 min.

2-Hydroxy(4-nitrophenyl)methyl)cyclohexan-1-one (7a)[22]
Yield: 114.7 mg (92%)

2-Hydroxy(2-nitrophenyl)methyl)cyclohexan-1-one (7b)[22]
Yield: 117.1 mg (94%)

2-Hydroxy(3-nitrophenyl)methyl)cyclohexan-1-one (7c)[22]
Yield: 112.2 mg (90%)

2-(Hydroxy-(4-cyanophenyl)methyl)cyclohexan-1-one (7d)[23]
Yield: 108.9 mg (95%)

2-(Hydroxy(4-(trifluoromethyl)phenyl)methyl)cyclohexan-1-one (7e)[4e]
Yield: 126.6 mg (93%)

2-(Hydroxy(perfluorophenyl)methyl)cyclohexan-1-one (7f)[24]
Yield: 145.7 mg (99%)

2-(Hydroxy(pyridin-3-yl)methyl)cyclohexan-1-one (7g)[24]
Yield: 92.4 mg (90%)

2-(Hydroxy(pyridin-4-yl)methyl)cyclohexan-1-one (7h)[23]
Yield: 97.5 mg (95%)

2-((4-Chloro-3-nitrophenyl)(hydroxy)methyl)cyclohexan-1-one (7i)[25]
Yield: 134.8 mg (95%)

2-((4-Chlorophenyl)(hydroxy)methyl)cyclohexan-1-one (7j)[23]
Yield: 79.9 mg (67%)

2-((3-Chlorophenyl)(hydroxy)methyl)cyclohexan-1-one (7k)[26]
Yield: 65.6 mg (55%)

2-((4-Bromophenyl)(hydroxy)methyl)cyclohexan-1-one (7l)[23]
Yield: 114.7 mg (81%)

2-(Hydroxy(phenyl)methyl)cyclohexan-1-one (7m)[22]
Yield: 53.1 mg (52%)

2-(Hydroxy(naphthalen-2-yl)methyl)cyclohexan-1-one (7n)[23]
Yield: 68.7 mg (54%)

2-(Hydroxy(3-phenoxyphenyl)methyl)cyclohexan-1-one (7o)[27]
Yield: 88.9 mg (60%)

2-(Hydroxy(4-methoxyphenyl)methyl)cyclohexan-1-one (7p)[23]
Yield: 41.1 mg (35%)

2-(Hydroxy(4-nitrophenyl)methyl)cyclopentan-1-one (9a)[23]
Yield: 116.4 mg (99%)

4-Hydroxy-4-(4-nitrophenyl)butan-2-one (9b)[22]
Yield: 83.7 mg (80%)

2-(Hydroxy(4-nitrophenyl)methyl)-4-methylcyclohexan-1-one (11)[4b]
Yield: 122.4 mg (93%)

Typical Procedure for Catalyst Recycling Studies (Table 2)

Method A

Cyclohexanone (**5**, 0.26 mL, 2.5 mmol) and water (50 μL, 2.8 mmol) were added to the catalyst **1b** (6.23 mg, 0.025 mmol) and the mixture was allowed to stir for 10 min at room temperature. 4-Nitrobenzaldehyde (**6a**, 75.5 mg, 0.5 mmol) was then added and the reaction mixture was allowed to stir for 6 h at room temperature. The excess cyclohexanone was removed under reduced pressure and the reaction mixture was dried under vacuum for 1 h. The reaction mixture was then extracted with Et_2O (2 mL × 4) following which the reaction flask was dried under vacuum for 1h. It was again charged with the reactants in identical amounts and order as above. The crude product was purified by evaporation of the combined organic extracts and subjecting the residue to silica gel chromatography to obtain the pure aldol **7a**.

Method B

Same as **Method A**, except that the excess cyclohexanone was not removed prior to the extraction; the reaction mixture was subjected directly to Et_2O extraction.

Supporting Information

The chiral HPLC data of the aldol adducts (determination of *ee*), the ^1H NMR spectra of the crude reaction mixtures (determination of diastereomeric ratio), the ^1H and ^{13}C NMR spectra of the purified aldol adducts and the spectral data of the catalyst and catalyst precursors are provided in the Supporting Information.

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