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Dry and wet prolines for asymmetric organic solvent-free aldehyde–aldehyde and aldehyde–ketone aldol reactions†

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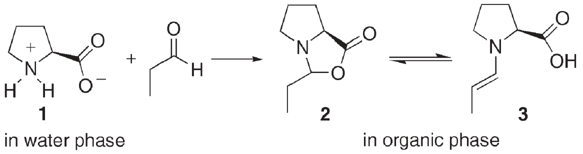
Dry and wet prolines were found to catalyze the direct aldol reactions of aldehyde–aldehyde and aldehyde–ketone, respectively, to afford aldols with excellent diastereo- and enantioselectivities, and an organic solvent-free reaction was realized in some cases.

Today "Green" is an increasingly important keyword and the development of green reactions is one of the most urgent and important topics in current chemistry.[1] The synthesis of enantiopure molecules is another important issue,[2] and the development of enantioselective reactions that proceed under environmentally benign conditions has grown into an extensively investigated field. Successful catalytic, enantioselective reactions have mostly used transition metal complexes, and hence may require toxic, rare and expensive metals and so suffer from possible metal contamination of the products, while most also require an organic solvent. Asymmetric catalytic reactions that proceed with a benign catalyst and without using an organic solvent would be highly desirable.[3] Proline is free from the problems associated with some metals, as it is safe, inexpensive, and stable to moisture and air.[4] Thus, the development of proline-mediated enantioselective reactions not requiring an organic solvent has become a highly sought-after goal in green chemistry.

The aldol condensation is a key carbon–carbon bond forming reaction creating the β-hydroxy carbonyl structural unit found in many natural products and drugs.[5] Several excellent asymmetric aldol reactions have been developed, and it is known that proline catalyzes such reactions in polar organic solvents such as DMSO and DMF,[6] a reaction that has been reported not to proceed in water.[7,8] Pihko *et al.* reported the highly enantioselective aldol reaction in aqueous DMF, in which the reaction proceeds efficiently in the presence of a large excess of water.[8c,l] It had been thought that modification of proline is required to achieve such aldol reactions in the presence of water without organic solvent, and recently we developed a highly lipophilic siloxyproline catalyst[9] and a combined proline–surfactant organocatalyst[10] to make possible aldehyde–ketone and aldehyde–aldehyde aldol reactions in the presence of water, respectively. Barbas and co-workers[11] have reported the combined use of a diamine and an acid to achieve aldol reaction in the presence of water. During the preparation of this manuscript, Lu and co-workers have reported a tryptophan-catalyzed reaction in the presence of water.[12] During our further investigation of aldol reaction in the presence of water, we happened to find that a highly enantioselective aldol reaction can proceed under *either dry or under wet conditions* without organic solvent, as we describe below.

It has generally been believed that proline does not catalyze the aldol reaction in the presence of water, or that even when the reaction does proceed, as in the presence of surfactant, a nearly racemic aldol product is obtained.[13] In fact, using the conditions under which we had previously investigated the self-aldol reaction of propanal,[14] or the aldol reaction of *o*-chlorobenzaldehyde and propanal,[10] catalyzed by proline in the presence of water no reaction was observed. However, when we examined the aldol reaction of *o*-chlorobenzaldehyde and propanal with higher catalyst loading and at higher temperature, we found that *the proline-mediated aldol reaction proceeded slowly in the presence of water to afford the product enantioselectively*. Even in the presence of a large excess (100 equiv.) of water, moderate yield and enantioselectivity were obtained (Table 1, entry 1). These results indicate that propanal can react with a reactive electrophilic aldehyde even in the presence of a large excess of water. In the present reaction, a two-phase system is formed, and the reaction is thought to proceed according to eqn. (1):



(1)

o-Chlorobenzaldehyde and some portion of the propanal form an organic phase. The remaining propanal dissolves in the aqueous phase, where it reacts with proline, most of which stays in the water in its zwitterionic form **1**, to generate neutral *N*,*O*-acetal **2**, which moves into the organic phase. Enamine **3** can be regenerated from **2** and react with *o*-chlorobenzaldehyde to generate the aldol product in the organic phase. Some water is dissolved in the organic phase, stabilizing **3** and reducing its reactivity, which is why **3** reacts with electron-deficient *o*-chlorobenzaldehyde but not with propanal. As propanal dissolves in both the aqueous and organic phases, in effect it extracts proline from water to the organic phase.

In order to improve the yield and enantioselectivity, the effect of amount of water on diastereo- and enantio-selectivities was investigated in detail. Reducing the amount of water increases both the yield and enantioselectivity. However with no water, the yield was reduced owing to over-reactions such as dehydration (entry 8). This side-reaction under neat conditions can be

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† Electronic supplementary information (ESI) available: Detailed experimental procedures, full characterization, ^{1}H, ^{13}C NMR and IR spectra of all new compounds. See DOI: 10.1039/b613262f

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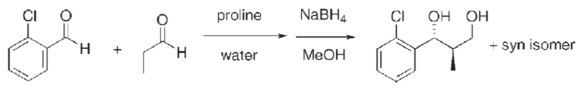
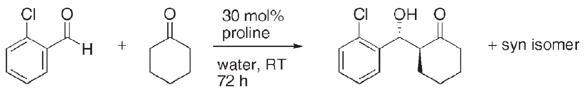
Table 1 The effect of amount of water on the yield, and diastereo- and enantio-selectivities in the aldol reaction of *o*-chlorobenzaldehyde and propanal[a]



Entry	Amount of water (equiv.)	Amount of proline (mol%)	Temp./°C	Time/h	Yield[b] (%)	*anti* : *syn*[c]	Ee[d] (%)
1	100	30	23	72	39	2.4 : 1	67
2	54	30	23	72	60	3.5 : 1	77
3	36	30	23	72	65	3.0 : 1	82
4	18	30	23	72	73	3.9 : 1	88
5	10	30	23	72	71	3.9 : 1	89
6	5	30	23	72	70	4.3 : 1	90
7	3	30	23	72	62	5.6 : 1	92
8	0	30	23	72	54	4.4 : 1	86
9	0	30	4	48	85	7.1 : 1	96
10	0	10	4	48	90	13 : 1	96
11[e]	0	10	4	60	76	9.7 : 1	96
12[f]	18	10	0	24	<5		
13[g]	0	10	4	48	79	12 : 1	98
14[h]	0	10	4	48	78	19 : 1	98

[a] Unless otherwise shown, the reaction was conducted with 0.4 mmol of *o*-chlorobenzaldehyde and 2 mmol of propanal. [b] Isolated yield. [c] Determined by ^{1}H NMR. [d] Ee of *anti*-isomer. Determined by chiral HPLC after conversion to the monobenzoyl ester (see ESI). [e] 3.0 equiv. of propanal was employed. [f] The data in ref 10. [g] 4-*tert*-Butyldiphenylsiloxyproline was employed instead of proline. [h] 4-Decanoyloxyproline was employed instead of proline.

Table 2 The effect of amount of water on the yield, and diastereo- and enantio-selectivities in the aldol reaction of *o*-chlorobenzaldehyde and cyclohexanone[a]



Entry	Amount of water (equiv.)	Yield[b] (%)	*anti* : *syn*[c]	Ee[d] (%)
1	0	75	3.0 : 1	84
2	1	70	9.5 : 1	96
3	3	71	13.9 : 1	98
4[e]	3	70	12.5 : 1	97
5	5	51	12.2 : 1	97
6	18	11	7.3 : 1	95

[a] Unless otherwise shown, the reaction was conducted with 0.4 mmol of *o*-chlorobenzaldehyde, 2 mmol of cyclohexanone and 0.12 mmol of proline at room temperature for 72 h. [b] Isolated yield. [c] Determined by ^{1}H NMR. [d] Ee of *anti*-isomer. Determined by chiral HPLC (see ESI). [e] 3.0 equiv. of cyclohexanone was employed.

suppressed by performing the reaction at the lower temperature of 4 °C, when the product is formed in good yield and with higher diastereo- and enantio-selectivities (entry 9). The amount of aldehyde and catalyst can be reduced to 3 equiv. and 10 mol%, respectively, with only a slight decrease in yield, and without compromising the enantioselectivity (entries 10, 11). When 4-*tert*-butyldiphenylsiloxyproline[9] or 4-decanoyloxyproline[10] was employed instead of proline, good yield and excellent enantioselectivity was obtained (entries 13, 14).

As the best conditions for the cross-aldol reaction of aldehydes had been established as neat at 4 °C, these were applied to aldehyde–ketone aldol reaction, for which the reaction of *o*-chlorobenzaldehyde and cyclohexanone was selected as a model (Table 2). In this case, a small amount of water has a beneficial effect on both diastereo- and enantio-selectivities. Though the reaction proceeds without solvents, the diastereomer ratio (dr) is low (3.0 : 1) and ee is moderate (84% ee). In the presence of 3 equiv. of water, dr and ee are increased to 13.9 : 1 and 98% ee, respectively. Wet proline is suitable and the reaction scarcely proceeded in the presence of an excess amount of water. The same positive effect of water has been observed in some cases,[8,9] but the reason of its effect is not clear at this moment.

The generality of the reactions under dry conditions for the aldehyde–aldehyde reaction and wet conditions for the aldehyde–ketone reaction was investigated with the results summarized in Table 3. Propanal reacts with reactive *o*-chlorobenzaldehyde and *p*-trifluoromethylbenzaldehyde enantioselectively under dry conditions. Not only electron-deficient aromatic aldehydes, but also benzaldehyde itself can be employed, though the yield is moderate. The heteroaromatic aldehyde 2-furaldehyde is also a suitable substrate. The water-soluble aldehyde dimethoxyacetaldehyde (60 wt% solution in water) can be used directly under wet conditions, and reacts with 3-phenylpropanal affording the aldol with excellent enantioselectivity. As for the aldehyde–ketone reaction, aqueous dimethoxyacetaldehyde reacts with cyclohexanone and cyclopentanone to provide β-hydroxyketones with excellent enantioselectivity. It should be noted that its reaction with 2,2-dimethyl-1,3-dioxan-5-one affords a polyfunctionalized ketone in excellent enantioselectivity, a useful intermediate for the synthesis of sugars.[15] Though cyclohexanone scarcely reacts with benzaldehyde, it reacts efficiently with reactive, electron-deficient aromatic aldehydes such as *o*-chloro-, *p*-nitro- and *p*-trifluoromethyl-benzaldehydes with excellent enantioselectivity.

Organic solvent is usually necessary not only during the reaction but also at the extraction and purification stages. A noteworthy advantage of the present reaction is the realization of an organic solvent-free system. As proline is soluble in water, it was easily removed and recovered from other organic materials by simply washing the organic phase with water. Direct distillation of the remaining organic phase afforded the pure aldols without compromising the enantioselectivity. By this procedure 11.7 g (75%) of the aldol product of cyclopentanone and *o*-chlorobenzaldehyde was obtained in >99% ee (*anti* : *syn* = 2 : 1) without using any organic solvent (for detailed procedure see ESI†).

When the aldols were crystalline, direct recrystallization of the organic phase after washing with water gave diastereomerically and enantiomerically pure aldols. By this procedure 11.4 g (73%) of the aldol adduct of *p*-trifluoromethylbenzaldehyde and cyclohexanone was obtained in >99% ee (*anti* : *syn* = >20 : 1), using 57.6 mL of cyclohexane as recrystallization solvent (for detailed procedure see ESI†).

Proline, which may have been present in the prebiotic era,[16] promotes the aldehyde–aldehyde aldol reaction in a presence of a large excess of water, affording the product in good enantioselectivity (Table 1, entry 1). This is a first example, in which an amino acid can promote the aldol reaction with high enantioselectivity in a presence of a large excess amount of water without organic solvent. This result may be evidence that proline could have promoted enantioselective aldol reactions in the presence of water and so created enantiomerically-enriched on the early Earth.[17]

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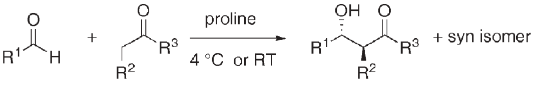
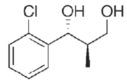
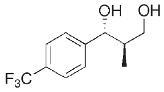
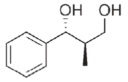
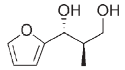
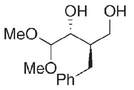
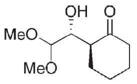
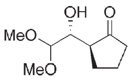
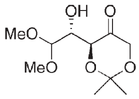
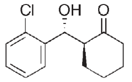
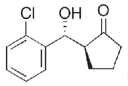
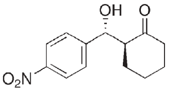
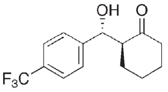
Table 3 Enantioselective direct, proline-mediated aldol reaction[a]



 Condition A 48h, 90% anti:syn 12.9:1 96% ee	 Condition A 48h, 91% anti:syn 14.1:1 98% ee	 Condition A 72h, 58% anti:syn 12.5:1 97% ee	 Condition A 96h, 74% anti:syn 5.7:1 96% ee
 Condition B[b] 32h, 40% anti:syn 3.3:1 92% ee	 Condition B 92h, 80% anti:syn 10:1 93% ee	 Condition B 13h, 75% anti:syn 1.0:1 94% ee	 Condition B 16h, 47% anti:syn > 20:1 83% ee
 Condition C 96h, 67% anti:syn 11:1 99% ee	 Condition C 24h, 89% anti:syn 2.8:1 >99% ee	 Condition C 96h, 73% anti:syn 9:1 >99% ee	 Condition C 96h, 83% anti:syn 12.4:1 96% ee

[a] Yields are for isolated compounds, and diastereomer ratios were determined by ^{1}H NMR. Ee refers to that of the *anti*-isomer, and were determined by chiral HPLC (see ESI). Condition A: acceptor aldehyde : donor aldehyde : proline = 1 : 5 : 0.1. The reaction was performed under neat conditions at 4 °C. The aldol product was reduced with $NaBH_4$ and isolated as a diol. Conditions B: acceptor aldehyde : carbonyl compound : proline = 1 : 5 : 0.3. Commercially available aqueous aldehyde was employed as received (3.8 equiv. of water), and the reaction was performed at room temperature. Conditions C: aldehyde : ketone : proline = 1 : 3 : 0.3. The reaction was performed in the presence of 3 equiv. amount of water at room temperature. [b]The aldol product was reduced with $NaBH_4$ and isolated as a diol.

In summary, we have found practical enantioselective aldehyde–aldehyde and aldehyde–ketone aldol reactions catalyzed by the inexpensive and safe catalyst proline under dry and wet conditions. There are several noteworthy synthetic advantages to the present reaction. (1) Any modification of proline is not required, and the proline catalyst can be used as it stands. (2) Commercially available aqueous aldehydes such as dimethoxyacetaldehyde can be employed directly. (3) In some cases a completely organic solvent-free procedure can be achieved. As operation is simple and scale-up is easy, the present method is suitable for the large-scale preparation of chiral aldols.

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