Proline-Catalyzed Asymmetric Direct Aldol Reaction Assisted by D-Camphorsulfonic Acid in Aqueous Media

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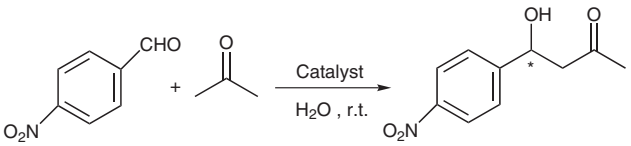
Abstract: Asymmetric aldol reactions of aromatic aldehydes with various ketones catalyzed by L-proline with D-camphorsulfonic acid as co-catalyst have been developed in aqueous media. High reactivity and modest to excellent enantioselectivity has been achieved.

Keywords: asymmetric direct aldol reaction, co-catalyst, proline, camphorsulfonic acid, aqueous media

Since the pioneer work reported by List and Barbas[1] that L-proline, a natural amino acid with stunning simplicity, can catalyze intermolecular asymmetric direct aldol reaction in DMSO or other aprotogenic solvents, extensive investigation has been conducted to increase the scope of both the substrates and solvents, as well as to optimize the catalytic efficiency and enantioselectivity of L-proline[2] and its derivatives.[3–5] However, it is noted that amino acids and amines are much more effective catalysts in non-aqueous or aprotogenic solvents where the amine functionality can be maintained in its reactive unprotonated state.[1b] Synthetically useful aldol reactions in aqueous media are rare and usually involve enzymes.[6] Indeed, even though it was reported that proline-catalyzed ketone-aldehyde aldol reactions are accelerated by water,[7] direct aldol reaction carried out in aqueous media catalyzed by native proline generally proceeded with low enantioselectivity.[2a,6–9] Proline-catalyzed aldol reactions in a phosphate buffer[6] and aqueous micelles[8] showed that there was no obvious enantioselectivity. While direct aldol reaction catalyzed by a proline-containing chiral Lewis acid, Zn-proline, in aqueous media was reported with moderate enantioselectivity and very limited substrate scope.[10] Therefore, native proline-catalyzed, synthetically useful asymmetric direct aldol reaction in aqueous media remains a challenging subject, which deserves to be explored in order to develop an environmentally benign and biomimetic aldol reaction. Aiming to explore the potential application of simple and readily available chiral compounds as organocatalysts for reactions carried out in aqueous media, we have employed camphorsulfonic acid (CSA) as a catalyst in direct Mannich reactions in aqueous media.[11] Herein, we wish to report that, by using the acid-base designing methodology[3b] to develop a multifunctional catalytic system, asymmetric aldol reactions with excellent enantioselectivity can be achieved in aqueous media by combining proline and CSA as co-organocatalysts. As far as we are aware, there is no report on the additive effect of CSA on the catalytic efficiency of proline itself in aqueous media.[3a,5]

Table 1 Different Types of Co-Catalyst for L-Proline-Catalyzed Asymmetric Aldol Reaction of Acetone with *p*-Nitrobenzaldehyde



Entry	Catalyst[a]	Time (h)	Yield (%)	ee (%)
1	L-Pro	24	47	34
2	D-CSA	24	n.d.	n.d.
3	L-Pro/D-CSA	24	74	61
4	L-Pro/ L-Tyr-SO_3H	24	61	47
5	L-Pro/ L-Try-SO_3H	24	58	43
6	L-Pro/1,5nds[b]	24	52	38
7	L-Pro/CF_3SO_3H	24	29	58
8	L-Pro/Tartaric acid	24	46	50
9	L-Tyr/D-CSA	24	n.d.[c]	n.d.
10	L-Phe/D-CSA	24	38	18
11	L-Try/D-CSA	24	33	8

[a] Amino acid–acid, 2:1.
[b] 1,5nds = 1,5-naphthalenedisulfonic acid.
[c] Not determined.

Table 2 Affect of the Ratio of L-Proline/D-CSA on the Asymmetric Aldol Reaction of Acetone with *p*-Nitrobenzaldehyde

Entry	Catalyst	Ratio (mol)	Time (h)	Yield (%)	ee (%)
1	L-Pro/D-CSA	1:0	24	47	34
2	L-Pro/D- CSA	4:1	24	70	57
3	L-Pro/D- CSA	3:1	24	70	34
4	L-Pro/D-CSA	2:1	24	74	61
5	L -Pro/D-CSA	1:1	24	44	59

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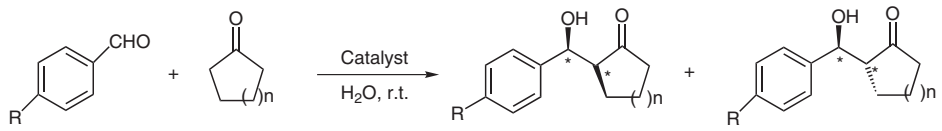
When catalyzed by 20mol% L-proline alone in acetone–water (4:1), the reaction between acetone and *p*-nitrobenzaldehyde proceeded in moderate yield 47% and enantiomeric excess 34%. CSA alone could not catalyze the reaction under the same reaction conditions. However, when CSA was added as a co-catalyst to proline (1:2 ratio), the yield and enantiomeric excess were increased significantly to 73% and 61%, respectively.[12] In order to identify the essential features of the co-catalyst leading to the improved activity and selectivity, achiral 1,5-naphthalenedisulfonic acid (1,5nds), CF_3SO_3H, chiral sulfonated amino acids, and tartaric acid were used instead of CSA. Either the yield or the enantioselectivity, or both of them, were increased, though to a lesser extent in comparison with that of CSA. On the other hand, when other natural amino acids, namely L-tyrosine, phenylalanine, and tryptophan were used instead of proline, both yield and enantiomeric excess diminished significantly. In the case of tyrosine, the reaction did not proceed at all. These results, shown in Table 1, indicate that proline is essential to achieve moderate to good enantioselectivity, while CSA carrying a sulfonic group adjacent to a chiral center is the best auxiliary co-catalyst to enhance the catalytic activity and enantioselectivity of proline.

The ratio of proline and CSA on the catalytic efficiency and selectivity was evaluated and the results are shown in Table 2. The best combination was as 2:1 mixture of proline and CSA. The solvent composition has a significant impact on both the catalytic efficiency and selectivity and the results are shown in Table 3; increasing the amount of water, resulted in a dramatic decrease in enantioselectivity. The reaction still proceeded with moderate yield, but no selectivity, when the amount of water exceeded 30% When the amount of water exceeded 50%, the reaction did not proceed.

Table 3 Influence of Water on the Asymmetric Aldol Reaction of Acetone with *p*-Nitrobenzaldehyde Catalyzed by L-Proline/D-CSA (2:1)

Entry	Acetone–Water	Time (h)	Yield (%)	ee (%)
1	4:1	24	74	61
2	3:1	24	63	54
3	2:1	24	39	1
4	1:1	24	n.d.	n.d.
5	1:2	24	n.d.	n.d.
6	No water	24	10	n.d.

Table 4 L-Proline/D-CSA (2:1) Catalyzed Aldol Reactions for Cyclic Ketones



1, **4**, **5**, **6** **7** n = 1 **8** n = 2 *Syn* **9–12** n = 1 **13–16** n = 2 *Anti* **9–12** n = 1 **13–16** n = 2

Entry	R	n	Time (h)	Yield (%)	*syn/anti*		ee (%)
					^{1}H NMR[a]	HPLC	
1	NO_2	1	12	83	77/23	75/25	*syn*: >99 *anti*: 88
2	NO_2	2	48	72	49/51	46/54	*syn*: >99 *anti*: >99
3	CN	1	12	76	70/30	80/20	*syn*: >99 *anti*: >99
4	CN	2	48	68	47/53	42/58	*syn*: >99 *anti*: >99
5	Br	1	12	51	55/45	54/46	*syn*: 88 *anti*: 76
6	Br	2	48	57	42/58	42/58	*syn*: 44 *anti*: 63
7	β-Na[b]	1	12	61	53/47	53/47	*syn*: 71 *anti:* >99
8	β-Na	2	48	56	35/65	34/66	*syn*: 61 *anti*: 77

[a] Procedure to determine the *syn/anti* ratio is described in ref. 12.
[b] β-Naphthyl aldehyde.

Remarkably, when cyclic ketones were employed as donors, excellent enantioselectivity for both *syn*- and *anti*-isomers was obtained with enantiomeric excess up to 99%. The results are shown in Table 4. In the case of cyclopentanone, after a reaction time of 12 hours, moderate to good yields were obtained with good to excellent enantioselectivity for both diastereoisomers. The reaction rate for cyclohexanone is slower in comparison to that of cyclopentanone, however, excellent enantioselectivity was also obtained. It is noted that the enantioselectivity for both *syn*- and *anti*-aldol adducts of *p*-nitrobenzaldehyde with cyclohexanone (99% ee for both *syn*- and *anti*-isomer) or cyclopentanone (99% and 88% ee for the *syn*- and *anti*-isomer respectively) are much higher than that obtained in DMSO catalyzed by native proline, where the best reported enantiomeric excess was 63% or 89% for the *anti*-aldol adduct of cyclohexanone and *p*-nitrobenzaldehyde; 53% or 69% for the *anti*-aldol adduct of cyclopentanone and *p*-nitrobenzaldehyde.[1b,3a] Interestingly, when the reaction of *p*-nitrobenzaldehyde and cyclopentanone was carried out without the addition of water, the reaction proceeded sluggishly, with only a 15% yield after 24 hours; the diastereoselectivity is moderate (*syn*/*anti* 75:25), but the enantioselectivity decreased significantly with only a 30% ee for the s*yn*-isomer and 70% ee for the *anti*-isomer.

In summary, we have developed an organo-cocatalyst which shows high reactivity and excellent enantioselectivity for a class of aldol reactions in aqueous media, especially with cyclic ketones as donors. Our results demonstrate that the acid-base methodology for designing an effective catalyst[3b] can be extended to develop chiral acid-chiral base co-catalyst for asymmetric direct aldol reaction. The chiral co-catalyst can fine-tune the activity and enantioselectivity of the native proline, and make direct asymmetric aldol reaction achievable in a more environmentally friendly manner.[13]

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(12) **Typical Procedure** (Table 1, entry 3): Anhyd acetone (2.0 mL, dried with K_2CO_3 before use) was added to *p*-nitrobenzaldehyde (75 mg, 0.5 mmol), followed by L-proline (20 mol%) and D-CSA (10 mol%) dissolved in water (0.5 mL). The resulting mixture was stirred at r.t. for 12 h. After treating the reaction mixture with saturated aq $NaHCO_3$ (5 mL), the aqueous layer was separated, and extracted with EtOAc three times. The combined organic extracts were washed with brine (5 mL), dried over anhyd Mg_2SO_4, and concentrated. The residue was purified by preparative thin layer chromatography (Silica gel plates GF254, hexane–EtOAc) to give the aldol product (76.3 mg). The *anti*/*syn* ratio is established by ^1H NMR; $\delta = 4.83$ ppm ($J = 9.0$ Hz) – CH of the *anti*-isomer; 5.42 ppm ($J = 2.7$ Hz) – CH of the *syn*-isomer (Table 4, entry 1). The ee values were determined by HPLC, Daicel chiralpak AS-RH.

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