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Chiral Diols: A New Class of Additives for Direct Aldol Reaction Catalyzed by L-Proline

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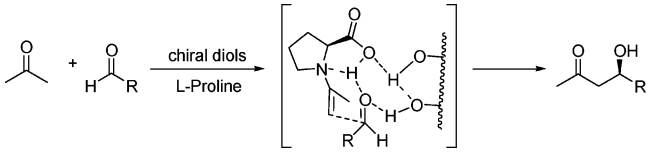

Nine C_2 symmetric diols have been examined as additives in the L-proline-catalyzed direct aldol reaction with significant improvement in enantioselectivity, conversion efficiency, and yield. Loading of 1 mol % of (*S*)-BINOL leads to the desired products in up to 98% ee and 90% yield. A transition state is proposed.

In the past decades, L-proline, the simplest "enzyme",[1] has become one of the most attractive molecules in green synthetic chemistry. As an effective organocatalyst,[2] it has been successfully applied in Diels−Alder reactions,[3] Baylis−Hillman reactions,[4] Michael reactions,[5] Mannich reactions,[6] direct electrophilic α-aminations,[7] Robinson annulations,[8] aldol reactions, and others.[9] Among them, the direct aldol reaction is particularly interesting.[10]

Since the pioneering work by List and Barbas that L-proline could act as an efficient catalyst in intermolecular direct aldol addition,[11] numerous efforts have been made to improve the stereoselectivity. Because of the poor solubility of proline in organic solvents, researchers strived to perform the reaction in water[12] and ionic liquids[13] and even utilized polymer-supported proline[14] which is hydrophilic or lipophilic. In the meantime, a great deal of endeavors were devoted to the design of different proline derivatives[15] or to simulation of the proline structure to construct new potential catalysts;[16] unfortunately, sometimes those new molecules failed to show satisfactory results. Therefore, much attention has been shifted to a practical strategy: to improve enantioselectivity or accelerate the reaction by using additives in the reaction system.[17] Additives reported

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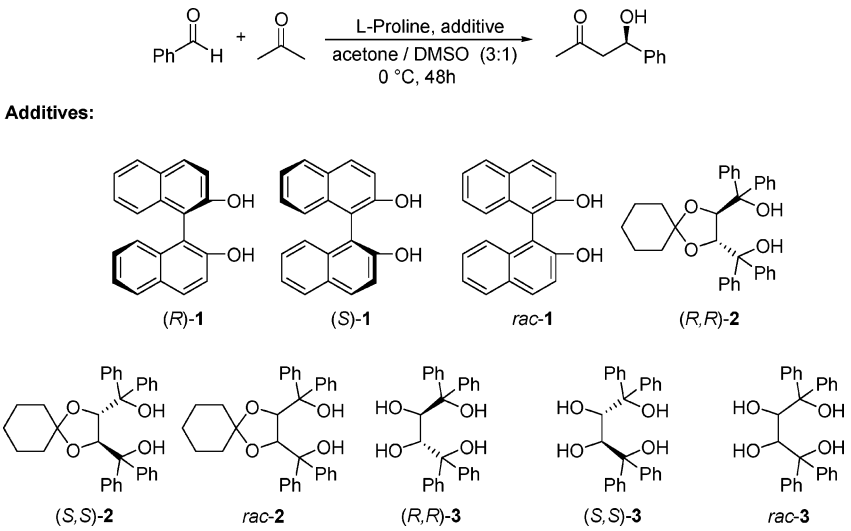

FIGURE 1. Additives evaluated in the reaction.

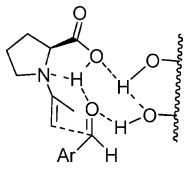

FIGURE 2. Possible supramolecular transition state.

TABLE 1. Screening of the Additives on the Direct Aldol Reaction[a]

entry	additive	sub./cat./additive	conversion (%)[b]	yield (%)[c]	ee (%)[d]
1	no	10:3:0	60	43	72
2	(*R*)-**1**	10:3:2	93	52	91
3	(*S*)-**1**	10:3:2	76	52	94
4	*rac*-**1**	10:3:2	72	50	76
5	(*R*,*R*)-**2**	10:3:2	94	54	97
6	(*S*,*S*)-**2**	10:3:2	96	59	96
7	*rac*-**2**	10:3:2	87	50	91
8	(*R*,*R*)-**3**	10:3:2	62	40	96
9	(*S*,*S*)-**3**	10:3:2	59	36	92
10	*rac*-**3**	10:3:2	70	54	89
11[e]	(*R*)-**1**	10:3:2	70	41	4
12[e]	(*S*)-**1**	10:3:2	72	43	5

[a] The entire reaction was carried out in acetone/DMSO (3:1) at 0 °C for 48 h. [b] Based on the aldehyde recovery after column chromatography. [c] Isolated yield after column chromatography. [d] The configuration was assigned as *R*. [e] Catalyzed by *rac*-proline

in the literature include bases, acids, and water.[18] It was believed that the additives could improve the rate and enantioselectivity of the reaction by promoting the enamine formation according to the theory revealed by Houk and co-workers.[19] Inspired by this, we chose readily available chiral diols as additives in the L-proline-catalyzed aldol reaction, and the desired products were obtained in up to 98% ee and 90% yield. Herein, we report the L-proline-catalyzed direct aldol reaction assisted by chiral diols.

To optimize the reaction conditions, the reaction of benzaldehyde and acetone was investigated as a model (Figure 1). The addition was allowed to perform at 0 °C for 48 h in the presence of L-proline and chiral diols or tetraols. In early studies, acetone itself was proved to be a good solvent. However,

TABLE 2. Screening of Additive Loadings on the Reaction[a]

entry	sub./cat./additive	additive	conversion (%)[b]	yield (%)[c]	ee (%)[d]
1	10:3:0	no	60	43	72
2	10:3:2.0	(*R*)-**1**	93	52	91
3	10:3:0.5	(*R*)-**1**	80	60	97
4	10:3:0.1	(*R*)-**1**	87	60	96
5	10:3:0.05	(*R*)-**1**	66	59	96
6	10:3:2.0	(*S*)-**1**	76	52	94
7	10:3:0.5	(*S*)-**1**	64	59	89
8	10:3:0.1	(*S*)-**1**	79	56	98
9	10:3:0.05	(*S*)-**1**	68	63	85
10	10:3:2.0	(*R*,*R*)-**2**	94	54	97
11	10:3:0.5	(*R*,*R*)-**2**	70	57	97
12	10:3:0.1	(*R*,*R*)-**2**	77	67	95
13	10:3:0.05	(*R*,*R*)-**2**	77	61	93

[a] The reaction was carried out in acetone/DMSO (3:1) at 0 °C for 48 h. [b] Based on the aldehyde recovery after column chromatography. [c] Isolated yield after column chromatography. [d] The configuration was assigned as *R*.

solubility of L-proline is poor in the acetone, so DMSO was employed as the cosolvent to improve the solubility.

Some representative diols and tetraols were screened, and the results are shown in Table 1. It clearly indicates that the enantioselectivity was improved (entries 2, 3, 5, 6, 8, and 9) compared with the original 72% ee in which no additive was used (entry 1). More significantly, the enantioselectivity was increased 25% from 72% ee to 97% ee in the best case (entry 5). It is notable that all the reactions afforded the aldol product in the same configuration and high enantioselectivity, regardless of the chirality of the additives (entries 2, 3, 5, 6, 8, and 9). Thereupon, three racemic additives, *rac*-**1**, *rac*-**2**, and *rac*-**3**, were also examined. The results indicated that the racemic additives gave the product with the same configuration, and the enantioselectivity was slightly dropped (entries 4, 7, and 10) compared with those with enantiopure additives. On the other hand, when racemic proline was used as catalyst, very poor chiral induction was observed even with enantiopure diols as additives (entries 11 and 12). On the basis of these results, we attributed the chiral induction in the aldol reaction to the chirality of L-proline, and probably, the additives only enhanced the chiral

TABLE 3. Direct Aldol Reaction Assisted by (*S*)-BINOL[a]

entry	R	additive	sub./cat./additive	product	configuration[b]	conversion (%)[c]	yield (%)[d]	ee (%)[e]
1	4-ClC_6H_4	(*S*)-**1**	10:3:0.1	**4a**	*R*	94	79	83
2		no	10:3:0		*R*	82	76	75
3	4-BrC_6H_4	(*S*)-**1**	10:3:0.1	**4b**	*R*	90	76	97
4		no	10:3:0		*R*	88	82	75
5	3-BrC_6H_4	(*S*)-**1**	10:3:0.1	**4c**	*R*	89	86	95
6		no	10:3:0		*R*	92	89	75
7	2,6-$Cl_2C_6H_3$	(*S*)-**1**	10:3:0.1	**4d**	*R*	95	90	96
8		no	10:3:0		*R*	94	80	89
13	Ph	(*S*)-**1**	10:3:0.1	**4e**	*R*	79	56	98
15		no	10:3:0		*R*	60	43	72
16	9-anthranyl	(*S*)-**1**	10:3:0.1	**4f**	*R*[f]	30	23	87
18		no	10:3:0		*R*[f]	14	10	92
19	*i*-Pr	(*S*)-**1**	10:3:0.1	**4g**	*R*	−	46	90
21		no	10:3:0		*R*	−	43	88

[a] The reaction was carried out in acetone/DMSO (3:1) at 0 °C for 48 h. [b] Assigned by comparison of the HPLC retention time of the product with reported data (ref 17b). [c] Based on the aldehyde recovery after column chromatography. [d] Isolated yield after column chromatography. [e] Determined by HPLC. [f] Assigned by analogy.

inductive ability of L-proline by the formation of a chiral supramolecular system through hydrogen-bonding interactions (Figure 2).

Next, the additive loading was screened and the diols (*R*)-**1**, (*S*)-**1**, and (*R*,*R*)-**2** were chosen for further optimization. The results are summarized in Table 2. It seems that a higher ratio of additives is favorable to the elevation of conversion of the starting material; however, the yield of the desired product is slightly lowered. Taking the conversion, yield, and enantioselectivity into consideration, we determined that the best additive loading is 1 mol % for (*S*)-**1** (entry 8) though the enantioselectivity did not fluctuate too much.

Having established the optimal reaction parameters, we evaluated several aldehydes and the results are summarized in Table 3. In most cases, the reactions afforded the desired products with improved enantiomeric excesses with the exception of the reaction of 9-anthranylaldehyde with acetone. Perhaps the bulky 9-anthranyl was unfavorable for the *re*-facial attack of the carbon anion in the transition state in the limited space. As for the reaction of *iso*-butyraldehyde, the enantioselectivity was only slightly improved. Perhaps, the catalyst system does not work well due to the flexibility of the aliphatic aldehyde.

In summary, as a new class of readily available additives, chiral diols were successfully applied to the asymmetric direct aldol reaction catalyzed by L-proline. When 1 mol % of the additive was used in the reaction, the enantioselectivity was improved considerably. It was proposed that the formation of a chiral supramolecular transition state through hydrogen bonding contributes to the improvement of the reaction.

Experimental Section

In a test tube fitted with a magnetic bar, L-proline (0.1725 g, 1.5 mmol) and (*S*)-BINOL (0.0143 g, 0.05 mmol) were charged, followed by injection of acetone (3 mL) and DMSO (1 mL). After stirring for 15 min in an ice bath, 4-chlorobenzaldehyde (0.7028 g, 5 mmol) was added, and stirring continued at 0 °C for 48 h. The reaction was quenched with saturated aqueous ammonium chloride and extracted with ethyl acetate (10 mL × 3). The combined extracts were dried over anhydrous Na_2SO_4. The following concentration and purification through flash column chromatography on a silica gel (200−300 mesh, eluent/petroleum ether/acetate 2:1) afforded the desired product (4*R*)-hydroxy-4-(4′-chlorophenyl)-butan-2-one (**4a**):[15b] white solid, mp 46−47 °C; 79% yield; $[\alpha]_D^{27}$ +52.9 (c = 1.3, in $CHCl_3$); 83% ee (determined by HPLC (Daicel chiralpak AS-H, *i*-PrOH/hexane 10:90), UV 220 nm, flow rate, 1 mL/min; major t_R 12.2 min and minor t_R 15.0 min); IR (KBr) ν 3430, 3051, 2883, 1700, 1594; ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 7.30−7.24 (m, 4H), 5.10 (s, 1H), 3.45 (s, 1H), 2.82−2.80 (m, 2H), 2.18 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm) 208.4, 141.2, 133.3, 128.7, 127.1, 69.7, 52.6, 31.7.

Compounds **4b**−**g** were afforded in a similar manner and were identical with the literature data.[15b,h] The conversion, yield, and enantiomeric excess are shown in Table 3.

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Supporting Information Available: General methods, ^{1}H NMR and ^{13}C NMR spectra, HPLC analysis data. This material is available free of charge via the Internet at http://pubs.acs.org.

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