Organocatalysis

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A Diarylprolinol in an Asymmetric, Catalytic, and Direct Crossed-Aldol Reaction of Acetaldehyde**

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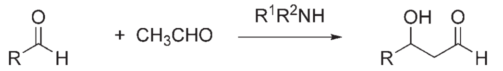
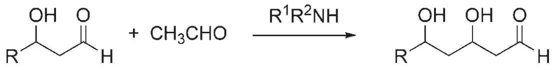
Dedicated to Professor E. J. Corey on the occasion of his 80th birthday

The aldol reaction is recognized to be one of the most important carbon–carbon bond-forming processes in organic synthesis.[1] Acetaldehyde, the simplest aldehyde, generates versatile β-hydroxy α-unsubstituted aldehydes when used as the nucleophilic component in this reaction [Eq. (1)]. In spite of its synthetic importance, we are not aware of any examples of a successful direct, enantioselective aldol reaction of this type except for the enzymatic reaction.[2] Indirect methods reported include the chiral Lewis base mediated aldol reaction of trimethyl siloxyethene, a synthetic equivalent of acetaldehyde described by Denmark and Bui,[3] while Yamamoto and Boxer have recently developed an acetaldehyde super silyl enol ether that reacts in racemic fashion.[4]

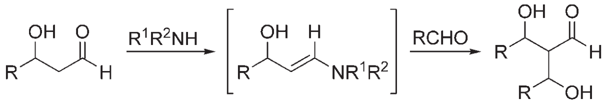


(1)

Even among organocatalyst-mediated[5] aldol reactions, there is no successful reaction of acetaldehyde in spite of the extensive research on this class of reactions in recent years.[6,7] As the aldol product generated when acetaldehyde is employed is unsubstituted at the α position, it is expected to act both as a reactive electrophile [Eq. (2)] and nucleophile [Eq. (3)]. Thus, the suppression of over-reactions is a difficult problem. In fact, Barbas and co-workers reported that 5-hydroxy-2-hexenal, a trimerization product of acetaldehyde, was obtained in 12% yield with 84% *ee* when acetaldehyde was treated with proline.[8] In this communication we disclose the first, direct, enantioselective crossed-aldol reaction of acetaldehyde.



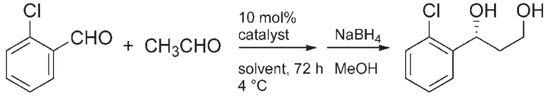
(2)



(3)

The aldol reaction of acetaldehyde with *o*-chlorobenzaldehyde was selected as a model (Table 1). As the aldol product was unstable, it was reduced to the corresponding diol, which was isolated. The efficacy of various catalysts was examined first. Proline is known to be a suitable catalyst for the crossed-aldol reactions of aldehyde/ketone[9] and aldehyde/aldehyde combinations.[10] When proline was employed under several different conditions, hardly any crossed-aldol product was obtained, and crotonaldehyde, generated by the self-aldol reaction followed by dehydration, was formed (entry 1, Table 1). While the diphenyl- and dixylylprolinols **3** and **4** (Figure 1) provided the aldol with good enantioselectivity, the yields were low (entries 4 and 5, Table 1). In contrast to these failures, when the trifluoromethyl-substituted diarylprolinol **1** was employed, the crossed-aldol product was generated in good yield with nearly complete enantiopurity (entry 2, Table 1). It should be noted that a

Table 1: The effect of catalyst and solvent on the aldol reaction of acetaldehyde and *o*-chlorobenzaldehyde[a]



Entry	Catalyst	Solvent	Yield [%][b]	*ee* [%][c]
1	proline[d]	DMF	12	47
2	**1**	DMF	85	99
3	**2**	DMF	15	75
4	**3**	DMF	33	85
5	**4**	DMF	11	78
6	**1**	neat[e]	40	83
7	**1**	H_2O[f]	86	93
8	**1**	DMSO	76	99
9	**1**	THF	40	95
10	**1**	CH_3CN	71	98

[a] Unless otherwise indicated, reactions were performed employing *o*-chlorobenzaldehyde (0.4 mmol), acetaldehyde (2.0 mmol), catalyst (0.04 mmol), and solvent (0.4 mL) at 4 °C for 72 h. [b] Yield of isolated product. [c] Optical purity was determined by HPLC analysis on a chiral phase. [d] Proline (30 mol%) was employed; structures of other catalysts shown in Figure 1. [e] Solvent was not employed. [f] Water (5 equiv) was added.

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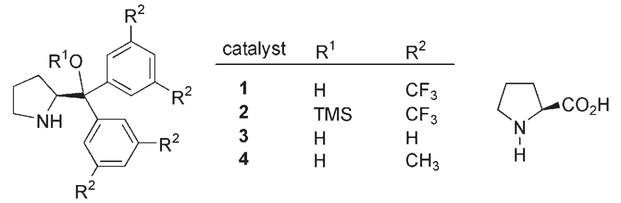


catalyst	R^1	R^2
1	H	CF_3
2	TMS	CF_3
3	H	H
4	H	CH_3

Figure 1. Organocatalysts examined in this study.

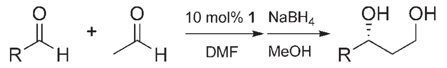
diarylprolinol silyl ether,[11–13] which has been developed independently by our[11] and Jørgensen's[12] groups, is not effective (entry 3, Table 1). This is in marked contrast to the Michael reactions of aldehydes with nitroalkenes,[11a] for which the silyl ether is more reactive than the corresponding alcohol (vide infra). Solvent screening using H_2O, CH_3CN, THF, DMSO, and DMF showed that while water affords good results,[14] the best combination of yield and enantioselectivity is realized with DMF (entry 2, Table 1). A second aldol reaction, in which the aldol product of acetaldehyde participates as an acceptor, was not observed because of the facile formation of the cyclic hemiacetal from the aldol product and acetaldehyde.[10b]

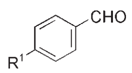
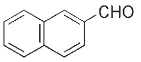
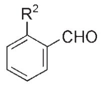
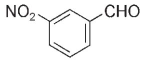
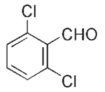
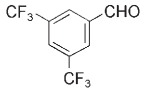
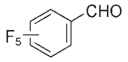
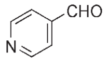
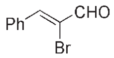
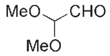
As excellent results had been obtained for the model system, the generality of the reaction was examined (Table 2). The reaction proceeds efficiently with both electron-deficient aromatic aldehydes and olefinic aldehydes, affording the corresponding aldol products in good to excellent yield with excellent enantioselectivity. The reaction also proceeds with non-activated aldehydes, such as benzaldehyde and 2-naphthaldehyde, though this requires the addition of 5 equiv of acetaldehyde every 24 h repeated three times to give the nearly optically pure aldol products in moderate yield. Heteroaromatic aldehydes such as 4-pyridinecarbaldehyde can also be employed as the electrophilic component. In the case of pentafluorobenzaldehyde, the reaction was performed in the presence of water in order to suppress the dehydration reaction. Dimethoxyacetaldehyde was also a useful electrophilic aldehyde, and it could be used as its commercially available aqueous solution to afford a highly functionalized aldol. Excellent enantioselectivity was observed in most cases. The results for the aliphatic aldehydes are not as good as aromatic aldehydes.

The aldol product of benzaldehyde (Table 2, entry 1) was reduced with $NaBH_4$ to afford the corresponding diol, which is a key intermediate in the synthesis of fluoxetine (Prozac),[15] a widely used selective serotonin-reuptake inhibitor. The absolute configuration of this aldol adduct was determined to be *R* by comparison of its optical rotation with that in the literature.[16]

The reaction is thought to proceed as follows: Diarylprolinol catalyst **1** reacts with acetaldehyde to generate enamine **5**, which reacts with an electrophilic aldehyde as shown in Figure 2. This model can explain the absolute configuration of the aldol product. Barbas and co-workers reported that prolinol is an effective organocatalyst in an enantioselective fluoroaldol reaction, in which a similar transition state was proposed.[17] Though the electrophile attacks from the side opposite to the bulky diphenylmethyl moiety in the reaction catalyzed by a diphenylprolinol silyl ether,[11] the aldehyde reacts on the more hindered face of the catalyst in the present case. This is because the aldehyde is activated by coordination to the proton of the hydroxy group through a hydrogen bond. This interaction would be stronger in the case of the trifluoromethyl-substituted catalyst **1** than in diphenylprolinol **3** owing to the higher acidity of its OH group. The importance of this hydrogen bond is also evident

Table 2: Catalytic asymmetric aldol reaction of acetaldehyde with various aldehydes[a]



Entry	Aldehyde		*T* [°C]	*t* [h]	Yield [%][b]	*ee* [%][c]
1[d]		$R^1 = H$	23	120	53	99
2		$R^1 = NO_2$	23	24	85	96
3		$R^1 = CF_3$	4	72	74	99
4[e]		$R^1 = Br$	23	96	77	97
5[e]		$R^1 = OTf$	23	96	71	98
6[d]			23	120	50	97
7		$R^2 = Cl$	4	72	85	99
8		$R^2 = NO_2$	23	72	89	97
9			23	72	89	97
10			23	72	82	96
11			4	96	76	99
12[f]			4	24	91	98
13			23	43	83	99
14[g]			4	120	53	98
15[h]			4	72	92	80

[a] Unless otherwise indicated, the reaction was performed employing electrophilic aldehyde (0.4 mmol), acetaldehyde (2.0 mmol), **1** (0.04 mmol) and DMF (400 μL) at the indicated temperature. [b] Yield of isolated product. [c] Optical purity was determined by HPLC analysis on a chiral stationary phase; see the Supporting Information for details. [d] Acetaldehyde (5 equiv) was added at 24-h intervals three times; see the Supporting Information. [e] 30% catalyst was employed. [f] Water (5 equiv) was added. [g] Starting material was recovered in 45% yield. [h] Commercially available aqueous solution (60 wt%) was employed.

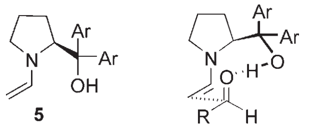


Figure 2. Intermediate enamine **5** and the transition state. Ar = 3,5-bis(trifluoromethyl)phenyl.

from the low reactivity of the corresponding silyl ether catalyst **2**.

Though diarylprolinol silyl ether is widely used as an effective organocatalyst, the present reaction is a rare example of its precursor, diarylprolinol, acting as an outstanding catalyst,[18] and the first example of the use of diarylprolinol in an enantioselective aldol reaction. The β-hydroxy α-unsubstituted aldehydes generated are versatile synthetic intermediates and are obtained with excellent enantioselectivity. Thus, the present aldol reaction of acetaldehyde is a synthetically useful process.

Experimental Section

Typical procedure (Table 2, entry 7): Acetaldehyde (112 μL, 2.0 mmol) was added to a mixture of (*S*)-2-{bis-[3,5-bis(trifluoromethyl)phenyl]hydroxymethyl}pyrrolidine (21 mg, 0.04 mmol) and 2-chlorobenzaldehyde (45 μL, 0.40 mmol) in anhydrous DMF (0.40 mL) in a sealed tube (ACE GLASS, product number 5027-05) at 4 °C. After the reaction mixture had been stirred for 72 h, MeOH (1 mL) and $NaBH_4$ (74 mg, 2.0 mmol) were added. The resulting reaction was stirred for an additional 1 h at 0 °C, before it was quenched with pH 7.0 phosphate buffer solution. The organic materials were extracted with ethyl acetate three times. The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated in vacuo after filtration. Purification by preparative thin layer chromatography (ethyl acetate/hexane 1:1) gave (1*R*)-1-(2-chlorophenyl)propane-1,3-diol (63 mg, 0.34 mmol) in 85 % yield. Enantiometric excess was 99 % *ee*.

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Keywords: acetaldehyde · aldol reaction · asymmetric catalysis · organocatalysis

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