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Special Issue

Diarylprolinol-Mediated Asymmetric Direct Cross-Aldol Reaction of α,β-Unsaturated Aldehyde as an Electrophilic Aldehyde

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Abstract: The diarylprolinol-mediated asymmetric direct cross-aldol reaction of α,β-unsaturated aldehyde as an electrophilic aldehyde was developed. The reaction becomes accelerated by an acid when a carbonyl group is introduced at the γ-position of the α,β-unsaturated aldehyde. Synthetically useful γ,δ-unsaturated β-hydroxy aldehydes were obtained with high *anti*-selectivity and excellent enantioselectivity.

Aldol reaction is one of the most important carbon-carbon bond-forming reactions.[1] Since the seminal paper of proline-mediated asymmetric direct aldol reaction between aldehyde and ketone by List, Lerner and Barbas in 2000,[2] the field of organocatalysis has developed rapidly, and many proline-based organocatalysts have been developed for the asymmetric aldol reaction of aldehyde and ketone with excellent results.[3] As for the cross-aldol reaction of two different aldehydes, although MacMillan and co-workers reported such a reaction catalyzed by proline for the first time in 2002,[4] to date it has not been thoroughly investigated.[5] Our group is interested in the asymmetric direct cross-aldol reaction promoted by the use of organocatalyst, and has found that the diarylprolinol-bearing 3,5-bis(trifluoromethyl)phenyl as the aryl moiety **1**[6] is an excellent aldol catalyst (Figure 1). It can catalyze the aldol reaction of acetaldehyde as a nucleophile,[7] and also catalyze the aldol reaction of ethyl glyoxylate,[8] chloral,[9] chloroacetaldehyde,[10] dichloroacetaldehdye,[11] and alkynyl aldehyde[12] as electrophilic aldehydes.[13]

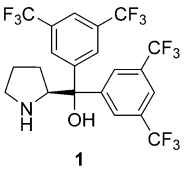

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Figure 1. Diarylprolinol catalyst.

On the other hand, allyl alcohol is an important building block in organic synthesis, and one of the synthetic methods for the generation of chiral allyl alcohol is the asymmetric cross-aldol reaction of α,β-unsaturated aldehyde, which affords γ,δ-unsaturated β-hydroxy aldehyde. To our knowledge, there are only three examples of the organocatalyst-mediated asymmetric cross-aldol reaction of α,β-unsaturated aldehyde; that is, the reactions of *tert-butyl*-4-oxo-2-butenoate,[14] 3-(*p*-nitrophenyl)prop-2-enal,[14] and 2-bromocinnamaldehyde.[7] All three reactions were catalyzed by the same diarylprolinol organocatalyst **1**. The cross-aldol reaction of α,β-unsaturated aldehyde is very useful but rare, and its generality has not been broadly investigated. In this paper, we describe the optimization of the cross-aldol reaction of α,β-unsaturated aldehyde with its generality.

We chose the reaction of 4-oxopent-2-enal (**2a**) and 3-phenylpropanal (**3a**) as a model reaction and investigated the reaction conditions (Table 1). As the generated β-hydroxyaldehyde was partially decomposed and epimerized during purification by silica gel column chromatography, it was treated with Wittig reagent ($Ph_3P=CHCO_2Et$) in situ to give the corresponding α,β-unsaturated ester **4a**, which was isolated and characterized. First, the reaction was carried out in the presence of catalyst **1** in THF, but the reaction was slow and could only afford the product in 22% yield after 96 h (entry 1). Water is known to accelerate the aldol reaction[15] and 10 equivalents of water were added, which led to an increased yield of 56% after 48 h (entry 2). To increase the reactivity, the additive was examined in detail. Although NaOAc was not effective,[16] acid was found to accelerate the reaction. Among the acids examined, good yield was obtained when acetic acid was employed as an additive to afford the product in 74% yield with high *anti*-selectivity and excellent enantioselectivity (entry 4). It shoud be noted that Michael products were not detected as a by-product under the present reaction conditions, although Michael reaction is a possible reaction because α,β-unsaturated aldehyde is a suitable Michael acceptor.

Then, solvent optimization was conducted, which revealed that THF was more suitable (entry 4). Next, the loading of the catalyst was investigated. Good results were obtained when 20 mol% of the catalyst was used (entry 9). It should be noted that the reaction also proceeds well in the presence of 10 mol% of the catalyst to afford the product without decreasing the enantioselectivity, although the reaction time was longer (entry 10). As for the molar ratio of the starting materials, good results were obtained in both cases when the nucleophilic aldehyde **3a** was used as two equivalents toward the electrophilic aldehyde **2a** and the opposite combination such as the electrophilic aldehyde **2a** was employed as two equivalents toward the nucleophilic aldehyde **3a** (entries 11, 12).

As the best reaction conditions were obtained, the generality of the reaction was investigated (Table 2). As for the nucleo-

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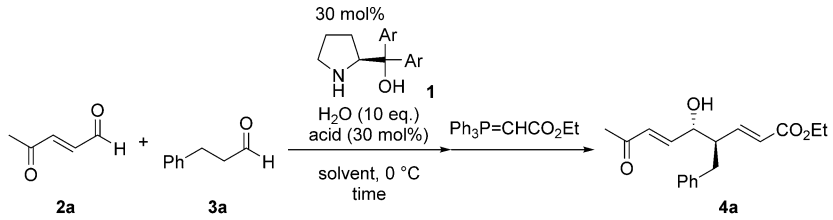
Table 1. The effect of additive and solvent in the asymmetric aldol reaction of **2a** and **3a**.[a]



2a 3a 4a

Entry	Solvent	Acid	*t* [h]	Yield [%][b]	*anti*:*syn*[c]	*Ee* [%][d]
1[e,f]	THF	none	96	22	1.2:1	76
2[e]	THF	none	48	56	2.6:1	86
3	THF	CCl_3CO_2H	28	64	10:1	97
4	THF	CH_3CO_2H	30	74	9.1:1	98
5	THF	$PhCO_2H$	30	64	6.7:1	96
6	dioxane	CH_3CO_2H	30	64	7.7:1	96
7	Et_2O	CH_3CO_2H	25	59	5.3:1	98
8	DMF	CH_3CO_2H	30	64	4.8:1	97
9[g]	THF	CH_3CO_2H	41	72	11:1	97
10[h]	THF	CH_3CO_2H	137	62	9.1:1	98
11[i]	THF	CH_3CO_2H	35	70	9.1:1	98
12[j]	THF	CH_3CO_2H	30	80	12:1	98

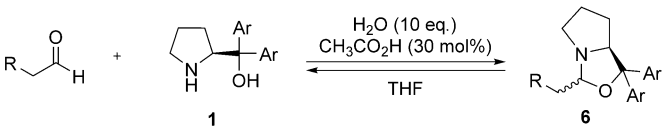
[a] Unless otherwise shown, reactions were performed by employing α,β-unsaturated aldehyde **2a** (0.3 mmol), 3-phenylpropanal (**3a**) (0.9 mmol), organocatalyst **1** (0.09 mmol) and additive (0.09 mmol), water (3 mmol) in solvent (0.3 mL) at 0 °C for the indicated time. The aldol product was treated with $Ph_3P{=}CHCO_2Et$. [b] Isolated yield of the ester **4a**. [c] Dr is determined by ^{1}H NMR analysis. [d] Enantiomeric excess (*ee*) of ester **4a** was as determined by HPLC analysis over a chiral solid phase. [e] The reaction was performed at room temperature. [f] Water was not used. [g] Catalyst **1** (20 mol%) was used. [h] Catalyst **1** (10 mol%) was used. [i] **2a** (0.3 mmol) and **3a** (0.6 mmol, 2 equivalents) were used. [j] **2a** (0.6 mmol, 2 equivalents) and **3a** (0.3 mmol) were used.

philic aldehyde, not only 3-phenylpropanal but also propanal, and isovaleraldehyde, and functionalized aldehyde such as β-alkoxyaldehyde, and aldehyde with *cis*-alkene moiety can be successfully employed in the reaction to afford the products with good *anti*-selectivity and excellent enantioselectivity (entries 1–5). As for the α,β-unsaturated aldehyde, the reaction of 3-chloro-4-oxo-2-pent-2-enal is fast owing to the electron-withdrawing group of chloride (entry 6). α-Methyl substituent does not disturb the reaction to provide the product with excellent enantioselectivity (entry 7). Not only methyl substituent, but also phenyl and furyl substituents are suitable and the reaction of these 4-substituted 4-oxopent-2-enal derivatives afforded the aldol products also with excellent enantioselectivity (entries 8, 9). As the solubility of **2e** is not good, dilute THF condition was employed (entry 9).

Although we have already reported several cross-aldol reactions catalyzed by diarylprolinol **1**, this is the first aldol reaction in which acid is an effective additive. In fact, when we carefully investigated the aldol reaction of alkynyl aldehyde such as 3-triethylsilylpropinal (**5**), the acceleration was not observed in the presence of acid. Given the special effect of acid in the present reaction, we further investigated its effect.

It is known that aldehyde and catalyst **1** react to generate *N,O*-acetal **6** (Scheme 1).[17] The acid might be involved in the generation speed of *N,O*-acetal **6**. Alkenyl aldehydes **2a** and **2d**, alkynyl aldehyde **5**, and alkyl aldehyde **3a** were treated with catalyst **1** in the presence of acetic acid and water. In all cases, the corresponding *N,O*-acetals **6** were generated instantly. Thus, there is no observable difference in the generation of *N,O*-acetals **6** between the various aldehydes (see SI).

Another possibility would be that the acid might be accelerating the exchange of *N,O*-acetals in **6**. To check this, *N,O*-acetal of alkenyl aldehyde **6d** was treated with alkynyl aldehyde **5** in the presence of acetic acid and water. As both aldehydes do not possess an α-proton, aldol reaction cannot proceed. When



Scheme 1.

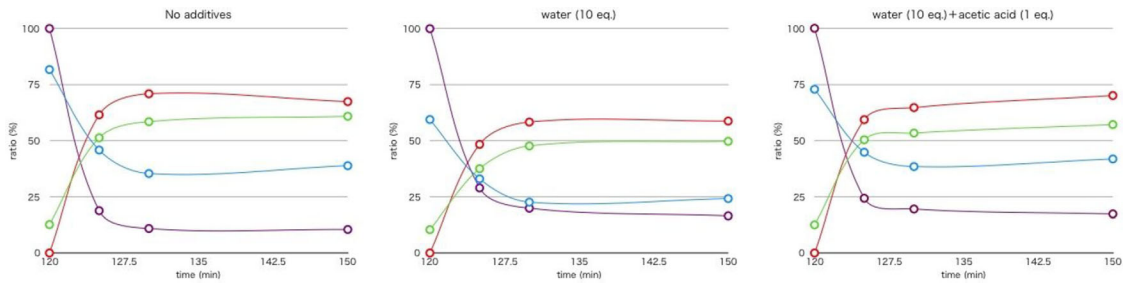
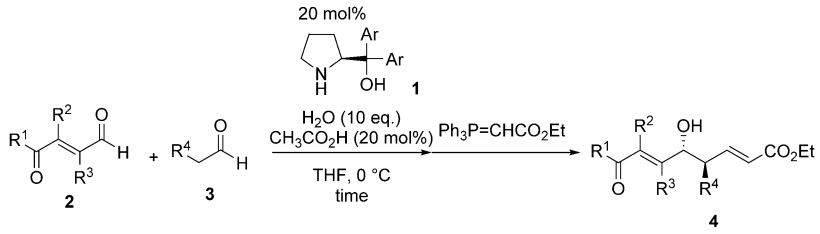
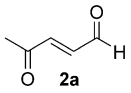
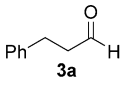
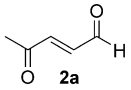
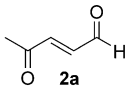
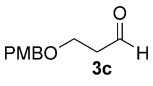
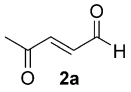
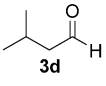
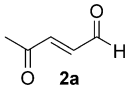
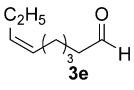
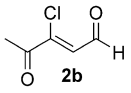
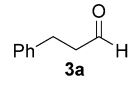
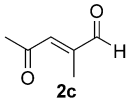
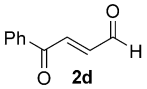
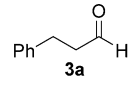
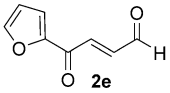
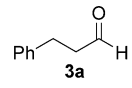


Figure 2. The effect of acid and water in the exchange reaction of **6d** and **7**. To a mixture of (*E*)-4-oxo-4-phenylbut-2-enal (**2d**) (0.4 mmol, 63.6 mg) and 1,3,5-trimethoxybenzene (0.1 mmol, 16.8 mg) as internal standard in THF (400 μL) was added catalyst **1** (0.4 mmol, 208 mg) at 23 °C. H_2O (4.0 mmol, 72 μL) and acetic acid (0.4 mmol, 24 μL) were added to the reaction mixture. After stirring the reaction mixture for 2 h at 23 °C, it was confirmed by NMR that *N,O*-acetal **6d** was formed. Then, alkynyl aldehyde **5** was added to the reaction mixture. The reaction was monitored by ^{1}H NMR spectroscopy. The ratio of each product was calculated by integration of selected peaks in the ^{1}H NMR spectra and plotted on the graph.

Table 2. The generality of the cross-aldol reaction of α,β-unsaturated aldehydes.[a]



Entry	Aldehyde **2**	Aldehyde **3**	*t* [h]	Yield [%][b]	*anti*:*syn*[c]	*Ee* [%][d]
1	 **2a**	 **3a**	55	70	9.0:1	97
2[e]	 **2a**	 **3b**	20	70	8.2:1	98
3	 **2a**	 **3c**	15	82	4.0:1	97
4[e]	 **2a**	 **3d**	123	61	6.2:1	89
5[e]	 **2a**	 **3e**	75	54	6.3:1	97
6	 **2b**	 **3a**	14	78	>20:1	98
7[e,f]	 **2c**	 **3b**	14	46	20:1	98
8[g,h]	 **2d**	 **3a**	32	62	4.8:1	92
9[g,h,i]	 **2e**	 **3a**	80	63	5.8:1	94

[a] Unless otherwise shown, reactions were performed by employing α,β-unsaturated aldehyde (0.3 mmol), nucleophilic aldehyde (0.6 mmol), organocatalyst **1** (0.06 mmol), water (3 mmol) and CH_3CO_2H (0.06 mmol) in THF (0.3 mL) at 0 °C for the indicated time. The aldol product was treated with $Ph_3P=CHCO_2Et$. [b] Isolated yield. [c] Dr is determined by ^1H NMR analysis. [d] Enantiomeric excess (*ee*) is determined by HPLC analysis over a chiral solid phase. See Supporting Information for details. [e] Nucleophilic aldehyde (0.9 mmol, 3 equiv) was used. [f] Reaction was performed at 23 °C. [g] The reaction was performed at 5 °C. [h] CH_3CO_2H (0.1 mmol) was used. [i] THF (0.6 mL) was used.

aldehyde **2d** and catalyst **1** were mixed, *N,O*-acetal **6d** was formed instantly. Then, alkynyl aldehyde **5** was added with or without water and/or CH_3CO_2H (Scheme 2). Exchange speeds of *N,O*-acetals **6d** and **5** were similar in all cases in the presence of water and CH_3CO_2H (Figure 2). Thus, the exchange of *N,O*-acetal **6** is sufficiently fast even without acid.

Next, we investigated the reaction of 3-(2,5-dichlorophenyl)propenal **2f** (Scheme 3). In this case, the effect of acid was not observed. An additional carbonyl group is necessary for the acceleration effect induced by acid. Thus, we propose that acid protonates the basic carbonyl moiety, to lower the LUMO level of α,β-unsaturated aldehyde **2**, which accelerates the reaction.

The reaction is thought to proceed as follows: The enamine, which is generated from the aldehyde, as shown in Figure 3, in which the alkenyl aldehyde is activated by the hydroxy group and acetic acid through a hydrogen bond.

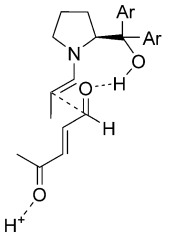
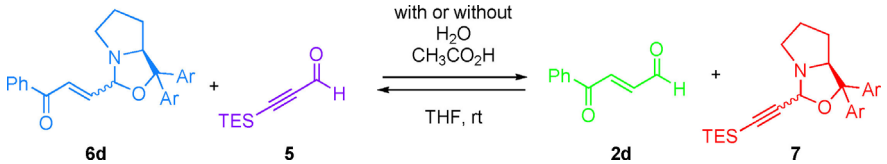
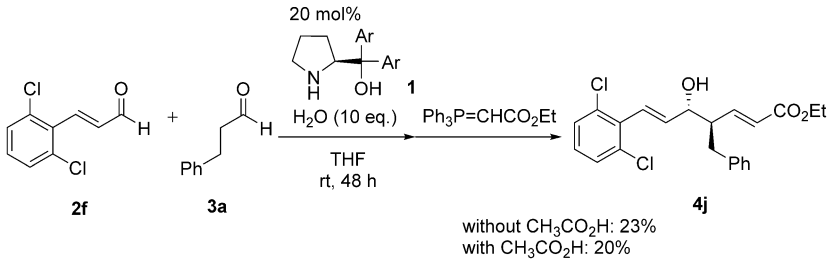


Figure 3. The proposed transition state between enamine and alkenyl aldehyde.

In summary, we have developed the asymmetric direct cross-aldol reaction of α,β-unsaturated aldehyde catalyzed by diarylprolinol **1**. Synthetically useful γ,δ-unsaturated β-hydroxy aldehydes were obtained with high *anti*-selectivity and excellent enantioselectivity. When there is a carbonyl group at the γ-position of the α,β-unsaturated aldehyde, acid accelerates the reaction by the protonation of the carbonyl moiety, leading to a lowering of the LUMO level of the electrophilic aldehyde. As the obtained aldol products possess several functional groups, they would be useful chiral synthetic intermediates.



Scheme 2.



Scheme 3.

Acknowledgements

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Conflict of interest

The authors declare no conflict of interest.

Keywords: aldehydes · aldol reaction · allyl alcohol · asymmetric synthesis · organocatalysis

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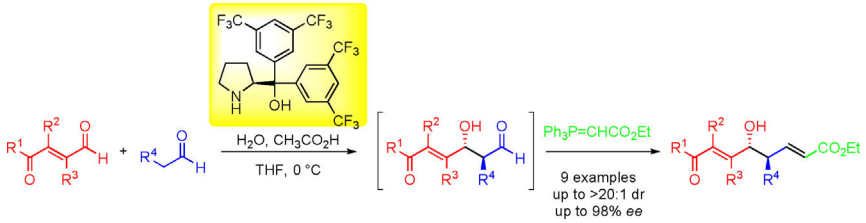

Asymmetric cross-aldol reaction: The asymmetric direct cross-aldol reaction of alkenyl aldehydes catalyzed by a trifluoromethyl-substituted diarylprolinol provides a synthetically useful γ,δ-unsaturated β-hydroxy aldehydes with high anti-selectivity and excellent enantioselectivity.

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Diarylprolinol-Mediated Asymmetric Direct Cross-Aldol Reaction of α,β-Unsaturated Aldehyde as an Electrophilic Aldehyde