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Asymmetric, Catalytic, and Direct Self-Aldol Reaction of Acetaldehyde Catalyzed by Diarylprolinol

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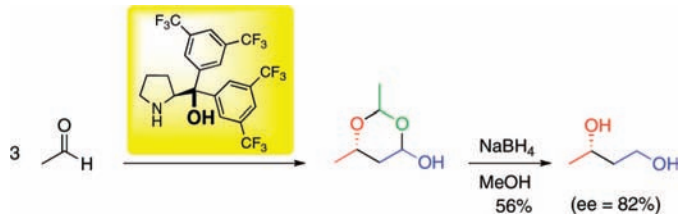
ABSTRACT



An asymmetric, catalytic, and direct self-aldol reaction of acetaldehyde was catalyzed by diarylprolinol in NMP, affording the trimer acetal, which was generated by the reaction of the self-aldol product with another acetaldehyde molecule in a moderate yield with good enantioselectivity. Acetal is the synthetic equivalent of the self-aldol product, which can be converted into other synthetically useful compounds in one pot without compromising the enantioselectivity.

The aldol reaction is one of the most important synthetic transformations in organic synthesis, and several asymmetric and catalytic versions have been developed.[1] The direct aldol reaction of acetaldehyde, which affords synthetically useful α,α-unsubstituted β-hydroxy aldehyde, is regarded as a difficult transformation because the generated aldehyde acts both as a reactive electrophile and as a nucleophile, causing overreactions. Indirect methods reported include the chiral Lewis base-mediated aldol reaction of trimethyl siloxyethene, a synthetic equivalent of acetaldehyde, by Denmark,[2] while Yamamoto has recently developed an acetaldehyde super silyl enol ether which reacts in racemic fashion.[3] Recently, the control of the reactivity and enantioselectivity of acetaldehyde has been reported by our group[4] and also by List and co-workers,[5] independently. Our group developed a diarylprolinol-mediated direct asymmetric cross-aldol reaction of acetaldehyde,[4a] while List's group reported on a proline-mediated Mannich reaction of acetaldehyde.[5a] Both groups reported on the Michael reaction of acetaldehyde catalyzed by diarylprolinol silyl ether.[4b,5b] Just recently, we also observed the Mannich reaction of acetaldehyde catalyzed by diarylprolinol silyl ether.[4c]

3-Hydroxy(or alkoxy)butanal is a synthetically useful chiral building block. Although the self-aldol reaction of acetaldehyde is a straightforward method for the preparation

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(1) (a) *Modern Aldol Reactions*; Mahrwald, R., Ed.; Wiley-VCH: Weinheim, 2004; Vols. 1 and 2. (b) Carreira, E. M. Mukaiyama Aldol Reaction. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999; Vol. III, Chapter 29.1. (c) Machajewski, T. D.; Wong, C.-H. *Angew. Chem., Int. Ed.* **2000**, *39*, 1352. (d) Alcaide, B.; Almendros, P. *Angew. Chem., Int. Ed.* **2003**, *42*, 858.

(2) Denmark, S. E.; Bui, T. *J. Org. Chem.* **2005**, *70*, 10190.

(3) (a) Boxer, M. B.; Yamamoto, H. *J. Am. Chem. Soc.* **2006**, *128*, 48. (b) Boxer, M. B.; Yamamoto, H. *J. Am. Chem. Soc.* **2007**, *129*, 2762.

(4) (a) Hayashi, Y.; Itoh, T.; Aratake, S.; Ishikawa, H. *Angew. Chem., Int. Ed.* **2008**, *47*, 2082. (b) Hayashi, Y.; Itoh, T.; Ohkubo, M.; Ishikawa, H. *Angew. Chem., Int. Ed.* **2008**, *47*, 4722. (c) Hayashi, Y.; Okano, T.; Itoh, T.; Urushima, T.; Ishikawa, H.; Uchimaru, T. *Angew. Chem., Int. Ed.* **2008**, *47*, 9053.

(5) (a) Yang, J. W.; Chandler, C.; Stadler, M.; Kampen, D.; List, B. *Nature* **2008**, *452*, 453. (b) G-Garcia, P.; Ladepeche, A.; Halder, R.; List, B. *Angew. Chem., Int. Ed.* **2008**, *47*, 4719.

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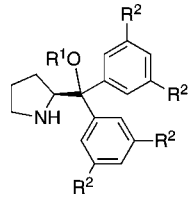
of this important molecule, as far as we are aware, there has been no successful, direct, asymmetric self-aldol reaction. Wong and co-workers obtained a cyclized trimer overreaction product of the aldol product via a double-aldol reaction when acetaldehyde was treated with 2-deoxyribose-5-phosphate aldolase.[6] Barbas and co-workers reported that (*S*,*E*)-5-hydroxy-2-hexenal, which was generated by the double-aldol reaction followed by a dehydration reaction, was obtained in a low yield with good enantioselectivity in the reaction of acetaldehyde catalyzed by proline.[7] Thus, it is difficult to obtain the self-aldol product because of these overreactions of the generated aldol product. Moreover, control of the enantioselectivity is also difficult. Arylaldehydes were employed as electrophiles in our previous cross-aldol reaction of acetaldehyde, in which the discrimination of a large aryl group and a small H atom was realized to generate excellent enantioselectivity. When acetaldehyde is used as an electrophile, both methyl group and H atom must be discriminated, and their sizes are similar, making this enantioselective reaction very difficult. In this paper, we describe the first successful realization of the direct, asymmetric self-aldol reaction of acetaldehyde.



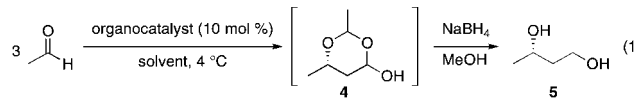
catalyst	R^1	R^2
1	H	CF_3
2	H	H
3	TMS	CF_3

Figure 1. Organocatalysts examined in this study.

First, the self-aldol reaction of acetaldehyde was examined using proline as a catalyst. Although the aldol reaction proceeded, the successive dehydration reaction was fast, generating crotonaldehyde as the major product in an 85% yield (Table 1, entry 1). Trifluoromethyl-substituted diarylprolinol, which gave an excellent result in the cross-aldol reaction of acetaldehyde,[4a] was employed as a catalyst. The aldol reaction was found to proceed, and the crude NMR of the reaction mixture suggested that acetal **4** was the main product (Table 1, eq 1); it was generated by the reaction of the generated aldol product **8** with another acetaldehyde molecule (Scheme 2). Acetal **4** is regarded as a synthetic equivalent of the self-aldol product **8**. We were able to isolate acetal **4**, and as acetal **4** is labile to acid, it was found to decompose on silica gel. The aldol product **8** was isolated as the corresponding diol **5** in a 61% yield after reduction of the aldol product **8** after treatment with $NaBH_4$ in MeOH. The enantiomeric excess was determined to be 64% from the chiral HPLC analysis of the bis-benzoate product (Table 1, entry 2). The reaction conditions were examined in detail in order to increase the enantioselectivity. The reaction

(6) Gijsen, H. J. M.; Wong, C.-H. *J. Am. Chem. Soc.* **1994**, *116*, 8422.
(7) Cordova, A.; Notz, W., III *J. Org. Chem.* **2002**, *67*, 301.

Table 1. Effects of Catalyst and Solvent in the Self-Aldol Reaction of Acetaldehyde[a]



entry	catalyst	solvent	time/day	yield (%)	ee[b] (%)
1	proline	neat	1	<5[c,d]	nd
2	**1**	neat	4	61[c]	64
3	**1**	hexane	4	68[c]	65
4	**1**	CH_3CN	4	63[c]	60
5	**1**	THF	4	59[c]	65
6	**1**	CH_2Cl_2	4	58[c]	51
7	**1**	DMF	5	55[e]	76
8	**1**	NMP	5	56[e]	82
9	**2**	NMP	5	46[e]	70
10	**3**	NMP	5	<5[e,f]	nd

[a] The reaction was performed using acetaldehyde (3 mmol), catalyst (0.2 mmol), and solvent (0.3 mL) at 4 °C for the indicated period of time, and MeOH and $NaBH_4$ were added to the reaction mixture at same temperature. nd = not determined. [b] The enantiomeric excess was determined by chiral HPLC analyses of bis-benzoate product. [c] Yield of the isolated product **5** after column chromatography. [d] Crotonaldehyde was formed in 85% yield. [e] Yield of the bis-benzoate (three steps) after the treatment of diol **5** with benzoyl chloride and Et_3N. [f] Crotonaldehyde was formed in 20% yield.

proceeded in most solvents, such as hexane, CH_3CN, THF, CH_2Cl_2, DMF, and NMP, and the yields were similar, as summarized in Table 1. However, the enantioselectivity was different. The best results were obtained when NMP was employed to afford the bis-benzoate in a 56% yield with good enantioselectivity (82% ee, entry 8).

Next, different catalysts were investigated. When diphenylprolinol **2** was employed, the reaction proceeded to afford the product in a 46% yield with lower enantioselectivity (70% ee, entry 9). The hydroxy group is essential, and the product was obtained in less than a 5% yield with the formation of crotonaldehyde in a 20% yield when diarylprolinol silyl ether **3**[8] was employed, which is an effective catalyst in the Mannich and Michael reactions of acetaldehyde (entry 10).[4b,c]

(8) Diarylprolinol silyl ether was developed by our group and Jørgensen's group, independently. For our contribution of diphenylrpolinol silyl ether, see: (a) Hayashi, Y.; Gotoh, H.; Hayashi, T.; Shoji, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 4212. (b) Gotoh, H.; Masui, R.; Ogino, H.; Shoji, M.; Hayashi, Y. *Angew. Chem., Int. Ed.* **2006**, *45*, 6853. (c) Hayashi, Y.; Okano, T.; Aratake, S.; Hazelard, D. *Angew. Chem., Int. Ed.* **2007**, *46*, 4922. (d) Gotoh, H.; Hayashi, Y. *Org. Lett.* **2007**, *9*, 2859. (e) Hayashi, Y.; Gotoh, H.; Masui, R.; Ishikawa, H. *Angew. Chem., Int. Ed.* **2008**, *47*, 4012. (f) Hayashi, Y.; Samanta, S.; Gotoh, H.; Ishikawa, H. *Angew. Chem., Int. Ed.* **2008**, *47*, 6634. For the contribution of Jørgensen's group, see: (g) Marigo, M.; Wabnitz, T. C.; Fielenbach, D.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2005**, *44*, 794. (h) Marigo, M.; Fielenbach, D.; Braunton, A.; Kjasgaard, A.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2005**, *44*, 3703. For a recent report of Jørgensen's group, see: (i) Franke, P. T.; Johansen, R. L.; Bertelsen, S.; Jørgensen, K. A. *Chem. Asian. J.* **2008**, *3*, 216. For selected examples of other groups' application of diarylprolinol ether, see: (j) Enders, D.; Huttl, M. R. M.; Grondal, C.; Raabe, G. *Nature* **2006**, *441*, 861. (k) Vesely, J.; Ibrahem, I.; Zhao, G.-L.; Rios, R.; Cordova, A. *Angew. Chem., Int. Ed.* **2007**, *46*, 778. (l) Xie, H.; Zu, L.; Li, H.; Wang, J.; Wang, W. *J. Am. Chem. Soc.* **2007**, *129*, 10886. (m) Vo, N. T.; Pace, R. D. M.; O'Hara, F.; Gaunt, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 404. For a review, see: (n) Palomo, C.; Mielgo, A. *Angew. Chem., Int. Ed.* **2006**, *45*, 7876. (o) Mielgo, A.; Palomo, C. *Chem. Asian J.* **2008**, *3*, 922.

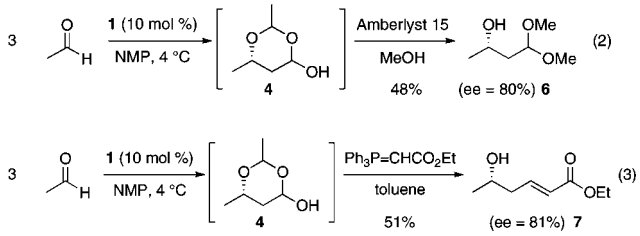
As the intermediate of the reaction is acetal **4**, the synthetic transformation of acetal **4** into other synthetically useful chiral building blocks in the same pot without compromising the enantioselectivity was investigated.

After a period of 5 d of stirring the reaction mixture composed of acetaldehyde and a catalytic amount of catalyst **1**, the excess acetaldehyde was removed under reduced pressure. Methanol and Amberlyst 15 were added to the residue, which generated 4,4-dimethoxy-2-butanol **6** in a 48% yield with an 80% ee (Scheme 1, eq 2).

Another transformation is the one-pot formation of the α,β-unsaturated ester. Addition of triphenylcarbethoxymethylenephosphorane to the reaction mixture of the acetal **4** produced ethyl 5-hydroxy-2-hexenoate **7** in a 51% yield with an 81% ee (Scheme 1, eq 3).

The optically active compounds **6** and **7** are synthetically useful as chiral building blocks and have been used in the synthesis of several natural products.[9]

Scheme 1

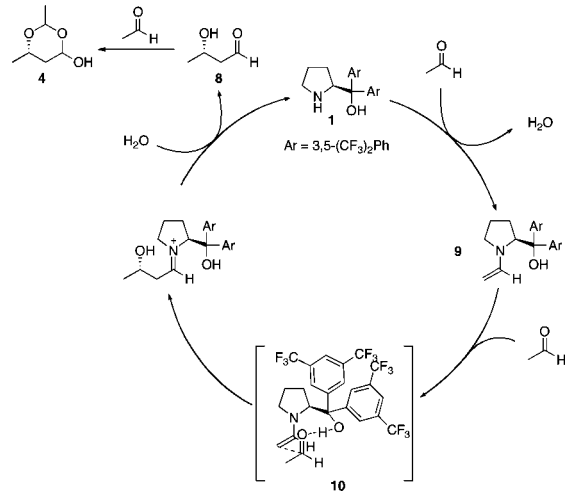


The reaction is thought to proceed via an enamine mechanism (Scheme 2). First, *anti*-enamine **9** is formed, thereby avoiding any steric interaction with the bulky diarylhydroxymethyl substituent. Second, the electrophilic acetaldehyde approaches from the crowded face of the enamine via a hydrogen-bond interaction, as shown in **10**. The aldol product **8** was obtained after hydrolysis, which reacted further with a third acetaldehyde molecule to produce acetal **4**, the generation of which was observed using NMR.

(9) Application of the compound **6** in natural product synthesis, see: (a) Ghiringhelli, D. *Tetrahedron Lett.* **1983**, *24*, 287. (b) Keck, G. E.; Murry, J. A. *J. Org. Chem.* **1991**, *56*, 6606. (c) Besse, P.; Ciblat, S.; Canet, J.-L.; Troin, Y.; Veschambre, H. *Tetrahedron: Asymmetry* **1999**, *10*, 2213. (d) Matsuda, M.; Yamazaki, T.; Fuhshuku, K.-I.; Sugai, T. *Tetrahedron* **2007**, *63*, 8752. (e) Garcia, A. B.; Lessmann, T.; Umarye, J. D.; Mamane, V.; Sommer, S.; Waldmann, H. *Chem. Commun.* **2006**, 3868. For application of the compound **7** in natural product synthesis, see: (f) Schnurrenberger, P.; Hungerbuhler, E.; Seebach, D. *Tetrahedron Lett.* **1984**, *25*, 2209. (g) Hills, L. R.; Ronald, R. C. *J. Org. Chem.* **1985**, *50*, 470. (h) Shimizu, I.; Omura, T. *Chem. Lett.* **1993**, *10*, 1759. (i) Keck, G. E.; Palani, A.; McHardy, S. F. *J. Org. Chem.* **1994**, *59*, 3113. (j) Hayes, J. C.; Heathcock, C. H. *J. Org. Chem.* **1997**, *62*, 2678. (k) Hunter, T. J.; O'Doherty, G. A. *Org. Lett.* **2001**, *3*, 2777. (l) Garaas, S. D.; Hunter, T. J.; O'Doherty, G. A. *J. Org. Chem.* **2002**, *67*, 2682. (m) Hunter, T. J.; O'Doherty, G. A. *Org. Lett.* **2002**, *4*, 4447. (n) Smith, C. M.; O'Doherty, G. A. *Org. Lett.* **2003**, *5*, 1959. (o) Ahmed, M. M.; Berry, B. P.; Hunter, T. J.; Tomcik, D.; O'Doherty, G. A. *Org. Lett.* **2005**, *7*, 745.

Whereas the generated aldol product **8** is expected to react as either a reactive nucleophile or electrophile to afford overreaction products, the aldol product **8** reacted immediately with another acetaldehyde molecule to generate acetal **4**, which suppressed the expected overreaction. As the reaction proceeded under neutral conditions, side reactions, such as dehydration reactions to afford 2-butenal, were not observed.

Scheme 2. Reaction Mechanism of the Self-Aldol Reaction Catalyzed by **1**



In summary, we have found the first, highly efficient, direct, asymmetric self-aldol reaction of acetaldehyde using diarylprolinol **1** as a catalyst to afford the protected 3-hydroxybutanal **4** in moderate yield with good enantioselectivity. Acetal **4** is the synthetic equivalent of the self-aldol product **8**, which can be converted into other synthetically useful compounds, such as 4,4-dimethoxy-2-butanol **6** and ethyl 5-hydroxy-2-hexenoate **7** by treatment with Amberlyst in MeOH and a Wittig reagent, respectively, in one pot without compromising the enantioselectivity.

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Supporting Information Available: Detailed experimental procedures, full characterization, and copies of ^{1}H and ^{13}C NMR and IR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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