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Polymeric Ethyl Glyoxylate in an Asymmetric Aldol Reaction Catalyzed by Diarylprolinol

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ABSTRACT

Diarylprolinol was found to be an effective organocatalyst of the direct, enantioselective aldol reaction of commercially available polymeric ethyl glyoxylate, affording γ-ethoxycarbonyl-β-hydroxy aldehydes, versatile synthetic intermediates, in good yield with excellent enantioselectivity.

Ethyl glyoxylate is a versatile electrophile. It can be converted into synthetically useful chiral building blocks in several asymmetric catalytic reactions. For example, it is a reactive ene component in the asymmetric glyoxylate−ene reaction,[1a] dienophile in the asymmetric hetero-Diels−Alder reaction,[2] and an electrophilic aldehyde in the reaction with ene−carbamates.[3]

Ethyl glyoxylate is commercially available in its polymeric form in toluene solution,[4] and a monomer is generated by pyrolysis of a polymer.[5] The monomer form is so reactive that it polymerizes easily and reacts readily with water to generate the hydrated form. Ethyl glyoxylate is therefore distilled just prior to use, after pyrolysis, and used under nonaqueous conditions. It would be a great synthetic advantage if ethyl glyoxylate could be directly used in the form of the commercially available toluene solution of its polymer under aqueous conditions.

To the best of our knowledge, there are three reports on the use of polymeric ethyl glyoxylate in asymmetric reactions, and in all cases Cu catalyst is used. Evans and coworkers[1d,g] used it in the asymmetric ene reaction catalyzed by a chiral Cu(II) complex, Kobayashi[3a] used it in the asymmetric reaction of ene-carbamates catalyzed by a Cu(I)-

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(4) We used ethyl glyoxylate polymer form (47% in toluene), which was purchased from TCI (Tokyo Chemical Inddustry Co., LTD.), Catalog no. G0242. Aldrich offers ethyl glyoxylate solution (∼50% in toluene), which exists partly in the polymerized form, Catalog no. 50705.

(5) For the generation of monomer via pyrolysis, see ref 3d for instance.

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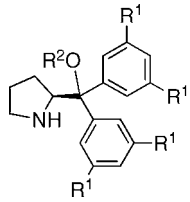
diimine complex, and Shair[6] used it in a decarboxylative aldol reaction catalyzed by Cu(II). The aldol reaction is one of the most useful carbon−carbon bond formation reactions in synthetic organic chemistry, for which several asymmetric catalysts have been developed.[7] The aldol reaction of ethyl glyoxylate as an electrophilic aldehyde is a useful synthesis reaction because the resulting aldol product, the β-ethoxycarbonyl-β-hydroxy carbonyl derivative, possesses polyfunctional groups. With regard to the asymmetric catalytic aldol reactions of ethyl glyoxylate, chiral Lewis acids[8] and TADDOL[9] have been used as catalysts to afford the aldol products with excellent enantioselectivity.



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

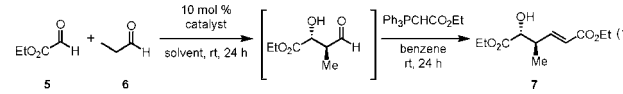
Figure 1. Organocatalysts investigated in the present study.

The field of organocatalysis[10] has developed very rapidly after the discovery of the proline-mediated intermolecular aldol reaction as reported by List, Lerner, and Barbas.[11] Many organocatalysts have been developed, and used in the direct, enantioselective aldol reaction (Figure 1). The enantioselective aldol reaction of ethyl glyoxylate in which monomeric ethyl glyoxylate is used has been investigated by several research groups.[12] While we were preparing this manuscript, a report appeared describing an example of the use of polymeric ethyl glyoxylate, but the enantioselectivity was moderate (65% ee).[13]

It is a great synthetic advantage, and a challenge, to use polymeric ethyl glyoxylate directly from the commercial source without pyrolysis and without the complete removal of water in the aldol reaction for the preparation of products with excellent enantioselectivity—as will now be described in this communication.

We chose the aldol reaction of propanal and polymeric ethyl glyoxylate as a model, and studied the catalyst (eq 1). As polymeric ethyl glyoxylate is commercially available as a toluene solution, our first investigations were performed in toluene. Because the diastereomer ratio of the aldol product is easily changed during the purification owing to the facile epimerization of the product, the determinations of yield and diastereo- and enantioselectivities were performed after conversion to the corresponding α,β-unsaturated ester **7** by the treatment of the aldol product with a Wittig reagent. The reaction proceeded with the polymeric ethyl glyoxylate, and the reactivity and enantioselectivity were found to be dependent on the catalyst (see Table 1). While a nearly racemic product was obtained in the case of proline as catalyst (entry 1), the enantioselectivity improved significantly to 86% when diphenylprolinol **3** was used as catalyst (entry 2). Diarylprolinol **1** with a trifluoromethyl group, which is also a suitable catalyst in the asymmetric aldol reaction of acetaldehdye as a nucleophile,[14] was found to be an effective catalyst and afforded the product with 92% ee (entry 5), while the corresponding trimethylsilyl ether **2** afforded the opposite enantiomer with 71% ee.

Table 1. Effects of Catalyst and Solvent in the Aldol Reaction of Propanal and Polymeric Ethyl Glyoxylate[a]



entry	catalyst	solvent	yield[b]/%	syn:anti[c]	ee[d]/%
1	proline	toluene	42	1.2:1	1
2	**3**	toluene	57	1:4.6	86
3	**4**	toluene	76	1.4:1	−20
4	**2**	toluene	80	1:1.4	−71
5	**1**	toluene	59	1:4.3	92
6	**1**	MeOH	18	1:4.9	90
7	**1**	DMF	41	1:2.0	62
8	**1**	$CHCl_3$	55	1:3.8	94
9	**1**	THF	50	1:3.7	95
10	**1**	H_2O	67	1:3.6	92
11	**1**	CH_3CN	73	1:4.4	98
12	**1**	aq CH_3CN[e]	86	1:4.1	96
13[f]	**1**	aq CH_3CN[e]	93	1:9.8	98

[a] Reaction conditions: propanal (2.5 mmol), ethyl glyoxylate polymer (47% in toluene, 0.5 mmol), catalyst (0.05 mmol), and solvent (0.5 mL) at room temperature for 24 h. See the Supporting Information for details. [b] Isolated yield of **7** (2 steps). [c] Determined by ^{1}H NMR spectroscopy. [d] Ee was determined by chiral HPLC analysis of **7**. [e] CH_3CN (0.5 mL) and H_2O (27 μL) were used as a solvent. [f] Propanal (0.75 mmol) was employed.

(6) Lalic, G.; Aloise, A. D.; Shair, M. D. *J. Am. Chem. Soc.* **2003**, *125*, 2852.

(7) *Modern Aldol Reactions*; Mahrwald, R., Ed.; Wiley-VCH, Weinheim, Germany, 2004; Vols. 1 and 2.

(8) Evans, D. A.; MacMillan, D. W. C.; Campos, K. R. *J. Am. Chem. Soc.* **1997**, *119*, 10859.

(9) Gondi, V. B.; Gravel, M.; Rawal, V. H. *Org. Lett.* **2005**, *7*, 5657.

(10) For selected reviews on organocatalysis, see: (a) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2004**, *43*, 5138. (b) *Asymmetric Organocatalysis*; Berkessel, A., Groger, H., Eds.; Wiley-VCH: Weinheim, Germany, 2005. (c) Hayashi, Y. *Yuki Gosei Kagaku Kyokaishi* **2005**, *63*, 464. (d) List, B. *Chem. Commun.* **2006**, 819. (e) Marigo, M.; Jørgensen, K. A. *Chem. Commun.* **2006**, 2001. (f) Gaunt, M. J.; Johansson, C. C. C.; McNally, A.; Vo, N. T. *Drug Discovery Today* **2007**, *12*, 8. (g) *Enantioselective Organocatalysis*; Dalko, P. I., Ed.; Wiley-VCH: Weinheim, Germany, 2007. (h) Mukherjee, S.; Yang, J. W.; Hoffmann, S.; List, B. *Chem. Rev.* **2007**, *107*, 5471. (i) Barbas, C. F., III *Angew. Chem., Int. Ed.* **2007**, *47*, 42. (j) Dondoni, A.; Massi, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 4638. (k) Melchiorre, P.; Marigo, M.; Carlone, A.; Bartoli, G. *Angew. Chem., Int. Ed.* **2008**, *47*, 6138. (l) Bertelsen, S.; Jørgensen, K. A. *Chem. Soc. Rev.* **2009**, *38*, 2178.

(11) List, B.; Lerner, R. A.; Barbas, C. F., III *J. Am. Chem. Soc.* **2000**, *122*, 2395.

(12) (a) Dodda, R.; Zhao, C.-G. *Synlett* **2007**, 1605. (b) Kano, T.; Yamaguchi, Y.; Tanaka, Y.; Maruoka, K. *Angew. Chem., Int. Ed.* **2007**, *46*, 1738. (c) Kano, T.; Yamaguchi, Y.; Maruoka, K. *Chem.—Eur. J.* **2009**, *15*, 6678.

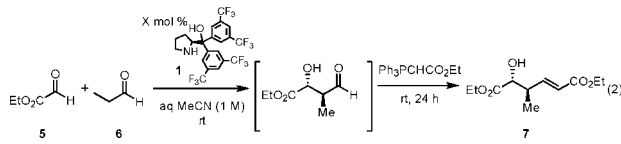
(13) Markert, M.; Scheffler, U.; Mahrwald, R. *J. Am. Chem. Soc.* **2009**, *131*, 16642.

(14) (a) Hayashi, Y.; Itoh, T.; Aratake, S.; Ishikawa, H. *Angew. Chem., Int. Ed.* **2008**, *47*, 2082. (b) Hayashi, Y.; Samanta, S.; Itoh, T.; Ishikawa, H. *Org. Lett.* **2008**, *10*, 5581. (c) Itoh, T.; Ishikawa, H.; Hayashi, Y. *Org. Lett.* **2009**, *11*, 3854.

Having identified a suitable catalyst, solvent screening was carried out next. After removal of toluene from the commercial solution under reduced pressure, the reaction was carried out after the addition of another solvent. The results are summarized in entries 6−13 of Table 1. Excellent enantioselectivity was obtained in all the solvents that were considered, except in DMF. Among the solvents used, MeCN was found to be suitable in terms of both the yield and enantioselectivity (entry 11). It should be noted that the reaction also proceeded when water was used as a reaction medium (entry 10). The addition of 3 equiv of water to MeCN increased the yield (entry 12). The quantity of propanal used was also important. When it was reduced from 5 equiv to 1.5 equiv the diastereoselectivity increased from 1:4.1 to 1:9.8, and the excellent enantioselectivity was maintained (entry 13).

The quantity of the catalyst was also investigated (Table 2). The reaction proceeded in the presence of 2 and 5 mol % of the catalyst (entries 2 and 3). Even in the presence of only 1 mol % of the catalyst, the reaction proceeded to afford the aldol product in 61% yield, with excellent diastereo- and enantioselectivity (entry 4).

Table 2. Effect of the Loading of the Catalyst **1** in the Aldol Reaction[a]

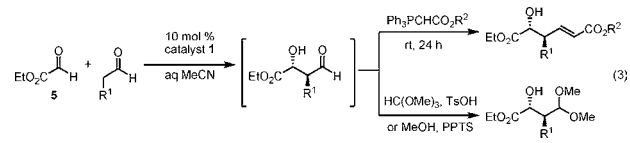


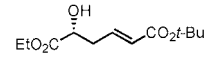
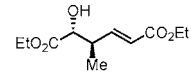
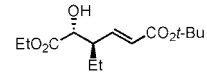
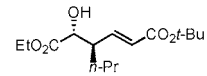
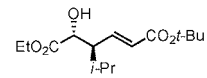
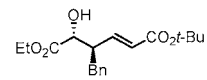
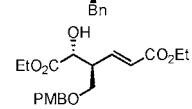
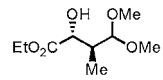
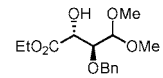
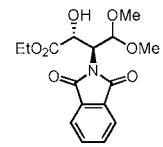
entry	X^b/mol %	time/h	yield[c]/%	syn:anti[d]	ee[e]/%
1	10	20	93	1:9.8	98
2	5	30	quant	1:7.6	98
3	2	40	quant	1:7.3	99
4	1	48	61	1:11.5	99

[a] The reaction was performed with propanal (0.75 mmol), ethyl glyoxylate polymer (47% in toluene, 0.5 mmol), catalyst **1**, CH_3CN (0.5 mL), and H_2O (27 μL) at room temperature for the indicated time. [b] Amount of the catalyst **1**. [c] Isolated yield of **7** (2 steps). [d] Determined by ^1H NMR spectroscopy. [e] Ee was determined by chiral HPLC analysis of **7**.

Having determined the best reaction conditions, the generality of the reaction was then investigated by using 10 mol % of the catalyst. The aldol product was converted to the α,β-unsaturated ester or dimethyl acetal, then isolated and characterized, and the enantiomeric excess determined. The results are summarized in Table 3. The diastereoselectivity and enantioselectivity of the α,β-unsaturated ester and dimethyl acetal were similar, indicating that there was no isomerization in the Wittig reaction and acetal formation

Table 3. Generality of the Aldol Reaction of Polymeric Ethyl Glyoxylate[a]



entry	product	yield/%[h]	syn:anti[c]	ee/%[d]
1		74	–	90
2		93	1:9.8	98
3		quant	1:16	92
4		89	1:19	96
5		quant	1:19	97
6		92	1:>20	>99
7[e]		95	1:6.8	99
8		74	1:9.7	99
9		78	1:>20	98
10		88	1:1.4	91,91

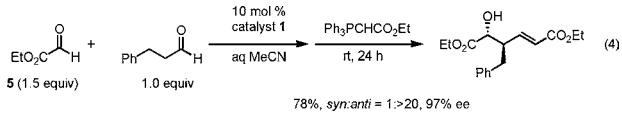
[a] Unless otherwise shown, reaction conditions: aldehyde (0.75 mmol), ethyl glyoxylate polymer (47% in toluene, 0.5 mmol), catalyst **1** (0.05 mmol), CH_3CN (0.5 mL) and H_2O (27 μL) at room temperature for 24 h. As for the procedure of Wittig and acetal formation, see the Supporting Information for details. [b] Isolated yield of the product over 2 steps. [c] Determined by ^1H NMR spectroscopy. [d] Ee was determined by chiral HPLC analysis, see the Supporting Information for details. [e] Aldehyde (0.5 mmol), ethyl glyoxylate polymer (47% in toluene, 0.75 mmol), catalyst **1** (0.05 mmol), CH_3CN (0.25 mL), and H_2O (27 μL) at 5 °C for 38 h.

reaction (entries 2 and 8). Although control of the reactivity of acetaldehyde as a nucleophile is difficult because of its high reactivity, both as a nucleophile and an electrophile,[14,15] acetaldehyde was found to be a suitable nucleophile in the present reaction—it afforded the product in good yield and excellent enantioselectivity (entry 1). α-Alkyl-substituted acetaldehydes, such as propanal, butanal, pentanal, and isovaleraldehyde, were used as nucleophilic aldehydes (entries 2−5). β-Alkoxy-substituted aldehydes such as 3-(*p*-methoxyphenylmethoxy)propanal, in which β-elimination is a possible side reaction, can be successfully used, which indicates the mild reaction conditions in the present reaction. Polyfunctional chiral intermediates can be synthesized with excellent diastereo- and enantioselectivity when α-hetero-

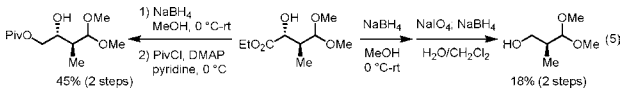
(15) (a) Yang, J. W.; Chandler, C.; Stadler, M.; Kampen, D.; List, B. *Nature* **2008**, *452*, 453. (b) G-Garcia, P.; Ladepeche, A.; Halder, R.; List, B. *Angew. Chem., Int. Ed.* **2008**, *47*, 4719. (c) Hayashi, Y.; Itoh, T.; Okubo, M.; Ishikawa, H. *Angew. Chem., Int. Ed.* **2008**, *47*, 4722. (d) Hayashi, Y.; Okano, T.; Itoh, T.; Urushima, T.; Ishikawa, H.; Uchimaru, T. *Angew. Chem., Int. Ed.* **2008**, *47*, 9053. (e) Kano, T.; Yamaguchi, Y.; Maruoka, K. *Angew. Chem., Int. Ed.* **2009**, *48*, 1838.

atom-substituted acetaldehydes, such as benzyloxyacetaldehyde and *N*-(formylmethyl)phthalimide, are used. The excellent diastereoselectivity in the present reaction is one of the noteworthy features, in contrast to the low diastereoselectivity achieved in reactions catalyzed by other organocatalysts.[12b,c]

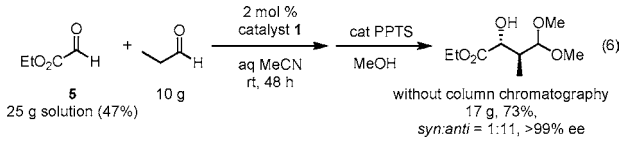
Whereas 1.5 equiv of aldehyde was used for the reactions tabulated in Table 3, we considered it desirable to use an excess of ethyl glyoxylate in the case of a precious aldehyde as a nucleophile. Thus, a procedure with 1.5 equiv of ethyl glyoxylate was developed. As shown in eq 4, good yield (78%) with excellent *anti*-selectivity and enantioselectivity was obtained.



The absolute configuration was determined by the comparison of the optical rotations of 4,4-dimethoxy-2-hydroxy-3-methylbutyl pivalate and 3,3-dimethoxy-2-methylpropanol, which were synthesized as shown in eq 5, with those described in the literature.[16]



The large-scale preparation was successfully performed in the presence of 2 mol % of the catalyst, using a 25 g solution of ethyl glyoxylate (47%), to afford the aldol product in its dimethyl acetal form in 73% yield (17 g) after distillation (eq 6). It should be noted that neither isomerization nor racemization occurred under the reaction conditions.



The reaction is thought to proceed as follows: Enamine, which is generated from aldehyde and diarylprolinol catalyst **1**, reacts with ethyl glyoxylate as shown in Figure 2, in which

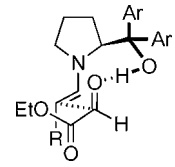


Figure 2. The transition state of intermediate enamine and **5**, Ar = 3,5-bis(trifluoromethyl)phenyl.

ethyl glyoxylate is activated by coordination to the proton of the hydroxy group via a hydrogen bond.[14a] This model can explain the absolute configuration of the aldol product. This interaction would be stronger in the case of the trifluoromethyl-substituted catalyst **1** than the diphenylprolinol **3** because of the higher acidity of its hydroxy group. Thus, the opposite enantiomer was generated when the corresponding silyl ether catalyst **2** was used.

In conclusion, we have developed an asymmetric, direct aldol reaction of ethyl glyoxylate and an aldehyde catalyzed by diarylprolinol to afford a synthetically useful β-ethoxycarbonyl-β-hydroxy aldehyde. There are several noteworthy features of this reaction: (1) the commercially available ethyl glyoxylate in its polymeric form was used directly without pyrolysis or distillation prior to use; (2) the reaction was conducted without the complete removal of water; (3) the *anti*-isomer was obtained with excellent diastereoselectivity; (4) excellent enantioselectivity was realized; and (5) this is one of the rare reactions in which diarylprolinol is successfully used as an efficient catalyst,[14,17] while its silyl ether is widely used as an effective organocatalyst.[18] As the generated product possesses several functional groups, with excellent diastereoselectivity and enantioselectivity, this method offers an efficient route for the preparation of the chiral intermediates.

Supporting Information Available: Detailed experimental procedures, full characterization, copies of ^{1}H, ^{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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