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Asymmetric Aldol Reaction of α,α-Disubstituted Acetaldehydes Catalyzed by Diphenylprolinol Silyl Ether for the Construction of Quaternary Stereogenic Centers

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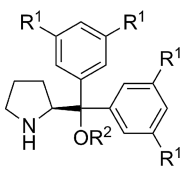
The asymmetric cross-aldol reaction of α,α-disubstituted acetaldehydes with commercial ethyl glyoxylate polymer was successfully catalyzed by diphenylprolinol silyl ether **3** to generate all-carbon quaternary stereogenic centers with good enantioselectivity.

The aldol reaction is one of the most useful carbon–carbon bond forming reactions in organic chemistry.[1] After the pioneering discovery of the intermolecular proline-mediated aldol reaction of aldehydes and ketones by List, Lerner and Barbas in 2000, there has been great progress in the field of organocatalysed asymmetric aldol chemistry.[2] The cross aldol reaction of two different aldehydes catalyzed by proline was reported by MacMillan in 2002.[3] Although the generated β-hydroxy aldehydes are synthetically useful and versatile chiral building blocks, the reaction is often limited to particular aldehydes. Our group has continuing interest to develop a general organocatalyst for the asymmetric cross-aldol reaction of aldehydes. Through our efforts, we have found trifluoromethyl-substituted diarylprolinol as an effective organocatalyst in the aldol reaction of not only acetaldehyde as the pro-nucleophile,[4] but also ethyl glyoxylate,[5] chloroacetaldehye,[6] trifluoroacetaldehyde ethyl acetal,[7] pyruvaldehyde,[8] succinaldehyde,[9] glyoxal,[10] alkynyl aldehyde,[11] and formaldehyde[12] as the electrophilic aldehyde.

An equally continuing challenge for contemporary synthetic organic chemistry is the asymmetric synthesis of all-carbon quaternary stereogenic centers.[13] In this context, there have been only two reports, as far as we are aware, that describe the intermolecular asymmetric aldol reaction to form all-carbon quaternary stereogenic centers. Tanaka and Barbas reported the aldol reaction catalyzed by the combination of a diamine and an acid.[14] Although excellent enantioselectivity was obtained, only *p*-nitrobenzaldehyde was examined as the electrophilic aldehyde. Mahrwald reported the aldol reaction catalyzed by histidine, which afforded the aldol product with moderate to good enantioselectivity.[15] Compared to the aldol reaction of α-monosubstituted acetaldehydes, the reaction of α,α-disubstituted acetaldehydes is significantly more difficult. Herein, we disclose the asymmetric aldol reaction of a range of α,α-aryl, alkyl disubstituted acetaldehydes with commercial ethyl glyoxylate.

Ethyl glyoxylate is a useful electrophilic aldehyde, because it possesses an ester moiety that can be converted into other functional groups.[16] Due to practical reasons, we have already adopted the direct use of commercially available polymer solutions of ethyl glyoxylate in the asymmetric aldol reaction of mono-substituted acetaldehydes catalyzed by diarylprolinol.[5] We thus began to investigate the aldol reaction of commercial ethyl glyoxylate with α,α-disubstituted acetaldehydes. For this purpose, 2-phenylpropanal was selected as a model nucleophilic aldehyde. First, the optimal catalyst was surveyed (Figure 1). Although diarylprolinol **1** is an effective catalyst in other aldol reactions of α-mono-substituted acetaldehydes,[5–12] it afforded products with low enantioselectivity (Table 1, entry 1). Use of the silyl ether **2** gave better results. As the reaction was slow,



	R^1	R^2
1	CF_3	H
2	CF_3	TMS
3	H	TMS
4	H	TBS
5	H	TIPS

Figure 1. Catalysts examined in this study.

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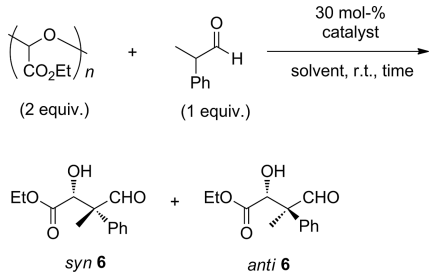
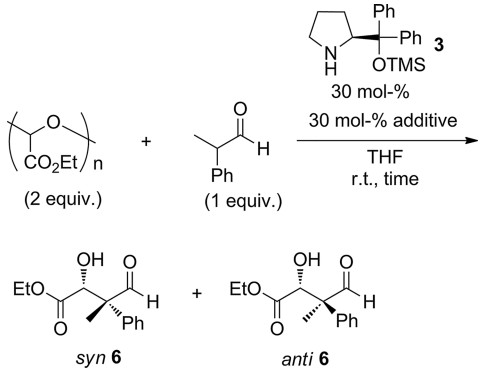
Table 1. Effect of catalyst and solvent in the asymmetric aldol reaction of 2-phenylpropanal and ethylglyoxylate.[a]



Entry	Catalyst	Solvent	Time [h]	Yield [%][b]	*syn*/*anti*[c]	*ee* [%][d]
1[e]	**1**	toluene	48	44	1:2.3	12:54
2[e]	**2**	toluene	48	70	1:1.4	80:3
3	**3**	toluene	24	86	1:1.3	74:44
4	**4**	toluene	36	72	1:1.1	71:59
5	**5**	toluene	48	65	1:1.2	73:35
6	**3**	MeOH	96	< 5		
7	**3**	CH_2Cl_2	15	55	1:1.1	39:11
8	**3**	MeCN	28	84	1:1	59:28
9	**3**	DMF	10	93	1:1.2	71:41
10	**3**	THF	18	86	1:1.3	82:13

[a] Unless noted otherwise, reactions were performed by employing a 47% toluene solution of ethyl glyoxylate polymer (0.46 mmol, 100 mg), 2-phenylpropanal (0.23 mmol) and organocatalyst (0.069 mmol, 30 mol-%) in the solvent (0.23 mL) at room temperature for the indicated time. [b] Yield of purified aldol product. [c] Diastereomer ratio, as determined by ^{1}H-NMR spectroscopy. [d] *ee* of the *syn*- and *anti*-aldol products, as determined by HPLC analysis over a chiral solid phase. [e] Reaction performed at 50 °C.

Table 2. Effect of additives in the asymmetric aldol reaction of 2-phenylpropanal and ethylglyoxylate.[a]

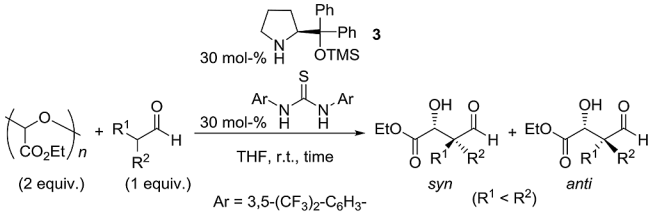


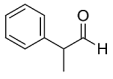
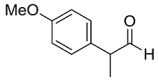
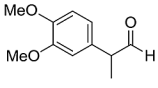
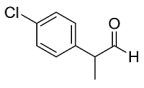
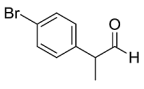
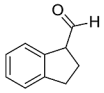
Entry	Additive	Time [h]	Yield [%][b]	*syn*/*anti*[c]	*ee* [%][d]
1	none	18	86	1:1.3	82:13
2	*p*-nitrophenol	8	75	1:1.2	58:26
3	AcOH	4	75	1:1.5	68:6
4	$PhCO_2H$	4	72	1:1.2	62:2
5	$ClCH_2CO_2H$	1.5	75	1:1.3	65:40
6	*N*,*N*′-bis[3,5-bis(trifluoro-methyl)-phenyl]thiourea	3	83	1:1.2	86:58

[a] Unless noted otherwise, reactions were performed by employing a 47% toluene solution of ethyl glyoxylate polymer (0.46 mmol, 100 mg), 2-phenylpropanal (0.23 mmol), organocatalyst **2** (0.069 mmol, 30 mol-%), and additive (0.069 mmol) in THF (0.23 mL) at room temperature for the indicated time. [b] Yield of purified aldol product. [c] Diastereomer ratio, as determined by ^{1}H-NMR spectroscopy. [d] *ee* of the *syn*- and *anti*-aldol products, as determined by HPLC analysis over a chiral solid phase.

the reaction was performed at 50 °C. This afforded the product in 70% yield with good enantioselectivity (80% *ee*, *syn* isomer, entry 2). By altering the silyl group on the catalyst, the reaction could be conducted at room temperature with good enantioselectivity by employing the diphenylprolinol silyl ether **3**, a catalyst developed independently by our group[17] and that of Jørgensen.[18] The trimethylsilyl, *tert*-butyldimethylsilyl and triisopropylsilyl ethers **3**–**5** gave similarly good enantioselectivity (entries 3–5). Next, the solvent was investigated using diphenylprolinol trimethylsilyl ether **3** as the catalyst (entries 6–10). While the reaction barely proceeded in MeOH, a lower enantioselectivity was obtained in CH_2Cl_2 and MeCN. Reactions in DMF gave a

Table 3. Asymmetric aldol reaction of α,α-disubstituted acetaldehyde and ethyl glyoxylate.[a]



Entry	Aldehyde	Time [h]	Yield [%][b]	*syn*/*anti*[c]	*ee* [%][d]
1		3	83	1:1.2	86:58
2		3	77	1:1	82:43
3		15	74	1:1.3	88:54
4		3	79	1:1.2	77:60
5		6	68	1:1	50:31
6		30	50	1:2.9	6:55
7		4	82	2:1	91:39

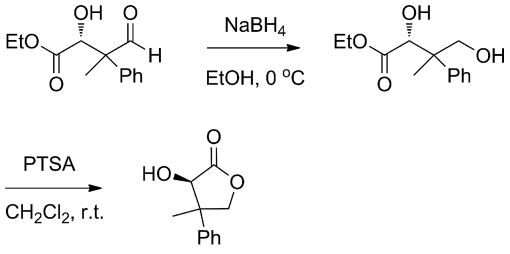
[a] Unless noted otherwise, reactions were performed by employing a 47% toluene solution of ethyl glyoxylate polymer (0.46 mmol, 100 mg), nucleophilic aldehyde (0.23 mmol), organocatalyst **3** (0.069 mmol, 30 mol-%) and thiourea derivative (0.069 mmol, 30 mol-%) in THF (0.23 mL) at room temperature for the indicated time. [b] Isolated yield of purified aldol product. [c] Diastereomer ratio, as determined by ^{1}H-NMR spectroscopy. [d] *ee* of the *anti* and *syn* aldol product, as determined by HPLC analysis over a chiral solid phase.

similarly good enantioselectivity to toluene. Optimal enantioselectivity was realized in THF, which afforded the product in 82% *ee* as for a *syn* isomer.

Although the best catalyst and solvent were determined, the reaction proceeded slowly over 18 hours before completion. As acid is sometimes effective in facilitating organocatalyst-mediated reactions, additives were examined next (Table 2). The reaction was found to be accelerated in the presence of acids such as *p*-nitrophenol, acetic acid, benzoic acid and chloroacetic acid, but the enantioselectivity decreased (entries 2–5). For instance, the reaction completed within 1.5 h in the presence of chloroacetic acid, but the enantioselectivity of the *syn* isomer was 65%. Instead of acid, Schreiner's thiourea[19] was selected as an additive. Here, the reaction not only accelerated, but also the enantioselectivity increased to 86%. As anticipated, the thiourea derivative presumably facilitated the reaction via hydrogen-bond activation of the ethyl ester carbonyl moiety.

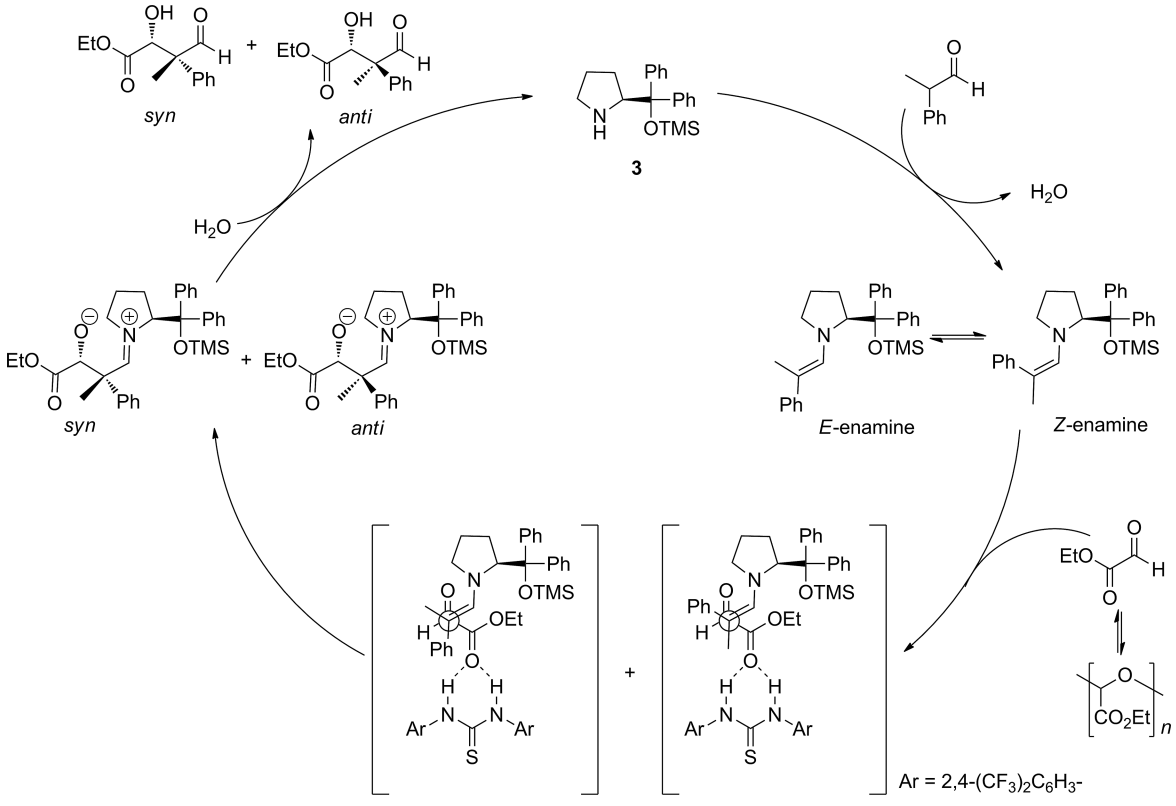
Having determined optimal reaction conditions, the generality of the reaction was investigated as summarized in Table 3. As for the aryl substituent of 2-arylpropanal acting as a pro-nucleophilic aldehyde, not only phenyl, but also phenyl groups substituted with electron-rich substituents such as *p*-methoxyphenyl and 3,4-dimethoxyphenyl were found suitable to afford the aldol products with good enantioselectivity (entries 2, 3). In the reaction of electron-deficient aryl moieties, such as 2-(*p*-chlorophenyl) and 2-(*p*-bromophenyl)propanal, the enantioselectivity was moderate (entries 4, 5). The reaction of 1,2,3,4-tetrahydro-1-naphthalenecarbaldehyde gave moderate enantioselectivity (entry 6), while the reaction of 2,3-dihydaro-1*H*-indene-1-carbaldehyde gave high enantioselectivity (entry 7).

The relative and absolute configurations of the aldol products were determined as follows: Aldol product of 2-phenylpropanal was reduced by $NaBH_4$ to afford diol, which was converted into lactone by the acid treatment, see Equation (1). *cis* and *trans* isomers were separated and then converted into MTPA esters by treatment with (*R*)- and (*S*)-MTPA-Cl. The absolute configurations were determined by comparison of literature data[15] and by the use of Kakisawa–Kusumi's modification of Mosher method.[20]

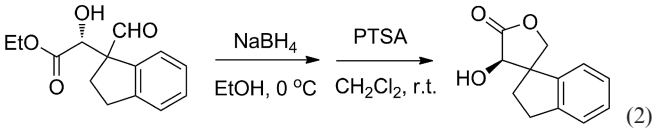


(1)

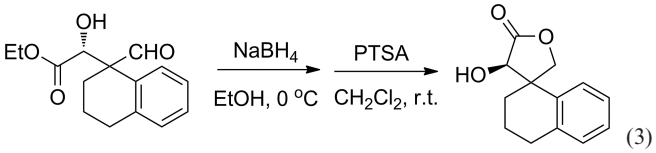
The relative stereochemistries of the aldol products of 1,2,3,4-tetrahydro-1-naphthalenecarbaldehyde and 2,3-dihydro-1*H*-indene-1-carbaldehyde were determined by the NOE analysis of the corresponding lactone, generated by the reduction with $NaBH_4$ and acid treatment; see Equations (2) and (3).



Scheme 1. Proposed reaction mechanism of 2-phenylpropanal and ethyl glyoxylate catalyzed by diphenylprolinlol silyl ether **3**.

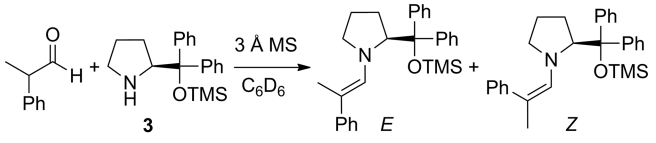


(2)



(3)

Since the chirality at the α-position of the ester moiety was found to be *R* in both the *syn*- and *anti*-isomers, the *Re*-face of the formyl moiety of ethyl glyoxylate reacts preferentially. An NMR study of 2-phenylpropanal with diphenylprolinol silyl ether indicated the generation of both *E*- and *Z*-enamines in nearly equal amounts, see Equation (4). We thus propose the reaction mechanism shown in Scheme 1.



2 h, 53%, *E*:*Z* = 1.0:1.3
4 h, 86%, *E*:*Z* = 1.1:1.0
9 h, 94%, *E*:*Z* = 1.2:1.0

(4)

Diphenylprolinol silyl ether **3** reacts with 2-phenylpropanal to generate both *E*- and *Z*-enamines. Both enamines react with ethyl glyoxylate from the opposite face of the bulky diphenylsiloxymethyl moiety to afford iminium ions, which are hydrolyzed with water to afford the aldol products. As both enamines react readily, the diastereoselectivity is not high. Because the bulky diphenylsiloxymethyl covers one of the enantiofaces of the enamine-catalyst intermediate,[17c] high enantioselectivity results in the aldol products.

In conclusion, we have developed a practical synthesis of chiral β-hydroxy-α,α-disubstituted aldehydes via an asymmetric, direct aldol reaction of α,α-disubstituted acetaldehydes, catalyzed by the diphenylprolinol silyl ether **3**. There are several noteworthy features of this reaction method: (1) Schreiner's thiourea is found to be an effective co-catalyst that not only accelerates the reaction, but also increases the enantioselectivity. (2) Synthetically useful all-carbon quaternary stereogenic centers can be constructed with good enantioselectivity.

Acknowledgments

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