Organocatalysis

DOI: 10.1002/anie.200801130

Asymmetric Michael Reaction of Acetaldehyde Catalyzed by Diphenylprolinol Silyl Ether**

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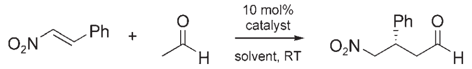
Reactions involving organocatalysis have developed rapidly in recent years.[1] Although many kinds of enantioselective reactions of aldehydes involving the enamine-type mechanism[2] have been developed, there has been no report of the successful use of acetaldehyde, despite its usefulness, in catalytic asymmetric reactions.[3] Control of the reactivity of acetaldehyde is difficult because of its high reactivity as both a nucleophile and an electrophile. Moreover, the addition product possesses a reactive α-unsubstituted aldehyde moiety that can potentially react with a nucleophile or an electrophile to give several side products. Recently, however, our group[4] and the group of List[5] independently developed the first enantioselective catalytic reactions of acetaldehyde. We reported a crossed-aldol reaction of acetaldehyde catalyzed by diarylprolinol, and List and co-workers reported the proline-catalyzed Mannich reaction of acetaldehyde.

The Michael reaction, a synthetically important carbon–carbon bond-forming reaction, is catalyzed enantioselectively by organocatalysts.[6] However, despite the many successful Michael reactions, in which aldehydes act as nucleophiles,[7] we are not aware of any report of a Michael reaction using acetaldehyde. Previously, we developed Michael reactions of aldehydes and nitroalkenes catalyzed by diphenylprolinol silyl ether[8] to afford α-substituted γ-nitro aldehydes in nearly optically pure form. The Michael adduct that is generated is synthetically useful; Enders and co-workers developed an elegant domino reaction based on the Michael reaction to generate chiral cyclohexene derivatives with excellent enantioselectivities.[9] In these previous Michael reactions, only α-substituted aldehyde derivatives were synthesized, but it is desirable to prepare chiral α-unsubstituted γ-nitro aldehydes with excellent enantioselectivity. Herein, we describe the first example of such a reaction.

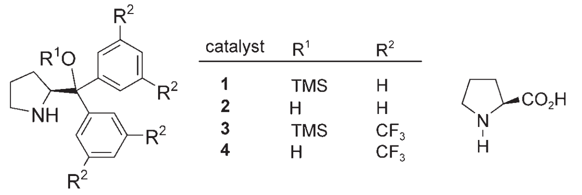
The Michael reaction of nitrostyrene and acetaldehyde was selected as a model reaction (Table 1). Organocatalysts were examined first and the results are summarized in Table 1. A reaction did not occur in the presence of either proline or trifluoromethyl-substituted diarylprolinol **4** (Figure 1), which afforded good results in the Mannich reaction[5] and the aldol reaction[4] of acetaldehyde, respectively. Although diphenylprolinol **2** did not promote the reaction, silyl ether **1**, which was developed by our group,[8,10] was effective and provided the Michael product in good yield with excellent enantioselectivity. Notably, the reactivity of diphenylprolinol silyl ether **1**[11] and that of trifluoromethyl-substituted diarylprolinol silyl ether **3**,[11] which is an effective organocatalyst in several asymmetric reactions developed by Jørgensen and co-workers,[12] are very different in the present reaction. After screening solvents, 1,4-dioxane was found to afford the best results.

Table 1: The effect of the catalyst and the solvent on the Michael reaction of acetaldehyde and nitrostyrene.[a]



Entry	Catalyst	Solvent	Yield [%][b]	*ee* [%][c]
1	proline	1,4-dioxane	<10	
2	**1**	1,4-dioxane	75	96
3	**2**	1,4-dioxane	<10	
4	**3**	1,4-dioxane	<10	
5	**4**	1,4-dioxane	<10	
6	**1**	hexane	53	95
7	**1**	toluene	47	93
8	**1**	H_2O	13	92
9	**1**	THF	53	95

[a] Unless otherwise shown, the reaction was performed with nitrostyrene (0.75 mmol), acetaldehyde (7.5 mmol), catalyst (0.075 mmol), and solvent (150 μL) at room temperature for 18 h. [b] Yield of isolated product. [c] Optical purity was determined by chiral GC analysis. See the Supporting Information for details.



catalyst	R1	R2
1	TMS	H
2	H	H
3	TMS	CF_3
4	H	CF_3

Figure 1. Organocatalysts examined in this study. TMS = trimethylsilyl.

After the reaction conditions were optimized the generality of the reaction was investigated, and the results summarized in Table 2 show that the reaction has broad applicability. Nitroalkenes with either phenyl or naphthyl substituents

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[**] This work was partially supported by the Toray Science Foundation and a Grant-in-Aid for Scientific Research from MEXT.

Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

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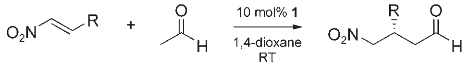
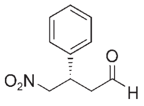
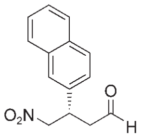
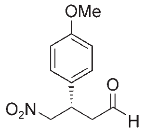
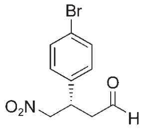
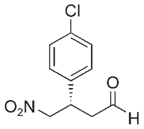
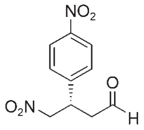
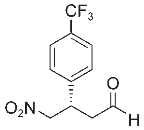
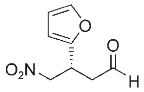
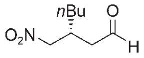
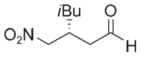
(Table 2, entry 2) gave excellent results. Aryl-substituted nitroalkenes, having both electron-rich and electron-deficient aryl groups, successfully afforded the Michael adducts in high yield with excellent enantioselectivity (Table 2, entries 3–7). Heteroaryl-substituted nitroalkenes were also suitable substrates (Table 2, entry 8). The reaction proceeded not only with aryl-substituted nitroalkenes, but also with alkyl-substituted nitroalkenes to give nearly optically pure Michael adducts (Table 2, entries 9 and 10).

Table 2: Catalytic asymmetric Michael reaction of acetaldehyde with various nitroalkenes.[a]



Entry	Product		t [h]	Yield [%][b]	*ee* [%][c]
1		**5a**	18	75	96
2		**5b**	28	70	92
3		**5c**	27	69	94
4		**5d**	18	73	93
5		**5e**	36	75	92
6		**5f**	42	72	95
7		**5g**	24	77	93
8		**5h**	48	72	97
9		**5i**	36	54	99
10		**5j**	72	61	>99

[a] Unless otherwise shown, the reaction was performed with nitroalkene (0.75 mmol), acetaldehyde (7.5 mmol), catalyst **1** (0.075 mmol), and 1,4-dioxane (150 μL) at room temperature. [b] Yield of isolated product. [c] Optical purity was determined by chiral HPLC analysis after conversion of the aldehyde into the corresponding alcohol by reduction with $NaBH_4$ or chiral GC analysis. See the SI for details.

The Michael addition products are important chiral intermediates that possess synthetically useful functional groups such as formyl and nitro groups. For instance, we have already established synthetic routes for baclofen,[13] a therapeutically useful $GABA_B$ receptor agonist, and pregabalin,[14] an important anticonvulsant drug, from **5e** and *ent*-**5j**, respectively.[15] Whereas the enantiomeric excess of *ent*-**5j** in our previous synthesis was 91 %,[15] that obtained by using the present method is over 99%, highlighting one of the superior features of the present Michael reaction.

In the crossed-aldol reaction of acetaldehyde, trifluoromethyl-substituted diarylprolinol is the effective catalyst, and hydrogen-bond interactions between the formyl oxygen atom and the hydroxy group of the catalyst may control the transition state. In the present Michael reaction, diphenylprolinol silyl ether is an efficient catalyst, but similar hydrogen-bonding interactions are not expected to occur. The reaction may proceed by the same transition state proposed for the reaction of propanal and nitroalkene catalyzed by the same catalyst (Figure 2):[8] The selectively generated *anti* enamine may react with the nitroalkene by Seebach's acyclic synclinal transition-state model.[16] It is remarkable that excellent enantioselectivity has been realized, even though a small enamine without a β substituent has been employed.

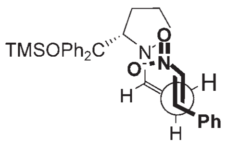


Figure 2. The transition-state model.

In summary, we have developed the first asymmetric Michael reaction of acetaldehyde to afford α-unsubstituted γ-nitro aldehyde in good yield with excellent enantioselectivity. The resulting product possesses useful functional groups, such as nitro and formyl groups, that make them synthetically important chiral building blocks. The present reaction also indicates that the enantiofacial selection of the enamine derived from acetaldehyde can be realized by the combination of acetaldehyde and diphenylprolinol silyl ether. This new finding will have broad application in synthetic organic chemistry.

Experimental Section

Typical procedure: Acetaldehyde (420 μL, 7.5 mmol) was added to a mixture of (*S*)-diphenyltrimethylsiloxymethyl pyrrolidine (24.4 mg, 0.075 mmol) and nitrostyrene (111.8 mg, 0.75 mmol) in 1,4-dioxane (0.15 mL) in a sealed tube (ACE GLASS, product number 5027-05) at 4 °C. The reaction mixture was stirred at room temperature for 18 h and then quenched with aq. 1N-HCl. The organic materials were extracted three times with ethyl acetate. The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. Purification by column chromatography (ethyl acetate/hexane = 1:20→1:6) gave (*S*)-4-nitro-3-phenylbutanal (108.1 mg, 0.56 mmol) in 75 % yield. The enantiometric excess was determined to be 96 %.

Received: March 8, 2008
Published online: April 25, 2008

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Keywords: acetaldehyde · asymmetric catalysis · Michael addition · synthetic methods

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