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Enantioselective Michael Reaction of Malonates and α,β-Unsaturated Aldehydes Using a *trans*-4-Hydroxyproline Derived Organocatalyst

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Asymmetric Michael addition of malonates to various α,β-unsaturated aldehydes using an organocatalyst derived from *trans*-4-hydroxyproline in MeOH proceeds smoothly to afford the corresponding Michael adducts in high yields with high to excellent enantioselectivities.

Organocatalytic asymmetric Michael addition[1] has widely been used for the stereocontrolled formation of carbon–carbon and carbon–heteroatom bonds. α,β-Unsaturated compounds are known as versatile Michael acceptors that provide important synthetic intermediates with various nucleophiles via Michael reaction. The organocatalytic asymmetric Michael addition of malonates to α,β-unsaturated aldehydes has been reported in recent years.[2] For example, Jørgensen et al. demonstrated that *O*-TMS diarylprolinol derived from (*S*)-proline was an effective organocatalyst.[3] Zlotin et al. have reported that *O*-TMS diphenylprolinol modified with an ionic liquid moiety can be used four times without any decrease in activity and enantioselectivity.[4] However, these reactions are very slow (1–4 d). Ma et al. have mentioned asymmetric Michael reaction catalyzed by *O*-TMS-protected diphenylprolinol and acetic acid in water.[5] In this case, the reaction reached completion in less than 24 h. However, more than 20 mol % of additive was needed for the reaction to be completed in reasonable time with high enantioselectivity. Therefore, the design and synthesis of more promising diarylprolinol silyl ethers[6] is a significant requirement for the organocatalytic asymmetric Michael reaction.

On the other hand, we reported the solvent-free organocatalytic asymmetric Michael addition of thiols to α,β-unsaturated aldehydes using an organocatalyst derived from *trans*-4-hydroxyproline in 2007.[7] This reaction proceeded smoothly without any organic solvent to give the corresponding chiral sulfides in almost enantiomerically pure form (up to 99% ee). We speculated that organocatalysts derived from *trans*-4-hydroxyproline may be extended to the enantioselective asymmetric Michael addition of malonates to α,β-unsaturated aldehydes. Herein, we disclose our fruitful results of these investigations.

First, we examined the reaction of cinnamaldehyde (0.45 mmol) with diethyl malonate (0.3 mmol) in MeOH as a model combination to optimize the organocatalyst (Figure 1 and Table 1). Organocatalyst **1** was found to be the most effective for this reaction (Entry 1). While a higher enantioselectivity was obtained with organocatalyst **3**, the chemical yield of Michael adduct was much lower compared to organocatalyst **1** (Entry 3). In the case of using organocatalyst **3**, a longer reaction time was required (Entry 4). In the presence of organocatalyst **4**, which has a free hydroxy group, yield and enantioselectivity of the Michael adduct were reduced (Entry 5). The reaction catalyzed by organocatalyst **5** also afforded the corresponding Michael adducts with 98% ee (Entry 6). When the reaction was carried out at 1.0 M, the chemical yield of the Michael adduct increased and the reaction was completed in 3 h (Entry 7). Decreasing the catalyst loading from 10 to 5 mol % resulted in a lower product yield (Entry 8). A reaction carried out at 0 °C did not improve the enantioselectivity (Entry 9).

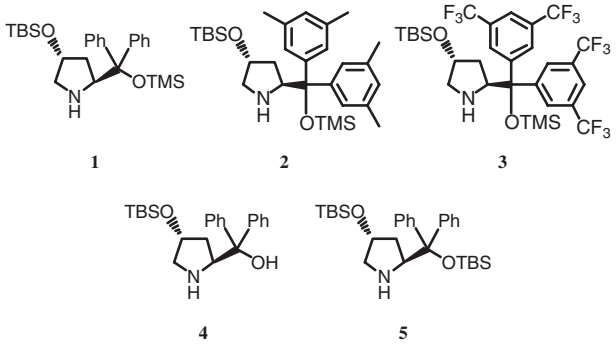
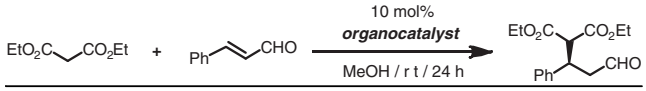


Figure 1. Organocatalysts examined in this study.

Table 1. Catalyst screening for the asymmetric Michael addition of diethyl malonate to cinnamaldehyde[a]

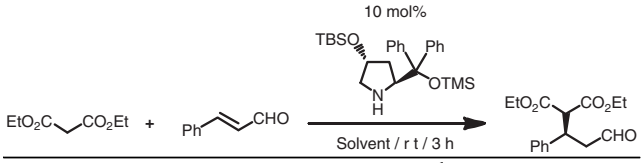


Entry	Organocatalyst	Yield/%[b]	Ee/%[c]
1	**1**	94	97
2	**2**	90	94
3	**3**	62	92
4[d]	**3**	80	94
5	**4**	53	62
6	**5**	75	98
7[e]	**1**	98	97
8[f]	**1**	74	96
9[g]	**1**	67	97

[a]Unless otherwise specified, the reactions were performed using cinnamaldehyde (0.45 mmol), diethyl malonate (0.3 mmol), and organocatalyst (0.03 mmol) in MeOH (0.5 mL). [b]Isolated yields. [c]Ee was determined by HPLC analysis using a chiral column after oxidation to the corresponding methyl ester.[3] [d]The reaction was carried out for 48 h. [e]The reaction was performed in MeOH (0.3 mL) for 3 h. [f]The reaction was carried out with 5 mol % catalyst for 12 h. [g]The reaction was carried out at 0 °C for 3 h.

Next, we investigated the effect of solvents in the presence of organocatalyst **1** (Table 2). As shown in Table 2, polar protic solvents, like MeOH and EtOH were effective and led to high enantioselectivities (Entries 1 and 2), whereas DMF, CH_3CN, CH_2Cl_2, and hexane were not effective from the viewpoint of

Table 2. Effect of solvents[a]



Entry	Solvent	Yield/%[b]	Ee/%[c]
1	MeOH	98	97
2	EtOH	70	97
3	DMF	8	96
4	CH_3CN	9	90
5	CH_2Cl_2	4	95
6	hexane	8	94
7	neat	46	97

[a]Unless otherwise specified, the reactions were performed using cinnamaldehyde (0.45 mmol), diethyl malonate (0.3 mmol), and organocatalyst **1** (0.03 mmol) in MeOH (0.3 mL). [b]Isolated yields. [c]Ee was determined by HPLC analysis using a chiral column after oxidation to the corresponding methyl ester.[3]

chemical yields (Entries 3–6). A similar solvent effect was observed in the Jørgensen's paper.[3] Interestingly, the desired Michael adduct was obtained in 46% yield with 97% ee under solvent-free conditions (Entry 7).

A variety of reactions were conducted under optimized conditions in the presence of 10 mol % of organocatalyst **1** in MeOH at room temperature to establish the scope and limitations of the present Michael reaction (Table 3).[8] Using dimethyl and dibenzyl malonates as Michael donors with cinnamaldehyde caused reactions to occur readily (Entries 1 and 3). The reaction of aromatic α,β-unsaturated aldehydes substituted with electron-donating (OMe) and electron-withdrawing groups (NO_2) afforded the corresponding Michael adduct in good to high yields with high enantioselectivities (Entries 4–11). It is notable that ortho substituted aromatic α,β-unsaturated aldehydes were found to be more effective in the enantioselectivity (Entries 5 vs. 7 and 9 vs. 11). This result might arise from steric hindrance between enals and two silyloxy groups of the organocatalyst molecule. Furthermore, heteroaromatic and aliphatic α,β-unsaturated aldehydes performed well in the presence of 10 mol % of organocatalyst **1**. Unfortunately, a longer reaction time was required for these aldehydes and the Michael adducts were obtained in moderate yields with good enantioselectivities (Entries 12 and 13).

In summary, we have developed a highly enantioselective Michael addition of malonates to various α,β-unsaturated aldehydes in the presence of an organocatalyst derived from *trans*-4-hydroxyproline in MeOH. In contrast to known methods, the reaction proceeds smoothly in a shorter reaction time to afford the corresponding Michael adducts with excellent enantioselectivities (up to 98% ee). Further studies on the development of environmentally benign reactions using organocatalysts derived from *trans*-4-hydroxyproline are currently in progress in our laboratory.

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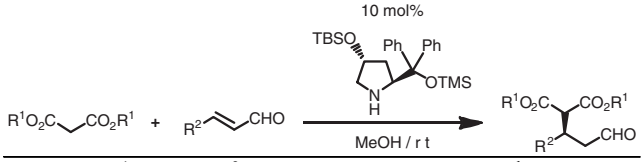
Table 3. Asymmetric Michael addition of malonates to various enals[a]



Entry	R^1	R^2	Time/h	Yield/%[b]	Ee/%[c]
1	Me	Ph	3	97	94
2	Et	Ph	3	98	97
3	Bn	Ph	3	87	94
4	Me	*o*-$MeOC_6H_4$	6	86	87
5	Et	*o*-$MeOC_6H_4$	6	73	95
6	Bn	*o*-$MeOC_6H_4$	6	85	92
7	Et	*p*-$MeOC_6H_4$	6	87	91
8	Me	*o*-$NO_2C_6H_4$	6	88	95
9	Et	*o*-$NO_2C_6H_4$	6	87	98
10	Bn	*o*-$NO_2C_6H_4$	6	77	95
11	Et	*p*-$NO_2C_6H_4$	6	76	92
12	Me	2-Furyl	13	30	82
13	Bn	Me	48	42	79

[a]All reactions were performed at a 0.3 mmol scale. [b]Isolated yields. [c]Ee was determined by HPLC analysis using a chiral column after oxidation to the corresponding methyl ester.[3]

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