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Enantioselective organocatalytic Michael addition of malonates to α,β-unsaturated aldehydes in water

Anqi Ma, Shaolin Zhu, Dawei Ma *

State Key Laboratory of Bioorganic and Natural Products Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Lu, Shanghai 200032, China

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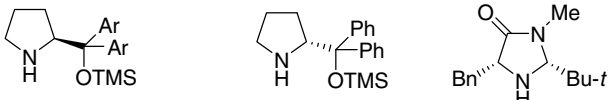
Abstract

The Michael addition of malonates to α,β-unsaturated aldehydes catalyzed by *O*-TMS protected diphenylprolinols and acetic acid in water occurs at 0 °C to rt. In most cases, the reaction runs to completion in less than 24 h. A wide range of aldehydes including β-aryl, β-alkyl and β-alkenyl acroleins are found to be compatible with these conditions, providing the corresponding adducts in good yields and with good to excellent enantioselectivities.

The catalytic asymmetric Michael addition is one of the most powerful and reliable tools for the stereocontrolled formation of carbon–carbon and carbon–heteroatom bonds.[1] Over the past years, significant progress in this area has been made using organocatalysts.[1] When α,β-unsaturated aldehydes were employed as Michael acceptors, chiral secondary amines such as *O*-TMS protected diarylprolinols **1**, **2**, and imidazolidinone **3** were proven to be effective catalysts by activating them through an iminium-ion mechanism.[2] Jørgensen and co-workers reported that the asymmetric Michael addition of malonates to aromatic α,β-unsaturated aldehydes could be achieved with good yields and enantioselectivities by using *O*-TMS protected diarylprolinol **1a** as catalyst, which provided a very useful approach to chiral lactones and lactams.[3] However, this reaction requires a long time (usually 4 days) and a relatively higher catalyst loading (10 mol %). Furthermore, the use of aliphatic α,β-unsaturated aldehydes as substrates was unsuccessful in this case due to predominant side reactions with the solvent ethanol.[3] Recently, we observed that the Michael addition of aldehydes to nitroalkenes could be greatly accelerated with improved stereochemical outcome by using *O*-TMS protected diphenylprolinol **2** and benzoic acid as catalytic system and water as the reaction medium.[4] Gratifyingly, application of these conditions to the Michael addition of malonates to α,β-unsaturated aldehydes gave similar effects. Both aromatic and aliphatic α,β-unsaturated aldehydes were found to be compatible with these reaction conditions. Herein, we wish to disclose our results.[5]



1a: Ar = 3,5-$(CF_3)_2C_6H_3$
1b: Ar = Ph

2

3

As indicated in Table 1, a model reaction between dimethyl malonate and cinnamaldehyde was used to evaluate the results under different conditions. A very good yield was obtained at room temperature with the additive $PhCO_2H$ using 10 mol % catalyst **2** within only 3 h (entry 1). We tried to reduce the amount of catalyst to 1 mol %, but the reaction became too slow to give reasonable yields even after 2 days (entry 2). Consequently, the amount of catalyst **2** was set to 5 mol % and it was found that the reaction ran smoothly now (entry 3). Further attempts demonstrated that the ee value could be slightly increased when the reaction was first kept at 0 °C for 1 h (entry 4).

* Corresponding author. Tel.: +86 2164163300; fax: +86 2164166128.
E-mail address: madw@mail.sioc.ac.cn (D. Ma).

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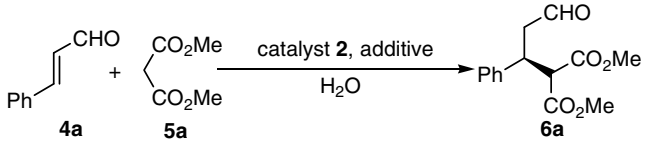
Table 1
Influence of additives on the addition of dimethyl malonate **5a** to cinnamaldehyde **4a** catalyzed by *O*-TMS protected diphenylprolinol **2**[a]



Entry	Compound **2** (mol %)	Time (h)	Additive	Yield[b] (%)	ee[c] (%)
1	10	3	$PhCO_2H$	91	91
2	1	48	$PhCO_2H$	<10	—
3	5	12	$PhCO_2H$	81	91
4	5	8	$PhCO_2H$	73[d]	97
5	5	24	NaOAc	85[d]	96
6	5	48	CF_3CO_2H	<5[d]	—
7	5	24	HOAc	96[d]	95

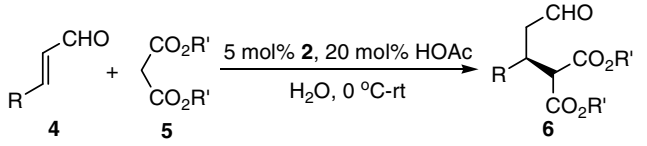
[a] Reaction conditions: **4a** (1.0 mmol), **5a** (0.5 mmol), 10 mol % acetic acid, 0.25 mL of water, rt.
[b] Isolated yield.
[c] Determined by chiral HPLC analysis of the isolated product.
[d] Reaction was carried out at 0 °C for 1 h, then rt for the indicated time.

Screening other additives including salt (entry 5) and acids (entries 6 and 7) revealed that they had an effect on the process. Because of the decomposition of the catalyst, there was barely any product when CF_3CO_2H (TFA) was used (entry 6). The use of acetic acid gave the best result with the highest yield and excellent enantioselectivity (entry 7).

With the optimized reaction conditions at hand, we examined a number of aromatic α,β-unsaturated aldehydes and two different malonates, and the results are summarized in Table 2. Generally, these reactions were complete in less than 12 h, and better yields and enantioselectivities were obtained compared to Jørgensen's conditions.[3] The electronic nature of the substituents at the aromatic ring seems to have little influence on this reaction process as evident from the fact that both substrates with a strong electron-donating group and a strong electron-withdrawing group gave similar results (compare entries 5 and 11). However, steric hindrance could greatly slow down this reaction, as indicated by the longer reaction time required in the case of the 2-bromophenyl substituted acrolein (entry 10). Noteworthy is that the excess amounts of aldehydes (entries 2, 3, 5–7, and 9) or malonates (entries 1, 4, 8, 10, and 11) had to be used to ensure better yields because incomplete conversion was met in most cases if equal molar amounts of the two partners were added (data not shown).

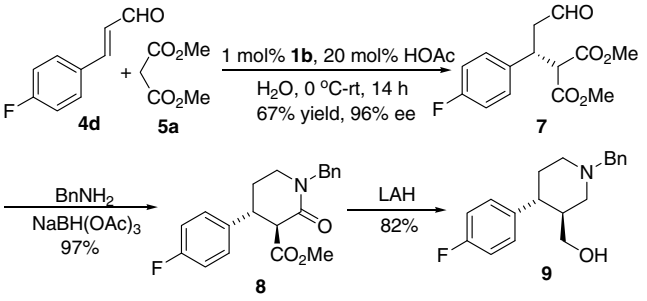
Based on Jorgensen's report[3], we assumed that using (*R*)-**2** as catalyst would afford (*S*)-configurated products. In order to confirm this hypothesis and demonstrate the practical application of this reaction, we decided to synthesize piperidine **9**, a known key intermediate for the assembly of antidepressant (−)-paroxetine.[3,6] As depicted in Scheme 1, we tried to use only 1 mol % catalyst **1b** to promote the reaction of β-(4-fluorophenyl) acrolein **4d** with dimethyl malonate **5a**. To our delight, this reaction worked well on a 20 mmol scale to provide **7**[7] in 67% yield with

Table 2
Enantioselective Michael addition of malonates **5** to β-aryl acroleins **4** catalyzed by *O*-TMS protected diphenylprolinol **2** and acetic acid[a]



Entry	R	R′	Time (h)	Product/yield[b] (%)	ee[c] (%)
1	Ph	Me	6	**6a**/90[d]	96
2	Ph	Bn	5	**6b**/93	95
3	2-Furyl	Me	3	**6c**/92	88
4	2-Furyl	Bn	3	**6d**/85[d]	90
5	4-$MeOC_6H_4$	Me	4	**6e**/81[e]	91
6	4-$MeOC_6H_4$	Bn	4	**6f**/88[e]	96
7	4-FC_6H_4	Me	2	**6g**/78[e]	97
8	4-BrC_6H_4	Me	4	**6h**/75[d]	94[f]
9	4-BrC_6H_4	Bn	4	**6i**/95	92[f]
10	2-BrC_6H_4	Me	12	**6j**/74[d]	90[f]
11	4-$NO_2C_6H_4$	Me	3	**6k**/78[d]	92

[a] Reaction conditions: **4** (1.0 mmol), **5** (0.5 mmol), 5 mol % **2**, 20 mol % acetic acid, 0.25 mL of water, 0 °C for 1 h, then rt for the indicated time.
[b] Isolated yield.
[c] Determined by chiral HPLC analysis of the isolated product.
[d] The reaction was carried out with 0.5 mmol of **4** and 1.0 mmol of **5**.
[e] The reaction was carried out with 0.75 mmol of **4** and 0.5 mmol of **5**.
[f] Determined by chiral HPLC analysis of the corresponding methyl ester that was obtained by oxidation and esterification of the adduct.

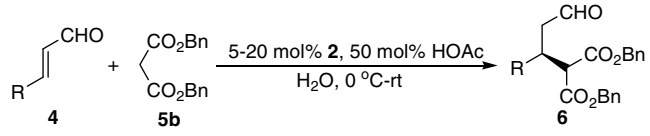


Scheme 1.

96% ee. Next, reductive amination of **7** and benzylamine mediated with $NaBH(OAc)_3$ followed by condensative cyclization delivered lactam **8** in 97% yield. No *cis*-isomer was determined by ^1H NMR, indicating that the diastereoselectivity in this step was greater than 97%. Finally, the reduction of **8** with LAH afforded **9**, whose optical rotation was identical to that previously reported, thereby indicating that intermediate **7** has the (*R*)-configuration.

Having achieved excellent results in the Michael addition of malonates to aromatic α,β-unsaturated aldehydes, we next explored the use of aliphatic α,β-unsaturated aldehydes as substrates since their products should be more useful for organic synthesis. As expected, these substrates were also compatible with our conditions, although relatively low yields and enantioselectivities were observed as illustrated in Table 3. Interestingly, β-alkyl substituted

Table 3
Enantioselective Michael addition of malonates **5** to β-alkyl or alkenyl acroleins **4** catalyzed by *O*-TMS protected diphenylprolinol **2** and acetic acid[a]



Entry	R	Time (h)	Product/yield[b] (%)	ee[c] (%)
1	Me	27	**6l**/55[d,e]	79
2	*i*-Pr	48	**6m**/70[d,e]	95
3	C_2H_5 $(CH_2)_2$	40	**6n**/44[e]	73
4		27	**6n**/62[d,e]	83
5	H_3C	20	**6o**/62	82
6	*n*-C_5H_{11}	20	**6p**/67	82

[a] Reaction conditions: **4** (1.0 mmol), **5b** (0.5 mmol), 5 mol % **2**, 50 mol % acetic acid, 0.25 mL of water, 0 °C for 1 h, then rt for the indicated time.
[b] Isolated yield.
[c] Determined by chiral HPLC analysis of the isolated product.
[d] The reaction was carried out with 2.0 mmol **4** and 0.5 mmol **5b**.
[e] The reaction was carried out with 20 mol % catalyst **2**.

acroleins showed a strongly reduced reactivity so that increased catalyst and aldehyde loadings were required to get satisfactory yields (entries 1 and 2). An unconjugated β-alkenyl substituted acrolein showed a similar behavior (entry 3), while two conjugated dienals displayed a reactivity similar to β-aryl acroleins (entries 5 and 6). These differences might arise from the bigger π-conjugated system that makes the imine intermediates more stable. The best enantioselectivity was obtained in the case of *i*-propyl as the β-substituent (entry 2). This implies that a bulkier β-substituent is favorable for asymmetric induction.

In conclusion, we have developed a new procedure for the asymmetric Michael addition of malonates to α,β-unsaturated aldehydes, which afforded the adducts in good yields with good to excellent enantioselectivities. Both aromatic and aliphatic α,β-unsaturated aldehydes worked in this process, thereby broadening the scope of this synthetically useful reaction. The short reaction time used here is also remarkable. These advantages presumably result from the combination of Brønsted acids as promoters[8] and water as the reaction medium.[9]

Acknowledgement

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7. *Selected data for* **7**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.59 (t, $J = 1.8$ Hz, 1H), 7.26–7.18 (m, 2H), 7.00–6.95 (m, 2H), 4.03–4.00 (m, 1H), 3.73 (s, 3H), 3.70 (d, $J = 9.3$ Hz, 1H), 3.51 (s, 3H), 2.95–2.86 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.5, 168.2, 167.7, 161.9, 135.5, 129.6, 115.6, 57.2, 52.7, 52.5, 47.3, 38.6; HRMS calcd for $C_{14}H_{15}O_5FNa$ $(M+Na)^+$ 305.0796, found 305.0794; $[\alpha]_D^{25}$ −30.5 (*c* 1.0, $CHCl_3$, 96% ee).
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