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Cinchona–diaminomethylenemalononitrile organocatalyst for asymmetric conjugate addition of 1,3-diketone to nitroalkene

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ABSTRACT

A diaminomethylenemalononitrile organocatalyst with a cinchona motif efficiently promotes the enantioselective conjugate addition of acetylacetone to various nitroalkenes to yield the corresponding addition products in high to excellent yields with up to 89% ee.

Organocatalytic conjugate addition is one of the most efficient methodologies for the formation of carbon—carbon bonds in the synthesis of enantiomerically enriched molecules.[1] Of numerous asymmetric Michael additions that are mediated by organocatalysts, the conjugate addition of 1,3-diketones to nitroalkenes plays an important role in modern organic chemistry because chiral intermediates with a nitrodicarbonyl motif can be readily prepared and easily converted to valuable synthetic scaffolds.[2] However, nearly all of the organocatalysts developed for this transformation are based on thiourea[3,4] or squaramide[5] derivatives as double hydrogen bond donating groups, and successful conjugate additions using organocatalysts with other types of double hydrogen bonding functional groups have rarely been reported.[6] Therefore, the development of organocatalysts bearing novel hydrogen bond donating groups other than thiourea and squaramide is a highly challenging theme in the field of organocatalysis. Recently, we reported that organocatalysts with the diaminomethylenemalononitrile (DMM) motif are excellent catalysts for conjugate additions.[7,8] DMM catalyst **1** with a primary amine group efficiently promotes the reaction of branched aldehydes with vinyl sulfone and the addition of malonates to enones, affording the corresponding adducts with excellent stereoselectivities.[7] Furthermore, pyrrolidine-DMM **2** with a secondary amine group catalyzes the conjugate addition of ketones to nitroalkenes to afford the desired addition products with excellent stereoselectivities (Fig. 1).[8]

To demonstrate the further efficiency of organocatalysts with the DMM skeleton, we envisaged the application of **1** and **2** to other types of asymmetric Michael additions. Thus, the application of DMM organocatalysts **1** and **2** to the conjugate addition of 1,3-diketones to nitroalkenes was investigated (Table 1). The conjugate additions were performed using nitrostyrene (**7a**) and acetylacetone (2 equiv) as test reactants in the presence of a catalytic amount of **1** or **2** in Et_2O at room temperature. Unfortunately, organocatalysts **1** and **2** were poor catalysts for this reaction and provided low yields and low enantioselectivities (entries 1 and 2). Given these results, it was predicted that a DMM catalyst with a tertiary amine group would be superior to catalysts **1** and **2** with their primary and secondary amines, respectively. Cinchona alkaloids, which are tertiary amines, are excellent and powerful chiral sources with nucleophilicity and are widely utilized as organocatalysts.[9] As expected, DMM organocatalyst **3** provided both a high yield and high enantioselectivity (entry 3). Herein, we describe the efficient conjugate addition of 1,3-diketones to nitroalkenes using the novel cinchona–DMM organocatalyst **3**.

Organocatalyst **3** was readily prepared as shown in Scheme 1. Treatment of **4**[10] with **5**[11] in THF provided intermediate **6** in quantitative yield. Intermediate **6** was then reacted with 3,5-bis(trifluoromethyl)benzylamine to give the desired DMM organocatalyst **3**[12] in 41% yield.

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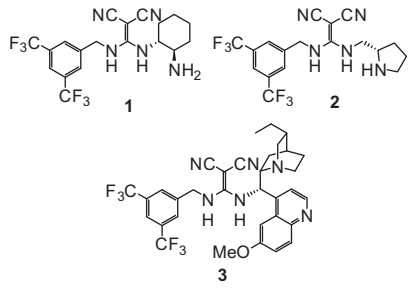
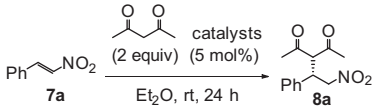


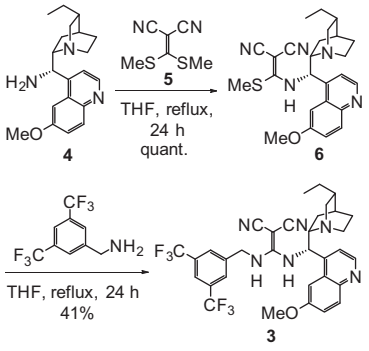
Figure 1. Structure of organocatalysts.

Table 1
Selection of organocatalysts



Entry	Catalyst	Yield[a] (%)	ee[b] (%)
1	**1**	23	1
2	**2**	48	−24
3	**3**	89	79

[a] Isolated yield.
[b] Determined by HPLC analysis.



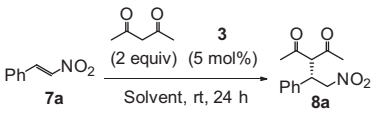
Scheme 1. Preparation of organocatalyst **3**.

First, the solvent conditions were examined for the Michael addition using **3**, as shown in Table 2. Among the representative solvents examined, diethyl ether was found to be the most suitable solvent considering both the yield and enantioselectivity (entry 6). Furthermore, more dilute conditions (0.5 M) led to a slight improvement in the enantioselectivity (entry 7).

Encouraged by these results, the reaction conditions for the Michael additions were then optimized by adding a representative protic acid as shown in Table 3. High enantioselectivity (87% ee) was obtained when 2.5 mol % benzoic acid was added (entry 3). The addition of other protic acids (2.5 mol %), including *p*-nitrobenzoic acid, formic acid, acetic acid, and trifluoroacetic acid, was also investigated; however, benzoic acid was found to be the most suitable additive (entries 7–10).

With these optimal conditions in hand, the scope and limitations of the Michael addition of acetylacetone to various nitroalkenes **7** were examined (Table 4).[13] Substrates **7b** and **7c** bearing methyl and methoxy substituents as representative electron-donating groups on the aromatic ring reacted with acetylacetone in the presence of catalyst **3**, affording the corresponding adducts

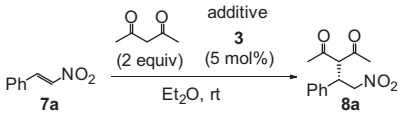
Table 2
Study of solvents



Entry	Solvent (1.0 M)	Yield[a] (%)	ee[b] (%)
1	DMF	92	1
2	MeOH	82	9
3	MeCN	53	47
4	EtOAc	67	70
5	THF	57	83
6	Et_2O	89	79
7[c]	Et_2O	71	81
8	Toluene	91	76
9	CH_2Cl_2	89	73
10	Neat	94	58

[a] Isolated yield.
[b] Determined by HPLC analysis.
[c] The reaction was carried out in Et_2O (0.5 M).

Table 3
Optimization of reaction conditions



Entry	Additive (mol %)	Time (h)	Yield[a] (%)	ee[b] (%)
1	—	24	71	81
2	$PhCO_2H$ (5)	24	53	86
3	$PhCO_2H$ (2.5)	48	76	87
4	$PhCO_2H$ (5)	48	80	81
5	$PhCO_2H$ (7.5)	48	51	90
6	$PhCO_2H$ (10)	48	46	87
7	*p*-$NO_2C_6H_4CO_2H$ (2.5)	48	21	68
8	HCO_2H (2.5)	48	95	75
9	AcOH (2.5)	48	86	75
10	TFA (2.5)	48	68	83

[a] Isolated yield.
[b] Determined by HPLC analysis.

8b and **8c** in high yields with high enantioselectivities (entries 2 and 3). The reaction of nitroalkenes **7d** and **7e** bearing electron-withdrawing bromo and chloro substituents, respectively, with acetylacetone proceeded to give the corresponding addition products **8d** and **8e** with high stereoselectivities (entries 4 and 5). The Michael addition of substrates with a chloro group at the *meta*- or *ortho*-position on the benzene ring also proceeded smoothly to afford the adducts **8f** and **8g**, respectively, in excellent yields with high stereoselectivities (entries 6 and 7). Moreover, **7h** with a naphthalene skeleton was a good substrate and provided the corresponding adduct **8h** in 99% yield with 89% ee (entry 8). The conjugate additions to **7i** and **7j** with heterocyclic skeletons also provided adducts **8i** and **8j** in 73% and 66% yields and 81% ee and 88% ee, respectively (entries 9 and 10).

It is presumed that the conjugate addition of acetylacetone to nitroalkenes using DMM organocatalyst **3** proceeds via the transition state shown in Figure 2. The tertiary amine group of **3** receives a proton from the enol group generated from acetylacetone. Two hydrogen bonding donor protons of the DMM motif then successfully interact with the two oxygen atoms in the nitro group in the nitroalkene to direct the approach of the enolate (attack on the *Si* face). This transition state subsequently affords the corresponding adduct with high stereoselectivity.

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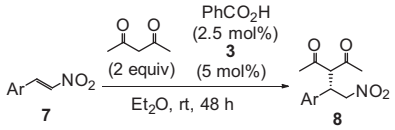
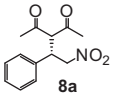
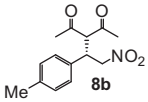
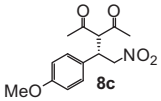
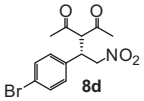
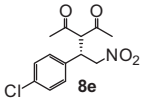
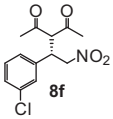
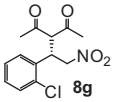
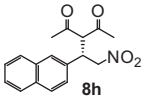
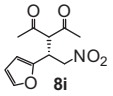
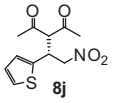
Table 4
Conjugate additions using organocatalyst **3**



Entry	Product	Yield[a] (%)	ee[b] (%)
1	 **8a**	76	87
2	 **8b**	83	81
3[c]	 **8c**	60	82
4	 **8d**	65	81
5	 **8e**	88	85
6	 **8f**	93	83
7	 **8g**	99	88
8	 **8h**	99	89
9	 **8i**	73	81
10	 **8j**	66	88

[a] Isolated yield.
[b] Determined by HPLC analysis.
[c] Catalyst (10 mol %) and benzoic acid (5 mol %) were used.

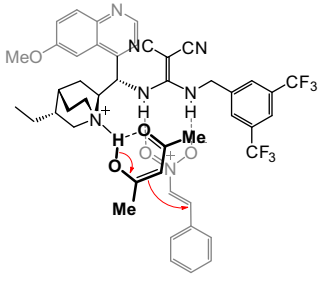


Figure 2. Plausible transition state model.

In conclusion, the novel readily prepared cinchona–DMM organocatalyst **3** efficiently catalyzes the conjugate addition of acetylacetone to nitroalkenes **7** at room temperature in diethyl ether to afford the corresponding addition products **8** in high yields with high enantioselectivities. On the other hand, the reaction of **7a** with acetylacetone using the similar cinchona–thiourea organocatalyst (10 mol %) provided high enantioselectivity; however, the yield of **8a** was modelate.[3b] Application of cinchona–DMM catalyst to other types of asymmetric reactions and the development of additional novel DMM-organocatalysts are currently underway in our laboratory.

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12. *Organocatalyst* ***3***: White powder; Mp = 104–106 °C; $[\alpha]_D^{20}$ −202.3 (*c* 1.00, MeOH); ^{1}H NMR (400 MHz, CD_3OD): δ = 0.79 (t, *J* = 7.3 Hz, 3H), 0.88–0.93 (m, 1H), 1.15–1.29 (m, 3H), 1.46–1.70 (m, 4H), 2.48 (ddd, *J* = 13.6, 6.0, 2.0 Hz, 1H), 2.67 (ddd, *J* = 14.6, 10.8, 4.3 Hz, 1H), 3.11–3.20 (m, 3H), 4.0 (s, 3H), 4.59–4.72 (m, 2H), 5.59 (br s, 1H), 7.37 (d, *J* = 4.5 Hz, 1H), 7.45 (dd, *J* = 9.3, 2.5 Hz, 1H),

7.65 (br s, 1H), 7.70 (br s, 2H), 7.87 (br s, 1H), 7.95 (d, J = 9.3 Hz, 1H), 8.53 (d, J = 4.8 Hz, 1H); ^{13}C NMR (100 MHz, CD_3OD): δ = 13.1, 27.0, 27.2, 29.3, 30.0, 36.4, 39.3, 42.8, 48.2, 57.4, 58.8, 80.3, 103.5, 120.3, 123.6, 124.9, 125.5 (q, $^1J_{C-F}$ = 272 Hz), 129.7, 132.7, 133.9 (q, $^2J_{C-F}$ = 33.7 Hz), 142.8, 146.0, 148.8, 160.8; HRMS (ESI): Calcd for $C_{33}H_{33}F_6N_6O$ $[M+H]^+$, 643.2620. Found, 643.2603; Anal. Calcd for $C_{33}H_{33}F_6N_6O$: C, 61.68; H, 5.02; N, 13.08. Found: C, 61.88; H, 5.23; N, 12.97.

13. *A typical procedure for the conjugate additions using* ***3*** *is as follows:* Acetylacetone (103 μL, 1.00 mmol) was added to a solution of nitrostyrene (**7a**, 74.6 mg, 0.500 mmol), benzoic acid (1.5 mg, 0.0125 mmol), and organocatalyst **3** (16.0 mg, 0.025 mmol) in Et_2O (1 mL) at room temperature. After stirring at room temperature for 48 h, the reaction mixture was directly purified by flash column chromatography on silica gel with hexane and ethyl acetate (gradually 5:1–2:1) to afford the pure **8a** (95.3 mg, 76%) as a white powder.

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