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Enantioselectively Organocatalytic Michael Addition of Ketones to Alkylidene Malonates

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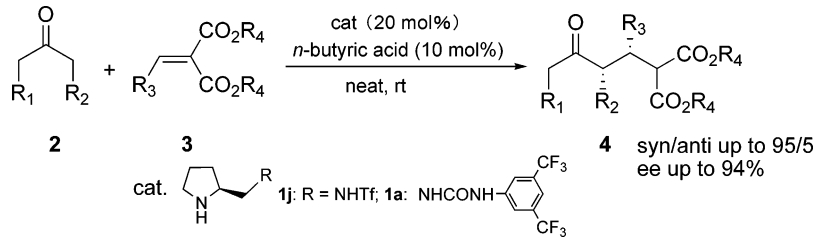

An organocatalytic asymmetric Michael addition of ketones to alkylidene malonates has been developed. In the presence of 20 mol % of urea **1a** or *N*-(pyrrolidin-2-ylmethyl)trifluoromethanesulfonamide **1j**, the reactions of ketones with alkylidene malonates afford the desired Michael adducts in moderate to good yields with good to high enantioselectivities under mild conditions.

Introduction

Asymmetric carbon−carbon bond formation reactions are among the most challenging endeavors in organic synthesis. The Michael reaction is one of the most efficient transformations, and thus, considerable attention has been given to its catalytic asymmetric version in the past decades.[1,2] Of the asymmetric reaction developed,[1−8] directly organocatalytic Michael addition[3−8] of ketones or aldehydes to α,β-unsaturated compounds provides a particular attractive method for the synthesis of versatile bifunctional products in an atom-economical manner. Recent studies on this subject show that α,β-unsaturated aldehyde,[4] ketone,[5] sulfone,[6] and nitrostyrene[7] are suitable substrates to give the desired adducts with high enantioselectivities. For

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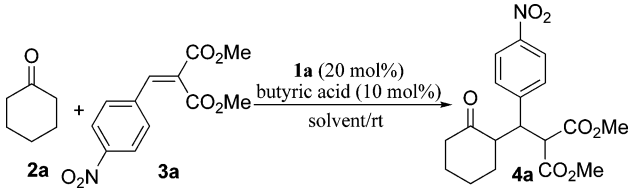
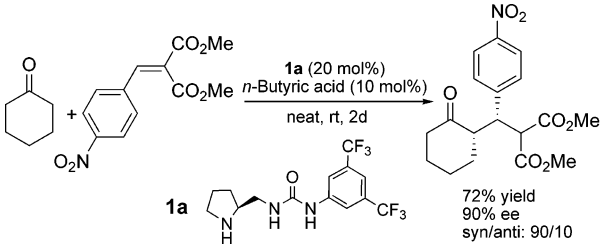
TABLE 1. Effects of Reaction Conditions on the Asymmetric Michael Addition[a]



entry	solvent	additive (10 mol %)	time (days)	conv[b] (%)	*syn*/*anti*[b]	ee[c] (%)
1	benzene	*n*-butyric acid	2	51	87/13	86
2	*i*-BuOH	*n*-butyric acid	2	50	90/10	87
3	*t*-BuOH	*n*-butyric acid	2	33	90/10	88
4	ethyl acetate	*n*-butyric acid	2	33	88/12	87
5	THF	*n*-butyric acid	2	26	82/18	88
6	CH_2Cl_2	*n*-butyric acid	2	25	88/12	86
7	neat	*n*-butyric acid	4	100	90/10	90
8	neat	*n*-butyric acid	2	72	90/10	90
9	neat	*i*-butyric acid	2	76	90/10	89
10	neat	heptanoic acid	2	68	91/9	87
11	neat	D-campher-10-sulfonic acid	2	15	–	–
12	neat	4-methylbenzenesulfonic acid	2	10	–	–

[a] Unless otherwise noted, all reactions were carried out using **2a** (474 mg, 5 mmol) and **3a** (0.25 mmol) in the presence of 20 mol % of catalyst in neat conditions, with *n*-butyric acid as an additive. [b] Determined by ^{1}H NMR. [c] Determined by chiral HPLC analysis.

alkylidene malonates as Michael acceptors, however, organocatalyst-promoted asymmetric Michael addition of ketones is less successful. So far, only pyrrolidine-based diamine catalysts were reported by Barbas and co-workers,[8] and they described that both ketones and aldehyde could react with alkylidene malonates[9] to afford the Michael adducts with moderate to good enantioselectivities (up to 73% ee). Very recently, we designed and synthesized two pyrrolidine−urea (thiourea)-based bifunctional organocatalysts **1a** and **1b**.[7k] These catalysts were successfully applied to the asymmetric Michael reaction of cyclohexanone with both aryl- and alkylnitroolefins to give the adducts in high yields with high diastereoselectivities and high enantioselectivities under operationally simple conditions. Further studies showed that the urea[10] could also catalyze the Michael addition of cyclohexanone with dimethyl 2-(4-nitrobenzylidene) malonate to afford the desired product in good yield with high enantiomeric excess as shown in eq 1. In this paper, we wish to report this reaction in detail.



(1)

Results and Discussion

Initially, it was found that a mixture of cyclohexanone and dimethyl 2-(4-nitrobenzylidene) malonate was stirred for 4 days to afford the Michael adduct in 72% yield with 90% ee in the presence of 10 mol % of *n*-butyric acid under solvent-free conditions. This result encouraged us to optimize the reaction conditions to further improve the diastereoselectivity and enantioselectivity. As shown in Table 1, although benzene, *i*-butanol, *tert*-butanol, ethyl acetate, THF, and CH_2Cl_2 could be employed as the solvents of the reaction to give good diastereoselectivity and high enantioselectivity (entries 1−6, Table 1), the optimal one is to perform the reaction in neat conditions (entries 7−12, Table 1). In addition to *n*-butyric acid, *i*-butyric acid, heptanoic acid, D-campher-10-sulfonic acid, and 4-methylbenzenesulfonic acid were tested as additives. Under the screened conditions, *n*-butyric acid gave the best results (entry 7, Table 1).

We also screened several readily accessible L-proline derivatives (**1a**−**1j**, Figure 1) as the catalysts using dimethyl 2-(4-nitrobenzylidene) malonate as a model substrate in solvent-free conditions at room temperature. As shown in Table 1, both pyrrolidine−urea **1a** and pyrrolidine−thiourea **1b** could promote the Michael reaction in moderate to good yield with high ee values (entries 1 and 2, Table 2). Although compounds **1c**−**1e** could catalyze the reaction to furnish the desired product, the reactions were sluggish (entries 3−5, Table 2). When **1f**−**1h** were employed (entries 6−8, Table 2), no Michael adduct was

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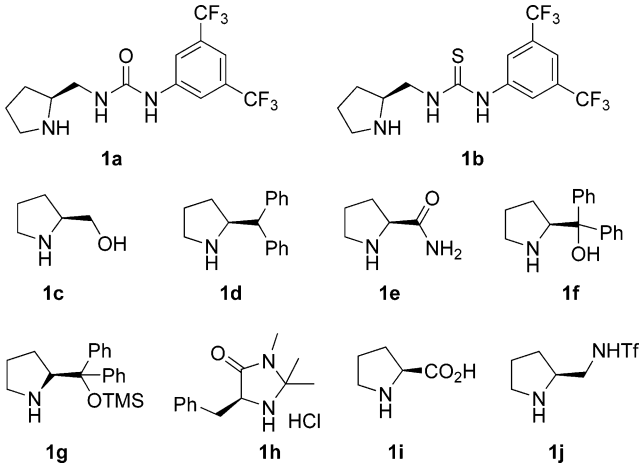
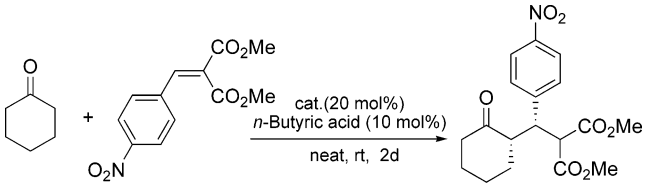


FIGURE 1. Structures of chiral catalysts.

TABLE 2. The Effects of Proline-Derived Catalysts on the Asymmetric Michael Addition of Cyclohexanone 2a to Alkylidene Malonate 3a[a]



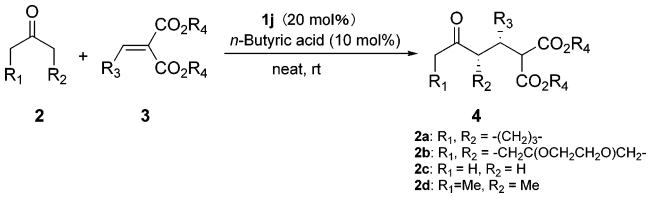
entry	catalyst	conv[b] (%)	*syn*/*anti*[b]	ee[c] (%)
1	**1a**	72	90/10	90
2	**1b**	43	80/20	88
3	**1c**	17	–	–
4	**1d**	17	–	–
5	**1e**	13	–	–
6	**1f**	NR	–	–
7	**1g**	NR	–	–
8	**1h**	NR	–	–
9	**1i**	85	85/15	33
10	**1j**	99	93/7	90
11[d]	**1j**	91	93/7	90

[a] Unless otherwise noted, all reactions were carried out for 2 days in the presence of 20 mol % of catalyst in neat conditions and 10 mol % of *n*-butyric acid using **2a** (474 mg, 5 mmol) and **3a** (0.25 mmol). [b] Determined by ^{1}H NMR. [c] Determined by chiral HPLC analysis. [d] Without *n*-butyric acid.

observed. L-Proline **1i** worked well to give good yield but with only 33% ee. To our delight, when pyrrolidine trifluoromethanesulfonamide **1j** was used, the product was isolated in nearly quantitative yield with high diastereoselectivity (93/7) and high enantioselectivity (90%) in the presence of 10 mol % of *n*-butyric acid (entry 10, Table 2). Without the acid, catalyst **1j** also gave the same diastereoselectivity and enantioselectivity with a slight reduction of the reaction rate (entry 11, Table 2).

Under the optimized conditions, a variety of ketones and alkylidene malonates with different structure were tested to investigate the generality of the present reaction, and the results are summarized in Table 3. All reactions were performed under solvent-free conditions at room temperature in the presence of 20 mol % of **1a** or **1j**[3c] with 10 mol % of butyric acid as an additive. Various alkylidene malonates reacted smoothly with cyclohexanone in moderate to good yields with high enantioselectivities. Substituents on aryl groups influenced slightly the

TABLE 3. Michael Addition Reactions of Ketones to Alkylidene Malonates[a]



entry	**2**	R_3	R_4	**4**	yield[b] (%)	*syn*/*anti*[b]	ee[c] (%)
1	**2a**	*p*-NO_2-C_6H_4	Me	**4a**	98	93/7	90
2	**2a**	C_6H_5	Et	**4b**	36	90/10	88
3	**2a**	*p*-Br-C_6H_4	Et	**4c**	71	93/7	90
4	**2a**	*o*-Cl-C_6H_4	Et	**4d**	48	95/5	88
5	**2a**	*m*-NO_2-C_6H_4	Et	**4e**	95	91/9	90
6	**2a**	α-$C_{10}H_7$	Et	**4f**	20	95/5	87
7	**2a**	*i*-Bu	Me	**4g**	27	nd	nd
8	**2b**	*p*-NO_2-C_6H_4	Me	**4h**	60	89/11	94
9	**2c**	*p*-NO_2-C_6H_4	Me	**4i**	74	–	54
10[d,e]	**2c**	*p*-NO_2-C_6H_4	Me	**4i**	36	–	62
11	**2d**	*p*-NO_2-C_6H_4	Me	**4j**	trace	–	–

[a] Unless otherwise noted, all reactions were carried out in neat conditions using **2** (0.5 mL, 5 mmol, 20 equiv) and **3** (0.25 mmol) in the presence of 20 mol % of **1j** and 10 mol % of *n*-butyric acid. [b] Determined by ^{1}H NMR. [c] Determined by chiral HPLC analysis. [d] **1a** as a catalyst. [e] At 0 °C.

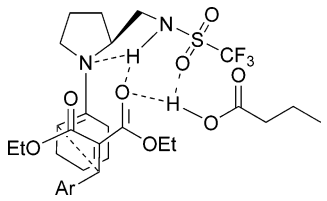


FIGURE 2. A proposed transition state.

diastereoselectivities and enantioselectivities (entries 1−6, Table 3) but affected strongly the yields. Generally, malonates with electron-withdrawing groups were more reactive than phenylidene malonate and gave higher yields (entries 1, 3, and 5 vs entry 2). Dimethyl 2-(3-methylbutylidene) malonate worked well to give the corresponding product in 27% yield, but the ee value was not determined since the racemic product could not be separated on a chiral column. The reaction of **2b** proceeded well to give good diastereoselectivity and enantioselectivity (entry 8, Table 3). Acetone also was a suitable Michael donor to produce the desired adducts in moderate yields with moderate ee values (entries 9 and 10, Table 3). For pentan-3-one, its reaction was very sluggish (entry 11, Table 3).

The relative and absolute configurations of the Michael adducts are shown in Table 2. The relative configurations were assigned by comparison of ^{1}H and ^{13}C NMR of the products with the known compounds. The absolute configurations were determined by comparing the optical rotations with those in literature.

In the reaction of cyclohexanone with chalcones catalyzed by **1j**, Wang et al. developed a transition state model to explain the stereochemistry. In the model, they proposed that the hydrogen bonding interactions of both NH in **1j** and *i*-PrOH with the chalcone carbonyl group brought out higher stereoselectivities.[5e] In the present reaction, a similar transition state model, as shown in Figure 2, could rationalize its high enantio- and diastereoselectivity. In this model, the hydrogen bonding of both NH in **1j** and *n*-butyric acid with the carbonyl group of

alkylidene malonates activated the substrate, explaining well that a catalytic amount of *n*-butyric acid can speed up the reaction.

In conclusion, we have developed a directly organocatalytic, asymmetric Michael addition reaction of ketones with alkylidene malonates. This reaction can be carried out under mild conditions to afford potentially useful 1,3-diester compounds in moderate to good yields with good to high enantio- and diastereoselectivities. Further investigations of the mechanism and synthetic applications of the current reaction are in progress.

Experimental Section

Representative Procedure for the Michael Addition of Cyclohexanone to Dimethyl 2-(4-nitrobenzylidene) Malonate. 1j (11.6 mg, 0.05 mmol) in cyclohexanone (474 mg, 5 mmol) was stirred for 10 min at room temperature, and then **3a** (66.25 mg, 0.25 mmol) was added. The reaction was allowed to be stirred at room temperature for 2 days. After the reaction was complete (monitored by TLC), the resulting mixture was concentrated under reduced pressure and the residue was then purified by flash chromatography (petroleum/EtOAc = 1/5) to give the product **4a**: yield 98%, 90% ee, determined by HPLC analysis (Chiralcel AD-H, *i*-PrOH/hexane = 10/90, 0.7 mL/min, 238 nm; t_r (minor) = 35.21 min, t_r (major) = 42.21 min); $[\alpha]_D^{20} = -46.7$ ($c = 1.045$, $CHCl_3$); *syn*/*anti* = 93/7; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.14 (d, $J = 8.4$ Hz, 2H), 7.48 (d, $J = 8.4$ Hz, 2H), 4.19−4.06 (m, 2H), 3.70 (s, 3H), 3.53 (s, 3H), 3.03−2.95 (m, 1H), 2.48−2.40 (m, 2H), 2.04 (m, 1H), 1.80−1.77 (m, 2H), 1.64−1.58 (m, 2H), 1.37−1.06 (m, 1H).

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Supporting Information Available: Characterization data for all new compounds noted in Table 3, and experimental procedures (PDF) are available. This material is available free of charge via the Internet at http://pubs.acs.org.

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