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Highly Enantioselective Conjugate Addition of Ketones to Alkylidene Malonates Catalyzed by a Pyrrolidinyl–Camphor-Derived Organocatalyst

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Pyrrolidinyl–camphor derivatives have been proven to be efficient organocatalysts for enantioselective conjugate addition of ketones to alkylidene malonates, affording high chemical yields (up to 95%) of the corresponding products with high to excellent levels of diastereoselectivity (up to >99:1 *dr*) and enantioselectivity (up to 96% *ee*) under solvent-free reaction conditions at ambient temperature.

Introduction

The development of organocatalysts in asymmetric reactions has attracted much attention, as catalytic systems are generally nontoxic, highly efficient and selective, environmentally friendly, and stable under aerobic and aqueous reaction conditions.[1] Asymmetric conjugate addition of carbon-centered nucleophiles to electron-deficient olefins is generally recognized as one of the most powerful, atom-economical, C–C bond-forming reactions in modern synthetic chemistry.[2] Remarkable advances have been realized in the development of asymmetric variants of this reaction, providing enantioenriched Michael adducts.[3] The organocatalytic conjugate addition of aldehydes and ketones to Michael acceptors is among the most elegant methods developed. Electron-deficient alkenes, such as nitrostyrenes,[4] α,β-unsaturated aldehydes,[5] enones,[6] vinyl sulfones,[7] maleimides,[8] benzoquinones,[9] and vinyl phosphonates,[10] have been successfully employed. On the other hand, alkylidene malonates represent alternative Michael acceptors because the functionalities are useful in the synthesis of important pharmaceutical molecules. For example, biologically active chiral substituted lactones and lactams are easily accessible from malonate-containing aldehydes.[11,12a]

Enantioselective Friedel–Crafts alkylations of indole with benzylidene malonates in the presence of chiral copper(II) complexes have been reported.[13] The organocatalytic reaction of carbonyl compounds with alkylidene malonates as efficient Michael acceptors has also been achieved.[12] Of these, the groups of Barbas and Tang have independently reported the efficient Michael addition of ketones to alkylidene malonates catalyzed by pyrrolidine-based diamine and trifluoromethanesulfonamide, respectively.[14a–14c] Recently Feng and co-workers reported the use of bispidine-derived organocatalysts for the Michael addition of ketones to alkylidene malonates and nitrostyrene.[15] In these processes, although the Michael adducts were obtained with high to excellent stereoselectivities, a large excess of ketones as donors (20 equiv.) and prolonged reaction times (weeks) were required to complete the reaction. For example, the reaction of cyclohexanone and diethyl 2-benzylidenemalonate catalyzed with *N*-(pyrrolidin-2-ylmethyl)trifluoromethanesulfonamide takes 14 d to give the desired product (36% yield, 90:10 *dr*, and 88% *ee*).[14b] The development of efficient catalytic systems for the Michael addition of ketones to alkylidene malonates remains a challenging goal in asymmetric synthesis. Herein, we present a highly enantioselective organocatalytic conjugate addition of ketones to alkylidene malonates by using novel pyrrolidinyl–camphor-based organocatalysts to afford Michael adducts in high chemical yields (up to 95%) with high to excellent levels of stereoselectivity (up to 99:1 *dr* and 96% *ee*). Moreover the reactions were carried out under operationally simple, solvent-free conditions in the absence of an additive.

Results and Discussion

We envisioned that the assembly of a rigid stereocontrolling camphor structure with a pyrrolidinyl group may constitute a well-defined scaffold. The motifs were linked with appropriate functional groups, such as amides (**1a**–**c**), sulfonamide (**1d**), sulfides (**1e** and **1f**), and thiourea (**1g**) to tune the intrinsic organocatalytic behaviors (Figure 1). For this, various pyrrolidinyl–camphor-based organocatalysts were designed and synthesized, and they have proven to be effective in catalyzing asymmetric transformations.[16] As a model reaction, we studied the Michael addition of cyclohexanone **2a** to dimethyl 2-(4-nitrobenzylidene)malonate

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(**3a**) catalyzed by pyrrolidinyl–camphor derivative **1a** (20 mol-%). The results are shown in Table 1. Resulting Michael adduct **4a** was obtained with moderate chemical yield, good diastereoselectivity, and good enantioselectivity when the reaction was carried out in polar solvents such as THF, CH_3CN, and $CHCl_3$ (Table 1, Entries 1–3). A slight improvement was observed when toluene was used as the reaction medium (Table 1, Entry 4). The reactivity was further improved and the stereoselectivity was retained under solvent-free reaction conditions (Table 1, Entry 5). Various acidic additives (20 mol-%) were then screened to further optimize the reaction. Comparable results were obtained when the reaction was carried out in the presence of citric acid, ketopinic acid, camphorsulfonic acid (CSA), propionic acid, and dodecylbenzenesulfonic acid (DBSA) (Table 1, Entries 6–10). In contrast, the diastereoselectivities and the chemical yields were marginally improved when the reaction was performed in the presence of PhCOOH, acetic acid, or TsOH (Table 1, Entries 11–13). Surprisingly, the reactivity dropped when trifluoroacetic acid (TFA) was used as an acidic additive (Table 1, Entry 14). This may due to the protonation of the secondary amine of the organocatalyst, which hampers enamine formation.

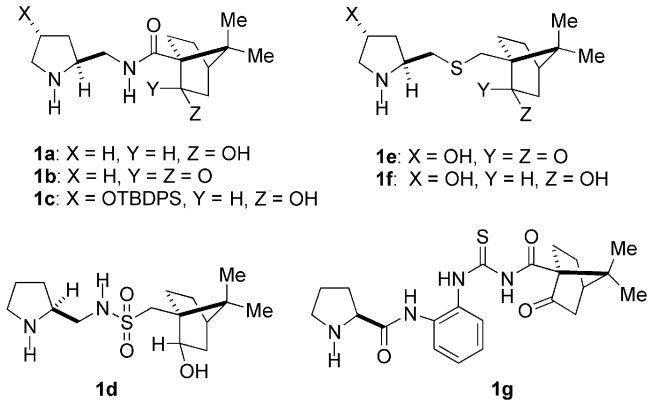
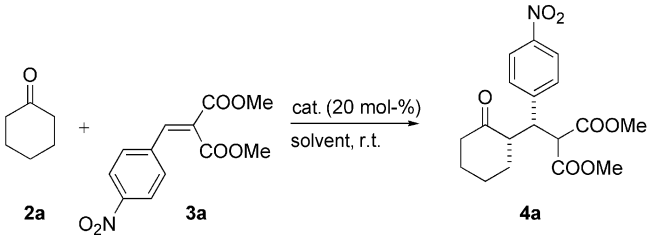


Figure 1. Structures of pyrrolidinyl–camphor-based organocatalysts.

Encouraged by these results, we further optimized the catalysis conditions by screening other catalysts that were synthesized from our laboratory. Only trace amounts of the Michael adducts were formed when amide-linked **1b** was used, whereas the use of silyl ether analogue **1c** failed to catalyze the reaction (Table 1, Entries 15 and 16). The use of sulfonamide **1d** yielded the desired product with high diastereoselectivity and enantioselectivity, with a modest chemical yield (Table 1, Entry 17). When sulfide-linked organocatalyst **1e** was used under the optimized conditions, desired addition product **4a** was generated with poor chemical yield but high enantioselectivity (96%*ee*) and diastereoselectivity (95:5 *dr*; Table 1, Entry 18). Surprisingly, increasing the ketone quantity (up to 20 equiv.) did not increase the chemical yield of the reaction (Table 1, Entry 19). Fortuitously, in the absence of TsOH the Michael adduct was obtained with excellent chemical yield with high levels of diastereo- and enantioselectivity (Table 1, Entry 20). Surprisingly, the reaction failed to proceed when C2-hydroxy (camphor numbering) analogue catalyst **1f** was used (Table 1, Entry 21). In contrast, catalyst **1f** worked well in the absence of an acidic additive (Table 1, Entry 22). Thiourea catalyst **1g** also failed to catalyze the reaction under the present catalysis conditions (Table 1, Entry 23).

Table 1. Optimization of the asymmetric Michael addition of cyclohexanone (**2a**) to dimethyl 2-(4-nitrobenzylidene)malonate (**3a**).[a]



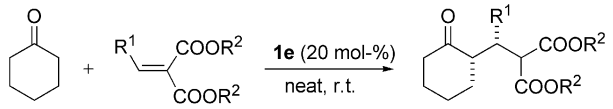
Entry	Solvent	Cat.	Additive	% Yield[b]	*dr*[c]	% *ee*[d]
1	THF	**1a**	–	70	92:8	84
2	CH_3CN	**1a**	–	64	91:9	84
3	$CHCl_3$	**1a**	–	62	90:10	84
4	toluene	**1a**	–	71	92:8	88
5	neat	**1a**	–	85	88:12	88
6	neat	**1a**	citric acid	76	91:9	88
7	neat	**1a**	ketopinic acid	80	85:15	88
8	neat	**1a**	CSA	70	93:7	90
9	neat	**1a**	propionic acid	74	87:13	90
10	neat	**1a**	DBSA	75	94:6	90
11	neat	**1a**	benzoic acid	90	91:9	88
12	neat	**1a**	AcOH	89	90:10	88
13	neat	**1a**	TsOH	90	93:7	89
14	neat	**1a**	TFA	20	95:5	88
15	neat	**1b**	TsOH	15	–	–
16	neat	**1c**	TsOH	nr	–	–
17	neat	**1d**	TsOH	56	95:5	92
18	neat	**1e**	TsOH	21	95:5	96
19[e]	neat	**1e**	TsOH	26	95:5	96
20[f]	neat	**1e**	–	95	95:5	96
21	neat	**1f**	TsOH	10	–	–
22	neat	**1f**	–	81	91:9	92
23	neat	**1g**	TsOH	nr	–	–

[a] Unless otherwise noted, all reactions were carried out with the use of **2a** (1.9 mmol, 10 equiv.) and **3a** (0.19 mmol) in the presence of the catalyst (20 mol-%) under neat conditions with the additive (20 mol-%) at ambient temperature. [b] Isolated yield. [c] Determined by ^{1}H NMR spectroscopy. [d] Determined by chiral HPLC analysis. [e] 20 equiv. of **2a** was used (3.8 mmol). [f] Reaction was carried out in the absence of TsOH.

With the optimal reaction conditions realized, a broad range of alkylidene malonates were investigated to establish the general utility of this asymmetric transformation. As illustrated in Table 2, various alkylidene malonates reacted smoothly to produce the corresponding Michael adducts with high chemical yields (up to 95%) and high to excellent levels of diastereoselectivity (up to 99:1 *dr*) and enantioselectivity (up to 96%*ee*). The steric or electronic nature of 3- and 4-substituents of the aryl substituents seemed to have no significant effect on the stereoselectivities (Table 2, Entries 1–5). However, the chemical yields decreased when dimethyl 2-(2-nitrobenzylidene)malonate and dimethyl 2-(4-methoxybenzylidene)malonate were used (Table 2, Entries 6

and 7). The former may be due to steric hindrance, whereas the latter was influenced by the presence of an electron-donating substituent in the phenyl ring. High enantioselectivities and diastereoselectivities were achieved with phenyl and 1-naphthyl groups (Table 2, Entries 8 and 9). Diethyl alkylidene malonates also reacted smoothly under the optimal conditions to afford the corresponding adducts with excellent yields and high selectivities (Table 2, Entries 10 and 11). High to excellent diastereoselectivities were observed at the expense of enantioselectivities when heteroarylidene malonates were used as Michael acceptors (Table 2, Entries 12 and 13). However, the desired product was not obtained when isopropylidene malonate was employed as the Michael acceptor (Table 2, Entry 14). The relative and absolute configurations of the Michael adducts were determined by comparing the ^1H and ^{13}C NMR spectroscopic data and the optical rotations of the products with those found in previous reports.[14b,15]

Table 2. Michael addition of cyclohexanone to the alkylidene malonates catalyzed by organocatalyst **1e**.[a]



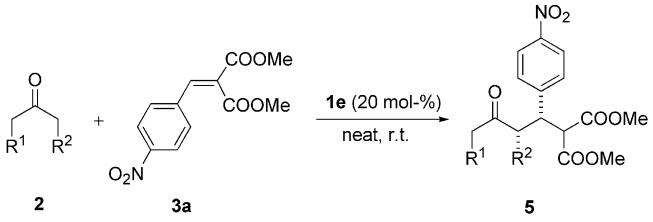
2a **3** **4**

Entry	R^1	R^2	**4**	% Yield[b]	*dr*[c]	% *ee*[d]
1	4-$O_2NC_6H_4$	Me	**4a**	95	95:5	96
2	3-$O_2NC_6H_4$	Me	**4b**	87	86:14	90
3	4-NCC_6H_4	Me	**4c**	84	88:12	92
4	4-ClC_6H_4	Me	**4d**	84	89:11	86
5	4-BrC_6H_4	Me	**4e**	88	91:9	94
6	2-$O_2NC_6H_4$	Me	**4f**	61	>99	96
7	4-$MeOC_6H_4$	Me	**4g**	64	91:9	92
8	Ph	Me	**4h**	86	91:9	90
9	1-naphthyl	Me	**4i**	80	91:9	86
10	4-$O_2NC_6H_4$	Et	**4j**	95	90:10	92
11	4-BrC_6H_4	Et	**4k**	90	90:10	94
12	2-pyridyl	Me	**4l**	87	>99	54
13	2-thiophene	Me	**4m**	88	90:10	82
14	*i*Pr	Me	**4n**	15	–	–

[a] Unless otherwise stated, all reactions were carried out with the use of **2a** (1.9 mmol, 10 equiv.) and **3** (0.19 mmol) in the presence of the catalyst (20 mol-%) under neat conditions at ambient temperature for 2–12 d. [b] Isolated yield. [c] Determined by ^1H NMR spectroscopy. [d] Determined by chiral HPLC analysis.

Furthermore, the asymmetric Michael addition of various ketones to dimethyl 2-(4-nitrobenzylidene)malonate (**3a**) was studied (Table 3). Various cyclic and acyclic ketones were subject to the optimal reaction conditions to give the desired Michael adducts with good to high chemical yields. However, only good diastereoselectivities and high enantioselectivities were obtained when tetrahydropyran-4-one (**2b**) and tetrahydrothiopyran-4-one (**2c**) were used (Table 3, Entries 1 and 2). The use of acetal-protected cyclohexanone **2d** afforded the desired product with good diastereoselectivity and reasonable enantioselectivity (Table 3, Entry 3). Moderate results were obtained when cyclopentanone, acetone, and acetophenone were employed (Table 3, Entries 4–6).

Table 3. Michael addition reaction of various ketones **2b–g** to alkylidene malonate **3a**.[a]



2 **3a** **5**

2b: R^1, R^2 = –(CH_2OCH_2)- **2e**: R^1, R^2 = –$(CH_2)_2$–
2c: R^1, R^2 = –(CH_2SCH_2)- **2f**: R^1 = H, R^2 = H
2d: R^1, R^2 = –$CH_2C(OCH_2CH_2O)CH_2$– **2g**: acetophenone

Entry	**2**	Product (% Yield)[b]	*dr*[c]	% *ee*[d]
1	**2b**	**5b** (87)	80:20	92
2[e]	**2c**	**5c** (88)	86:14	94
3[e]	**2d**	**5d** (84)	90:10	60
4[e]	**2e**	**5e** (73)	75:25	50
5	**2f**	**5f** (76)	–	61
6	**2g**	**5g** (75)	–	20

[a] Unless otherwise stated, all reactions were carried out with the use of **2** (1.9 mmol, 10 equiv.) and **3a** (0.19 mmol) in the presence of the catalyst (20 mol-%) under neat condition at room temperature, for 2–5 d. [b] Isolated yield. [c] Determined by ^1H NMR spectroscopy. [d] Determined by chiral HPLC analysis. [e] Reaction was carried out in toluene (0.5 mL).

To rationalize the high stereoselectivities of the Michael adducts obtained in the catalytic system, a plausible transition-state model was proposed (Figure 2). The reaction of cyclohexanone and the organocatalyst to form a nucleophilic enamine under solvent-free conditions was conducted. The rigid and bulky bicyclic camphor moiety selectively shielded the approach of the Michael acceptor from the enamine *Si* face. This was assisted by the hydrogen-bond interactions between the *trans*-4-hydroxy group of the pyrrolidine and the alkylidene malonates, which projected the aromatic group away from the camphor scaffold.[14b,16b] Thus, the alkylidene malonates would approach from the less-hindered *Re* face of the enamine to give the observed stereochemistry of the Michael adducts.

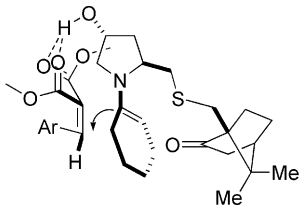
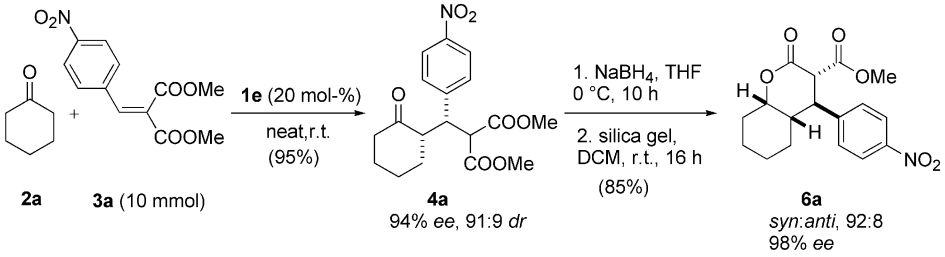


Figure 2. Plausible transition-state model.

The utility of the catalytic process is illustrated by the easy scale-up of the reaction and further chemical transformations that can be performed to prepare highly substituted lactones. As shown in Scheme 1, under the optimized conditions, we carried out the Michael addition of **2a** with



Scheme 1. Synthesis of chiral lactone **6a**.

3a on a 10-mmol scale, affording desired product **4a** with excellent chemical yield and high stereoselectivities. Michael adduct **4a** was converted into chiral lactone **6a** by following a reductive cyclization process without incident (85% chemical yield, 92:8 *dr*, and 98% *ee*). The structural characterization of lactone **6a** was confirmed by ^{1}H and ^{13}C NMR spectroscopy and NOESY experiments (see Supporting Information).

Conclusions

In summary, we have presented an efficient asymmetric Michael addition of ketones with various alkylidene malonates catalyzed by novel pyrrolidinyl–camphor organocatalysts. The structurally well-defined organocatalysts were easily accessible from inexpensive natural materials. The reaction proceeded smoothly under neat conditions, and the corresponding Michael products were generally obtained with high chemical yields (up to 95%) and high to excellent levels of diastereoselectivity (up to >99:1 *dr*) and enantioselectivity (up to 96% *ee*). A reasonable mechanistic model was proposed to explain the stereochemical outcome. The exploration of these novel organocatalysts in organocatalytic transformations is under active investigation.

Experimental Section

General Procedure for the Michael Addition of Ketones to Alkylidene Malonates: To cyclohexanone (184.5 mg, 1.90 mmol) and alkylidene malonate **3a** (50 mg, 0.19 mmol) was added organocatalyst **1e** (10.77 mg, 0.038 mmol, 20 mol-%) in one portion at ambient temperature. The resulting mixture was allowed to stir at ambient temperature and monitored by thin-layer chromatography. After the disappearance of the alkylidene malonate, the reaction mixture was purified through flash column chromatography on silica gel (petroleum ether/ethyl acetate, 10:1 to 5:1) to give desired product **4a** (95% yield, 96% *ee*). The stereoselectivity was determined by HPLC analysis. HPLC (Chiralcel AS-H; *i*PrOH/hexanes, 6:94; 1.0 mL min^{-1}): t_R = 26.16 (minor), 31.20 (major) min. *syn*/*anti* = 95/5. $[\alpha]_D^{20}$ = –49.5 (*c* = 0.393, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.14 (d, *J* = 8.7 Hz, 2 H), 7.47 (d, *J* = 8.7 Hz, 2 H), 4.16–4.04 (m, 2 H), 3.68 (s, 3 H), 3.51 (s, 3 H), 2.99–2.95 (m, 1 H), 2.43–2.37 (m, 2 H), 2.03–2.02 (m, 1 H), 1.78–1.75 (m, 2 H), 1.61–1.55 (m, 2 H), 1.12–1.09 (m, 1 H) ppm.

Supporting Information (see footnote on the first page of this article): Experimental procedures; spectral and analytical data for the Michael adducts and lactone.

Acknowledgments

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