Enantioselective Organocatalytic Michael Addition of Ketones to Alkylidene Malonates

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ABSTRACT Organocatalysts bearing sulfide or sulfone functions (**1a–d**) were studied for the direct asymmetric Michael addition of ketones and alkylidene malonates. The organocatalyst (*S*)-2-((naphthalen-2-ylthio)methyl)pyrrolidine, bearing a pyrrolidine and a sulfide moiety, showed a very high catalytic activity in the absence of additives. The reaction condition is mild, and the Michael adducts were obtained in very good enantioselectivities (up to 96%), diastereoselectivities (up to >95:5), and chemical yields (up to 95%). *Chirality 00:000–000, 2012.* © 2012 Wiley Periodicals, Inc.

KEY WORDS: organocatalysis; Michael addition; ketones; alkylidene malonate; stereoselectivity

INTRODUCTION

Asymmetric carbon–carbon bond formation is of great importance in organic synthesis, and it is especially useful for the generation of stereogenic centers in optically active nature products.[1–4] Among all the developed methodologies, organocatalysis attracts much attention because of some intrinsic properties of organocatalysts such as low toxicities and good stabilities in the air.[5–8] Organocatalytic Michael addition is one of the well-known reactions successfully applied in asymmetric organic syntheses.[9–15] To construct a carbon–carbon bond, Michael donors, such as aldehydes or ketones, and electron-deficient Michael acceptors such as nitroolefins[16–27], α,β-unsaturated ketones[28–33] or aldehyes[34–38], vinyl sulfones[39–45], maleimides[46,47], and vinyl phosphonates[42,48] are employed and well studied. However, the asymmetric Michael additions of ketones toward the alkylidene malonates with high diastereoselectivities and enantioselectivities have been reported only in a few literatures.[49–54] In addition, because of their low reactivities, acidic additives are often necessary to be used for accelerating the reaction rates and improving stereoselectivities of the Michael adducts.[50–52] Recently, we have reported highly stereoselective Michael addition of ketones to nitroolefins on water by using a new type of organocatalyst bearing a pyrrolidine and sulfone moieties.[55] With successes of the use of sulfones as organocatalysts in Michael additions, we envisioned that our sulfur-based catalysts could be also applied for the Michael addition of cyclohexanone to alkylidene malonates (Fig. 1). Furthermore, only one report to the best of our knowledge was published for the asymmetric Michael additions of ketones toward the alkylidene malonates with sulfur-based catalysts. In 2010, Chen and coworkers demonstrated that pyrrolidinyl-camphor-derived catalysts could be used for enantioselective addition of ketones to alkylidene malonates.[56] However, their application has been limited because the preparation of their catalysts takes long time with multiple steps, even though the protocol is general and well known. Therefore, we wish to report a study of the pyrrolidine-type organocatalysts with a sulfone or a sulfide functionality for this Michael reaction. Fortunately, the organocatalyst **1b** gave the most satisfactory results (up to 95% yield, >95:5 dr, 96% ee) (Scheme 1).

EXPERIMENTAL

All starting materials were commercially available and used without purification. Yields refer to isolated yields of compounds estimated to be >95% pure as determined by ^{1}H nuclear magnetic resonance (NMR). Analytical thin layer chromatography was performed using Merck 60 F_{254} precoated silica-gel plate (0.2 mm thickness). Flash chromatography was performed using Merck silica gel 60 (70–230 mesh). NMR data was recorded on a 400 or 500 MHz NMR spectrometer. The ionization method used was electron impact ionization (20 eV). Enantioselectivities were determined by high-performance liquid chromatography (HPLC) analysis employing a Daicel Chiralpak AD-H, OJ-H, IA, or AS-H column. Optical rotations were measured in $CHCl_3$ on a JASCO co.DIP-1000 Digital polarimeter with a 50-mm cell (*c* given in g/100 ml). Alkylidene malonates **3** were prepared according to literature procedures.[57] Absolute configuration and spectroscopic data (NMR or HPLC spectra) of the products were determined by comparison with reported compounds and were given in the Supplementary data.[49]

General Procedure for Organocatalytic Michael Addition Reaction

Cyclohexanone (**2a**) (311 μl, 10.0 equiv, 3.0 mmol) and organocatalyst **1b** (14.6 mg, 20 mol%, 0.06 mmol) were mixed in 0.3 ml of ethyl acetate at 35 °C. Alkylidene (**3a**) (79.5 mg, 0.3 mmol) was then added, and the resulting mixture was stirred at 35 °C for 5 days. After that, it was purified by flash chromatography (hexanes/ethyl acetate = 6/1) to give the product **4a** as a yellow sticky liquid (95.9 mg, 88%).

Dimethyl 2-((S)-(4-nitrophenyl)((S)-2-oxocyclohexyl) methyl)malonate (4a)

Yellow sticky liquid; HPLC analysis: Chiralpak AD-H column (hexane-isopropanol (IPA) = 90:10, flow rate = 0.4 ml min^{-1}, λ = 254 nm): T_R = 75.19 min (minor, *syn*), 95.21 min (major, *syn*), 96% ee.

R_f 0.24 (hexanes/ethyl acetate = 3/1); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ/ppm: 8.15–8.04 (m, 2H + 2H),7.53 (*pseudo* d, 2H, *J* = 8.6 Hz) 7.44 (*pseudo* d, 2H, *J* = 8.6 Hz), 4.51 (d, 1H, *J* = 10.6 Hz) 4.20–4.00 (m, 2H), 3.76–3.70 (m, 1H), 3.70 (s, 3H), 3.66 (s, 3H), 3.49 (s, 3H), 3.45 (s, 3H), 3.03–2.90 (m, 1H + 1H), 2.47–2.24 (m, 2H + 2H), 2.08–1.93 (m,1H + 1H),

Additional Supporting Information may be found in the online version of this article.

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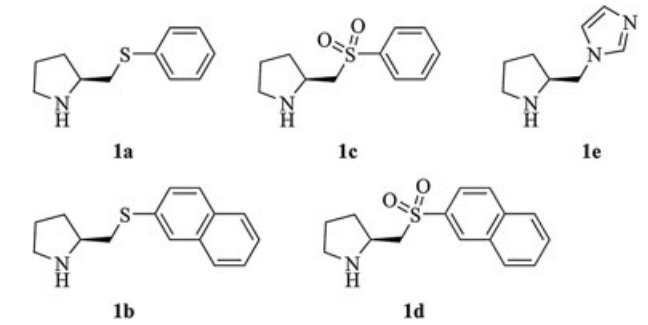
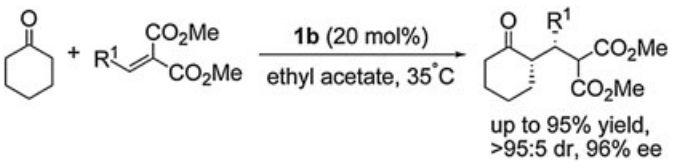


Fig. 1. Structures of organocatalysts.



Scheme 1. Michael addition of cyclohexanone to alkylidene malonates.

1.90–1.70 (m, 2H + 2H), 1.65–1.46 (m, 2H + 2H), 1.20–1.03, (1H + 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ/ppm: 210.8, 168.4, 168.0, 146.8, 146.5, 130.4, 123.1, 54.6, 52.6, 52.4, 52.3, 43.3, 42.1, 31.7, 27.7, 24.8 (major). 210.6, 168.6, 168.2, 147.3, 130.6, 53.5, 52.0, 46.0, 42.5, 41.8, 31.9, 27.0, 26.9, 25.1 (minor); mass spectrometry (MS) (electron ionization (EI), 20 eV) *m/z* (%): 364 $[M+1]^+$ (100), 232 (47), 132 (45).

Characterization of Michael Addition Products

Dimethyl 2-((*S*)-(3-nitrophenyl)((*S*)-2-oxocyclohexyl)methyl)malonate (4b). Yellow sticky liquid; HPLC analysis: Chiralpak IA column (hexane-IPA = 77:23, flow rate = 0.8 ml min^{-1}, λ = 238 nm): T_R = 11.56 min (minor, *syn*), 13.02 min (major, *syn*), 86% ee.

R_f 0.27 (hexanes/ethyl acetate = 3/1); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) □/ppm: 8.24–8.03 (m, 2H + 2H), 7.75, (*pseudo* d, 1H, *J* = 7.6 Hz), 7.68 (*pseudo* d, 1H, *J* = 7.5 Hz), 7.50–7.39 (m, 1H + 1H), 4.51 (d, 1H, *J* = 10.4 Hz), 4.13–4.07 (m, 2H), 3.76–3.75 (m, 1H), 3.72 (s, 3H), 3.68 (s, 3H), 3.52 (s, 3H), 3.48 (s, 3H), 3.06–2.95 (m, 1H + 1H), 2.50–2.20 (m, 2H + 2H), 2.12–1.95 (m, 1H + 1H), 1.91–1.71 (m, 2H + 2H), 1.71–1.48 (m, 2H + 2H), 1.20–1.04 (m, 1H + 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) □/ppm: 211.0, 168.5, 168.1, 148.0, 140.9, 136.3, 129.0, 124.0, 122.2, 54.6, 52.6, 52.3, 52.2, 43.4, 42.3, 32.0, 27.9, 24.9 (major). 210.7, 168.7, 168.2, 141.6, 136.1, 128.9, 124.5, 122.1, 53.6, 52.7, 52.4, 52.1, 45.9, 42.5, 32.0, 27.1, 25.1 (minor); MS (EI, 20 eV) *m/z* (%): 364 $[M+1]^+$ (100), 232 (68), 132 (27).

Dimethyl 2-((*S*)-(2-nitrophenyl)((*S*)-2-oxocyclohexyl)methyl)malonate (4c). Yellow sticky liquid; HPLC analysis: Chiralpak AD-H column (hexane-IPA = 90:10, flow rate = 1.0 ml min^{-1}, λ = 254 nm): T_R = 26.82 min (minor, *syn*), 42.21 min (major, *syn*), 92% ee. $[\alpha]_{30}^{D} = -7.74$ (*c* 1, $CHCl_3$).

R_f 0.35 (hexanes/ethyl acetate = 2/1); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) □/ppm: 7.73 (*pseudo* d, 1H, *J* = 8.2 Hz), 7.55–7.45 (m, 2H), 7.40–7.31 (m, 1H), 4.53 (*pseudo* t, 1H, *J* = 8.7 Hz), 4.14 (d, 1H, *J* = 8.0 Hz), 3.60 (s, 3H), 3.53 (s,3H), 3.10–3.24 (m, 1H), 2.50–2.32 (m, 2H), 2.10–1.98 (m, 1H), 1.84–1.75 (m, 1H), 1.75–1.64 (m, 2H), 1.64–1.52 (m, 1H), 1.51–1.36 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) □/ppm: 211.5, 168.6, 168.4, 134.1, 132.2, 127.8, 124.4, 55.1, 53.0, 52.6, 52.3, 42.5, 32.9, 28.4, 25.3. MS (EI, 20 eV) *m/z* (%): 363 [M] + (13), 232 (100), 132 (51).

Dimethyl 2-((*S*)-(4-cyanophenyl)((*S*)-2-oxocyclohexyl)methyl) malonate (4d). Yellow sticky liquid; HPLC analysis: Chiralpak AS-H column (hexane-IPA = 90:10, flow rate = 0.8 ml min^{-1}, λ = 238 nm): T_R = 30.53 min (minor, *syn*), 36.76 min (major, *syn*), 85% ee.

R_f 0.24 (hexanes/ethyl acetate = 3/1); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) □/ppm: 7.58 (d, 2H, *J* = 8.2 Hz), 7.41 (d, 2H, *J* = 8.2 Hz), 4.11–4.00 (m, 2H), 3.68 (s, 3H), 3.51 (s, 3H), 3.02–2.90 (m, 1H), 2.49–2.26 (m, 2H), 2.08–1.99 (m, 1H), 1.85–1.72 (m, 2H), 1.64–1.52 (m, 2H), 1.18–1.04 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) □/ppm: 210.9, 168.4, 168.0, 144.4, 131.7, 130.3, 118.5, 110.9, 54.7, 52.6, 52.4, 52.2, 43.6, 42.1, 31.7, 27.7, 24.8; MS (EI, 20 eV) *m/z* (%): 344 $[M+1]^+$ (100), 212 (31), 132 (19).

Dimethyl 2-((*S*)-(4-chlorophenyl)((*S*)-2-oxocyclohexyl)methyl) malonate (4e). Yellow sticky liquid; HPLC analysis: Chiralpak OJ-H column (hexane-IPA = 99:1, flow rate = 0.5 ml min^{-1}, λ = 230 nm): T_R = 53.53 min (minor, *syn*), 61.06 min (major, *syn*), 86% ee.

R_f 0.33 (hexanes/ethyl acetate = 4/1); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) □/ppm: 7.26–7.16 (m, 4H), 4.00–3.93 (m, 2H), 3.66 (s, 3H), 3.49 (s, 3H), 2.96–2.85 (m, 1H), 2.48–2.40 (m, 1H), 2.40–2.30 (m, 1H), 2.05–1.93 (m, 1H), 1.81–1.69 (m, 2H), 1.61–1.48 (m, 2H), 1.20–1.07 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) □/ppm: 211.7, 168.8, 168.3, 137.3, 132.9, 130.8, 128.3, 55.4, 52.9, 52.5, 52.2, 43.2, 42.2, 32.0, 27.9, 24.7; MS (EI, 20 eV) *m/z* (%): 355 $[M+3]^+$ (16), 353 $[M+1]^+$ (56), 261 (25), 221 (100), 98 (33).

Dimethyl 2-((*S*)-(4-bromophenyl)((*S*)-2-oxocyclohexyl)methyl) malonate (4f). Yellow sticky liquid; HPLC analysis: Chiralpak AS-H column (hexane-IPA = 97:3, flow rate = 0.7 ml min^{-1}, λ = 238 nm): T_R = 25.32 min (minor, *syn*), 30.48 min (major, *syn*), 73% ee.

R_f 0.33 (hexanes/ethyl acetate = 4/1); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) □/ppm: 7.39 (*pseudo* d, 2H, *J* = 8.4 Hz), 7.13 (*pseudo* d, 2H, *J* = 8.4 Hz), 3.99–3.94 (m, 2H), 3.66 (s, 3H), 3.50 (s, 3H), 2.97–2.85 (m, 1H), 2.49–2.30 (m, 2H), 2.05–1.95 (m, 1H), 1.81–1.70 (m, 2H), 1.65–1.52 (m, 2H), 1.19–1.07 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) □/ppm: 211.7, 168.8, 168.3, 137.8, 131.3, 131.2, 121.1, 55.3, 52.8, 52.6, 52.3, 43.3, 42.2, 32.0, 27.9, 24.8; MS (EI, 20 eV) *m/z* (%): 399 $[M+3]^+$ (76), 397 $[M+1]^+$ (100), 267 (92), 265 (88).

Dimethyl 2-((*S*)-((*S*)-2-oxocyclohexyl)(phenyl)methyl)malonate (4g). Yellow sticky liquid; HPLC analysis: Chiralpak AD-H column (hexane-IPA = 90:10, flow rate = 0.5 ml min^{-1}, λ = 225 nm): T_R = 24.59 min (minor, *syn*), 26.39 min (major, *syn*), 71% ee.

R_f 0.33 (hexanes/ethyl acetate = 4/1); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) □/ppm: 7.35–7.16 (m, 5H), 4.00–3.94 (m, 2H), 3.66 (s, 3H), 3.46 (s, 3H), 3.00–2.88 (m, 1H), 2.51–2.43 (m, 1H), 2.42–2.31 (m, 1H), 2.02–1.19 (m, 1H), 1.76–1.53 (m, 4H), 1.20–1.12 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) □/ppm: 212.3, 169.0, 168.5, 138.9, 129.3, 128.2, 127.1, 56.0, 53.3, 52.5, 52.1, 44.0, 42.1, 32.2, 28.1, 24.6; MS (EI, 20 eV) *m/z* (%): 318 $[M]^+$ (23), 187 (100).

Dimethyl 2-((*S*)-((*S*)-2-oxocyclohexyl)(thiophen-2-yl)methyl) malonate (4i). Yellow sticky liquid; HPLC analysis: Chiralpak IA column (hexane-IPA = 98:2, flow rate = 0.4 ml min^{-1}, λ = 238 nm): T_R = 54.69 min (major, *syn*), 59.45 min (minor, *syn*), 79% ee.

R_f 0.22 (hexanes/ethyl acetate = 5/1); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) □/ppm: 7.19–7.12 (m, 1H), 6.96–6.84 (m, 2H), 4.29 (*pseudo* t, 1H, *J* = 7.9 Hz), 4.05 (d, 1H, *J* = 8.2 Hz), 3.68 (s, 3H), 3.59 (s, 3H), 2.97–2.87 (m, 1H), 2.49–2.32 (m, 2H), 2.04–1.95 (m, 1H), 1.93–1.77 (m, 2H), 1.66–1.55 (m, 2H), 1.15–1.00 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) □/ppm: 211.4, 168.6, 168.3, 141.3, 126.9, 126.2, 124.6, 55.6, 53.3, 52.6, 52.4, 42.2, 39.3, 31.8, 27.9, 24.8; MS (EI, 20 eV) *m/z* (%): 324 $[M]^+$ (90), 233 (100), 193 (97).

Dimethyl 2-((*S*)-((*S*)-2-oxocyclohexyl)(pyridin-2-yl)methyl)malonate (4j). Yellow sticky liquid; HPLC analysis: Chiralpak AS-H column (hexane-IPA = 95:5, flow rate = 0.7 ml min^{-1}, λ = 254 nm): T_R = 23.37 min (major, *syn*), 25.74 min (minor, *syn*), 32% ee. $[\alpha]_D^{30} = -1.40$ (*c* 1, $CHCl_3$).

R_f 0.28 (hexanes/ethyl acetate = 2/1); ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C) □/ppm: 8.46 (*pseudo* d, 1H, *J* = 4.5 Hz), 7.57 (*pseudo* dt, 1H, *J* = 7.7, 1.4 Hz), 7.38 (d, 1H, *J* = 7.8 Hz), 7.11–7.06 (m, 1H), 4.25–4.15 (m, 2H), 3.70 (s, 3H), 3.53 (s, 3H), 3.06–2.99 (m, 1H), 2.43–2.35 (m, 2H), 2.04–1.97 (m, 1H), 1.77–1.53 (m, 4H), 1.11–1.01 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C) □/ppm: 211.8, 169.5, 168.8, 159.5, 148.6, 136.0, 126.1, 121.7, 54.2, 52.7, 52.5, 52.0, 44.3, 42.4, 31.5, 28.0, 25.2; MS (EI, 20 eV) *m/z* (%): 320 $[M+1]^+$ (30), 223 (72), 188 (51), 164 (100), 132 (13).

Dimethyl 2-((*S*)-(4-nitrophenyl)((*R*)-4-oxotetrahydro-2H-pyran-3-yl)methyl)malonate (5b). Yellow sticky liquid; HPLC analysis: Chiralpak OJ-H column (hexane-IPA = 80:20, flow rate = 1.0 ml min^{-1}, λ = 254 nm): T_R = 41.36 min (minor, *syn*), 45.94 min (major, *syn*), 93% ee.

R_f 0.35 (hexanes/ethyl acetate = 2/1); ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C) δ/ppm: 8.15 (d, 2H, *J* = 8.7 Hz), 8.11 (d, 2H, *J* = 8.7 Hz), 7.50 (d, 2H, *J* = 8.7 Hz), 7.46 (d, 2H, *J* = 8.7 Hz), 4.54 (d, 1H, *J* = 10.6 Hz), 4.17–4.10 (m, 1H + 2H), 4.06–4.01 (m, 2H), 3.81–3.72 (m, 2H + 4H), 3.68 (s, 3H), 3.57–3.51 (m, 1H), 3.48 (s, 3H), 3.47 (3H), 3.33 (t, 1H, *J* = 10.6 Hz), 3.22–3.18 (m, 1H + 1H), 3.11–3.06 (m, 1H), 2.63–2.52 (m, 2H + 1H), 2.29–2.25 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C) δ/ppm: 206.8, 168.1, 167.6, 147.2, 145.3, 130.2, 123.6, 70.7, 68.7, 54.9, 53.9, 52.8, 52.5, 42.3, 41.7 (major). 206.2, 168.3, 167.8, 147.1, 146.1, 130.4, 123.5, 70.8, 67.9, 53.6, 52.9, 52.6, 52.4, 43.3, 42.8 (minor); MS (EI, 20 eV) *m/z* (%): 366 $[M+1]^+$ (24), 365 $[M]^+$ (20), 233 (100), 132 (45), 99 (100).

Dimethyl 2-((*R*)-(4-nitrophenyl)((*S*)-4-oxotetrahydro-2H-thiopyran-3-yl)methyl)malonate (5c). Yellow sticky liquid; HPLC analysis: Chiralpak AD-H column (hexane-IPA = 90:10, flow rate = 0.6 ml min^{-1}, λ = 254 nm): T_R = 80.75 min (minor, *syn*), 86.87 min (major, *syn*), 87% ee.

R_f 0.40 (hexanes/ethyl acetate = 2/1); ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C) δ/ppm: 8.16 (d, 2H, *J* = 8.7 Hz), 8.12 (d, 2H, *J* = 8.7 Hz), 7.52–7.48 (m, 2H + 2H), 4,37 (d, 1H, *J* = 10.1 Hz), 4.26 (t, 1H, *J* = 8.7 Hz), 4.00–3.94 (m, 1H + 1H), 3.72 (s, 3H), 3.68 (s, 3H), 3.52–3.50 (m, 3H + 3H), (m, 1H + 1H), 2.94–2.82 (m, 3H + 3H), 2.78–2.56 (m, 2H + 3H), 2.33 (dd, 1H, *J* = 13.8, 9.6 Hz); ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C) δ/ppm: 209.0, 168.1, 167.6, 147.3, 145.5, 130.3, 123.7, 55.3, 55.0, 52.8, 52.5, 43.9, 43.7, 34.3, 30.9 (major). 207.9, 168.4, 167.8, 147.1, 146.3, 130.5, 123.5, 54.8, 53.4, 52.9, 52.6, 45.7, 44.7, 33.5, 30.0 (minor); MS (EI, 20 eV) *m/z* (%): 381 $[M]^+$ (5), 267 (10), 132 (17), 115 (100).

Dimethyl 2-((*S*)-(4-nitrophenyl)((*S*)-2-oxocyclopentyl)methyl) malonate (5d). Yellow sticky liquid; HPLC analysis: Chiralpak IA column (hexane-IPA = 90:10, flow rate = 1.0 ml min^{-1}, λ = 238 nm): T_R = 25.40 min (minor, *syn*), 27.71 min (major, *syn)*, 63% ee.

R_f 0.40 (hexanes/ethyl acetate = 3/1); ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C) δ/ppm: 8.11 (d, 2H, *J* = 8.7 Hz), 7.39 (d, 2H, *J* = 8.7 Hz), 4.19 (d, 1H, *J* = 10.6 Hz), 4.08 (dd, 1H, *J* = 10.6, 6.0 Hz), 3.74 (s, 3H), 3.47 (s, 3H), 2.59–2.54 (m, 1H), 2.26–2.21 (m, 1H), 2.08–2.02 (m, 1H), 1.92–1.65 (m, 3H), 1.51–1.43 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C) δ/ppm: 217.4, 168.2, 167.7, 147.0, 146.0, 130.2, 123.3, 54.3, 52.9, 52.5, 51.4, 43.9, 38.3, 26.4, 20.3; MS (EI, 20 eV) *m/z* (%): 350 $[M+1]^+$ (100), 349 $[M]^+$ (42), 218 (30), 132 (100).

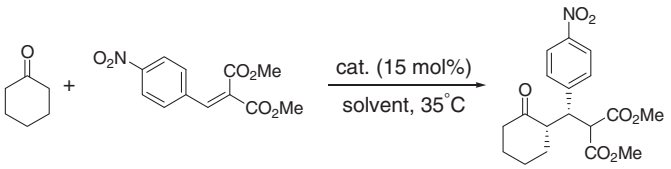
Dimethyl 2-((*S*)-1-(4-nitrophenyl)-3-oxobutyl)malonate (5e). Yellow sticky liquid; HPLC analysis: Chiralpak AD-H column (hexane-IPA = 90:10, flow rate = 1.0 ml min^{-1}, λ = 238 nm): T_R = 28.69 min (minor), 41.78 min (major), 66% ee, $[\alpha]_D^{30} = +11.17$ (*c* 1, $CHCl_3$).

R_f 0.35 (hexanes/ethyl acetate = 4/1); ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C) δ/ppm: 8.11 (d, 2H, *J* = 8.7 Hz), 7.42 (d, 2H, *J* = 8.7 Hz), 4.07 (dt, 1H, *J* = 9.2, 4.6 Hz), 3.75 (d, 1H, *J* = 9.6 Hz), 3.71 (s, 3H), 3.51 (s, 3H), 3.03 (dd, 1H, *J* = 17.9, 4.6 Hz), 2.96 (dd, 1H, *J* = 17.9, 8.7 Hz), 2.04 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C) δ/ppm: 217.4, 168.2, 167.7, 147.0, 146.0, 130.2, 123.3, 54.3, 52.9, 52.5, 51.4, 43.9, 38.3, 26.4, 20.3; MS (EI, 20 eV) *m/z* (%): 323 $[M]^+$ (100), 232 (64), 132 (92).

RESULTS AND DISCUSSION

Initial screening of different organocatalysts (**1a–e**, 15 mol %) demonstrated encouraging results with good diastereoselectivities and high enantioselectivities over 3 days under solvent-free and additive-free conditions in case of using cyclohexanone (**2a**) and dimethyl 2-(4-nitrobenzylidene)-malonate (**3a**) as reaction partners (entries 1–5, Table 1). The organocatalyst **1b** emerged as our choice because of

TABLE 1. Screening of reaction conditions for the organocatalytic Michael addition of cyclohexanone (2a) to dimethyl 2-(4-nitrobenzylidene)malonate (3a)[a]



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

Entry	Solvent	Catalyst	Additive	Yield (%)[b]	dr[c]	ee[d] (*syn*)
1	neat	**1a**	—	17	88:12	89
2	neat	**1b**	—	89	90:10	90
3	neat	**1c**	—	81	94: 6	90
4	neat	**1d**	—	75	90:10	84
5	neat	**1e**	—	39	75:25	91
6	H_2O	**1b**	—	30	95: 5	95
7	MeOH	**1b**	—	88	95: 5	93
8	CH_3CN	**1b**	—	74	90:10	94
9	ethyl acetate	**1b**	—	72	88:12	96
10	THF	**1b**	—	89	90:10	94
11	CH_2Cl_2	**1b**	—	66	90:10	94
12	$CHCl_3$	**1b**	—	41	95: 5	90
13	ether	**1b**	—	68	86:14	95
14	toluene	**1b**	—	66	96: 4	94
15	hexane	**1b**	—	nr	-	-
16	ethyl acetate	**1b**	phenol	71	83:17	94
17	ethyl acetate	**1b**	benzoic acid	67	87:13	94
18	ethyl acetate	**1b**	AcOH	74	90:10	95
19	ethyl acetate	**1b**	piperidine	90	93: 7	95
20	ethyl acetate	**1b**	NEt_3	85	92: 8	93
21[e]	ethyl acetate	1b	—	82	88:12	96

[a]Unless stated otherwise, all the reactions were carried out using **2a** (3 mmol, 10 equiv) and **3a** (0.3 mmol) in the presence of a catalyst (15 mol%) and an additive (15 mol%) in ethyl acetate (0.3 ml) at 35 °C for 3 days.
[b]Isolated yield.
[c]Determined by ^{1}H NMR of crude product.
[d]Determined by high-performance liquid chromatography by using a chiral column.
[e]20 mol% of catalyst was used.

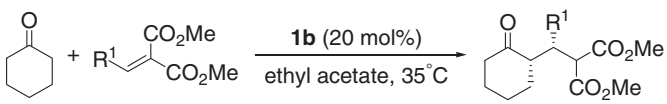
the resulting high enantioselectivity (90%), good diastereoselectivity (90:10), and good chemical yield (89%) (entry 2). The solvents were found to have very little effect on the enantioselectivities, and almost all the solvents gave good enantioselectivities ranging from 90% to 96% ee (entries 6–14). Although the reactions provided good enantioselectivities and diastereoselectivities in case of solvents such as water and chloroform, the chemical yields were relatively low (entries 6 and 12). The best enantioselectivity was obtained when ethyl acetate was used as a solvent (entry 9). Furthermore, various acidic and basic additives were screened to optimize the reaction conditions. A slight decrease in enantioselectivity was observed in the presence of acidic and basic additives although diastereoselectivity and chemical yield remained almost similar (entries 16–20). An increase of chemical yield of **4a** was obtained as well when 20 mol% of **1b** was applied (entry 21).

With having the optimal reaction conditions in hand, the scope of the catalytic asymmetric Michael addition was explored. As summarized in Table 2, the reactions catalyzed by **1b** have broad applicability with respect to cyclohexanone (**2a**) and alkylidene malonates (**3**) as Michael acceptors. A wide variety of alkylidene malonates (**3a–j**) having different substitution profiles at various positions can be tolerated in our optimized reaction condition (20 mol% of **1b**) with **2a**, providing the corresponding Michael adducts (**4a–j**) in moderate to excellent enantioselectivities and good diastereoselectivities. The effects of substitution position in R^1 (4-, 3-, or 2-$NO_2C_6H_4$) remained similar as far as enantioselectivities or diastereoselectivities were concerned, but the chemical yield was very poor in case of *ortho*-substituted dimethyl alkylidene malonate **3c** (entries 1–3, Table 2), indicating the steric influence. The reactions also worked well in case of different electron-withdrawing substituents in *para*-position of R^1 (entries 4–6). The phenyl group also gave moderate yield with good diastereoselectivity and medium enantioselectivity (entry 7). However, dimethyl 2-(4-methoxybenzylidene)malonate (**3h**) had very low reactivity and did not proceed under our reaction condition (entry 8). The dimethyl heteroarylidene malonate, such as **3i**, was also employed as the Michael acceptor, but only 59% yield of the adduct **4i** with good diastereoselectivity (80:20 dr) and moderate enantioselectivity (79% ee) was afforded (entry 9). Interestingly, in case of **3j** as the dimethyl heteroarylidene malonate, excellent diastereoselectivity (>95:5 dr) of **4j** albeit with the low enantioselectivity and chemical yield was furnished (entry 10).

Having demonstrated the suitability of this process for the Michael addition of cyclohexanone (**2a**) to different alkylidene malonates (**3a–j**), we then turned our attention toward various cyclic and acyclic ketones (**2b–e**) with 2-(4-nitrobenzylidene)malonate (**3a**) as a model substrate in our optimized reaction condition to provide the corresponding Michael adducts **5b–e** (Table 3). All the ketones **2b–e** responded well as judged from the chemical yield of **5**. Good diastereoselectivities and high enantioselectivities were obtained when tetrahydropyran-4-one (**2b**) and tetrahydrothiopyran-4-one (**2c**) were employed (entries 1 and 2). Moderate enantioselectivity but good diastreoselectivity was obtained when cyclopentanone (**2d**) was used (entry 3). Acetone (**2e**) was also a suitable substrate in our protocol, and the adduct **5e** was furnished in good yield with a moderate enantioselectivity (entry 4).

A transition-state model was proposed to account for the observed stereochemical outcome of our results (Fig. 2). Cyclohexanone is believed to be activated through an enamine intermediate. The resulting enamine can attack the

TABLE 2. Asymmetric Michael addition of cyclohexanone (2a) to alkylidene malonates (3) catalyzed by organocatalyst 1b[a]

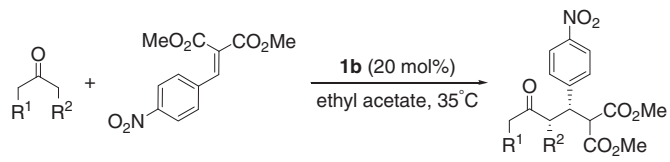


2a **3** **4**

Entry	R^1	Time (days)	4	Yield (%)[b]	dr[c]	ee[d] (*syn*)
1	4-$NO_2C_6H_4$	3	4a	82	88:12	96
2	3-$NO_2C_6H_4$	7	4b	89	75:25	86
3	2-$NO_2C_6H_4$	14	4c	10 (30)[e]	>95:05	92
4	4-CNC_6H_4	8	4d	95	78:22	85
5	4-ClC_6H_4	14	4e	59	86:14	86
6	4-BrC_6H_4	14	4f	54	85:13	73
7	Ph	14	4g	52	86:14	71
8[f]	4-$MeOC_6H_4$	14	4h	10	-	-
9	2-thiophene	14	4i	59	80:20	79
10	2-pyridyl	14	4j	22 (39)[e]	>95:05	32

[a]Unless stated otherwise, all the reactions were carried out using **2a** (3 mmol, 10 equiv) and **3** (0.3 mmol) in the presence of catalyst **1b** (20 mol%) in ethyl acetate (0.3 ml) at 35 °C for 3–14 days.
[b]Isolated yield.
[c]Determined by ^{1}H NMR of crude product.
[d]Determined by high-performance liquid chromatography by using a chiral column.
[e]Conversion yield (the ratio of the amounts between product **4** and consumed alkylidene malonates **3**).
[f]NMR yield (a known amount of CH_2Br_2 was added to the crude products and used as an internal reference for calculating the ratio of NMR integrals and consequently yields).

TABLE 3. Asymmetric Michael addition of ketones (2b–e) to 2-(4-nitrobenzylidene)malonate (3a) catalyzed by organocatalyst 1b[a]



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

2b: R^1, R^2 = -(CH_2OCH_2)-; **2c**: R^1, R^2 = -(CH_2SCH_2)-
2d: R^1, R^2 = -$(CH_2)_2$-; **2e**: R^1 = H, R^2 = H

Entry	2	Time (days)	5	Yield (%)[b]	dr[c]	ee[d] (*syn*)
1	2b	3	5b	77	73:30	93
2	2c	3	5c	74	80:20	87
3	2d	3	5d	83	71:29	63
4	2e	4	5e	79	—	66

[a]Unless stated otherwise, all the reactions were carried out using **2** (5 mmol, 10 equiv) and **3a** (0.5 mmol) in the presence of catalyst **1b** (20 mol%) in ethyl acetate (0.3 ml) at 35 °C for 3–4 days.
[b]Isolated yield.
[c]Determined by ^{1}H NMR of crude product.
[d]Determined by high-performance liquid chromatography by using a chiral column.

Fig. 2. A proposed transition state (blue is on upside).

alkylidene malonates **3** from the *Re*-face with opposite orientation of naphthyl group of **1b** to aryl group of **3**, providing the highly enantioselective and diastereoselective corresponding adducts **4**.[52,54,58]

CONCLUSION

In conclusion, organocatalysts that were earlier developed in our laboratory and can be easily prepared from (*S*)-proline and beared sulfide or sulfone functions (**1a–e**) were studied for the direct asymmetric Michael addition of ketones (**2**) and dialkyl alkylidene malonates (**3**). The organocatalyst **1b**, bearing a pyrrolidine and a sulfide moiety, showed high catalytic activity in the absence of any additives. The reaction condition was mild and the Michael adducts **4** or **5** were obtained in good enantioselectivities (up to 96%), diastereoselectivities (up to >95:5), and chemical yields (up to 95%). Further investigation and application of this potential organocatalyst and its derivatives into a wider range of substrates are currently underway.

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