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Stereoselective conjugate addition of ketones to alkylidene malonates using thiourea-sulfonamide organocatalyst

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Abstract

In this study, stereoselective conjugate addition of ketones to alkylidene malonates using organocatalyst has been developed. The reaction in the presence of 20 mol% of a novel thiourea-sulfonamide organocatalyst afforded conjugate adducts in moderate to high yields (up to 81%) under mild reaction conditions. Excellent diastereoselectivity (up to 98:2 *dr*) and enantioselectivity (up to 88% *ee*) were achieved.

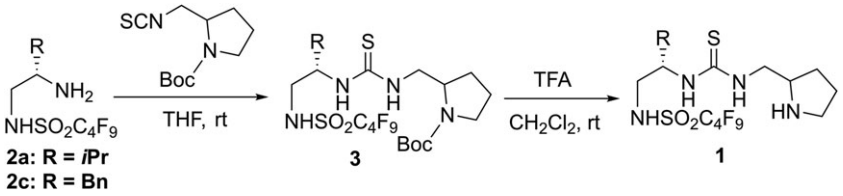
KEYWORDS

asymmetric conjugate addition, alkylidene malonate, organocatalysis, organocatalyst, thiourea-sulfonamideIntroduction

1 | INTRODUCTION

Conjugate addition promoted by organocatalysts is an attractive synthetic methodology owing to their low toxicities and stabilities under air atmosphere. Asymmetric conjugate addition of carbon nucleophile to electron poor olefin using an organocatalyst is one of the most important reactions to form carbon—carbon bonds in modern organic chemistry.[1-4] Useful synthetic intermediates can be produced by selecting the combination of different Michael donors and acceptors. The organocatalytic reactions of Michael donors such as aldehydes and ketones with electron deficient Michael acceptors such as α,β-unsaturated aldehydes,[5,6] ketones,[7-10] sulfones,[11,12] and nitrostylenes[13-32] are well investigated. However, alkylidene malonates are rarely used as a Michael acceptor in organocatalysis despite their availability as a synthetic intermediate for access to remarkable pharmaceutical compounds. In 2001, Barbas and coworkers reported the first asymmetric conjugate additions of ketones to alkylidene malonates in moderate to good enantioselectivities using pyrrolidine-based organocatalyst.[33,34] Some groups demonstrated the asymmetric Michael addition of ketones to alkylidene malonates using pyrrolidine-derived urea or thiourea catalyst and sulfonamide organocatalysts.[35-40] On the contrary, Wang et al[41] reported a thiourea-sulfonamide organocatalyst that rapidly promoted the conjugate addition of 1,3-diketones to nitroalkenes. Thiourea-sulfonamide organocatalysts bearing multiple hydrogen bonding donors were able to efficiently accelerate asymmetric reactions, improving yields and enantioselectivities.[42-44]

Recently, we reported that organocatalysts **2a** and **2c** bearing perfluorobutanesulfonamide groups are good catalysts for several attractive asymmetric reactions (Scheme 1).[45-47] Furthermore, we demonstrated that the organocatalyst bearing both perfluorobutanesulfonamide and squaramide motifs effectively promote the asymmetric direct vinylogous aldol reaction of furan-2(5*H*)-ones with aldehydes.[48] In addition, the organocatalyst in combination of perfluorobutanesulfonamide and thiourea motifs efficiently provides enantiomerically enriched addition products between nitroalkanes and α,β-unsaturated ketones.[49] To further demonstrate the value of organocatalysts having both perfluorobutanesulfonamide and thiourea motifs, we attempted the development of efficient conjugate addition of ketones to alkylidene malonates using the thiourea-perfluorobutanesulfonamide organocatalyst.



SCHEME 1 Preparation of organocatalyst **1**

2 | MATERIALS AND METHODS

2.1 | General

^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance III Nanobay 400 MHz spectrometer (400 MHz for ^{1}H NMR and 100 MHz for ^{13}C NMR). The chemical shifts were reported in ppm on the δ scale relative to Me_4Si (δ = 0.00 for ^{1}H NMR) and $CDCl_3$ (δ = 77.0 for ^{13}C NMR). Mass spectra were recorded by an electrospray ionization-time of flight (ESI-TOF) mass spectrometer (Micromass LCT). For thin layer chromatographic (TLC) analyses, Merck precoated TLC plates (silica gel 60 F254) were used. Flash column chromatography was performed on neutral silica gel (40-50 μm)

2.1.1 | Preparation of the organocatalyst 1a

To a stirred solution of *tert*-butyl (*S*)-2-(isothiocyanatomethyl)pyrrolidine-1-carboxylate[50] (1.12 g, 4.62 mmol) in THF (46 mL) was added (*S*)-*N*-(2-amino-3-methylbutyl)-perfluorobutanesulfonamide (**2a**)[46] (1.78 g, 4.62 mmol). The reaction mixture was stirred at room temperature for 5 days. The solvent was removed under reduced pressure. The residue was purified by flash column chromatography on silica gel with a 5:1 mixture of hexane and ethyl acetate to afford the pure **3a** (2.11 g, 73%). White powder; mp 53-55°C; $[\alpha]^{26}_D$ = −9.4° (c 0.50, $CHCl_3$), ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.02 (d, *J* = 6.3 Hz, 3H), 1.03 (d, *J* = 6.3 Hz, 3H), 1.46 (s, 9H), 1.78-1.92 (m, 3H), 2.00-2.05 (m, 2H), 2.91 (brs, 1H), 3.22-3.24 (m, 1H), 3.34-3.40 (m, 1H), 3.45-3.51 (m, 1H), 3.55 (brs, 1H), 3.61-3.64 (m, 1H), 3.80 (brs, 1H), 7.15 (brs, 1H), 8.17 (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.2, 19.3, 23.5, 28.4, 29.9, 30.1, 46.6, 47.6, 56.6, 60.0, 81.3, 106.1-119.0 (Complex signals of —CF_2— and —CF_3), 156.3, 181.6; HRMS (ESI-TOF): calcd for $C_{20}H_{31}N_4O_4F_9S_2Na$ $(M + Na)^+$: 649.1535, found: 649.1545.

To a stirred solution of compound **3a** (2.11 g, 3.37 mmol) in CH_2Cl_2 (34 mL) was added TFA (2.7 mL) at 0°C. After stirring at room temperature for 24 hours, the reaction mixture was added saturated aqueous $NaHCO_3$ and extracted three times with $CHCl_3$. The $CHCl_3$ layers were combined, washed with brine, dried over anhydrous Na_2SO_4, and evaporated. The residue was purified by recrystallization from MeOH to afford the pure **1a** (1.04 g, 59%). White crystal; mp 193°C (decompose); $[\alpha]^{28}_D$ = −15.9° (c 0.50, DMSO); ^{1}H NMR (400 MHz, DMSO-d_6): δ = 0.85 (d, *J* = 6.4 Hz, 3H), 0.86 (d, *J* = 6.4 Hz, 3H), 1.64 (brs, 1H), 1.74-1.98 (m, 4H), 3.11-3.14 (m, 4H), 3.59-3.62 (m, 1H), 3.68 (brs, 2H), 4.06 (brs, 1H), 5.76 (brs, 2H), 7.58 (brs, 1H), 7.74 (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.6, 19.1, 23.3, 27.4, 28.9, 44.8, 45.1, 46.4, 59.2, 60.7, 110.6-118.6 (Complex signals of —CF_2— and —CF_3), 182.9; HRMS (ESI-TOF): calcd for $C_{15}H_{24}N_4O_2F_9S_2$ $(M + H)^+$: 527.1191, found: 527.1197; Anal. Calcd for $C_{15}H_{23}N_4O_2F_9S_2$: C, 34.22; H, 4.40; N, 10.64. Found: C, 34.35; H, 4.45; N, 10.57

2.1.2 | Preparation of the organocatalyst 1b

To a stirred solution of *tert*-butyl (*R*)-2-(isothiocyanatomethyl)pyrrolidine-1-carboxylate[50] (297 mg, 1.23 mmol) in THF (12 mL) was added (*S*)-*N*-(2-amino-3-methylbutyl)-perfluorobutanesulfonamide (**2a**)[46] (557 mg, 1.45 mmol). The reaction mixture was stirred at room temperature for 15 hours. The solvent was removed under reduced pressure. The residue was purified by flash column chromatography on silica gel with a 5:1-3:1 mixture of hexane and ethyl acetate to afford the pure **3b** (575 mg, 75%). White powder; mp 160-161°C; $[\alpha]^{26}_D$ = − 13.0° (c 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 50°C): δ = 1.02 (d, *J* = 6.8 Hz, 6H), 1.46 (s, 9H), 1.76-1.79 (m, 1H), 1.83-1.89 (m, 2H), 2.00-2.07 (m, 2H), 3.30 (brs, 2H), 3.35-3.40 (m, 1H), 3.43-3.45 (m, 1H), 3.88 (brs, 1H), 4.55 (brs, 1H), 7.01 (brs, 1H), 8.08 (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 50°C): δ = 19.3, 23.7, 28.5, 30.1, 30.2, 47.0, 47.6, 56.7, 60.0, 81.1, 107.4-121.7 (Complex signals of —CF_2— and —CF_3), 156.6, 182.4; HRMS (ESI-TOF): calcd for $C_{20}H_{31}N_4O_4F_9S_2Na$ $(M + Na)^+$: 649.1535, found: 649.1542

To a stirred solution of compound **3b** (470 mg, 0.75 mmol) in CH_2Cl_2 (10 mL) was added TFA (0.6 mL) at 0°C. After stirring at room temperature for 9 hours, the reaction mixture was added saturated aqueous $NaHCO_3$ and extracted two times with $CHCl_3$. The $CHCl_3$ layers were combined, washed with brine, dried over anhydrous Na_2SO_4, and evaporated. The residue was

purified by flash column chromatography on silica gel with a 50:1-20:1 mixture of $CHCl_3$ and MeOH to afford the pure **1b** (342 mg, 87%). White powder; mp 124-125°C; $[\alpha]^{25}_D$ = − 82.2° (c 0.50, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.92 (d, *J* = 6.8 Hz, 3H), 0.94 (d, *J* = 6.8 Hz, 3H), 1.62-1.72 (m, 1H), 1.7-1.83 (m, 1H), 2.02-2.10 (m, 2H), 2.20 (brs, 1H), 3.22-3.28 (m, 2H), 3.40 (d, *J* = 12.2 Hz, 2H), 3.70-3.84 (m, 3H), 4.23 (brs, 1H), 6.83 (brs, 1H), 7.05 (brs, 1H), 8.13 (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.3, 18.9, 23.8, 28.6, 32.3, 44.6, 47.0, 47.7, 59.4, 61.8, 109.2-119.0 (Complex signals of —CF_2— and —CF_3), 183.4; HRMS (ESI-TOF): calcd for $C_{15}H_{24}N_4O_2F_9S_2$ $(M + H)^+$: 527.1191, found: 527.1201; Anal. Calcd for $C_{15}H_{23}N_4O_2F_9S_2$: C, 34.22; H, 4.40; N, 10.64. Found: C, 33.98; H, 4.36; N, 10.45

2.1.3 | Preparation of the organocatalyst 1c

To a stirred solution of *tert*-butyl (*S*)-2-(isothiocyanatomethyl) pyrrolidine-1-carboxylate[50] (769 mg, 3.17 mmol) in THF (32 mL) was added (*S*)-*N*-(2-amino-3-phenylpropyl)-perfluorobutanesulfonamide (**2c**)[45] (1.37 g, 3.17 mmol). The reaction mixture was stirred at room temperature for 20 hours. The solvent was removed under reduced pressure. The residue was purified by flash column chromatography on silica gel with a 5:1-1:1 mixture of hexane and ethyl acetate to afford the pure **3c** (1.36 g, 64%). White powder; mp 69-71°C; $[\alpha]^{26}_D$ = − 12.8° (c 1.00, $CHCl_3$), ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.49 (s, 9H), 1.77-2.00 (m, 4H), 2.78 (brs, 1H), 2.94-2.99 (m, 1H), 3.06-3.11 (m, 1H), 3.21 (brs, 1H), 3.29-3.38 (m, 2H), 3.47 (brs, 1H), 3.63 (d, *J* = 12.2 Hz, 1H), 3.77 (brs, 1H), 5.05 (brs, 1H), 7.19-7.23 (m, 1H), 7.26-7.28 (m, 4H), 7.57 (brs, 1H), 8.21 (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.5, 28.5, 30.2, 37.8, 46.7, 48.7, 55.6, 56.6, 81.4, 108.4-118.7 (Complex signals of —CF_2— and —CF_3), 126.9, 128.7, 129.3, 137.0, 156.4, 180.9; HRMS (ESI-TOF): calcd for $C_{24}H_{31}N_4O_4F_9S_2Na$ $(M + Na)^+$: 697.1535, found: 649.1543

To a stirred solution of compound **3c** (1.36 mg, 2.00 mmol) in CH_2Cl_2 (20 mL) was added TFA (1.6 mL) at 0°C. After stirring at room temperature for 20 hours, the reaction mixture was added saturated aqueous $NaHCO_3$ and extracted three times with $CHCl_3$. The $CHCl_3$ layers were combined, washed with brine, dried over anhydrous Na_2SO_4, and evaporated. The residue was purified by flash column chromatography on silica gel with a 50:1-10:1 mixture of $CHCl_3$ and MeOH to afford the pure **1c** (1.09 g, 95%). White powder; mp 204°C (decompose); $[\alpha]^{26}_D$ = − 19.1° (c 0.50, DMSO-d_6); ^{1}H NMR (400 MHz,DMSO-d_6): δ = 1.59-1.64 (m, 1H), 1.77-1.93 (m, 2H), 1.95-2.03 (m, 1H), 2.78-2.83 (m, 2H), 3.05 (brs, 2H), 3.08-3.20 (m, 2H), 3.61 (brs, 1H), 3.70 (brs, 2H), 4.30 (brs, 1H), 7.15-7.19 (m, 1H), 7.24-7.30 (m, 3H), 7.60 (d, *J* = 7.8 Hz, 1H), 7.92 (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.0, 27.3, 37.3, 44.5, 45.0, 46.7, 57.2, 59.1, 108.4-118.9 (Complex signals of -CF_2- and -CF_3), 125.8, 128.0, 129.2, 139.3, 182.2; HRMS (ESI-TOF): calcd for $C_{19}H_{24}N_4O_2F_9S_2$ $(M + H)^+$: 575.1191, found: 527.1196; Anal. Calcd for $C_{19}H_{23}N_4O_2F_9S_2$: C, 39.72; H, 4.04; N, 9.75. Found: C, 39.73; H, 4.11; N, 9.75

2.2 | Typical procedure for a conjugate addition using organocatalyst 1a (Table 3)

To a solution of dimethyl 2-(4-nitrobenzylidene)malonate (**5a**, 53.1 mg, 0.200 mmol) and organocatalyst **1a** (21.1 mg, 0.040 mmol) in cyclohexanone (311 μL, 3.00 mmol) was added water (0.2 mL) at room temperature. After stirring at room temperature for 48 hours, the reaction mixture was directly purified by flash column chromatography on silica gel with a 5:1 mixture of hexane and AcOEt to afford the pure **6a** (57.5 mg, 72%) as a white powder

2.2.1 | Dimethyl 2-{(*S*)-(4-nitrophenyl) [(1*S*)-2-oxocyclohexyl]methyl} propanedioate (6a)[39]

87% ee: Enantiomeric excess was determined by HPLC with ChiralPak AS-H column (hexane/2-propanol = 94:6), flow rate = 1.0 mL/min; λ = 254 nm; t_{major} = 35.2 min, t_{minor} = 42.6 min.

2.2.2 | Dimethyl 2-{(*S*)-(3-nitrophenyl) [(1*S*)-2-oxocyclohexyl]methyl} propanedioate (6b)[39]

85% ee: Enantiomeric excess was determined by HPLC with ChiralPak AS-H column (hexane/2-propanol = 80:20), flow rate = 0.4 mL/min; λ = 254 nm; t_{major} = 35.1 min, t_{minor} = 37.3 min.

2.2.3 | Dimethyl 2-{(*S*)-(2-nitrophenyl) [(1*S*)-2-oxocyclohexyl]methyl} propanedioate (6c)[39]

84% ee: Enantiomeric excess was determined by HPLC with ChiralCel OJ-H column (hexane/2-propanol = 90:10), flow rate = 0.8 mL/min; λ = 254 nm; t_{major} = 37.9 min, t_{minor} = 39.5 min.

2.2.4 | Dimethyl 2-{(*S*)-(4-cyanophenyl)[(1*S*)-2-oxocyclohexyl]methyl}propanedioate (6d)[39]

87% ee: Enantiomeric excess was determined by HPLC with ChiralPak AS-H column (hexane/2-propanol = 90:10), flow rate = 0.8 mL/min; λ = 210 nm; t_{major} = 35.5 min, t_{minor} = 45.9 min.

2.2.5 | Dimethyl 2-{(*S*)-(4-bromophenyl)[(1*S*)-2-oxocyclohexyl]methyl}propanedioate (6e)[39]

65% ee: Enantiomeric excess was determined by HPLC with ChiralPak AD-H column (hexane/2-propanol = 95:5), flow rate = 0.5 mL/min; λ = 210 nm; t_{minor} = 45.9 min, t_{major} = 82.7 min.

2.2.6 | 2.3.6. Dimethyl 2-{(*S*)-(4-methoxycarbonylphenyl)[(1*S*)-2-oxocyclohexyl]methyl}propanedioate (6f)[51]

88% ee: Enantiomeric excess was determined by HPLC with ChiralPak AD-H column (hexane/2-propanol = 90:10), flow rate = 0.5 mL/min; λ = 210 nm; t_{major} = 52.5 min, t_{minor} = 64.1 min.

2.2.7 | 2.3.7. Dimethyl 2-{(*S*)-phenyl[(1*S*)-2-oxocyclohexyl]methyl}propanedioate (6g)[39]

87% ee: Enantiomeric excess was determined by HPLC with ChiralPak IC column (hexane/2-propanol = 90:10), flow rate = 0.8 mL/min; λ = 210 nm; t_{major} = 77.1 min, t_{minor} = 115.3 min.

2.2.8 | Dimethyl 2-{(*S*)-(4-methylphenyl)[(1*S*)-2-oxocyclohexyl]methyl}propanedioate (6h)[51]

81% ee: Enantiomeric excess was determined by HPLC with ChiralPak IC column (hexane/2-propanol = 90:10), flow rate = 1.0 mL/min; λ = 210 nm; t_{major} = 44.3 min, t_{minor} = 61.1 min.

2.2.9 | Dimethyl 2-{(*S*)-[(1*S*)-2-oxocyclohexyl] (pyridin-3-yl)methyl}propanedioate (6i)[40]

87% ee: Enantiomeric excess was determined by HPLC with ChiralPak AD-H column (hexane/2-propanol = 90:10), flow rate = 0.8 mL/min; λ = 254 nm; t_{major} = 37.9 min, t_{minor} = 39.5 min.

2.2.10 | Diethyl 2-{(*S*)-(4-nitrophenyl)[(1*S*)-2-oxocyclohexyl]methyl}propanedioate (6j)[51]

88% ee: Enantiomeric excess was determined by HPLC with ChiralPak AS-H column (hexane/2-propanol = 95:5), flow rate = 0.5 mL/min; λ = 254 nm; t_{major} = 47.5 min, t_{minor} = 62.2 min.

2.2.11 | Dimethyl 2-{(*S*)-(4-nitrophenyl)[(1*S*)-2-oxocyclopentyl]methyl}propanedioate (6k)[39]

84% ee: Enantiomeric excess was determined by HPLC with ChiralPak AS-H column (hexane/2-propanol = 94:6), flow rate = 1.0 mL/min; λ = 254 nm; t_{major} = 42.8 min, t_{minor} = 47.8 min.

2.2.12 | Dimethyl 2-[(*S*)-(4-nitrophenyl)-3-oxobutyl]propanedioate (6l)[39]

51% ee: Enantiomeric excess was determined by HPLC with ChiralPak AD-H column (hexane/2-propanol = 90:10), flow rate = 1.0 mL/min; λ = 254 nm; t_{minor} = 24.5 min, t_{major} = 47.1 min.

3 | RESULTS AND DISCUSSION

We initially conducted screening of organocatalysts (**1a**-**1c**) for the asymmetric conjugate addition of cyclohexanone (**4a**) to dimethyl 2-(4-nitrobenzylidene)malonate (**5a**) as a model reaction (Figure 1, Table 1). Thiourea-sulfonamide organocatalyst **1a** in the presence of catalytic amount of benzoic acid resulted in low yield but high stereoselectivity (entry 1). No decrease in stereoselectivity was observed in the reaction without

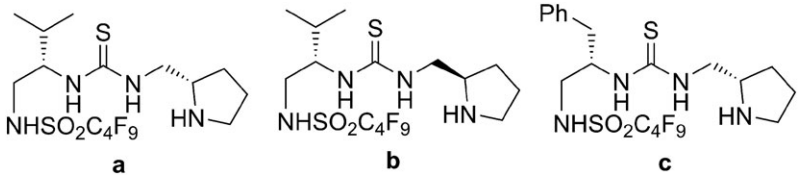
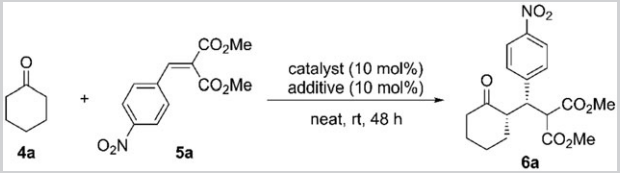


FIGURE 1 Structure of organocatalysts

TABLE 1 Selection of organocatalysts[a]



Entry	Catalyst	Additive, mol%	Yield, %[b]	syn/anti[c]	ee (%)[d]
1	1a	Benzoic acid (10)	32	94/6	85
2	1a	None	30	94/6	85
3	1b	None	31	93/7	−80
4	1c	None	13	94/6	80
5	2a	None	3	93/7	56
6	2c	None	7	92/8	39

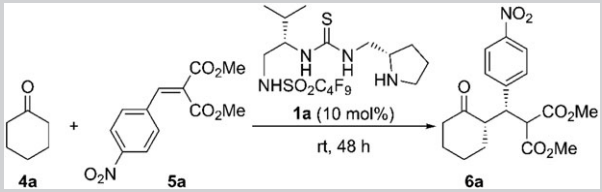
[a]Reactions conditions: **4a** (2.0 mmol), **5a** (0.20 mmol), and catalyst (0.020 mmol) were stirred at rt.

[b]Isolated yields.

[c]Determined by ^{1}H NMR.

[d]Determined by chiral HPLC analysis.

TABLE 2 Optimization of reaction conditions[a]



Entry	Solvent	4a (eq.)	Yield, %[b]	Syn/anti[c]	ee, %[d]
1	CH_2Cl_2	10	9	95/5	82
2	Toluene	10	11	97/3	86
3	Hexane	10	10	97/3	84
4	Et_2O	10	7	98/2	81
5	THF	10	14	98/2	75
6	MeCN	10	2	96/4	76
7	MeOH	10	Trace	…	…
8	Neat	10	30	94/6	85
9	Brine	10	53	93/7	86
10	H_2O	10	51	94/6	87
11[e]	H_2O	10	14	95/5	88
12	H_2O	15	57	93/7	87
13	H_2O	20	56	92/8	87
14[f]	H_2O	15	72	93/7	87

[a]Reaction conditions (unless otherwise noted): **4a** (2.0 mmol), **5a** (0.20 mmol), and catalyst **1a** (0.020 mmol) in solvent (0.2 mL) were stirred at rt for 48 hours.

[b]Isolated yields.

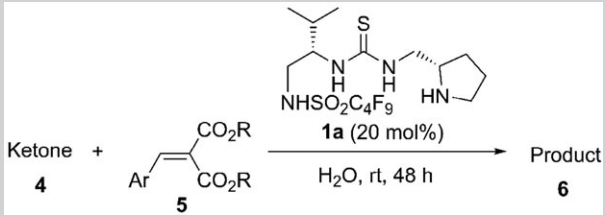
[c]Determined by ^{1}H NMR.

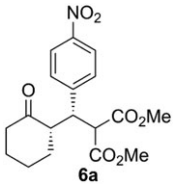
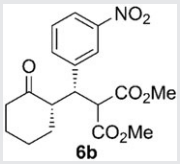
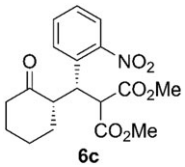
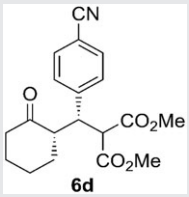
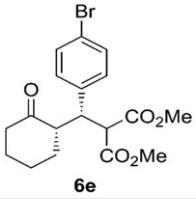
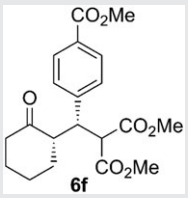
[d]Determined by chiral HPLC analysis.

[e]Benzoic acid (10 mol%) was added.

[f]Catalyst **1a** (20 mol%) was used.

TABLE 3 Michael reactions of various alkylidene malonates with ketones in the presence of oraganocatalyst **1a**[a]



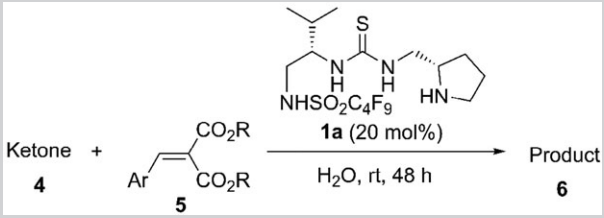
Entry	Product	Yield, %[b]	syn/anti[c]	ee, %[d]
1	 **6a**	72	93/7	87
2	 **6b**	58	92/8	85
3[e]	 **6c**	27	98/2	84
4	 **6d**	81	92/8	87
5	 **6e**	43	93/7	65
6[e]	 **6f**	51	93/7	88

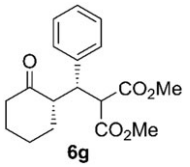
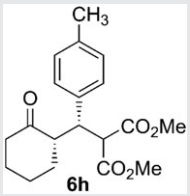
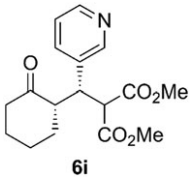
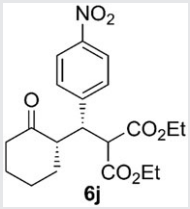
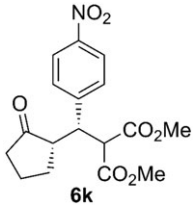
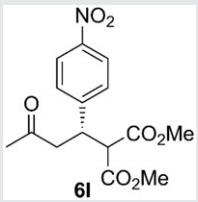
(Continues)

additives (entry 2). Both organocatalyst **1b** as a diastereoisomer of **1a** and thiourea-sulfonamide **1c** derived from L-phenylalanine exhibited low enantioselectivities (entries 3 and 4). Sulfonamides **2a** and **2c** were poor catalyst to provide low enantioselectivities, respectively (entries 5 and 6).

The preparation of organocatalyst **1a** is shown in Scheme 1. *N*-(β-Aminoalkyl)sulfonamide **2a** was coupled with isothiocyanate derived from L-proline, affording the intermediate **3a** in good yield. The Boc group of **3a** was removed by TFA treatment to generate the desired thiourea-sulfonamide organocatalyst **1a**.

TABLE 3 (Continued)



Entry	Product	Yield, %[b]	syn/anti[c]	ee, %[d]
7[e]	 6g	21	89/11	84
8	 6h	17	92/8	81
9	 6i	61	90/10	87
10[e]	 6j	68	94/6	88
11[e]	 6k	30	86/14	84
12[f]	 6l	52	…	51

[a]Reaction conditions (unless otherwise noted): **4** (2.0 mmol), **5** (0.20 mmol), and catalyst **1a** (0.040 mmol) in solvent (0.2 mL) were stirred at rt for 48 hours.

[b]Isolated yields.

[c]Determined by ^{1}H NMR.

[d]Determined by chiral HPLC analysis.

[e]The reaction was carried out at 40°C.

[f]The reaction was carried out without H_2O.

Organocatalysts **1b** and **1c** also were prepared by the similar procedure.

Further improvement of the yield and stereoselectivity was conducted using organocatalyst **1a** (Table 2). We examined the asymmetric Michael addition reactions using **4a** and **5a** as test reactants in the presence of a catalytic amount of **1a** at room temperature. A number of representative solvents were examined. Except for methanol, most solvents afforded low to moderate yields and good stereoselectivities (entries 1-8). The Michael adduct **6a** yield was improved in brine (entry 9) and water (entry 10). We infer that the reaction in water increased the yield of product **6a** because the hydration of iminium intermediate between catalyst **1a** and product **6a** is accelerated in the presence of water. Addition of benzoic acid as an additive resulted in low yield (entry 11). When the amount of added cyclohexanone (**4a**) increased to 15 equiv, the yield was slightly improved (entry 12). Best result was obtained by increasing the catalyst loading to 20 mol% (entry 14).

After the determination of optimal conditions, the scope and limitations of Michael additions between carbonyl compounds **4** and various alkylidene malonates **5** were examined (Table 3). Various alkylidene malonates reacted with cycloalkanones to afford the corresponding Michael adducts (**6a-k**) in moderate to good yield as well as high diastereoselectivities and enantioselectivities. Substitution position in aromatic group (4-, 3-, 2-$NO_2C_6H_4$) affected negligibly on diastereoselectivity and enantioselectivity; however, 2-substituted alkylidene malonate **5c** gave low yield (entries 1-3). Alkylidene malonates having electron-withdrawing groups, such as cyano, bromo, and ester groups (entries 4-6), were more reactive than benzylidene malonate **5g** (entry 7). Alkylidene malonate **5h** bearing methyl group was poor substrate to give low yield; however, high stereoselectivity was obtained (entry 8). The malonate **5i** having heterocycle such as pyridine ring also reacted with **4a**, providing good yield and high stereoselectivity (entry 9). Diethyl alkylidene malonate **5j** gave the corresponding product in good yield with high stereoselectivity (entry 10). Moderate yield and high stereoselectivity were observed when cyclopentanone (**4b**) was used as a Michael donor (entry 11). Acetone as an aliphatic ketone reacted with **5a** in the presence of **1a**, affording the adduct **6l** in moderate yield with moderate enantioselectivity (entry 12). The stereochemistry of the addition product **6** was determined by comparison with the reported chiral-phase HPLC retention time.

The secondary amine group in **1a** condensed with ketones **4** to form the enamine intermediate. We inferred that the three acidic protons of **1a** can function as hydrogen-bond donors, providing a rigid interaction with the oxygen atoms of malonates **5** via a plausible transition state similar to that proposed by Cao et al. (Figure 2).[35] These successful interactions can control the direction from which alkylidene malonates approached the enamine intermediate.

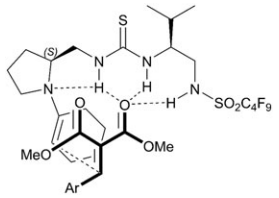


FIGURE 2 Plausible transition state

4 | CONCLUSION

The thiourea-sulfonamide organocatalyst **1a** efficiently promoted the Michael additions of cyclic ketones to alkylidenemalonates to afford the corresponding addition products **6** in moderate to high yields with high enantioselectivities (up to 88% ee). We demonstrated that the combination of perfluorobutanesulfonamide and thiourea groups was a good motif for organocatalysis. Application of organocatalysts with thiourea-sulfonamide to other types of asymmetric reactions, and the development of additional novel organocatalysts are currently underway.

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