Supporting Information

Enantioselectively Organocatalytic Michael Addition of Ketones to Alkylidene Malonates

*Chun-Li Cao, Xiu-Li Sun , jiaolong zhou and Yong Tang**

State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry,

Chinese Academy of Sciences, 354 Fenglin Lu, Shanghai 200032, P. R. China

tangy@mail.sioc.ac.cn

Contents:

General methods.....	S2
General procedures for catalytic Michael addition.....	S2
Copies of ¹H NMR and ¹³C NMR of compounds.....	S5
Copies of HPLC spectra of Micheal addition products.....	S20

General Methods. Commercial Reagents were used as received, unless otherwise noted. All reactions unless otherwise noted were carried out directly in air atmosphere. Ketone and cyclohexanone were distilled prior to use. Alkylidene malonates were prepared according to literature procedures¹.

Typical Procedure for Michael Addition Reaction:

A mixture of catalyst (0.05 mmol, 0.2eq) in cyclohexanone (0.5 mL, 20eq) was stirred for 10 min at desired temperature and alkylidene malonates (0.25 mmol, 1eq) was added. After the reaction was complete (monitored by TLC), the resulting mixture was concentrated under reduced pressure and the residue was purified by flash chromatography (petroleum: EtOAc = 1/5) to give the product.

Relative and absolute configurations of the products were determined by comparison with the known ¹H NMR, chiral HPLC analysis, and optical rotation values. Compounds **4a**², **4b**² are known.

4a: reaction time 2d, 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, CHCl₃); syn/anti = 93/7; ¹H NMR (300 MHz, CDCl₃): 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).

4b: reaction time 14d, yield: 36%. 88% ee, determined by HPLC analysis (Chiralcel AD, *i*-PrOH/hexane = 2/100, 1.0mL/min, 238 nm; *t_r*(minor) = 33.17 min, *t_r*(major) = 40.91 min), $[\alpha]_D^{20} = -38.3$ (*c* = 1.380, CHCl₃); syn/anti = 90/10; ¹H NMR (300 MHz, CDCl₃): δ 7.35-7.17 (m, 5H), 4.21-3.99 (m, 3H), 3.95-3.88 (m, 3H), 2.95-2.84 (m, 1H), 2.51-2.23 (m, 2H), 1.97-1.93 (m, 1H), 1.78-1.50 (m, 4H), 1.23 (m, 4H), 0.98 (t, *J* = 7.2 Hz, 3H).

4c: reaction time: 10d, yield: 71%. 90% ee, determined by HPLC analysis (Chiralcel AD-H, *i*-PrOH/hexane = 10/90, 0.8 mL/min, 238 nm; *t_r*(minor) = 16.51 min, *t_r*(major) = 21.95 min), $[\alpha]_D^{20} = -41.1$ (*c* = 1.016, CHCl₃); syn/anti = 93/7; ¹H NMR (300 MHz, CDCl₃): δ 7.38 (d, *J* = 8.7 Hz, 2H), 7.16 (d, *J* = 8.7 Hz, 2H), 4.21-4.09 (m, 2H), 4.04-3.91 (m, 4H), 2.91-2.83 (m, 1H), 2.47-2.28 (m, 2H), 1.97 (m, 1H), 1.81-1.76 (m, 2H), 1.57 (m, 2H), 1.23 (m, 4H), 1.03 (t, *J* = 7.2 Hz, 3H). ¹³C NMR (75 MHz, CDCl₃): 211.2, 168.2, 167.6, 137.6, 131.2, 130.9, 120.7, 61.4, 61.0,

55.2, 52.7, 42.7, 41.9, 31.3, 27.6, 24.5, 13.8, 13.6 ; IR (film): 2980 , 2938 , 2731 , 1489 , 1306 , 1176 cm^{-1} ; MS (ESI, m/z): 425 ($\text{M}+\text{H}^+$) ; Anal. Calcd for $\text{C}_{20}\text{H}_{25}\text{BrO}_5$: C, 56.48; H, 5.92. Found: C, 56.35; H, 5.76. Mp: 43°C.

4d: reaction time: 10d, yield: 48%. 88% ee, determined by HPLC analysis (Chiralcel AD-H, *i*-PrOH/hexane = 10/90, 1.0 mL/min, 238 nm; t_r (minor) = 9.06 min, t_r (major) = 17.65 min) , $[\alpha]_D^{20} = -86$ ($c = 0.757$, CHCl_3); syn/anti = 95/5; ^1H NMR (300 MHz, CDCl_3): δ 7.39-7.31 (m, 2H), 7.24-7.13 (m, 2H), 4.55 (m, 1H), 4.11-3.94 (m, 5H), 2.99 (m, 1H), 2.55-2.49 (m, 1H), 2.41-2.37 (m, 1H) , 1.97-1.93 (m, 1H), 1.78-1.56 (m, 4H), 1.28-1.18 (m, 4H), 1.06 (t, $J = 6.6$ Hz, 3H). ^{13}C NMR (75 MHz, acetone- d_6): 211.4, 168.5, 167.9, 138.7, 135.5, 129.9, 128.7, 127.6, 61.5, 61.0, 56.5, 54.5, 42.3, 39.5, 33.0, 28.7, 25.0, 13.8, 13.7 ; IR (film): 2981, 2939, 1731, 1364, 1309, 1257, 1035, 751 cm^{-1} ; MS (ESI, m/z): 403 ($\text{M}+\text{Na}^+$) ; Anal. Calcd for $\text{C}_{20}\text{H}_{25}\text{ClO}_5$: C, 63.07; H, 6.62. Found: C, 63.05; H, 6.67.

4e: reaction time: 10d, yield: 95%. 90% ee, determined by HPLC analysis (Chiralcel AD-H, *i*-PrOH/hexane = 10/90, 1.0 mL/min, 238 nm; t_r (minor) = 17.16 min, t_r (major) = 22.89 min) , $[\alpha]_D^{20} = -37.1$ ($c = 1.860$, CHCl_3); syn/anti = 91/9; ^1H NMR (300 MHz, CDCl_3): δ 8.09 (t, $J = 1.8$ Hz, 1H), 8.02-7.98 (m, 1H), 7.65 (d, $J = 7.5$ Hz, 1H), 7.40 (t, $J = 7.5$ Hz, 1H), 4.12-3.87 (m, 6H), 2.95-2.87 (m, 1H), 2.39-2.25 (m, 2H) , 1.97-1.93 (m, 1H), 1.80-1.74 (m, 2H), 1.60-1.47 (m, 2H), 1.16 (m, 4H), 0.96 (t, $J = 7.2$ Hz, 3H). ^{13}C NMR (75 MHz, CDCl_3): 210.8, 168.0, 167.6, 147.8, 140.8, 136.5, 128.8, 124.2, 122.0, 61.6, 61.3, 54.7, 52.3, 43.0, 42.1, 31.4, 27.6, 24.8, 13.8, 13.6 ;IR (film): 2936, 2864, 1731, 1530, 1350, 1249, 1178 cm^{-1} ; MS (ESI, m/z): 392 ($\text{M}+\text{H}^+$) ; Exact mass calcd for $\text{C}_{20}\text{H}_{25}\text{NO}_7\text{Na}^+$: 414.1535. Found: 414.1523.

4f: reaction time: 14d, yield: 20%. 87% ee, ee determined by HPLC analysis (Chiralcel AD-H, *i*-PrOH/hexane = 10/90, 1.0 mL/min, 238 nm; t_r (minor) = 14.89 min, t_r (major) = 34.20 min) , $[\alpha]_D^{20} = -102.8$ ($c = 0.860$, CHCl_3); syn/anti = 95/5; ^1H NMR (300 MHz, CDCl_3): δ 8.39 (d, $J = 8.7$ Hz, 1H), 7.81 (dd, $J = 8.7, 1.8$ Hz, 1H), 7.72 (m, 1H), 7.55-7.41 (m, 4H), 4.99 (t, $J = 9.0$ Hz, 1H), 4.09-4.04 (m, 3H), 3.77-3.72 (m, 2H), 3.10 (dt, $J = 10.5, 4.5$ Hz, 1H), 2.57-2.37 (m, 2H) , 1.70 (m, 1H), 1.49-1.26 (m, 4H), 1.20-1.08 (m, 4H), 0.74 (t, $J = 7.2$ Hz, 3H). ^{13}C NMR (75 MHz, CDCl_3): 212.8, 168.8, 168.0, 136.8, 133.7, 132.8, 128.5, 127.4, 126.0, 125.5, 125.1, 124.6, 124.0, 61.5, 60.9, 57.5, 55.1, 42.1, 36.7, 32.7, 28.4, 24.8, 13.8, 13.3 ; IR (film): 2980 , 2938 , 1729, 1250, 1033, 803, 784 cm^{-1} ; MS (ESI, m/z): 419 ($\text{M}+\text{Na}^+$) ; Anal. Calcd for $\text{C}_{24}\text{H}_{28}\text{O}_5$: C, 72.70; H,

7.11. Found: C, 72.63; H, 7.16. Mp: 82°C.

4g: reaction time: 10d, yield: 27%. ¹H NMR (300 MHz, CDCl₃): δ 3.72 (s, 3H), 3.71 (s, 3H), 3.57 (d, *J* = 6.0 Hz, 1H), 2.92 (m, 1H), 2.66-2.59 (m, 1H), 2.43-2.27 (m, 2H), 2.10-2.00 (m, 2H), 1.94-1.88 (m, 1H), 1.70-1.59 (m, 2H), 1.47-1.36 (m, 2H), 1.25-1.21 (m, 2H), 0.93-0.86 (m, 6H). ¹³C NMR (75 MHz, CDCl₃): 211.2, 169.5, 53.5, 52.3, 52.2, 52.1, 42.3, 38.5, 33.6, 29.9, 27.5, 26.1, 25.4, 22.8, 22.2 ; IR (film): 2954, 2868, 1736, 1710, 1436, 1310, 1157 cm⁻¹.

4h: reaction time: 10d, yield: 60%. 94% ee, determined by HPLC analysis (Chiralcel AD-H, *i*-PrOH/hexane = 10/90, 1.0 mL/min, 238 nm; *t_r* (minor) = 39.32 min, *t_r* (major) = 53.29 min) , [α]_D²⁰ = -14.4 (c = 1.238, CHCl₃); syn/anti = 89/11; ¹H NMR (300 MHz, CDCl₃): δ 8.14 (d, *J* = 9.0 Hz, 2H), 7.48 (d, *J* = 9.0 Hz, 2H), 4.28-4.22 (m, 1H), 4.05-3.91 (m, 5H), 3.74 (s, 3H), 3.52 (s, 3H), 3.31-3.22 (m, 1H) , 2.72-2.59 (m, 1H), 2.45-2.35 (m, 1H), 2.05-1.80 (m, 3H), 1.50 (m, 1H). ¹³C NMR (75 MHz, CDCl₃): 209.1, 168.2, 167.7, 146.8, 145.9, 130.5, 123.2, 106.9, 64.7, 64.5, 54.4, 52.7, 52.4, 48.2, 42.7, 38.0, 37.7, 34.2 ; IR (film): 2956, 2874, 1756, 1736, 1519, 1348, 731 cm⁻¹; MS (ESI, *m/z*): 444 (M+Na⁺) ; Anal. Calcd for C₂₀H₂₃NO₉: C, 57.00; H, 5.50; N, 3.32; Found: C, 56.90; H, 5.58; N, 3.24; Mp: 155°C.

4i: reaction time: 7d, yield: 36%. 62% ee, determined by HPLC analysis (Chiralcel AD-H, *i*-PrOH/hexane = 40/60, 0.6mL/min, 238 nm; *t_r* (minor) = 11.49 min, *t_r* (major) = 15.90 min) , [α]_D²⁰ = +10.3 (c = 0.815, CHCl₃); ¹H NMR (300 MHz, CDCl₃): δ 8.14 (d, *J* = 8.7 Hz, 2H), 7.45 (d, *J* = 8.7 Hz, 2H), 4.14-4.07 (m, 1H), 3.78 (d, *J* = 9.6 Hz, 1H), 3.75 (s, 3H), 3.55 (s, 3H), 3.11-2.94 (m, 2H) , 2.08 (s, 3H). ¹³C NMR (75 MHz, CDCl₃): 205.0, 168.0, 167.6, 148.3, 146.9, 129.1, 123.6, 56.1, 52.8, 52.6, 46.4, 39.7, 30.2 ; IR (film): 2955, 1736, 1521, 1348, 1157, 857, 700 cm⁻¹; MS (ESI, *m/z*): 346 (M+Na⁺) ; Anal. Calcd for C₁₅H₁₇NO₇: C, 55.73; H, 5.30; N, 4.33; Found: C, 55.76; H, 5.32; N, 4.23.

1 Zhou, J.; Tang, Y. *J. Am. Chem. Soc.* **2002**, *124*, 9030.

2 Blarer, S. J.; Seebach, D. *Chem. Ber.* GE, **1983**; *116*, 2250

Chemical Formula: C₂₀H₂₅BrO₅
Molecular Weight: 425.31
Elemental Analysis: C, 56.48; H, 5.92; Br, 18.79; O, 18.81

Compound 4c
300 MHz in CDCl₃

Chemical Formula: $C_{20}H_{25}ClO_5$
 Molecular Weight: 380.86
 Elemental Analysis: C, 63.07; H, 6.62; Cl, 9.31; O, 21.00

Compound 4d
300 MHz in $CDCl_3$

cc1-66556a.c
Pulse Sequence: s2pu1

Compound 4d
75 MHz in acetone-d6

210.185

167.976
167.584

147.754

140.800

136.490

128.816

124.168

121.980

77.418
77.000
76.575

61.614

61.294

54.737

52.314

43.012

42.119

31.388

27.605

24.785

13.620

13.621

Chemical Formula: $C_{20}H_{25}NO_7$
Molecular Weight: 391.4

Compound 4e
75 MHz in $CDCl_3$

Compound 4f
300 MHz in CDCl₃

Chemical Formula: C₂₄H₂₈O₅
Molecular Weight: 396.48
Elemental Analysis: C, 72.70; H, 7.12; O, 20.18

211.235

169.540

77.430
77.000
76.58353.487
52.348
52.183
52.142

42.256

38.534

33.589

29.868

27.542

26.124

25.394

22.797

22.186

Chemical Formula: $C_{16}H_{26}O_5$

Exact Mass: 298.178

Elemental Analysis: C, 64.41; H, 8.78; O, 26.81

Compound 4g
75 MHz in $CDCl_3$

Chemical Formula: C₂₀H₂₃NO₉

Exact Mass: 421.14

Molecular Weight: 421.4

Elemental Analysis: C, 57.00; H, 5.50; N, 3.32; O, 34.17

Compound 4h
75 MHz in CDCl₃

No.	R. Time	PeakHeight	PeakArea	PerCent
1	33.722	4125.2	250423.9	6.7532
2	35.637	23008.3	1596396.0	43.0501
3	40.210	3400.9	258524.0	6.9716
4	43.710	19035.2	1602886.0	43.2251
Total		49569.7	3708229.9	100.0000

No.	R. Time	PeakHeight	PeakArea	PerCent
1	33.127	34716.4	2105835.4	6.5730
2	35.210	23390.3	1483811.5	4.6315
3	39.460	16199.6	1139858.7	3.5579
4	42.210	288572.2	27308167.3	85.2377
Total		362878.4	32037672.9	100.0000

ccl

ccl-6-51b-race-biao

Peak #	Time [min]	Area [uV*sec]	Height [uV]	Area [%]	Norm. Area [%]
1	32.65	805984.3154	1.147e+04	49.69	49.69
2	41.15	816054.9727	9408.4042	50.31	50.31
		1.6220e+06	2.088e+04	100.00	100.00

Chiralcel ad Column; i-PrOH/n-Hex =2/100; Flow rate = 1.0mL/min; 238 nm.

ccl

ccl-6-51a-biao

Peak #	Time [min]	Area [uV*sec]	Height [uV]	Area [%]	Norm. Area [%]
1	33.17	121073.3974	1918.0276	6.04	6.04
2	40.91	1.8836e+06	1.937e+04	93.96	93.96
		2.0046e+06	2.129e+04	100.00	100.00

Chiralcel ad Column; i-PrOH/n-Hex =2/100; Flow rate = 1.0mL/min; 238 nm.

ccl

ccl-6-55b-race-biao

Peak #	Time [min]	Area [uV*sec]	Height [uV]	Area [%]	Norm. Area [%]
1	15.41	2.6649e+06	1.198e+05	6.94	6.94
2	16.45	1.6258e+07	6.226e+05	42.35	42.35
3	22.41	1.6721e+07	4.733e+05	43.55	43.55
4	29.35	2.7496e+06	6.329e+04	7.16	7.16
		3.8393e+07	1.279e+06	100.00	100.00

Chiralcel adh Column; i-PrOH/n-Hex =90/10; Flow rate = 0.8mL/min; 238 nm.

ccl

ccl-7-98b-biao-0.8ml/min

Peak #	Time [min]	Area [uV*sec]	Height [uV]	Area [%]	Norm. Area [%]
1	16.51	1.9122e+06	5.698e+04	4.86	4.86
2	21.95	3.7439e+07	5.901e+05	95.14	95.14
		3.9351e+07	6.471e+05	100.00	100.00

Chiralcel adh Column; i-PrOH/n-Hex =10/90; Flow rate = 0.8mL/min; 238 nm.

ccl

ccl-7-96a-race-biao-1.0ml/min

Peak #	Time [min]	Area [uV*sec]	Height [uV]	Area [%]	Norm. Area [%]
1	9.01	2.8140e+06	1.287e+05	49.61	49.61
2	17.59	2.8579e+06	6.065e+04	50.39	50.39
		5.6719e+06	1.893e+05	100.00	100.00

Chiralcel adh Column; i-PrOH/n-Hex =10/90; Flow rate = 1.0mL/min; 238 nm

ccl

ccl-7-96a-biao-1.0ml/min

Peak #	Time [min]	Area [uV*sec]	Height [uV]	Area [%]	Norm. Area [%]
1	9.06	126364.9436	5884.6156	6.18	6.18
2	17.65	1.9196e+06	4.236e+04	93.82	93.82
		2.0459e+06	4.824e+04	100.00	100.00

Chiralcel adh Column; i-PrOH/n-Hex =10/90; Flow rate = 1.0mL/min; 238 nm.

ccl

ccl-7-96b-race-biao-1.0ml/min

Peak #	Time [min]	Area [uV*sec]	Height [uV]	Area [%]	Norm. Area [%]
1	17.23	3.2840e+06	8.818e+04	40.26	40.26
2	18.64	818527.6359	1.788e+04	10.03	10.03
3	23.13	3.3795e+06	6.445e+04	41.43	41.43
4	25.84	675857.3241	1.148e+04	8.28	8.28
		8.1579e+06	1.820e+05	100.00	100.00

Chiralcel adh Column; i-PrOH/n-Hex =10/90; Flow rate = 1.0mL/min; 238 nm.

ccl

ccl-7-96b-biao-1.0ml/min

Peak #	Time [min]	Area [uV*sec]	Height [uV]	Area [%]	Norm. Area [%]
1	17.16	2.3479e+06	6.344e+04	4.56	4.56
2	18.59	2.8187e+06	6.429e+04	5.47	5.47
3	22.89	4.3561e+07	7.701e+05	84.61	84.61
4	25.72	2.7562e+06	3.678e+04	5.35	5.35
		5.1483e+07	9.346e+05	100.00	100.00

Chiralcel adh Column; i-PrOH/n-Hex =10/90; Flow rate = 1.0mL/min; 238 nm.

ccl

ccl-6-89a-biao-1.0

Peak #	Time [min]	Area [uV*sec]	Height [uV]	Area [%]	Norm. Area [%]
1	14.51	2.9945e+06	8.009e+04	49.72	49.72
2	33.63	3.0288e+06	4.471e+04	50.28	50.28
		6.0233e+06	1.248e+05	100.00	100.00

Chiralcel Ad-h Column; Hex/i-PrOH: 90/10; Flow rate = 1.0mL/min; 238 nm;

ccl

ccl-6-89a-biao-1.0

Peak #	Time [min]	Area [uV*sec]	Height [uV]	Area [%]	Norm. Area [%]
1	14.89	600527.8830	1.471e+04	6.47	6.47
2	34.20	8.6806e+06	1.181e+05	93.53	93.53
		9.2811e+06	1.328e+05	100.00	100.00

Chiralcel Ad-h Column; Hex/i-PrOH: 90/10; Flow rate = 1.0mL/min; 238 nm;

ccl

ccl-8-1a-race-biao

Peak #	Time [min]	Area [uV*sec]	Height [uV]	Area [%]	Norm. Area [%]
1	40.09	2.4908e+07	2.535e+05	50.46	50.46
2	55.15	2.4454e+07	1.940e+05	49.54	49.54
		4.9362e+07	4.476e+05	100.00	100.00

Chiralcel adh Column; i-PrOH/n-Hex =10/90; Flow rate = 1.0mL/min; 238 nm.

ccl

ccl-8-1a-biao

Peak #	Time [min]	Area [uV*sec]	Height [uV]	Area [%]	Norm. Area [%]
1	39.32	7.4746e+06	8.305e+04	97.08	97.08
2	53.29	224961.6892	2442.5867	2.92	2.92
		7.6995e+06	8.549e+04	100.00	100.00

Chiralcel adh Column; i-PrOH/n-Hex =10/90; Flow rate = 1.0mL/min; 238 nm.

ccl

ccl-6-70b-biao

Peak #	Time [min]	Area [uV*sec]	Height [uV]	Area [%]	Norm. Area [%]
1	11.72	2.1742e+07	1.379e+06	49.21	49.21
2	16.20	2.2440e+07	8.704e+05	50.79	50.79
		4.4182e+07	2.249e+06	100.00	100.00

Chiralcel adh Column; i-PrOH/n-Hex =40/60; Flow rate = 0.6mL/min; 238 nm.

ccl

ccl-6-81-biao

Peak #	Time [min]	Area [uV*sec]	Height [uV]	Area [%]	Norm. Area [%]
1	11.49	598855.3991	4.013e+04	19.18	19.18
2	15.90	2.5228e+06	1.004e+05	80.82	80.82
		3.1216e+06	1.406e+05	100.00	100.00

Chiralcel adh Column; i-PrOH/n-Hex =40/60; Flow rate = 0.6mL/min; 238 nm.