

Asymmetric Michael Reaction of Malonate Derivatives with α,β -Unsaturated Ketones Using Chiral Quaternary Ammonium Salts

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The catalytic enantioselective Michael reaction promoted by quaternary ammonium salts from Cinchona alkaloids as a phase-transfer catalyst is described. Treatment of malonates with α,β -unsaturated ketones under mild reaction conditions afforded the corresponding Michael adducts in good yields with good to moderate enantiomeric excesses.

Key Words : Phase-transfer catalyst, Michael reactions, Asymmetric reactions, Malonates, Fluoromalones

Introduction

Phase-transfer catalysis is a clean and efficient processes involving high yields, operational simplicity, mild conditions, low cost, safety, and environmental profit.¹ During the past decade, the development of asymmetric phase-transfer catalysis based on the use of structurally well defined chiral, nonracemic catalysts has resulted in notable achievements, making it feasible to perform various bond formation reactions under mild phase-transfer catalyzed conditions.²

The formation of carbon-carbon bonds by conjugated addition of appropriate carboanionic reagents to α,β -unsaturated carbonyl compounds is one of the most useful methods of remote functionalization in organic synthesis.³ Therefore, their catalytic asymmetric version have been studied extensively.⁴ Efforts toward achieving asymmetric conjugate addition of malonates to chalcones in the presence of chiral catalysts have been the subject of several reports. For example, the reaction of malonates with chalcones catalyzed by La-BINOL complexes,⁵ L-proline derivatives,⁶ chiral metal complexes,⁷ pyrrolidylalkyl ammonium hydroxide,⁸ and chiral ammonium salts.⁹

As part of our research program related to the development of synthetic methods for the enantioselective construction of stereogenic carbon centers,¹⁰ we reported the catalytic enantioselective Michael reaction promoted by quaternary ammonium salts from cinchonidine as a phase-transfer catalyst.¹¹ Herein we wish to report on the catalytic asymmetric conjugate addition of malonates **2** and fluoro-malonates **7** to α,β -unsaturated ketones **1** using *N*-(3,5-di-*tert*-butyl-4-methoxy)benzylcinchonidinium bromide (**4**) in more details, providing information on its scopes and limitations.

Results and Discussion

Asymmetric Michael Reactions of Malonates to α,β -Unsaturated Ketones. The introduction of the bulky subunit at the bridged nitrogen of Cinchona alkaloids leads to enhancement of the stereoselectivity in catalytic phase-

transfer reactions.² We introduced a bulky environment at the bridgehead nitrogen using (3,5-di-*tert*-butyl-4-methoxy)benzyl moiety which can be prepared in two steps starting from BHT. Phase-transfer catalysts **4** were easily prepared from cinchonine or cinchonidine.¹²

In order to determine suitable reaction conditions for the catalytic asymmetric conjugate addition of malonates **2** to chalcones **1**, we initially investigated the reaction system using 10 mol% of catalyst, with malonate as the Michael donor and chalcone **1a** as the Michael acceptor (Table 1). Catalysts **4a** and **4d** having O-allyl group showed higher catalytic efficiencies than other catalysts in terms of yields and enantioselectivity (entries 1-5, and 13-14). It has been also found that K₂CO₃ was the more effective base in this

Table 1. Catalytic asymmetric Michael reaction of malonates **2** to chalcone **1a** with phase-transfer catalysts

entry	malonate 2 , R	catalyst	base	yield ^a (%)	ee ^b (%)
1	Et	4a	<i>t</i> -BuOK	3a , 74	35 (<i>R</i>)
2	Et	4b	<i>t</i> -BuOK	3a , 68	13 (<i>R</i>)
3	Et	4c	<i>t</i> -BuOK	3a , 76	22 (<i>R</i>)
4	Et	4d	<i>t</i> -BuOK	3a , 68	9 (<i>S</i>)
5	Et	4e	<i>t</i> -BuOK	3a , 72	31 (<i>S</i>)
6	Et	4a	KOH	3a , 74	40 (<i>R</i>)
7 ^c	Et	4a	KOH	3a , 68	43 (<i>R</i>)
8	Et	4a	K ₂ CO ₃	3a , 70	46 (<i>R</i>)
9 ^d	Et	4a	K ₂ CO ₃	3a , 68	40 (<i>R</i>)
10	Me	4a	K ₂ CO ₃	3b , 92	27 (<i>R</i>)
11	<i>i</i> -Pr	4a	K ₂ CO ₃	3c , 77	55
12	Bn	4a	K ₂ CO ₃	3d , 91	70

^aYield of isolated product. ^bEnantiopurities of **3a-3d** were determined by HPLC analysis with Chiralcel AD (for **3a** and **3c**) and Chiralpak AS (for **3b** and **3d**) columns, 2-propanol-hexane (1 : 9), 1.2 mL/min, λ_{\max} = 254 nm. It were established by analyses of racemic **3** that the enantiomers were fully resolved. ^cReaction carried out in CH₂Cl₂ at 0 °C. ^dReaction carried out at 0 °C.

reaction than others such as KOH or *t*-BuOK (entries 1, 6, 8). Compound (*R*)-**3a** was formed using cinchonine-derived catalysts (**4a-4c**) as the excessive enantiomer, which should be the case because all of these catalysts possess the same chirality. The cinchonidine-derived catalysts **4d-4e** leading to formation of (*S*)-**3a** in excess. The absolute configuration of the major enantiomer of **3** was determined by comparison of the optical rotation and chiral HPLC analysis with those previously reported.⁵⁻⁹ Toluene as solvent was effective in this reaction. The reaction temperature is not critical in this reaction (entries 8 and 9). The structure of the malonate plays a key role in influencing the enantioselectivity. Dibenzyl malonate gave high selectivity in this reaction (entries 9-12).

Under the optimized reaction conditions described above (10 mol% of catalyst **4a**, K₂CO₃, toluene, rt), we investigated catalytic asymmetric Michael reaction of dibenzyl malonate to chalcone derivatives **1**. The reaction smoothly proceeded to afford the corresponding adducts **3** with good enantioselectivities. Reaction of 1.5 equiv of dibenzyl malonate with chalcone derivatives **1**, cinchonidinium salt **4** (10 mol%), and K₂CO₃ in toluene at room temperature with stirring for 18-24 h afforded the Michael adducts **3** in good yields with moderate enantioselectivities (45-70% ee) (Table 2). In all cases the enantiomeric excesses were determined by HPLC analysis.

Having established the scope with respect to the Michael reaction of malonates with α,β -unsaturated ketones, we next turned our attention to the reaction of malonates with 2-cyclohexenone (Table 3). We subsequently tested catalysts **4a-4f**. Catalyst **4d** exhibited high chiral efficiency in the reaction of dibenzyl malonate with 2-cyclohexenone to afford **3l** with 63% ee. Under the optimum conditions (10 mol% of catalyst **4d**, K₂CO₃, toluene, 72 h), the reaction of malonate derivatives with 2-cyclohexenone (**1l**) furnished adducts **3m-3o** with 67-75% ee, respectively (Table 3, entries 7-9). Compound (*R*)-**3l** was formed using cinchonidine-derived catalysts (**4a-4c**) as the excessive enantiomer, which

Table 2. Catalytic asymmetric Michael reaction of dibenzyl malonate (**2d**) to chalcones **1** with phase-transfer catalyst **4a**

1	2d	3		
Ar ¹	Ar ²	time (h)	yield (%)	ee ^a (%)
Ph	Ph	18	3d , 91	70
Ph	<i>p</i> -OMe, Ph	18	3e , 91	45
Ph	2-thienyl	18	3f , 94	51
Ph	<i>p</i> -tolyl	10	3g , 88	47
Ph	2-furyl	10	3h , 92	49
<i>p</i> -OMe, Ph	Ph	18	3i , 88	47
2-naphthyl	<i>m</i> -Br, Ph	24	3j , 60	67
2-naphthyl	<i>p</i> -Br, Ph	24	3k , 58	59

^aEnantiopurities of **3d-3k** were determined by HPLC analysis with chiral column (Chiralpak AS for **3d-3i**, Chiralcel OD-H for **3j** and **3k**), 2-propanol-hexane (1 : 9), 1.2 mL/min, λ_{\max} = 254 nm. In each case, it was established by analyses of racemic **3** that the enantiomers were fully resolved.

Table 3. Catalytic asymmetric Michael reaction of malonate **2** to 2-cyclohexenone (**1l**) with phase-transfer catalysts **4**

entry	malonate 2 R ¹ , R ²	catalyst	yield (%)	ee ^{a,b} (%)
1	Bn, H	4a	3l , 66	33 (<i>R</i>)
2	Bn, H	4b	3l , 76	17 (<i>R</i>)
3	Bn, H	4c	3l , 60	29 (<i>R</i>)
4	Bn, H	4d	3l , 74	63 (<i>S</i>)
5	Bn, H	4e	3l , 65	27 (<i>S</i>)
6	Bn, H	4f	3l , 74	43 (<i>S</i>)
7	Me, H	4d	3m , 73	67 (<i>S</i>)
8	Et, H	4d	3n , 83	75 (<i>S</i>)
9	Bn, Me	4d	3o , 76	73 (<i>S</i>)

^aEnantiopurities of **3l-3o** were determined by HPLC analysis with Chiralpak AS, 2-propanol-hexane (1 : 9), 1.2 mL/min, λ_{\max} = 215 nm.

^bThe absolute configuration was established through comparison of its optical rotation and HPLC data with chiral columns to that reported in the literature.^{5,7}

should be the case because all of these catalysts possess the same chirality. The cinchonine-derived catalysts **4d-4f** leading to formation of (*S*)-**3l** in excess.

Asymmetric Michael reactions of fluoromalonates to chalcones. Organic fluorine compounds are of importance in organic synthesis because of their use as medicinals, agrochemicals, and in fundamental studies of biochemical and metabolic process.¹³ However, enantioselective Michael reactions of fluoromalonate to α,β -unsaturated carbonyl compounds have scarcely been studied. In analogy with above reaction previously studied, we initially investigated the reaction system using 10 mol% of catalyst, with diethyl fluoromalonate **7a** as the Michael donor and chalcone **1a** as the Michael acceptor.

To examine the generality of the enantioselective Michael reaction using chiral phase-transfer catalysts, we investigated catalytic asymmetric Michael reaction of diethyl fluoromalonate **7a** to chalcone derivatives **1a** under the optimized reaction conditions described above (10 mol% of catalyst **4a**, K₂CO₃, toluene, rt). The reaction smoothly proceeded to afford the corresponding adduct **8** with moderate enantioselectivities (Table 4). Reaction of 1.0 equiv of diethyl fluoromalonate **2** with chalcone derivatives

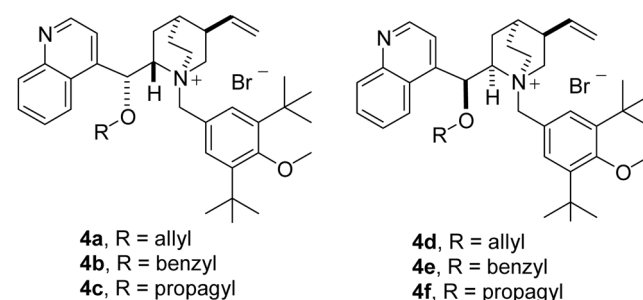


Figure 1. Chiral phase-transfer catalysts.

Table 4. Catalytic asymmetric Michael reaction of diethyl fluoromalonates **7** to chalcones **1** with phase-transfer catalyst **4a**

Ar ¹	Ar ²	R	time (h)	yield ^a (%)	ee ^b (%)
Ph	Ph	Et	15	8a , 63	39
Ph	<i>p</i> -CF ₃ , Ph	Et	18	8b , 60	45
Ph	<i>p</i> -OCH ₃ , Ph	Et	18	8c , 58	47
Ph	<i>p</i> -OCH ₃ , Ph	Bn	23	8d , 64 ^c	51
<i>p</i> -Cl, Ph	Ph	Et	18	8e , 77	37
<i>p</i> -Cl, Ph	Ph	Bn	36	8f , 76 ^c	37
<i>p</i> -Cl, Ph	<i>m</i> -Br, Ph	Et	9	8g , 64	37
2-naphthyl	<i>m</i> -Br, Ph	Et	18	8h , 76	47

^aIsolated yields are based on chalcone. ^bEnantiomeric excess was determined by HPLC analysis using Chiralcel OD-H (for **8a**, **8b**, **8e**, **8g**, and **8h**), AS (for **8d** and **8f**), and Whelk-O1 (for **8c**) columns. ^cReaction carried out using Rb₂CO₃ as base.

1, cinchonidinium salt **4a** (10 mol%), and K₂CO₃ in toluene at room temperature with stirring for 15-18 h afforded the Michael adducts **8** in good yields with moderate enantioselectivities (35-47% ee) (Table 2).

In conclusion, we have developed a new class of asymmetric phase-transfer catalyst, which shows good enantioselectivity in the Michael reaction of malonate and fluoromalonate to α,β -unsaturated ketones. We are currently involved in the further development of these catalyst systems and investigating their applicability to other asymmetric phase-transfer processes.

Experimental Section

General. All reactions were carried out in oven-dried glassware under an atmosphere of dry nitrogen unless otherwise noted. All reaction were magnetically stirred and monitored by analytical thin layer chromatography using Merck pre-coated silica gel plates with F₂₅₄ indicator. Flash column chromatography was performed using silicagel 60 (mesh 230-400) supplied by E. Merck. ¹H NMR and ¹³C NMR spectra were recorded on a Bruker AC 200 (200 MHz for ¹H, 50 MHz for ¹³C) or Bruker DRS 400 (400 MHz for ¹H, 100 MHz for ¹³C). Chemical shift values (δ) are reported in ppm relative to Me₄Si (δ 0.0 ppm). Multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet) and br (broad). Mass spectra were measured on a Jeol HX110/110A using electrospray ionization technique. Optical rotations were measured with a JASCO-DIP-1000 digital polarimeter. High-performance liquid chromatography (HPLC) was performed on a Younglin M930 Series equipped with variable wavelength detector using chiral stationary column (250 mm, 4.6 mm) such as Chiralpak AS, Chiralcel OD-H, and Whelk O1 columns.

General Procedure for Michael Addition of Malonates to Chalcones. A mixture of malonate derivatives (0.45 mmol), K₂CO₃ (0.16 g, 2.0 mmol), chiral cinchonidinium salt **4a** (18.0 mg, 0.03 mmol), and chalcones (0.3 mmol) in

toluene (2 mL) was stirred at room temperature for 9-24 h. The mixture was diluted with water (10 mL) and extracted with ethyl acetate (2 \times 10 mL). The combined organic layers were dried over MgSO₄, filtered, concentrated, and purified by flash chromatography (silica gel, ethyl acetate : hexane = 1 : 5) to afford Michael adducts.

2-(3-Oxo-1,3-diphenylpropyl)dibenzylmalonate (3d).^{9b} R_f 0.32 (EtOAc : hexane = 1 : 5); [α]_D²⁰ -25.9 (c 1.0 CHCl₃, 70% ee); ¹H NMR (CDCl₃, 200 MHz) δ 3.42-3.45 (m, 2H), 3.94 (d, *J* = 9.6 Hz, 1H), 4.16-4.28 (m, 1H), 4.91 (s, 2H), 5.14 (s, 2H), 7.03-7.83 (m, 20H); ¹³C NMR (CDCl₃, 50 MHz) δ 197.3, 167.9, 167.4, 140.2, 136.6, 135.0, 133.0, 128.4, 128.3, 128.1, 128.0, 127.1, 67.3, 67.1, 57.4, 42.2, 40.7; R_t HPLC (90 : 10, hexane : *iso*-PrOH, 254 nm, 0.5 mL/min) Chiralpak AS column, t_R = 45.2 min (minor), t_R = 49.5 min (major).

2-[3-(4-Methoxyphenyl)-3-oxo-1-phenylpropyl]dibenzylmalonate (3e). R_f 0.26 (EtOAc : hexane = 1 : 5); [α]_D²⁵ -5.9 (c 1.0 CHCl₃, 45% ee); ¹H NMR (CDCl₃, 200 MHz) δ 3.37-3.48 (m, 2H), 3.73 (s, 3H), 3.89 (d, *J* = 17.7 Hz, 1H), 4.13-4.22 (m, 1H), 4.91 (s, 2H), 5.15 (s, 2H), 6.69-7.82 (m, 19H); ¹³C NMR (CDCl₃, 50 MHz) δ 197.5, 168.0, 167.5, 136.6, 135.1, 132.9, 132.0, 129.1, 128.4, 128.3, 128.1, 128.0, 113.7, 67.2, 67.0, 57.7, 55.0, 42.4, 40.1; R_t HPLC (90 : 10, hexane : *iso*-PrOH, 254 nm, 0.5 mL/min) Chiralpak AS column, t_R = 36.4 min (minor), t_R = 39.5 min (major).

2-(3-Oxo-1-phenyl-3-thiophen-2-yl-propyl)dibenzylmalonate (3f). R_f 0.35 (EtOAc : hexane = 1 : 5); [α]_D²⁵ -8.3 (c 1.1 CHCl₃, 51% ee); ¹H NMR (CDCl₃, 200 MHz) δ 3.34-3.38 (m, 2H), 3.96 (d, *J* = 11.2 Hz, 1H), 4.17-4.22 (m, 1H), 4.89 (s, 2H), 5.15 (d, *J* = 2.2 Hz, 2H), 7.04-7.63 (m, 18H); ¹³C NMR (CDCl₃, 50 MHz) δ 195.3, 167.9, 167.3, 139.8, 134.9, 133.6, 132.0, 128.5, 128.4, 128.2, 128.1, 127.2, 67.3, 67.1, 57.3, 42.9, 41.0; R_t HPLC (90 : 10, hexane : *iso*-PrOH, 254 nm, 1.2 mL/min) Chiralpak AS column, t_R = 15.8 min (minor), t_R = 16.8 min (major).

2-(3-Oxo-1-phenyl-3-*p*-tolylpropyl)dibenzylmalonate (3g). R_f 0.32 (EtOAc : hexane = 1 : 5); [α]_D²⁰ -11.4 (c 1.0 CHCl₃, 49% ee); ¹H NMR (CDCl₃, 200 MHz) δ 2.38 (s, 3H), 3.44-3.55 (m, 1H), 3.99 (d, *J* = 10.2 Hz, 1H), 4.16-4.21 (m, 1H), 4.92 (s, 2H), 5.16 (d, *J* = 7.4 Hz, 2H), 7.03-7.87 (m, 19H); ¹³C NMR (CDCl₃, 50 MHz) δ 196.9, 167.9, 167.4, 128.5, 128.4, 128.2, 128.1, 127.1, 67.2, 67.0, 57.5, 42.1, 40.7; R_t HPLC (90 : 10, hexane : *iso*-PrOH, 254 nm, 1.2 mL/min) Chiralpak AS column, t_R = 10.5 min (major), t_R = 12.7 min (minor).

2-(3-Furan-2-yl-3-oxo-1-phenylpropyl)dibenzylmalonate (3h). R_f 0.35 (EtOAc : hexane = 1 : 5); ¹H NMR (CDCl₃, 200 MHz) δ 3.26-3.36 (m, 1H), 3.94 (d, *J* = 11.2 Hz, 1H), 4.13-4.22 (m, 1H), 4.89 (s, 2H), 5.14 (d, *J* = 1.8 Hz, 2H), 6.44-6.47 (m, 1H), 7.02-7.59 (m, 17H); ¹³C NMR (CDCl₃, 50 MHz) δ 186.3, 167.7, 167.3, 146.2, 139.9, 134.9, 128.4, 128.1, 127.2, 117.1, 112.1, 67.3, 67.1, 57.3, 42.1, 40.6; R_t HPLC (90 : 10, hexane : *iso*-PrOH, 254 nm, 1.2 mL/min) Chiralpak AS column, t_R = 18.2 min (minor), t_R = 20.2 min (major).

2-[1-(4-Methoxyphenyl)-3-oxo-3-phenylpropyl]dibenzyl-

malonate (3i). R_f 0.32 (EtOAc : hexane = 1 : 5); $[\alpha]_D^{25}$ -10.8 (c 2.1 CHCl₃, 47% ee); ¹H NMR (CDCl₃, 200 MHz) δ 3.36-3.45 (m, 2H), 3.85 (s, 3H), 3.94 (d, J = 9.5 Hz, 1H), 4.15-4.23 (m, 1H), 4.90 (s, 2H), 5.13 (d, J = 2.2 Hz, 2H), 6.83-7.82 (m, 19H); ¹³C NMR (CDCl₃, 50 MHz) δ 196.7, 168.7, 167.7, 130.2, 128.4, 127.1, 113.5, 67.2, 67.0, 57.5, 55.4, 41.9, 40.9; R_t HPLC (90 : 10, hexane : *iso*-PrOH, 254 nm, 1.2 mL/min) Chiralpak AS column, t_R = 18.5 min (minor), t_R = 24.9 min (major).

2-[3-(3-Bromophenyl)-1-naphthalen-2-yl-3-oxopropyl]dibenzylmalonate (3j). R_f 0.25 (EtOAc : hexane = 1 : 5); $[\alpha]_D^{25}$ -9.0 (c 1.0 CHCl₃, 67% ee); ¹H NMR (CDCl₃, 200 MHz) δ 3.40-3.47 (m, 2H), 4.04 (d, J = 9.79 Hz, 1H), 4.33-4.37 (m, 1H), 4.87 (s, 2H), 5.22 (d, J = 2.0 Hz, 2H), 6.88-7.73 (m, 21H); ¹³C NMR (CDCl₃, 50 MHz) δ 197.7, 167.9, 167.4, 137.5, 131.7, 129.5, 128.5, 128.4, 128.2, 128.0, 127.8, 127.5, 127.0, 126.0, 125.8, 67.4, 67.2, 57.4, 42.2, 40.8; R_t HPLC (90 : 10, hexane : *iso*-PrOH, 254 nm, 1.2 mL/min) Chiralcel OD-H column, t_R = 29.8 min (major), t_R = 46.9 min (minor).

2-[3-(4-Bromophenyl)-1-naphthalen-2-yl-3-oxopropyl]dibenzylmalonate (3k). R_f 0.25 (EtOAc : hexane = 1 : 5); $[\alpha]_D^{22}$ -6.1 (c 1.0 CHCl₃, 59% ee); ¹H NMR (CDCl₃, 200 MHz) δ 3.46-3.49 (m, 2H), 4.02 (d, J = 9.6 Hz, 1H), 4.33-4.41 (m, 1H), 4.95 (s, 2H), 5.15 (d, J = 2.0 Hz, 2H), 6.88-7.74 (m, 21H); ¹³C NMR (CDCl₃, 50 MHz) δ 194.4, 167.9, 167.1, 131.7, 129.5, 128.5, 128.4, 128.2, 128.0, 127.8, 127.5, 127.0, 126.0, 125.8, 67.4, 67.2, 57.4, 42.2, 40.8; R_t HPLC (90 : 10, hexane : *iso*-PrOH, 254 nm, 1.2 mL/min) Chiralcel OD-H column, t_R = 26.9 min (major), t_R = 36.3 min (minor).

(S)-3-[Bis(benzyloxycarbonyl)methyl]cyclohexanone (3l).^{5c,7c} R_f 0.3 (EtOAc : hexane = 1 : 4); $[\alpha]_D^{22}$ -1.4 (c 1.5 CHCl₃, 63% ee); ¹H NMR (CDCl₃, 200 MHz) δ 1.42-1.63 (m, 2H), 1.86-2.62 (m, 7H), 3.41 (d, J = 7.8 Hz, 1H), 5.14 (s, 2H), 5.15 (s, 2H), 7.28-7.40 (m, 10H); ¹³C NMR (CDCl₃, 50 MHz) δ 24.5, 28.6, 38.1, 40.9, 45.0, 56.7, 67.3, 128.3, 128.5, 128.6, 135.1, 167.5, 209.4; R_t HPLC (90 : 10, hexane : *iso*-PrOH, 215 nm, 1.2 mL/min) Chiralcel AS column, t_R = 23.9 min (minor), t_R = 29.1 min (major).

(S)-3-[Bis(methyloxycarbonyl)methyl]cyclohexanone (3m).^{5d,5e} R_f 0.3 (EtOAc : hexane = 1 : 2); $[\alpha]_D^{22}$ -2.7 (c 2.5 CHCl₃, 67% ee); ¹H NMR (CDCl₃, 200 MHz) δ 1.46-1.82 (m, 2H), 1.92-2.51 (m, 7H), 3.36 (d, J = 7.8 Hz, 1H), 3.76 (d, J = 1.7 Hz, 6H); ¹³C NMR (CDCl₃, 50 MHz) δ 24.5, 28.7, 38.0, 40.9, 45.0, 52.5, 56.6, 168.2, 209.4; R_t HPLC (90 : 10, hexane : *iso*-PrOH, 215 nm, 1.2 mL/min) Chiralcel AS column, t_R = 20.5 min (minor), t_R = 26.3 min (major).

(S)-3-[Bis(ethyloxycarbonyl)methyl]cyclohexanone (3n).^{7d} R_f 0.3 (EtOAc : hexane = 1 : 5); $[\alpha]_D^{20}$ -2.2 (c 1.7 CHCl₃, 75% ee); ¹H NMR (CDCl₃, 200 MHz) δ 1.28 (t, J = 7.3 Hz, 6H), 1.19-1.66 (m, 2H), 2.01-2.50 (m, 7H), 3.30 (d, J = 7.9 Hz, 1H), 4.15-4.27 (m, 4H); ¹³C NMR (CDCl₃, 50 MHz) δ 14.1, 24.5, 28.8, 38.0, 41.0, 45.1, 56.9, 60.4, 61.5, 167.86, 209.7; R_t HPLC (90 : 10, hexane : *iso*-PrOH, 215 nm, 1.2 mL/min) Chiralcel AS column, t_R = 12.3 min (minor), t_R = 14.7 min (major).

(S)-3-[Bis(benzyloxycarbonyl)ethyl]cyclohexanone (3o).^{5d} R_f 0.25 (EtOAc : hexane = 1 : 4); $[\alpha]_D^{20}$ -0.4 (c 1.8 CHCl₃, 73% ee); ¹H NMR (CDCl₃, 200 MHz) δ 1.35-1.83 (m, 2H), 1.44 (s, 3H), 1.97-2.63 (m, 7H), 5.11 (s, 4H), 7.21-7.38 (m, 10H); ¹³C NMR (CDCl₃, 50 MHz) δ 16.8, 24.6, 26.6, 41.0, 42.6, 43.2, 57.0, 67.1, 67.2, 128.1, 128.6, 128.5, 135.2, 170.5, 210.0; R_t HPLC (90 : 10, hexane : *iso*-PrOH, 215 nm, 1.2 mL/min) Chiralcel AS column, t_R = 11.2 min (minor), t_R = 19.0 min (major).

2-Fluoro-2-(3-oxo-1,3-diphenylpropyl)diethylmalonate (8a). R_f 0.25 (EtOAc : hexane = 1 : 6); $[\alpha]_D^{25}$ -16.3 (c = 1.0, CHCl₃, 39% ee); ¹H NMR (CDCl₃, 200 MHz) δ 1.03 (t, J = 7.2 Hz, 3H), 1.31 (t, J = 7.3 Hz, 3H), 3.38 (dd, J = 3.6, 17.6 Hz, 1H), 3.68 (dd, J = 9.6, 17.5 Hz, 1H), 3.95-4.09 (m, 2H), 4.32 (q, J = 7.2 Hz, 2H), 4.54 (ddd, J = 3.6, 9.6, 32.9 Hz, 1H), 7.24 (d, J = 7.8 Hz, 2H), 7.36-7.46 (m, 5H), 7.55 (d, J = 9.5 Hz, 1H), 7.90 (d, J = 5.3 Hz, 2H); ¹³C NMR (CDCl₃, 50 MHz) δ 197.3, 167.9, 167.4, 140.2, 136.6, 135.0, 133.0, 128.4, 128.3, 128.1, 128.0, 127.1, 67.3, 67.1, 57.4, 42.2, 40.7; HRMS calcd for C₂₂H₂₃FO₅Na ([M+Na]⁺) 409.1427, found 409.1425; R_t HPLC (90 : 10, hexane : *iso*-PrOH, 254 nm, 0.5 mL/min) Chiralcel OD-H column, t_R = 14.0 min (major), t_R = 15.5 min (minor).

2-Fluoro-2-[3-oxo-1-phenyl-3-(4-trifluoromethylphenyl)propyl]diethylmalonate (8b). R_f 0.29 (EtOAc : hexane = 1 : 6); $[\alpha]_D^{25}$ -13.5 (c = 1.0, CHCl₃, 45% ee); ¹H NMR (CDCl₃, 400 MHz) δ 1.02 (t, J = 7.2 Hz, 3H), 1.32 (t, J = 7.2 Hz, 3H), 3.43 (dd, J = 4.0, 17.2 Hz, 1H), 3.64 (dd, J = 9.6, 17.2 Hz, 1H), 3.93-4.06 (m, 2H), 4.31 (q, J = 7.2 Hz, 2H), 4.49 (ddd, J = 3.6, 9.6, 32.4 Hz, 1H), 7.19-7.25 (m, 3H), 7.34 (d, J = 8.4 Hz, 2H), 7.67 (d, J = 8.0 Hz, 2H), 7.97 (d, J = 8.0 Hz, 2H); ¹³C NMR (CDCl₃, 50 MHz) δ 196.3, 167.9, 167.3, 139.0, 137.4, 135.2, 134.9, 134.7, 133.1, 132.5, 131.7, 128.9, 128.5, 128.3, 128.2, 128.1, 128.0, 127.8, 127.5, 126.9, 126.0, 125.7, 67.3, 67.1, 57.3, 42.2, 40.8; HRMS calcd for C₂₃H₂₂F₄O₅Na ([M+Na]⁺) 477.1301, found 477.1307; R_t HPLC (90 : 10, hexane : *iso*-PrOH, 254 nm, 0.5 mL/min) Chiralcel OD-H column, t_R = 13.7 min (major), t_R = 19.7 min (minor).

2-Fluoro-2-[3-(4-methoxyphenyl)-3-oxo-1-phenylpropyl]diethylmalonate (8c). R_f 0.13 (EtOAc : hexane = 1 : 6); $[\alpha]_D^{25}$ -7.4 (c = 1.0, CHCl₃, 47% ee); ¹H NMR (CDCl₃, 400 MHz) δ 1.02 (t, J = 7.2, 3H), 1.30 (t, J = 7.2, 3H), 3.30 (dd, J = 3.6, 17.0, 1H), 3.60 (dd, J = 9.6, 17.0, 2H), 3.83 (s, 3H), 3.92-4.10 (m, 2H), 4.30 (q, J = 7.6, 2H), 4.51 (ddd, J = 3.2, 9.8, 33.2 Hz, 1H), 6.87 (d, J = 8.8, 2H), 7.17-7.24 (m, 4H), 7.35 (d, J = 8.4, 1H), 7.85 (d, J = 9.2, 2H); ¹³C NMR (CDCl₃, 50 MHz) δ 194.4, 167.9, 167.1, 137.5, 131.7, 129.5, 128.5, 128.4, 128.2, 128.0, 127.8, 127.5, 127.0, 126.0, 125.8, 67.4, 67.2, 57.4, 42.2, 40.8; HRMS calcd for C₂₃H₂₅FO₆Na ([M+Na]⁺) 439.1533, found 439.1533; R_t HPLC (90 : 10, hexane : *iso*-PrOH, 254 nm, 1.0 mL/min) Whelk-O1 column, t_R = 24.5 min (major), t_R = 28.5 min (minor).

2-Fluoro-2-[3-(4-methoxyphenyl)-3-oxo-1-phenylpropyl]dibenzylmalonate (8d). R_f 0.34 (EtOAc : hexane = 1 : 4); $[\alpha]_D^{25}$ -20.7 (c = 1.0, CHCl₃, 51% ee); ¹H NMR (CDCl₃,

200 MHz) δ 3.16 (dd, $J = 3.5, 17.5$ Hz, 1H), 3.57 (dd, $J = 9.8, 17.5$ Hz, 1H), 3.85 (s, 3H), 4.52 (ddd, $J = 3.5, 9.8, 33.1$ Hz, 1H), 4.90 (d, $J = 3.2$ Hz, 2H), 5.25 (d, $J = 2.2$ Hz, 2H), 6.86 (d, $J = 6.9$ Hz, 2H), 7.03-7.08 (m, 1H), 7.16-7.19 (m, 2H), 7.24-7.33 (m, 12H), 7.79 (d, $J = 6.8$ Hz, 2H); HRMS calcd for $C_{33}H_{29}FO_6Na$ ($[M+Na]^+$) 563.1846, found 563.1848; R_t HPLC (50 : 50, hexane : *iso*-PrOH, 254 nm, 1.0 mL/min) Chiralpak AS column, $t_R = 8.6$ min (minor), $t_R = 13.7$ min (major).

2-[1-(4-Chlorophenyl)-3-oxo-3-phenylpropyl]-2-fluorodiethylmalonate (8e). R_f 0.25 (EtOAc : hexane = 1 : 6); $[\alpha]_D^{25} -22.0$ ($c = 1.0$, $CHCl_3$, 37% ee); 1H NMR ($CDCl_3$, 400 MHz) δ 1.07 (t, $J = 7.2$, 3H), 1.31 (t, $J = 7.2$, 3H), 3.36 (dd, $J = 3.2, 17.6$, 1H), 3.62 (dd, $J = 10.0, 17.6$, 1H), 3.96-4.09 (m, 2H), 4.31 (q, $J = 7.2$, 2H), 4.50 (ddd, $J = 3.6, 9.8, 32.6$ Hz, 1H), 7.21 (d, $J = 8.4$ Hz, 2H), 7.31 (d, $J = 7.6$ Hz, 2H), 7.39-7.43 (m, 2H), 7.52 (m, 1H), 7.86 (d, $J = 6.8$ Hz, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 196.7, 168.7, 167.7, 130.2, 128.4, 127.1, 113.5, 67.2, 67.0, 57.5, 55.4, 41.9, 40.9; HRMS calcd for $C_{22}H_{22}FCIO_5Na$ ($[M+Na]^+$) 443.1037, found 443.1039; R_t HPLC (90 : 10, hexane : *iso*-PrOH, 254 nm, 0.5 mL/min) Chiralcel OD-H column, $t_R = 12.7$ min (major), $t_R = 14.6$ min (minor).

2-[1-(4-Chlorophenyl)-3-oxo-3-phenylpropyl]-2-fluorodibenzylmalonate (8f). R_f 0.43 (EtOAc : hexane = 1 : 4); $[\alpha]_D^{25} -19.0$ ($c = 1.0$, $CHCl_3$, 37% ee); 1H NMR ($CDCl_3$, 200 MHz) δ 3.16 (dd, $J = 3.2, 17.8$ Hz, 1H), 3.55 (dd, $J = 10.2, 17.8$ Hz, 1H), 4.48 (ddd, $J = 3.2, 10.2, 32.8$ Hz, 1H), 4.96 (s, 2H), 5.26 (d, $J = 4.7$ Hz, 2H), 7.03-7.10 (m, 4H), 7.17-7.32 (m, 10H), 7.41 (d, $J = 7.6$ Hz, 2H), 7.52 (d, $J = 7.2$ Hz, 1H), 7.77 (d, $J = 7.0$ Hz, 2H); HRMS calcd for $C_{32}H_{26}FCIO_5Na$ ($[M+Na]^+$) 567.1350, found 567.1347; R_t HPLC (50 : 50, hexane : *iso*-PrOH, 254 nm, 0.7 mL/min) Chiralpak AS column, $t_R = 9.9$ min (minor), $t_R = 11.1$ min (major).

2-[3-(3-Bromophenyl)-1-(4-chlorophenyl)-3-oxo-propyl]-2-fluorodiethylmalonate (8g). R_f 0.22 (EtOAc : hexane = 1 : 6); $[\alpha]_D^{25} -18.7$ ($c = 1.0$, $CHCl_3$, 37% ee); 1H NMR ($CDCl_3$, 400 MHz) δ 1.07 (t, $J = 7.2$ Hz, 3H), 1.32 (t, $J = 7.2$ Hz, 3H), 3.35 (dd, $J = 3.2, 17.6$ Hz, 1H), 3.56 (dd, $J = 10.0, 17.6$ Hz, 1H), 3.97-4.10 (m, 2H), 4.31 (q, $J = 7.6$ Hz, 2H), 4.47 (ddd, $J = 3.6, 9.8, 32.4$ Hz, 1H), 7.20-7.31 (m, 5H), 7.65 (d, $J = 8.0$ Hz, 1H), 7.79 (d, $J = 8.0$ Hz, 1H), 7.97 (s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 195.3, 167.9, 167.3, 139.8, 134.9, 133.6, 132.0, 128.5, 128.4, 128.2, 128.1, 127.2, 67.3, 67.1, 57.3, 42.9, 41.0; HRMS calcd for $C_{22}H_{21}BrClFO_5Na$ ($[M+Na]^+$) 521.0143, found 521.0139; R_t HPLC (90 : 10, hexane : *iso*-PrOH, 254 nm, 0.5 mL/min) Chiralcel OD-H column, $t_R = 12.8$ min (major), $t_R = 15.6$ min (minor).

2-[3-(3-Bromophenyl)-1-naphthalen-2-yl-3-oxopropyl]-2-fluorodiethylmalonate (8h). R_f 0.19 (EtOAc : hexane = 1 : 6); $[\alpha]_D^{25} -19.7$ ($c = 1.0$, $CHCl_3$, 47% ee); 1H NMR ($CDCl_3$, 400 MHz) δ 0.94 (t, $J = 7.2$, 3H), 1.33 (t, $J = 7.2$, 3H), 3.45 (dd, $J = 3.2, 17.6$ Hz, 1H), 3.72 (dd, $J = 9.6, 17.4$ Hz, 1H), 3.88-3.98 (m, 2H), 4.33 (q, $J = 7.6$ Hz, 2H), 4.67 (ddd, $J = 3.6, 9.6, 32.8$ Hz, 1H), 7.26 (d, $J = 15.6$ Hz, 1H),

7.40-7.42 (m, 2H), 7.50 (d, $J = 8.4$ Hz, 1H), 7.61 (d, $J = 8.0$ Hz, 1H), 7.72-7.81 (m, 5H), 7.97 (s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 197.5, 168.0, 167.5, 136.6, 135.1, 132.9, 132.0, 129.1, 128.4, 128.3, 128.1, 128.0, 113.7, 67.2, 67.0, 57.7, 55.0, 42.4, 40.1; HRMS calcd for $C_{26}H_{24}BrFO_5Na$ ($[M+Na]^+$) 537.0689, found 537.0681; R_t HPLC (90 : 10, hexane : *iso*-PrOH, 254 nm, 0.5 mL/min) Chiralcel OD-H column, $t_R = 14.8$ min (major), $t_R = 18.8$ min (minor).

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