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Enantioselective synthesis of α-halo-α-alkylmalonates *via* phase-transfer catalytic α-alkylation†

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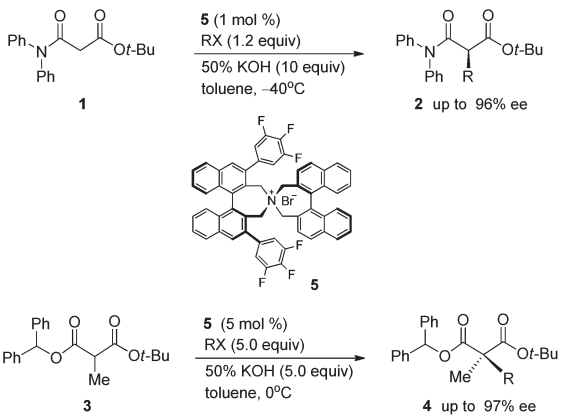
A new enantioselective synthetic method for α-halo-α-alkylmalonates is reported. α-Alkylation of diphenylmethyl *tert*-butyl α-halomalonates under phase-transfer catalytic conditions (solid KOH, toluene, −40 °C) in the presence of (*S*,*S*)-3,4,5-trifluorophenyl-NAS bromide (5 mol%) afforded diphenylmethyl *tert*-butyl α-halo-α-alkylmalonates in very high chemical yields (up to 99%) and optical yields (up to 93% ee).

Introduction

Malonates possessing α-halogenated quaternary carbon center have been recognized as privileged elements in organic synthesis for the following reasons. First, α-halogenated quaternary carbon center cannot be racemized. Second, the high electronegativity of halogens provides molecules with biophysical features such as increased bond energy and lipophilicity. Especially, because fluorine has the highest electronegativity among all elements and the second smallest van der Waals radius after hydrogen, fluorine can replace hydrogen without changing its steric environment, however it greatly changes the electronic environment by the bioisostere mimic effect.[1] Third, malonate can be easily modified according to the chemical conversion of the two esters. Although construction of chiral α-halogenated quaternary carbon centers by enantioselective α-halogenation or α-alkylation of a β-ketoester system[2] and chiral induction from a stereogenic center in β-position of malonates by enantioselective conjugate addition[3] have been frequently reported, to date, the enantioselective synthesis of the α-halomalonate system has not yet been extensively studied, with only few reported studies using organometallic catalysts or chiral auxiliaries.[4]

Recently, we reported a new enantioselective synthetic method for chiral α-mono-alkylmalonamide esters (**2**) by phase-transfer catalytic (PTC) mono-α-alkylation of *N*,*N*-diarylmalonamide esters (**1**) in the presence of Maruoka catalyst (*S*,*S*)-3,4,5-trifluorophenyl-NAS bromide (**5**) and successfully proved its usefulness in applications involving synthesis of various chiral building blocks (Scheme 1).[5] We could also expand the PTC alkylation to the malonate system for the construction of quaternary carbon center. The enantioselective α-alkylation of diphenylmethyl *tert*-butyl α-methylmalonates (**3**) under the condition of phase-transfer catalysis afforded α-methyl-α-alkylmalonates (**4**) in high chemical and optical yields.[6] Based on a series of our previous studies, we attempted to further extend the PTC alkylation to the enantioselective construction of the quaternary α-halomalonate system.[7] Here we report a new and highly efficient enantioselective synthetic method for α-halo-α-alkylmalonates under phase-transfer catalytic conditions[8] (Scheme 2).



Scheme 1 Previous chiral phase-transfer catalysis of malonate type substrates.

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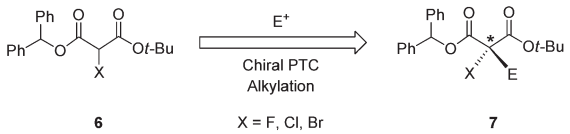
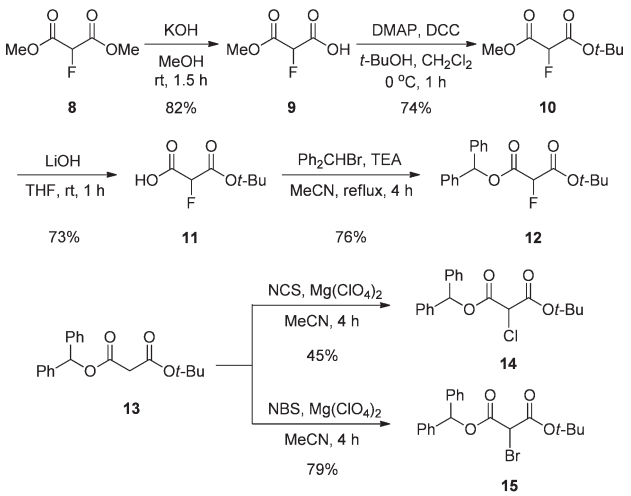


Scheme 2 PTC α-alkylation of α-halomalonates.

Results and discussion

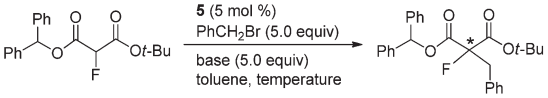
First, we needed to synthesize α-halomalonates as substrates for the initial study. Since both diphenylmethyl and *tert*-butyl ester groups shown to be necessary for high enantioselectivity in a previous report,[6] we chose diphenylmethyl *tert*-butyl malonate (**6**) as a template of substrates (**12**, **14**, **15**). Substrate **12** could be prepared from commercially available dimethyl α-fluoromalonate (**8**) in 4 steps (Scheme 3).[6] Partial hydrolysis of dimethyl α-fluoromalonate (**8**) using KOH in methanol afforded the corresponding mono-acid **9** (82%). DCC coupling of **9** with *tert*-BuOH in the presence of DMAP (74%), followed by methyl ester hydrolysis using LiOH in THF (73%) provided mono-acid **11**. Finally, the treatment of **11** with diphenylmethyl bromide under triethylamine basic condition gave α-fluoro substrate **12** (76%). α-Chloromalonate **14** and α-bromomalonate **15** were successfully prepared from malonate **13** *via* direct α-halogenation by following the procedure developed by Yang and coworkers.[9] The efficiency of the prepared α-halosubstrates was examined by α-benzylation of **12** under typical PTC conditions. The enantioselective PTC benzylation of **12** was performed in the presence of Maruoka catalyst **5**[10] optimized in our previous study, along with benzyl bromide (5.0 equiv.) and 50% KOH (aq. 5.0 equiv.) at 0 °C in toluene (Table 1).[6]

As shown in Table 1, the α-benzylated product **12c** could be obtained in 87% ee which is slightly less than that of the corresponding α-benzylated product of α-methyl substrate **3** (95% ee in Scheme 1).[6] We speculated that the smaller size of the α-substituent might provide less benefit to form optimal tight binding conformation with catalyst **5**. In fact, α-benzylation



Scheme 3 Preparation of α-halomalonates (**12**, **14**, **15**).

Table 1 Optimization of reaction conditions of temperature and base

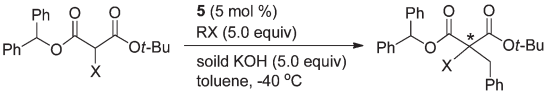


Entry	Base	T (°C)	Time (h)	Yield[a] (%)	ee[b] (%)
1	50% KOH	0	13	80	87
2	50% KOH	−20	14	99	89
3	Solid KOH	0	2	98	87
4	Solid KOH	−20	3	98	88
5	Solid KOH	−40	20	99	90
6[c]	Solid KOH	−78	96	0	—
7	Solid CsOH	−78	96	99	92

[a] Yield of isolated product. [b] The enantiopurity was determined by HPLC analysis of α-benzylated product using a chiral column (Chiralpak AD-H) with hexanes/2-propanol as eluents. [c] No reaction.

of non-substituted diphenylmethyl *tert*-butyl malonate (**13**) under PTC condition in the presence of weak base K_2CO_3 gave the corresponding mono-benzylated product in 65% ee.[11] Also, the electronic property of fluorine might be responsible for the difference of enantioselectivity. The optimization of base and temperature conditions was performed. As shown in Table 1, solid alkali base (solid–liquid PTC system) and 50% alkali base (liquid–liquid PTC system) provided comparable enantioselectivity (entries 1–4). Generally, a lower temperature affords a slightly higher enantioselectivity, but no reaction was observed at −78 °C with solid KOH (entries 3–6). Also the lower amount of solid KOH or benzyl bromide gave lower chemical yield with longer reaction time. The best enantioselectivity was observed in the case of solid CsOH base condition at −78 °C (entry 7, 99%, 92% ee), however, the reaction time was quite long (96 h). We finally chose solid KOH at −40 °C as the optimal reaction condition (entry 5).[12] The α-benzylation of **14** and **15** were also performed under the optimized PTC condition. Similar enantioselectivities and chemical yields were observed as shown in Table 2. The scope and limitations of enantioselective PTC alkylation with various electrophiles (Table 3) was investigated. As shown in Table 3, high enantioselectivities were observed except for methylation of **12** (entry 1, 30% ee) and allylation of **15** (entry 4, 42% ee).

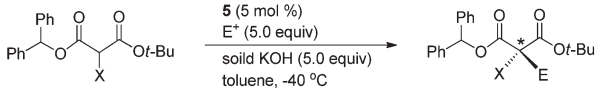
Table 2 PTC benzylation of α-halomalonates (**12**, **14**, **15**)

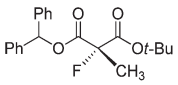
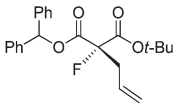
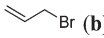
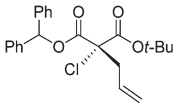
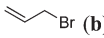
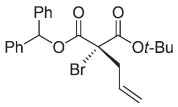
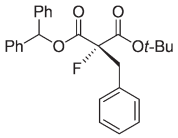
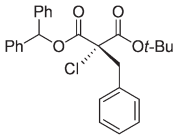
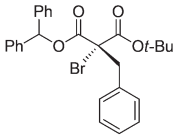
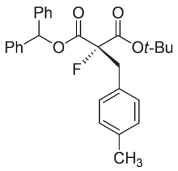
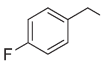
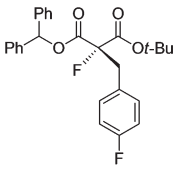
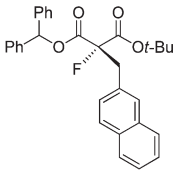


Entry	X	Time (h)	Yield[a] (%)	ee[b] (%)
1	F (**12**)	20	99	90
2	Cl (**14**)	5	98	93
3	Br (**15**)	9	99	86

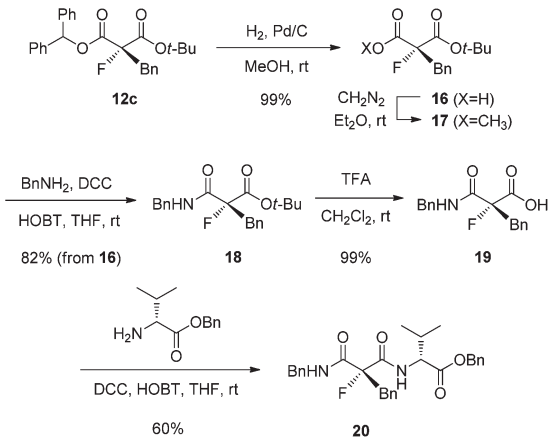
[a] Yield of isolated product. [b] The enantiopurity was determined by HPLC analysis of α-benzylated product using a chiral column (Chiralcel OJ-H or Chiralpak AD-H) with hexanes/2-propanol as eluents.

Table 3 Enantioselective phase-transfer α-alkylation of α-halomalonates with various alkyl halides



Entry	X	E^+	Product		Time (h)	Yield[a] (%)	ee[b] (%)
1	F	CH_3I (**a**)		**12a**	48	38	30 (+)
2	F	 (**b**)		**12b**	48	82	87 (+)
3	Cl	 (**b**)		**14b**	7	99	70 (+)
4	Br	 (**b**)		**15b**	4	78	42 (+)
5	F	 (**c**)		**12c**	20	99	90 (+) (*R*)[c]
6	Cl	 (**c**)		**14c**	5	98	93 (+)
7	Br	 (**c**)		**15c**	9	99	86 (+)
8	F	 (**d**)		**12d**	18	91	91 (+)
9	F	 (**e**)		**12e**	14	86	80 (+)
10	F	 (**f**)		**12f**	16	97	93 (+)

[a] Yield of isolated product. [b] The enantiopurity was determined by HPLC analysis of α-alkylated products (**12a–f**, **14b–c**, **15b–c**) using a chiral column (Chiralcel OJ-H or Chiralpak AD-H) with hexanes/2-propanol as eluents. [c] The absolute configuration was confirmed as *R* by comparison of the specific optical rotation value of **17** derivatized from **12c** with a reported value.[13a]



Scheme 4 Conversion of **12c** into a precursor of Welch's (*R,R*)-HIV-1 protease inhibitor (**20**).

The very high enantioselectivities (up to 93% ee) indicates that this reaction method is a very efficient enantioselective synthetic method for quaternary α-halo-α-alkylmalonates.

The synthetic potential of this method has been demonstrated *via* the synthesis of a precursor of Welch's (*R,R*)-HIV-1 protease inhibitor (**20**[13]) from **12c** as outlined in Scheme 4. Hydrogenolysis of **12c** under one atmosphere of H_2 in the presence of Pd/C in methanol provided the corresponding mono acid **16** (99%). To confirm the absolute configuration of **12c**, the methyl ester **17** was prepared by treatment of **16** with an excess of diazomethane and comparing the specific optical rotation value of **17** {$[\alpha]_D^{23}$ = −10.9 (*c* 1.0, MeOH)} with a reported value[13a] {(*S*)-**17**, $[\alpha]_D^{23}$ = +13.9 (*c* 1.0, MeOH), 98% ee} revealed that the absolute configuration of **12c** is *R*. The DCC coupling of **16** with benzylamine in the presence of HOBT in THF, followed by the deprotection of *tert*-butyl group afforded the mono acid **19** (82%). Finally, the precursor of Welch's (*R,R*)-HIV-1 protease inhibitor (**20**) could be obtained by the amide formation of **19** and *O*-benzylated L-valine using DCC in the presence of HOBT in THF (60%).

Conclusions

In summary, enantioselective synthetic methods of α-halo-α-alkylmalonates were developed. The enantioselective PTC α-alkylation of diphenylmethyl *tert*-butyl α-halomalonates afforded the corresponding diphenylmethyl *tert*-butyl α-halo-α-alkylmalonates in high chemical (up to 99%) and optical yields (up to 93% ee). Additionally, the synthetic potential of this method was successfully demonstrated by the synthesis of a precursor of Welch's (*R,R*)-HIV-1 protease inhibitor.

Experimental section

General methods

All reagents bought from commercial sources were used without further purification. Organic solvents were concentrated under reduced pressure using a Büchi rotary evaporator. As the commercially available KOH is a pellet type, solid KOH should be grinded to the powder form and stored under Ar gas for successful reaction and high enantiopurity. Phase-transfer catalysts (**5**) were purchased from the commercial source (Wako). Flash column chromatography was carried out using silica gel (230–400 mesh). Nuclear magnetic resonance spectra were measured on 300 MHz, 400 MHz or 500 MHz instrument. All ^{1}H-NMR spectra were reported in ppm relative to $CHCl_3$ (δ 7.24) or CD_3OD (δ 3.30). All ^{13}C-NMR spectra were reported in ppm relative to the central $CDCl_3$ (δ 77.23) or CD_3OD (δ 49.15). All HPLC analyses were performed using 4.6 mm × 250 mm chiral column as the stationary phase.

Preparation of halomalonates (12, 14, 15)

2-Fluoro-3-methoxy-3-oxopropanoic acid (9). KOH 1.0 M in MeOH (29.98 mL) was added to a stirred solution of dimethyl fluoromalonate (**8**, 5 g, 33.31 mmol) in MeOH at room temperature. After 1.5 hours, the reaction mixture was evaporated and diluted by 5% $NaHCO_3$, then acidified by 1N HCl in ice-water bath. Then extracted by DCM, dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The residue **9** (3.72 g, 82% yield) was obtained as a pale yellow oil. ^{1}H-NMR (300 MHz, CDCl3) δ 5.37 (d, J = 47.62 Hz, 1H), 3.86 (s, 3H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 167.74 (d, J = 24.30 Hz), 164.40 (d, J = 23.80 Hz), 84.65 (d, J = 196.10 Hz), 53.68 ppm; IR (KBr) 3542, 2965, 1965, 1757, 1631, 1442, 1267, 1117, 1014, 928, 811 cm^{-1}; HRMS (FAB): calcd for $[C_4H_6FO_4]^+$: 137.0250, found: 137.0245.

1-*tert*-Butyl 3-methyl 2-fluoromalonate (10). *t*-BuOH (28.7 mL) was added to a stirred solution of **9** (1.17 g, 8.60 mmol) in dichloromethane (28.7 mL) at room temperature. And DMAP (52.52 mg, 0.43 mmol), DCC (3.55 g, 17.2 mmol) was added to the reaction mixture at 0 °C and stirred for 1 hour. The *N,N*′-dicyclohexylurea formed during the reaction was removed by filtration and the filtrate was poured in to a mixture of EtOAc (700 mL) and brine (100 mL). The organic phase was washed with brine and water. The solution was dried over $MgSO_4$ and concentrated. The resulting residue was purified by column chromatography (silica gel, hexane–EtOAc = 15 : 1) to afford **10** (1.23 g, 74% yield) as a colorless oil. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 5.14 (d, J = 48.55 Hz, 1H), 3.82 (s, 3H), 1.47 (s, 9H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 164.79 (d, J = 23.8 Hz), 162.73 (d, J = 23.7 Hz), 86.46, 84.46 (d, J = 8.3 Hz), 53.01, 27.75 ppm; IR (KBr) 2982, 2934, 2856, 1754, 1680, 1440, 1396, 1371, 1297, 1255, 1207, 1155, 1122, 1018, 842, 760 cm^{-1}. The spectral data were identical to the reported data.[6]

1-Benzhydryl 3-(*tert*-butyl) 2-fluoromalonate (12). LiOH 1 M in H_2O (5.20 mL) was added to a stirred solution of **10** (1.0 g, 5.20 mmol) in tetrahydrofuran (5.20 mL) at room temperature. After 40 minutes, the reaction mixture was evaporated and diluted by 5% $NaHCO_3$, then acidified by 1N HCl in ice-water bath. Then it was extracted by DCM, dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The residue (crude

11) was diluted with acetonitrile (17.35 mL), and triethylamine (0.73 mL, 5.72 mmol) was added at room temperature. Then diphenylmethyl bromide was added at room temperature and refluxed for 4 hours. The reaction mixture was diluted with EtOAc (700 mL), washed with brine (2 × 100 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, hexane–EtOAc = 50 : 1) to afford **12** (985 mg, 55% yield) as a white solid. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.34–7.28 (m, 10H), 7.00 (s, 1H), 5.23 (d, J = 48.33 Hz, 1H), 1.38 (s, 9H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 163.28 (d, J = 24.3 Hz), 162.51 (d, J = 24.1 Hz), 138.83 (d, J = 3.1 Hz), 128.56, 128.50, 128.31, 128.25, 127.17, 127.11, 86.59, 84.64, 84.45, 78.74, 27.65 ppm; IR (KBr) 2981, 1771, 1751, 1469, 1454, 1370, 1251, 1152, 1122, 987, 838, 748, 700 cm^{-1}; HRMS (FAB): calcd for $[C_{20}H_{22}FO_4]^+$: 345.1502, found: 345.1487; m.p. = 72 °C. The spectral data were identical to the reported data.[6]

1-Benzhydryl 3-(*tert*-butyl) 2-chloromalonate (14). A solution of **13** (750 mg, 2.298 mmol) in dry MeCN (23 mL) was added to *N*-chlorosuccinimide (368 mg, 2.757 mmol) and magnesium perchlorate (154 mg, 0.689 mmol). The reaction mixture was stirred for 4 hours. After the solvent was removed on a rotary evaporator, the mixture was diluted with EtOAc (400 mL) and washed with brine (100 mL). The organic layers were dried with $MgSO_4$, and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, hexane–EtOAc = 40 : 1–20 : 1) to afford α-chloromalonate substrates as a colorless oil (373 mg, 45% yield). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.34–7.25 (m, 10H), 6.96 (s, 1H), 4.84 (s, 1H), 1.36 (s, 9H) ppm; ^{13}C-NMR (125 MHz, $CDCl_3$) δ 163.79, 162.90, 138.89, 138.86, 128.58, 128.53, 128.35, 128.23, 127.34, 127.08, 84.55, 79.22, 56.70, 27.54 ppm; IR (KBr) 2921, 2850, 1745, 1598, 1457, 1371, 1299, 1252, 1147, 988, 753, 699 cm^{-1}; HRMS (CI): calcd for $[C_{20}H_{20}ClO_4]^+$: 359.1050, found: 359.1046.

1-Benzhydryl 3-(*tert*-butyl) 2-bromomalonate (15). A solution of **13** (750 mg, 2.298 mmol) in dry MeCN (23 mL) was added to *N*-bromosuccinimide (490 mg, 2.757 mmol) and magnesium perchlorate (154 mg, 0.69 mmol). The reaction mixture was stirred for 4 hours. After the solvent was removed on a rotary evaporator, the mixture was diluted with EtOAc (400 mL) and washed with brine (100 mL). The organic layers were dried with $MgSO_4$, and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, hexane–EtOAc = 40 : 1–20 : 1) to afford α-bromomalonate substrates as a colorless oil (736 mg, 79% yield). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.35–7.27 (m, 10H), 6.94 (s, 1H), 4.48 (s, 1H), 1.36 (s, 9H) ppm; ^{13}C-NMR (125 MHz, $CDCl_3$) δ 163.77, 162.90, 138.91, 138.89, 128.52, 128.48, 128.28, 128.17, 127.29, 127.04, 84.40, 79.26, 44.24, 27.47 ppm; IR (KBr) 2981, 1740, 1496, 1455, 1370, 1294, 1256, 1139, 989, 848, 748, 699 cm^{-1}; HRMS (CI): calcd for $[C_{20}H_{20}FO_4]^+$: 403.0545, found: 403.0545.

General procedure for enantioselective phase-transfer catalytic alkylation

Alkyl halides (0.29 mmol) was added to a solution of α-halomalonate substrates (0.058 mmol) and (*S*,*S*)-3,4,5-trifluorophenyl-NAS bromide (**5**, 2.66 mg, 0.003 mmol) in toluene (0.2 mL). At the designated temperature, solid KOH (16.29 mg, 0.29 mmol) was quickly added to the reaction mixture and stirred for the designated time. EYELA PSL-1400 was used for low temperature stirring and the stirring rate was 7. The reaction mixtures was diluted with EtOAc (10 mL), washed with brine (2 × 3 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, hexane–EtOAc = 50 : 1) to afford alkylated malonates.

(*R*)-1-Benzhydryl 3-*tert*-butyl 2-fluoro-2-methylmalonate (12a). Following the general procedure, the reaction was started from **12** (20 mg, 0.058 mmol) using iodomethane (18 μL, 0.29 mmol). After 48 hours, **12a** was obtained as a yellow oil (7.90 mg, 38% yield). HPLC analysis (Chiralpak AD-H, hexane–2-propanol = 96 : 4, flow rate = 1.0 mL min^{-1}, 23 °C, λ = 254 nm) retention time = major 6.70 min, minor 8.82 min, 30% ee; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.35–7.25 (m, 10H), 6.96 (s, 1H), 1.75 (d, J = 21.78 Hz, 3H), 1.32 (s, 9H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 166.05 (d, J = 25.60 Hz), 165.42 (d, J = 24.90 Hz), 139.13, 139.01, 128.56, 128.53, 128.26, 128.20, 127.24, 127.11, 92.44 (d, J = 193.00 Hz), 83.90, 78.52, 27.56, 20.50 (d, J = 23.20 Hz) ppm; IR (KBr) 2927, 1750, 1455, 1372, 1254, 1146, 1123, 1075, 958, 841, 743, 700 cm^{-1}; HRMS (CI): calcd for $[C_{21}H_{22}FO_4]^+$: 357.1502, found: 357.1501; $[\alpha]_D^{25}$ = +1.53 (c 1, $CHCl_3$).

(*R*)-1-Benzhydryl 3-*tert*-butyl 2-fluoro-2-allylmalonate (12b). Following the general procedure, the reaction was started from **12** (20 mg, 0.058 mmol) using allyl bromide (25 μL, 0.29 mmol). After 48 hours, **12b** was obtained as a colorless oil (18.30 mg, 82% yield). HPLC analysis (Chiralpak AD-H, hexane–2-propanol = 96 : 4, flow rate = 1.0 mL min^{-1}, 23 °C, λ = 254 nm) retention time = major 7.38 min, minor 10.96 min, 87% ee; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.33–7.26 (m, 10H), 6.96 (s, 1H), 5.78–5.64 (m, 1H), 5.10 (d, J = 11.55 Hz, 2H), 2.87 (dd, J_1 = 23.61 Hz, J_2 = 7.14 Hz, 2H), 1.33 (s, 9H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 165.14 (d, J = 25.7 Hz), 164.36 (d, J = 25.2 Hz), 139.05, 138.96, 129.13 (d, J = 2.9 Hz), 128.53, 128.50, 128.30, 128.17, 127.40, 127.05, 120.64, 93.95 (d, J = 197.4 Hz), 84.09, 78.60, 38.51 (d, J = 21.2 Hz), 27.64 ppm; IR (KBr) 2981, 2930, 1750, 1455, 1371, 1303, 1249, 1150, 1032, 928, 840, 743, 700 cm^{-1}; HRMS (CI): calcd for $[C_{23}H_{24}FO_4]^+$: 383.1659, found: 383.1654; $[\alpha]_D^{25}$ = +13.57 (c 1, $CHCl_3$).

(*R*)-1-Benzhydryl 3-*tert*-butyl 2-chloro-2-allylmalonate (14b). Following the general procedure, the reaction was started from **14** (21 mg, 0.058 mmol) using allyl bromide (25 μL, 0.29 mmol). After 7 hours, **14b** was obtained as a colorless oil (23 mg, 99% yield). HPLC analysis (Chiralpak AD-H, hexane–2-propanol = 99 : 1, flow rate = 1.0 mL min^{-1}, 23 °C, λ = 254 nm) retention time = major 15.82 min, minor 18.06 min, 69% ee; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.35–7.26 (m, 10H), 6.93 (s, 1H), 5.81–5.67 (m, 1H), 5.11–5.01 (m, 2H), 2.96 (d, J = 6.96 Hz, 2H), 1.28 (s, 9H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 165.72, 164.71, 139.03, 138.96, 130.28, 128.51, 128.48, 128.34, 128.11, 127.62, 126.97, 120.45, 84.19, 79.07, 70.56, 42.02, 27.46 ppm; IR (KBr) 2981, 2929, 1744, 1456, 1371, 1278, 1237, 1155, 1029, 972, 839,

742, 699 cm^{-1}; HRMS (ESI): calcd for $[C_{23}H_{25}ClO_4Na]^+$: 423.1334, found: 423.1336; $[\alpha]_D^{20}$ = +8.97 (*c* 1, $CHCl_3$).

(*R*)-1-Benzhydryl 3-*tert*-butyl 2-bromo-2-allylmalonate (15b). Following the general procedure, the reaction was started from **15** (23.50 mg, 0.058 mmol) using allyl bromide (25 μL, 0.29 mmol). After 4 hours, **15b** was obtained as a colorless oil (20.20 mg, 99% yield). HPLC analysis (Chiralpak AD-H, hexane–2-propanol = 99 : 1, flow rate = 1.0 mL min^{-1}, 23 °C, λ = 254 nm) retention time = major 11.45 min, minor 10.07 min, 42% ee; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.37–7.25 (m, 10H), 6.92 (s, 1H), 5.81–5.67 (m, 1H), 5.11–5.02 (m, 2H), 3.02 (d, *J* = 6.6 Hz, 2H), 1.28 (s, 9H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 165.81, 164.74, 139.09, 138.99, 131.20, 128.49, 128.45, 128.30, 128.09, 127.59, 127.03, 120.25, 84.16, 79.21, 63.35, 42.64, 27.43 ppm; IR (KBr) 2980, 2929, 1740, 1496, 1455, 1370, 1271, 1234, 1154, 1130, 964, 927, 842, 759, 699, 649 cm^{-1}; HRMS (CI): calcd for $[C_{23}H_{26}BrO_4]^+$: 445.1014, found: 445.1008; $[\alpha]_D^{20}$ = +0.57 (*c* 1, $CHCl_3$).

(*R*)-1-Benzhydryl 3-*tert*-butyl 2-fluoro-2-benzylmalonate (12c). Following the general procedure, the reaction was started from **12** (20 mg, 0.058 mmol) using benzyl bromide (34.5 μL, 0.29 mmol). After 20 hours, **12c** was obtained as a yellow oil (25 mg, 99% yield). HPLC analysis (Chiralpak AD-H, hexane–2-propanol = 96 : 4, flow rate = 1.0 mL min^{-1}, 23 °C, λ = 254 nm) retention time = major 13.82 min, minor 24.40 min, 90% ee; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.31–7.16 (m, 15H), 6.92 (s, 1H), 3.44 (d, *J* = 15.33 Hz, 2H), 1.28 (s, 9H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 165.20 (d, *J* = 25.8 Hz), 164.30 (d, *J* = 25.1 Hz), 139.02, 138.92, 133.08, 130.33, 128.54, 128.45, 128.30, 128.24, 128.06, 127.51, 127.32, 126.95, 94.57 (d, *J* = 199.6 Hz), 84.10, 78.67, 39.94 (d, *J* = 20.5 Hz), 27.56 ppm; IR (KBr) 3033, 2979, 2929, 1752, 1469, 1455, 1370, 1302, 1251, 1156, 1085, 1053, 953, 840, 742, 699 cm^{-1}; HRMS (CI): calcd for $[C_{27}H_{26}FO_4]^+$: 433.1815, found: 433.1828; $[\alpha]_D^{25}$ = +16.69 (*c* 1, $CHCl_3$). The spectral data were identical to the reported data.[6]

(*R*)-1-Benzhydryl 3-*tert*-butyl 2-chloro-2-benzylmalonate (14c). Following the general procedure, the reaction was started from **14** (21 mg, 0.058 mmol) using benzyl bromide (34.5 μL, 0.29 mmol). After 5 hours, **14c** was obtained as a colorless oil (25.60 mg, 98% yield). HPLC analysis (Chiralpak AD-H, hexane–2-propanol = 99 : 1, flow rate = 1.0 mL min^{-1}, 23 °C, λ = 254 nm) retention time = major 23.44 min, minor 21.80 min, 93% ee; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.29–7.04 (m, 15H), 6.87 (s, 1H), 3.48 (s, 2H), 1.21 (s, 9H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 165.85, 164.88, 138.94, 138.89, 133.74, 130.60, 128.54, 128.42, 128.36, 128.03, 127.74, 127.39, 126.95, 84.25, 79.20, 71.44, 42.89, 27.40 ppm; IR (KBr) 3032, 2980, 1745, 1496, 1455, 1370, 1272, 1149, 1082, 984, 840, 743, 699 cm^{-1}; HRMS (CI): calcd for $[C_{27}H_{26}ClO_4]^+$: 449.1520, found: 449.1518; $[\alpha]_D^{20}$ = +20.10 (*c* 1, $CHCl_3$).

(*R*)-1-Benzhydryl 3-*tert*-butyl 2-bromo-2-benzylmalonate (15c). Following the general procedure, the reaction was started from **15** (23.5 mg, 0.058 mmol) using benzyl bromide (34.5 μL, 0.29 mmol). After 9 hours, **15c** was obtained as a colorless oil (28.50 mg, 99% yield). HPLC analysis (Chiralcel OJ-H, hexane–2-propanol = 99 : 1, flow rate = 1.0 mL min^{-1}, 23 °C, λ = 254 nm) retention time = major 15.54 min, minor 11.68 min, 86% ee; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.47–7.36 (m, 10H), 7.32–7.22 (m, 5H), 7.04 (s, 1H), 3.73 (d, *J* = 1.65 Hz, 2H), 1.39 (s, 9H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 165.95, 165.07, 139.00, 138.92, 134.42, 130.52, 128.54, 128.43, 128.33, 128.05, 128.01, 127.72, 127.41, 127.05, 84.26, 79.41, 64.51, 43.43, 27.38 ppm; IR (KBr) 3033, 2980, 1745, 1496, 1455, 1370, 1272, 1149, 984, 840, 743, 699 cm^{-1}; HRMS (ESI): calcd for $[C_{27}H_{27}BrO_4Na]^+$: 517.0985, found: 517.0889; $[\alpha]_D^{20}$ = +6.91 (*c* 1, $CHCl_3$).

(*R*)-1-Benzhydryl 3-*tert*-butyl 2-fluoro-2-(4-methylbenzyl)-malonate (12d). Following the general procedure, the reaction was started from **12** (20 mg, 0.058 mmol) using 4-methylbenzyl bromide (53.70 mg, 0.29 mmol). After 18 hours, **12d** was obtained as a white solid (23.80 mg, 91% yield). HPLC analysis (Chiralpak AD-H, hexane–2-propanol = 96 : 4, flow rate = 1.0 mL min^{-1}, 23 °C, λ = 254 nm) retention time = major 14.54 min, minor 18.27 min, 91% ee; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.62–7.45 (m, 10H), 7.35–7.24 (m, 5H), 7.19 (s, 1H), 3.67 (d, *J* = 25.48 Hz, 2H), 2.55 (s, 3H), 1.57 (s, 9H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 165.26 (d, *J* = 25.90 Hz), 164.36 (d, *J* = 25.10 Hz), 139.04, 138.95, 136.87, 130.17, 129.92, 128.94, 128.52, 128.41, 128.27, 128.03, 127.51, 126.98, 94.65 (d, *J* = 199.00 Hz), 84.03, 78.59, 39.55 (d, *J* = 20.80 Hz), 27.59, 21.05 ppm; IR (KBr) 2979, 2925, 1752, 1517, 1454, 1371, 1251, 1157, 1061, 953, 841, 745, 699 cm^{-1}; HRMS (FAB): calcd for $[C_{28}H_{30}FO_4]^+$: 449.2128, found: 449.2143; $[\alpha]_D^{25}$ = +14.29 (*c* 1, $CHCl_3$); m.p. = 82 °C.

(*R*)-1-Benzhydryl 3-*tert*-butyl 2-fluoro-2-(4-fluorobenzyl)malonate (12e). Following the general procedure, the reaction was started from **12** (20 mg, 0.058 mmol) using 4-fluorobenzyl bromide (36.2 μL, 0.29 mmol). After 14 hours, **12e** was obtained as a yellow solid (22.60 mg, 86% yield). HPLC analysis (Chiralpak AD-H, hexane–2-propanol = 96 : 4, flow rate = 1.0 mL min^{-1}, 23 °C, λ = 254 nm) retention time = major 14.24 min, minor 22.01 min, 80% ee; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.31–7.06 (m, 15H), 6.91 (s, 1H), 3.39 (d, *J* = 25.30 Hz, 2H), 1.30 (s, 9H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 165.07 (d, *J* = 25.50 Hz), 164.22 (d, *J* = 25.00 Hz), 138.95, 138.81, 131.94, 131.85, 128.57, 128.46, 128.36, 128.13, 127.52, 126.93, 115.21 115.00, 94.49 (d, *J* = 199.60 Hz), 84.27, 78.71, 39.12 (d, *J* = 20.70 Hz), 27.59 ppm; IR (KBr) 2927, 1751, 1606, 1511, 1455, 1371, 1289, 1226, 1157, 1101, 1059, 953, 841, 795, 744, 700, 647 cm^{-1}; HRMS (FAB): calcd for $[C_{27}H_{25}F_2O_4]^+$: 451.1721, found: 451.1719; $[\alpha]_D^{25}$ = +11.68 (*c* 1, $CHCl_3$); m.p. = 99 °C.

(*R*)-1-Benzhydryl 3-*tert*-butyl 2-fluoro-2-(naphthalen-2-yl-methyl)malonate (12f). Following the general procedure, the reaction was started from **12** (20 mg, 0.058 mmol) using 2-(bromomethyl) naphthalene (64.10 mg, 0.29 mmol). After 16 hours, **12f** was obtained as a white solid (27.30 mg, 97% yield). HPLC analysis (Chiralpak AD-H, hexane–2-propanol = 96 : 4, flow rate = 1.0 mL min^{-1}, 23 °C, λ = 254 nm) retention time = major 19.39 min, minor 27.39 min, 93% ee; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.78–7.16 (m, 22H), 6.90 (s, 1H), 3.60 (d, *J* = 25.26 Hz, 2H), 1.28 (s, 9H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 165.21 (d, *J* = 25.70 Hz), 164.34 (d, *J* = 25.10 Hz),

138.98, 138.85, 133.21, 132.63, 130.67, 129.29, 128.55, 128.38, 128.30, 128.04, 127.85, 127.77, 127.55, 127.45, 126.90, 125.90, 125.77, 94.77 (d, J = 199.90 Hz), 84.20, 78.71, 40.08 (d, J = 20.50 Hz), 27.59 ppm; IR (KBr) 2928, 1751, 1496, 1455, 1370, 1255, 1155, 1063, 951, 839, 746, 699 cm^{-1}; HRMS (FAB): calcd for $[C_{31}H_{29}FO_4]^+$: 484.2050, found: 484.2059; $[\alpha]_D^{25}$ = +16.88 (c 1, $CHCl_3$); m.p. = 76 °C.

Confirmation of absolute configuration

(*R*)-1-*tert*-Butyl 3-methyl 2-fluoro-2-benzylmalonate (17). 10% Pd/C (47.50 mg) was added to a stirred solution of **12c** (95 mg, 0.219 mmol) in MeOH (2.80 mL), and H_2 gas was substituted. After 1 hour, the reaction mixture was filtered by celite 545 using MeOH, and the filtrate was evaporated to afford crude **16**. The crude **16** was diluted by a toluene–MeOH = 5 : 2 mixture (2.20 mL), and TMS-diazomethane (0.36 mL, 0.72 mmol) was added. After 1 hour, the reaction mixture was quenched by AcOH (added to the mixture until the yellow color was converted to colorless) and evaporated. The residue was diluted with EtOAc (50 mL), washed with brine (2 × 10 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. Then the residue was purified by column chromatography (silica gel, hexane–EtOAc = 20 : 1) to afford **17** (47.20 mg, 76% yield) as a yellow oil. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.28–7.24 (m, 5H), 3.76 (s, 3H), 3.41 (d, J = 25.62 Hz, 2H), 1.39 (s, 9H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 166.64 (d, J = 25.30 Hz), 164.46 (d, J = 25.10 Hz), 133.20, 130.31, 128.28, 127.42, 94.69 (d, J = 199.80 Hz), 84.13, 53.06, 40.07 (d, J = 20.60 Hz), 27.68 ppm; IR (KBr) 2980, 2929, 1753, 1456, 1371, 1308, 1255, 1157, 1087, 1058, 842, 745, 701 cm^{-1}; HRMS (FAB): calcd for $[C_{15}H_{20}FO_4]^+$: 283.1346, found: 283.1347; {$[\alpha]_D^{25}$ = −10.93 (c 1, MeOH); lit. $[\alpha]_D^{25}$ = +13.92 (c 1.0, MeOH, 98% ee (*S*)-form)}.[4c] The spectral data were identical to the reported data.[4c]

Conversion of 12c into a precursor of Welch's (*R*,*R*)-HIV-1 protease inhibitor (20)[4c,13]

(*R*)-*tert*-Butyl 2-benzyl-3-(benzylamino)-2-fluoro-3-oxopropanoate (18). 10% Pd/C (47.50 mg) was added to a stirred solution of **12c** (95 mg, 0.22 mmol) in MeOH (2.80 mL), and H_2 gas was substituted. After 1 hour, the reaction mixture was filtered by celite 545 using MeOH, and the filtrate was evaporated to afford crude **16**. The crude **16** was vacuumed for 3 hours, and dry tetrahydrofuran (0.73 mL) was added at room temperature. Then, HOBt (32.60 mg, 0.24 mmol), benzylamine (26.3 μL, 0.24 mmol), DCC (49.70 mg, 0.24 mmol) were added in order at 0 °C. The reaction mixture was stirred for 2 hours at 0 °C and then stirred for 20 h more at room temperature. The reaction mixture was evaporated and diluted with EtOAc (50 mL), washed with brine (2 × 10 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, hexane–EtOAc = 9 : 1) to afford **18** (64.20 mg, 82% yield) as a white solid. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.28–7.22 (m, 8H), 7.09–7.07 (m, 2H), 6.57 (s, 1H), 4.40 (d, J = 5.88 Hz, 2H), 3.38 (d, J = 26.00 Hz, 2H), 1.54 (s, 9H) ppm; ^{13}C-NMR (75 MHz, $CDCl_3$) δ 165.75 (d, J = 21.38 Hz), 165.06 (d, J = 24.60 Hz), 137.24, 133.64, 130.54, 128.59, 128.27, 127.51, 127.49, 127.23, 96.92 (d, J = 199.66 Hz), 84.00, 43.17, 39.68 (d, J = 19.96 Hz), 27.73 ppm; IR (KBr) 3330, 2925, 2852, 1739, 1684, 1542, 1454, 1365, 1217, 1085, 697 cm^{-1}; HRMS (FAB): calcd for $[C_{21}H_{25}FNO_3]^+$: 358.1818, found: 358.1816; $[\alpha]_D^{25}$ = +29.02 (c 1, $CHCl_3$); m.p. = 106 °C. The spectral data were identical to the reported data.[4c]

(*R*)-2-Benzyl-3-(benzylamino)-2-fluoro-3-oxopropanoic acid (19). A solution of **18** (35 mg, 0.098 mmol), TFA (75.4 μL, 0.98 mmol) in DCM (1.40 mL) was stirred for 3 hours at room temperature. Then, the reaction mixture was evaporated and purified by column chromatography (silica gel, DCM–MeOH = 9 : 1) to afford **19** (29.20 mg, 99% yield) as a white solid. ^{1}H-NMR (300 MHz, CD_3OD) δ 7.28–7.14 (m, 8H), 6.92–6.89 (m, 2H), 4.51 (d, J = 15 Hz, 1H), 4.14 (d, J = 15.21 Hz, 1H), 3.70–3.55 (m, 2H) ppm; ^{13}C-NMR (75 MHz, CD_3OD) δ 169.17 (d, J = 22.28 Hz), 167.50 (d, J = 24.52 Hz), 140.23, 135.89, 132.42, 130.17, 130.05, 129.12, 129.09, 128.90, 98.73 (d, J = 200.56 Hz), 44.51, 41.41 (d, J = 20.48 Hz) ppm; IR (KBr) 3404, 1661, 1546, 1496, 1391, 1209, 1140, 1088, 802, 742, 699 cm^{-1}; HRMS (ESI): calcd for $[C_{17}H_{16}FNO_3Na]^+$: 324.1006, found: 324.1029; {$[\alpha]_D^{25}$ = −24.26 (c 1, $CHCl_3$); lit. $[\alpha]_D^{25}$ = −24 (c 0.5, CH_2Cl_2, (*R*)-form)}[13b]; m.p. = 107 °C. The spectral data were identical to the reported data.[4c]

A precursor of Welch's (*R*,*R*)-HIV-1 protease inhibitor (20). A solution of acid **19** (15 mg, 0.05 mmol), D-valine benzyl ester *p*-toluenesulfonate (20.78 mg, 0.055 mmol), HOBt (7.40 mg, 0.055 mmol) and *N*-methylmorpholine (5.54 mg, 0.055 mmol) in dry THF (0.17 mL) was stirred and cooled in an ice-water bath while DCC (11.30 mg, 0.055 mmol) was added. Stirring was continued for 2 hours at 0 °C and for an additional 20 hours at room temperature. The *N*,*N*′-dicyclohexylurea formed during the reaction was removed by filtration and the filtrate was poured in to a mixture of EtOAc (35 mL) and brine (5 mL). The organic phase was washed with brine and water. The organic solution was dried over $MgSO_4$ and concentrated. The resulting residue was purified by column chromatography (silica gel, hexane–EtOAc = 9 : 1) to afford **20** (14.80 mg, 60% yield) as a white solid. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.54 (d, J = 8.61 Hz, 1H), 7.35–7.21 (m, 12H), 6.96–6.95 (m, 2H), 6.82 (bs, 1H), 5.11 (d, J = 2.55 Hz, 2H), 4.51 (dd, J_1 = 8.91 Hz, J_2 = 4.77 Hz, 1H), 4.42 (dd, J_1 = 14.28 Hz, J_2 = 5.67 Hz, 1H), 4.22 (dd, J_1 = 15.03 Hz, J_2 = 5.31 Hz, 1H), 3.46 (d, J = 20.31 Hz, 1H), 3.37 (d, J = 11.16 Hz, 1H), 2.19–2.15 (m, 1H), 0.90 (d, J = 6.78 Hz, 3H), 0.85 (d, J = 6.96 Hz, 3H) ppm; ^{13}C-NMR (125 MHz, $CDCl_3$) δ 170.56, 166.86 (d, J = 8.44 Hz), 166.68 (d, J = 9.35 Hz), 136.79, 135.18, 132.79, 130.30, 128.59, 128.54, 128.42, 128.34, 128.29, 127.54, 127.50, 127.47, 96.25 (d, J = 198.93 Hz), 67.01, 57.27, 43.34, 42.93 (d, J = 21.24 Hz), 31.23, 18.95, 17.51 ppm; IR (KBr) 3333, 2925, 2852, 1740, 1688, 1626, 1538, 1455, 1378, 1260, 1187, 1153, 1086, 1029, 803, 745, 698 cm^{-1}; HRMS (EI): calcd for $[C_{29}H_{31}F\ N_2O_4]^+$: 490.2268, found: 490.2291; {$[\alpha]_D^{25}$ = +6.43 (c 1.5, $CHCl_3$); lit. $[\alpha]_D^{25}$ = +7.3 (c 1.5, CH_2Cl_2, (*R*,*R*)-form)}[13b]; m.p. = 104 °C. The spectral data were identical to the reported data.[4c]

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Notes and references

1 K. Mikami, Y. Itoh and M. Yamanaka, *Chem. Rev.*, 2004, **104**, 1.

2 (*a*) H. Li, S. Zhang, C. Yu, X. Song and W. Wang, *Chem. Commun.*, 2009, 2136; (*b*) X. Wang, Q. Lan, S. Shirakawa and K. Maruoka, *Chem. Commun.*, 2010, **46**, 321.

3 (*a*) T. Okino, Y. Hoashi, T. Furukawa, X. Xu and Y. Takemoto, *J. Am. Chem. Soc.*, 2005, **127**, 119; (*b*) P. J. Nichols, J. A. DeMattei, B. R. Barnett, N. A. LeFur, T.-H. Chuang, A. D. Piscopio and K. Koch, *Org. Lett.*, 2006, **8**, 1495; (*c*) J. M. Andrés, R. Manzano and R. Pedrosa, *Chem.–Eur. J.*, 2008, **14**, 5116; (*d*) Y.-n. Xuan, S.-z. Nie, L.-t. Dong, J.-m. Zhang and M. Yan, *Org. Lett.*, 2009, **11**, 1583; (*e*) Z. Jiang, Y. Pan, Y. Zhao, T. Ma, R. Lee, Y. Yang, K.-W. Huang, M. W. Wong and C.-H. Tan, *Angew. Chem., Int. Ed.*, 2009, **48**, 3627; (*f*) Z. Wang, D. Chen, Z. Yang, S. Bai, X. Liu, L. Lin and X. Feng, *Chem.–Eur. J.*, 2010, **16**, 10130; (*g*) S. Kobayashi, M. M. Salter, Y. Yamazaki and Y. Yamashita, *Chem.–Asian J.*, 2010, **5**, 493; (*h*) M. Hatano, T. Horibe and K. Ishihara, *Org. Lett.*, 2010, **12**, 3502; (*i*) N. Shibata, T. Nishimine, N. Shibata, E. Tokunaga, K. Kawada, T. Kagawa, A. E. Sorochinskycde and V. A. Soloshonok, *Chem. Commun.*, 2012, **48**, 321.

4 (*a*) M. Ihara, T. Kawabuchi, Y. Tokunaga and K. Fukumoto, *Tetrahedron: Asymmetry*, 1994, **5**, 1041; (*b*) T. Suzuki, T. Goto, Y. Hamashima and M. Sodeoka, *J. Org. Chem.*, 2007, **72**, 246; (*c*) D. S. Reddy, N. Shibata, J. N. S. Nakamura, T. Toru and S. Kanemasa, *Angew. Chem., Int. Ed.*, 2008, **47**, 164; (*d*) K. Shibatomi, Y. Soga, A. Narayama, I. Fujisawa and S. Iwasa, *J. Am. Chem. Soc.*, 2012, **134**, 9836; (*e*) A. Narayama, K. Shibatomi, Y. Soga, T. Muto and S. Iwasa, *Synlett*, 2013, 375.

5 (*a*) M.-h. Kim, S.-H. Choi, Y.-J. Lee, J. Lee, K. Nahm, B.-S. Jeong, H.-g. Park and S.-s. Jew, *Chem. Commun.*, 2009, 782; (*b*) Y. Park, Y. J. Lee, S. Hong, M.-h. Kim, M. Lee, T.-S. Kim, J. K. Lee, S.-s. Jew and H.-g. Park, *Adv. Synth. Catal.*, 2011, **353**, 3313.

6 S. Hong, J. Lee, M. Kim, Y. Park, C. Park, M.-h. Kim, S.-s. Jew and H.-g. Park, *J. Am.Chem. Soc.*, 2011, **133**, 4924.

7 As a preliminary result, one sample (**12c**) of the enantioselective α-benzylation of α-fluoromalonate (**12**) was reported in ref. 6.

8 For recent reviews on the phase-transfer catalysis, see: (*a*) K. Maruoka and T. Ooi, *Chem. Rev.*, 2003, **103**, 3013; (*b*) M. J. O'Donnell, *Acc. Chem. Res.*, 2004, **37**, 506; (*c*) B. Lygo and B. I. Andrews, *Acc. Chem. Res.*, 2004, **37**, 518; (*d*) T. Hashimoto and K. Maruoka, *Chem. Rev.*, 2007, **107**, 5656; (*e*) S.-s. Jew and H.-g. Park, *Chem. Commun.*, 2009, 7090.

9 D. Yang, Y.-L. Yan and B. Lui, *J. Org. Chem.*, 2002, **67**, 7429.

10 T. Ooi, M. Kameda and K. Maruoka, *J. Am. Chem. Soc.*, 2003, **125**, 5139.

11 S. Hong, J. Lee, M. Kim, Y. Park, C. Park and H.-g. Park, unpublished results.

12 The same chemical yield and enantioselectivity in PTC α-benzylation of **12** were confirmed with 0.5 g scale synthesis under the optimized reaction conditions.

13 (*a*) A. Abouabdellah, L. Boros, F. Gyenes and J. T. Welch, *J. Fluorine Chem.*, 1995, **72**, 255; (*b*) A. Abouabdellah and J. T. Welch, *Tetrahedron: Asymmetry*, 1994, **5**, 1005.