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Note

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Enantioselective Synthesis of Chiral α-Thio-Quaternary Stereogenic Centers via Phase-Transfer-Catalyzed α-Alkylation of α-Acylthiomalonates

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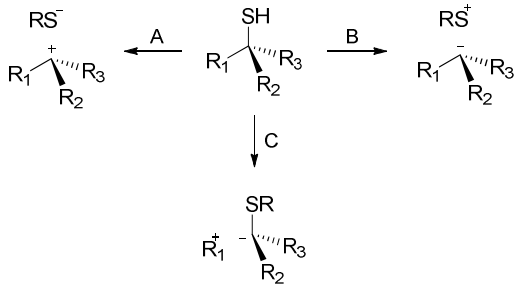
Abstract

An efficient synthetic method for establishing chiral α-thio-α-quaternary stereogenic center was successfully developed. The enantioselective α-alkylation of α-acylthiomalonates under phase-transfer catalytic conditions [50% aq. KOH, toluene, –20 °C and (*S*,*S*)-3,4,5-trifluorophenyl-NAS bromide] provided the corresponding α-acylthio-α-alkylmalonates in high chemical yields (up to 99%) and high optical yields (up to 98% ee).

Organosulfur compounds play important roles in biological systems. Two natural amino acids contain sulfur residues (cysteine and methionine), and their functional groups mediate various biological processes in the enzymes of living organisms. Additionally, many commercially available organosulfur compounds are best-selling drugs.[1] As the need for variable sulfur-containing compounds for the development of new drugs increases, the development of asymmetric synthetic methods for organosulfur compounds having chirality at the sulfur carbon has become increasingly important. The asymmetric preparation of secondary chiral sulfur (II) compounds via stereospecific substitution is well developed.[2] However, few methods are available for the asymmetric synthesis of tertiary thiols. Although chiral tertiary alcohols are generally obtained by the enantioselective addition of a nucleophile to a prochiral ketone[3], the analogous approach to the preparation of chiral tertiary thiols is difficult due to the instability of thioketones and the possibility of nucleophilic attack occurring at the sulfur rather than at the carbon.[4] Therefore, the synthesis of enantiomerically pure tertiary thiols is very challenging despite the simplicity of their structures.

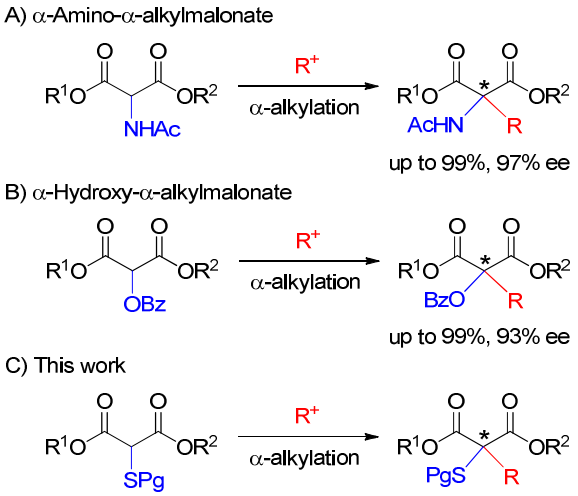


Scheme 1. Synthetic methods for tertiary thiol or thioether

Three general synthetic approaches are available for the preparation of a chiral tertiary thiol, and they are classified according to the disconnection of either a C–S (A and B) or a C–C bond (C) (Scheme 1).[5] The thiol can be obtained by stereoselective attack of either a sulfur nucleophile on an electrophilic carbon (A)[6] or a nucleophilic carbon on an electrophilic sulfur (B)[7]. Additionally, the stereoselective α-alkylation of a secondary organosulfur substrate can generate a quaternary

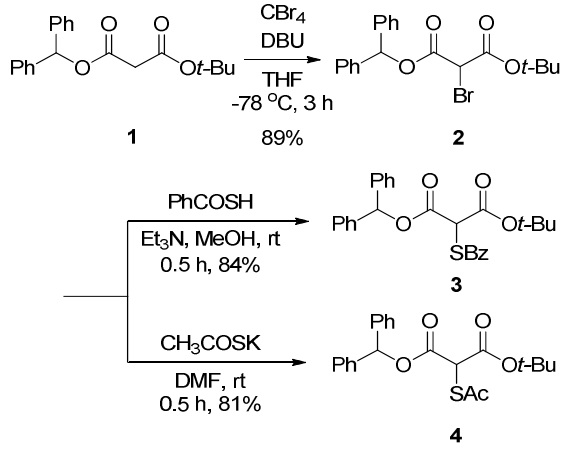
stereogenic center (C).[8] Generally, the C-C bond formation methods (C) use a chiral auxiliary, a stoichiometric chiral base, a rearrangement reaction or self-regeneration of a chiral secondary sulfide to impart tertiary chirality. However, a catalytic synthesis of a chiral tertiary sulfur system via C-C bond formation has not yet been reported.

In 2011, we reported the asymmetric synthesis of quaternary chiral α,α-dialkylmalonates as versatile chiral starting materials in both high chemical and optical yields via enantioselective phase-transfer catalytic (PTC)[9] α-alkylation of malonates with chiral quaternary ammonium salts.[10] The established synthetic method was applied to the preparation of chiral quaternary α-aminomalonates[11] (Scheme 2, A) and α-hydroxymalonates[12] (Scheme 2, B), which were successfully converted to useful chiral molecules bearing quaternary stereogenic centers. To expand our enantioselective PTC α-alkylation methodology, we planned to synthesize chiral quaternary α-thiomalonates that have not yet been reported. As shown in the synthetic strategy illustrated in Scheme 2, a sulfur group is incorporated into the α-position of malonates, and the subsequent enantioselective PTC α-alkylations with various electrophiles afford a versatile library of quaternary chiral α-thiomalonates (Scheme 2, C). Herein, we report efficient enantioselective synthetic method for the preparation of quaternary α-thio-α-alkylmalonates.



Scheme 2. Synthetic strategy for chiral quaternary α-thiomalonates.

First, we designed enantiotopic unsymmetrical α-thiomalonates, bearing non nucleophilic sulfur as substrate for the PTC α-alkylation. Since both diphenylmethyl and tert-butyl ester groups were shown to be necessary for high enantioselectivity in previous reports[11,12], we chose diphenylmethyl tert-butyl malonate (1) as a template. Two α-acylthiomalonates were prepared by α-bromination using CBr_4 in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) followed by substitution with benzothiolic acid or potassium thioacetate to afford α-benzoylthiomalonate (**3**) or α-acetylthiomalonate (**4**), respectively (Scheme 3).



Scheme 3. Preparation of α-acylthiomalonates.

The phase-transfer catalytic α-allylation of the prepared α-acylthiomalonates were performed to examine their efficiency as substrates. The enantioselective PTC allylations of **3** and **4** were carried out under typical PTC conditions[12] [allyl bromide (5.0 equiv.), 50% KOH (aq., 5.0 equiv.), toluene, room temperature] in the presence of chiral quaternary ammonium salts (**5** – **9**)[13] (Figure 1). As shown in Table 1, both α-acylthiomalonates successfully afforded their corresponding α-allylated products in the presence of the Maruoka's catalyst, (*S*,*S*)-3,4,5-trifluorophenyl-NAS

bromide (**5**) (entries 1 – 2). The acetylthio group (**4**, 78% ee) gave a higher enantioselectivity than that of the benzoylthio group (**3**, 72% ee). This result is opposite of that obtained for the α-hydroxymalonates system[12], which may be due to the difference in size between the two atoms (oxygen and sulfur).

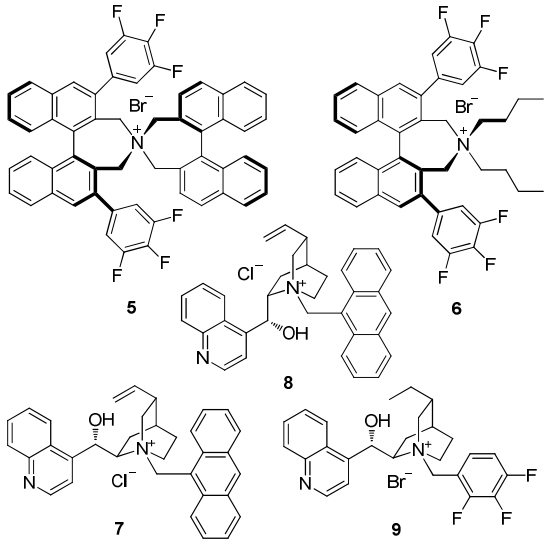
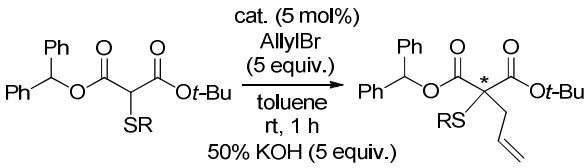


Figure 1. Representative chiral phase-transfer catalysts.

Table 1. Enantioselective PTC α-alkylation of α-acylthiomalonates.[a]

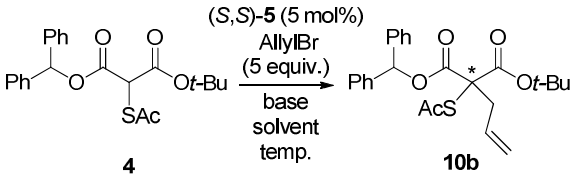


entry	substrate	cat.	yield (%)[b]	ee (%)[c]
1	**3**	**5**	97	72
2	**4**	**5**	99	78
3	**4**	**6**	91	11
4	**4**	**7**	77	15
5	**4**	**8**	40	–14
6	**4**	**9**	96	24

[a]Reactions were performed with 5.0 equiv. of allyl bromide and 5.0 equiv. of 50% KOH(*aq*.) under the given conditions. [b]Isolated yields. [c]Enantiopurity was determined by HPLC analysis using a chiral column (DAICEL Chiralpak AD-H).

Among the examined chiral PTC catalysts, the Maruoka's catalyst (**5**) gave the highest enantioselectivity (entries 1 and 2). The lower enantioselectivities obtained for the other catalysts (**6** – **9**), including Lygo's catalysts (**7**, **8**), were consistent with the trends observed in the previous reports.[11,12]

Table 2. Optimization of the reaction conditions for the enantioselective PTC α-allylation of α-acetylthiomalonate.[a]



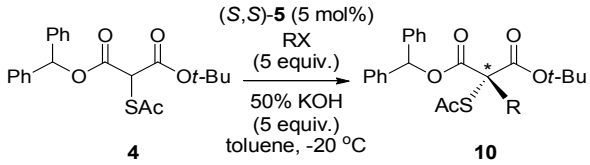
entry	base	solvent	*T* (°C)	time (h)	yield (%)[b]	ee (%)[c]
1	50% KOH	toluene	rt	1	99	78
2	50% CsOH	toluene	rt	1	87	71
3	s-KOH	toluene	rt	1	96	72
4	s-CsOH	toluene	rt	1	36	76
5	50% KOH	CH_2Cl_2	rt	1	75	65
6	50% KOH	THF	rt	1	85	45
7	50% KOH	toluene	0	20	95	84
8	50% KOH	toluene	–20	40	95	89
9	50% KOH	toluene	–40	144	33	90

[a]Reactions were performed with 5.0 equiv. of allyl bromide and 5.0 equiv. of base under the given conditions. [b]Isolated yields. [c]Enantiopurity was determined by HPLC analysis using a chiral column (DAICEL Chiralpak AD-H).

Next, the optimization of the base and temperature conditions were performed using substrate **4** and the best catalyst (*S*,*S*)-**5** (Table 2). Chemical yield and enantioselectivity were dependent on the base and solvent conditions at room temperature (entries 1 – 6). The highest enantioselectivity was observed with 50% KOH base in toluene (entries 1). In case of temperature, higher enantioselectivities were observed at lower reaction temperatures (entry 1, entries 7 – 9). However, a longer reaction time resulted in a lower chemical yield at –40 °C (entry 9). When the PTC reaction was kept for 1 week, the alkylated product was partially hydrolyzed and immediately desulfurized to mono-alkylated malonate that was further alkylated to α,α-dialkylated malonate as a side product. Consequentially, 50% KOH base in toluene at –20 °C was selected as the optimal reaction conditions based on the chemical yield, optical yield, and reaction time (entry 8; 95% yield, 89% ee).

We then turned our attention to determine the scope and limitations of electrophiles in the optimized enantioselective PTC alkylation of **4**. As shown in Table 3, most of the alkylating agents afforded very high enantioselectivities (**10c**–**p**, 90–98% ee). However, an unactivated alkylating reagent gave no alkylated product (data not shown), and propargyl bromide (**10a**) resulted in a relatively poor enantioselectivity, which may be due to geometrical constraints. The achievement of very high enantioselectivities (up to 98% ee) shows that this methodology is very efficient for the enantioselective synthesis of quaternary α-thio-α-alkylmalonates. Note that the enantioselectivities were higher than those of the α-acyloxymalonate system (up to 93% ee).[12] To the best of our knowledge, this is the first report to accomplish the enantioselective catalytic synthesis of quaternary α-thio-α-alkylmalonates.

Table 3. Enantioselective synthesis of α-acetylthio-α-alkylmalonates via PTC α-alkylation[a]



entry	RX	time (h)	yield (%)[b]	ee (%)[c]
1	CH≡CBr (**a**)	23	81	61
2	CH_2=$CHCH_2Br$ (**b**)	40	95	89
3	CH_2=$C(CH_3)CH_2Br$ (**c**)	23	91	94
4	CH_2=$C(Br)CH_2Br$ (**d**)	23	86	92
5	$PhCH_2Br$ (**e**)	8	99	95
6	4-Me-$PhCH_2Br$ (**f**)	4	96	96
7	4-F-$PhCH_2Br$ (**g**)	4	99	97
8	4-Cl-$PhCH_2Br$ (**h**)	7	99	98
9	4-Br-$PhCH_2Br$ (**i**)	5	99	97
10	4-NO_2-$PhCH_2Br$ (**j**)	4	98	95
11	4-t-Bu-$PhCH_2Br$ (**k**)	7	99	96
12	4-CF_3-$PhCH_2Br$ (**l**)	6	99	96
13	4-CF_3O-$PhCH_2Br$ (**m**)	5	86	96(*R*)[d]
14	4-CO_2Me-$PhCH_2Br$ (**n**)	6	99	96
15	3-CH_3O-$PhCH_2Br$ (**o**)	9	96	96
16	β-naphthyl-CH_2Br (**p**)	30	91	90

[a]Reactions were performed with 5.0 equiv. of alkyl bromide and 5.0 equiv. of 50% KOH(*aq*.) under the given conditions. [b]Isolated yields. [c]Enantiopurity was determined by HPLC analysis using a chiral column (DAICEL Chiralpak AD-H). [d]Absolute configuration of **10m** was determined as *R* by X-ray crystallography (Figure 2)[14] and the absolute configuration of other compounds were tentatively assigned as *R* based on the X-ray crystallography of **10m**.

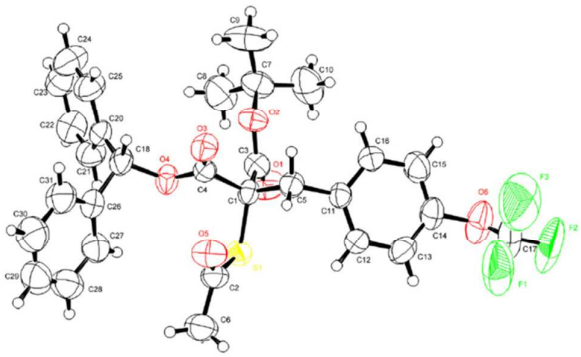
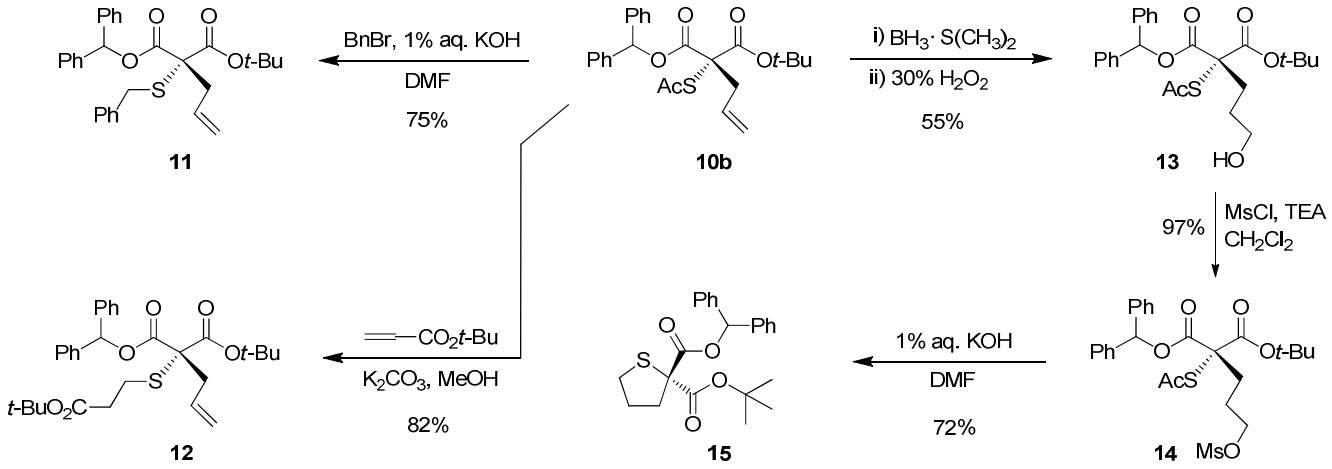


Figure 2. X-ray Crystallographic Structure of **10m**.[14]



Scheme 4 Derivatizations of chiral acetylthiomalonate **10b**

As a demonstration of the synthetic potential of this methodology, derivatizations of **10b** were performed, as illustrated in Scheme 4. The hydrolysis of chiral acetylthiomalonate **10b** under 1% aq-KOH or aq-K_2CO_3 conditions in the presence of benzyl bromide or tert-butyl acrylate directly provided the corresponding *S*-alkylated products **11** and **12**, respectively.[15] Additionally, the hydroboration of **10b** by borane and hydrogenperoxide afforded the corresponding alcohol **13**. The mesylation of **13** followed by hydrolysis using 1% aq-KOH in dimethylformamide (DMF) successively afforded the cyclized tetrahydrothiofuran **15**.[16]

In conclusion, a new asymmetric synthetic method was successfully developed for the preparation of α-acylthio-α-alkylmalonates via PTC α-alkylation. The enantioselective PTC α-alkylations of diphenylmethyl-*tert*-butyl α-acetylthiomalonate provided the corresponding α-acetylthio-α-alkylmalonates in high chemical yields (up to 99%) and optical yields (up to 98% ee). Our newly established PTC reaction provides an efficient method to prepare useful versatile chiral molecules containing α-sulfur quaternary stereogenic centers.

Experimental Section

General Methods

All reagents purchased from commercial sources were used without further purification. Commercially available KOH pellet (99%) was grinded to prepare Solid KOH as powder form. 50% w/v aqueous KOH was used as stock solution. Phase-transfer catalysts (**8** and **9**) were prepared according to the reported procedure. Phase-transfer catalysts (**5**, **6**, and **7**) were purchased from the commercial sources. TLC analyses were performed using pre-coated TLC plate (silica gel 60 GF_{254}, 0.25 mm). Flash column chromatography was performed on flash silica gel 230~400 mesh size. The values of enantiomeric excess (ee) of chiral products were determined by HPLC using 4.6 mm × 250 mm Daicel Chiralpak AD-H. Infrared analyses (KBr pellet) were performed by FT-IR. ^{1}H-NMR spectra was recorded at 300MHz, 400MHz, or 500MHz with reference to $CHCl_3$ (δ 7.24) or CH_3OH (δ 3.31). ^{13}C-NMR spectra was obtained by 100 MHz, 125 MHz, or 150MHz spectrometer relative to the central $CDCl_3$ (δ 77.0) or CD_3OD (δ 49.0) resonance. Coupling constants (*J*) in ^{1}H-NMR are in Hz. Low-resolution mass spectra (LRMS) and high-resolution mass spectra (HRMS) were measured on positive-ion FAB, CI, or Q-TOF (ESI) spectrometer. Melting points were measured on melting point apparatus and were uncorrected. Optical rotations were measured on polarimeter and calibrated with pure solvent as blank.

(A) Procedure for preparation of PTC substrates

To a stirred solution of benzhydryl *tert*-butyl malonate (**1**, 1.63 g, 5.0 mmol) prepared according to the already reported procedure in dry THF (100 mL) was added DBU (822 µL, 5.5 mmol) at -78 °C under argon atmosphere. After stirring for 1 hour at the designated temperature, carbon tetrabromide (2 g, 6.0 mmol) was added little by little, and the reaction mixture was stirred for 3 hours at the same temperature. When the starting material was consumed, a saturated ammonium chloride solution was

added. Extraction using dichloromethane (150 mL x 2), drying over anhydrous $MgSO_4$, filtration, and concentration were performed to yield the residue which can be purified by flash column chromatography (silica gel, Hexane : EtOAc = 30:1) to afford the α-mono-brominated malonate, **2** (1.8 g, 89%) as a pale yellow oil. Potassium thioacetate (423 mg, 3.7 mmol) was added to a stirred solution of α-bromomalonate, **2** (1.0 g, 2.47 mmol) in dry dimethylformamide (10 mL) at room temperature under argon atmosphere. The reaction was stirred until the TLC analysis showed that the reaction was complete. The reaction solvent was evaporated and diluted with EtOAc (100 ml), extracted with brine (100 ml x 2), dried over anhydrous $MgSO_4$, filtered, and concentrated in *vacuo*. The residue was purified by column chromatography (silica gel, Hexane : EtOAc = 10:1) to afford 1-benzhydryl 3-(*tert*-butyl) 2-(acetylthio)malonate (**4**, 801 mg, 81% yield) as a white solid. 1-benzhydryl 3-(*tert*-butyl) 2-(benzoylthio)malonate **(3)** was synthesized in the same manner using 1.5 equivalent of benzothiolic acid and triethylamine in anhydrous methanol instead of potassium thioacetate in DMF.

(B) Typical experimental procedure for enantioselective phase-transfer catalytic alkylation.

To a solution of 1-benzhydryl 3-(*tert*-butyl) 2-(acetylthio)malonate (**4**, 30 mg, 0.075 mmol) and (*S*,*S*)-3,4,5-trifluorophenyl-NAS bromide (**5**, 3.4 mg, 0.0037 mmol) in toluene (250 μL) was added allyl bromide (32.5 μL, 0.38 mmol) at room temperature. At the designated low temperature, aqueous 50% w/v aqueous KOH (32.6 μL, 0.38 mmol) was added to the reaction mixture and stirred until the starting material disappeared. After completion of the reaction, the reaction mixture was diluted with ethyl acetate (20 mL), washed with brine (10 mL x 2), dried over anhydrous $MgSO_4$, filtered, and concentrated in *vacuo*. The residue was purified by flash column chromatography on silica gel eluting with Hexane-EtOAc solution (15:1) to afford **10b** (32.7 mg, 99% yield) as a colorless oil.

(C) Analytical data

1-Benzhydryl 3-(*tert*-butyl) 2-(benzoylthio)malonate (3)

Following the procedure **(A)** from the compound **2** (1.0 g, 2.47 mmol), the title molecule **3** was obtained as a colorless oil (960 mg, 84% yield). ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.95 (d, J = 7.85 Hz, 2H), 7.59 (t, J = 7.35 Hz, 1H), 7.45 (t, J = 7.73 Hz, 2H), 7.36 ~ 7.26 (m, 10H), 6.96 (s, 1H), 5.31 (s, 1H), 1.38 (s, 9H) ppm; ^{13}C-NMR (125 MHz, $CDCl_3$) δ 188.6, 165.3, 164.3, 139.20, 139.18, 135.7, 134.0, 128.7, 128.5, 128.4, 128.08, 128.06, 127.5, 127.2, 127.1, 83.9, 78.9, 51.6, 27.6 ppm; IR (KBr) 3033, 2980, 1738, 1675, 1449, 1288, 1144, 906, 772 cm^{-1}; HRMS (FAB) m/z: $[M+Na]^+$ Calcd for $C_{27}H_{26}O_5SNa$ 485.1399; found 485.1404.

1-Benzhydryl 3-(*tert*-butyl) 2-(acetylthio)malonate (4)

Following the procedure **(A)** from the compound **2** (1.0 g, 2.47 mmol), the title molecule **4** was obtained as a white solid (801mg, 81% yield). mp 70 ^{o}C ; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.32 ~ 7.24 (m, 10H), 6.90 (s, 1H), 5.07 (s, 1H), 2.37 (s, 3H), 1.33 (s, 9H) ppm; ^{13}C-NMR (125 MHz, $CDCl_3$) δ 192.2, 165.2, 164.3, 139.2, 139.1, 128.48, 128.45, 128.13, 128.09, 127.2, 127.1, 83.9, 78.8, 51.6, 29.9, 27.6 ppm; IR (KBr) 3033, 2981, 1738, 1545, 1446, 1220, 1139, 948, 767 cm^{-1}; HRMS (FAB) m/z: $[M+Na]^+$ Calcd for $C_{22}H_{24}O_5SNa$ 423.1242; found 423.1247.

1-Benzhydryl 3-(*tert*-butyl) 2-(benzoylthio)-2-allylmalonate (3')

Following the procedure **(B)** from the substrate **3** (30 mg, 0.065 mmol), the title molecule **3'** (not numbered in the manuscript) was obtained as a colorless oil (31.7 mg, 97% yield). ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.84 (d, J = 7.40 Hz, 2H), 7.56 (t, J = 7.40 Hz, 1H) 7.41 (t, J = 7.78 Hz, 2H), 7.35 ~ 7.24 (m, 8H), 7.14 ~ 7.12 (m, 3H), 6.98 (s, 1H), 5.84 ~ 5.75 (m, 1H), 5.06 ~ 5.03 (m, 2H), 3.23 ~ 3.15 (m, 2H), 1.27 (s, 9H) ppm; ^{13}C-NMR (125 MHz, $CDCl_3$) δ 190.0, 166.4, 165.5, 139.5, 139.3, 136.5, 133.6, 132.1, 128.6, 128.4, 128.2, 128.1, 127.8, 127.6, 127.20, 127.16, 119.7, 84.0, 78.6, 66.0,

39.1, 27.6 ppm; IR (KBr) 3033, 2979, 1732, 1665, 1449, 1370, 1219, 911, 772 cm^{-1}; HRMS (FAB) m/z: $[M+Na]^+$ Calcd for $C_{30}H_{30}O_5SNa$ 525.1712; found 525.1707. The enantioselectivity was determined by chiral HPLC analysis (DAICEL Chiralpak AD-H, hexane : 2-propanol = 80 : 20, flow rate = 1.0 ml/min, 23 °C, λ = 254 nm) retention time; major isomer 15.34 min, minor isomer 19.55 min, 72% ee, $[\alpha]^{20}_D = -16.21$ (*c* 1.0, $CHCl_3$).

(*R*)-1-Benzhydryl 3-(*tert*-butyl)-2-(acetylthio)-2-(prop-2-yn-1-yl)malonate (10a)

Following the procedure **(B)** from the substrate **4** (30 mg, 0.075 mmol) using propargyl bromide, the title molecule **10a** was obtained as a yellow oil (26.6 mg, 81% yield). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.32 ~ 7.26 (m, 10H), 6.94 (s, 1H), 3.32 (ddd, J_1 = 23.66 Hz, J_2 = 17.45 Hz, J_3 = 2.60 Hz, 2H), 2.23 (s, 3H), 2.01 ~ 2.00 (m, 1H), 1.30 (s, 9H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 194.2, 165.2, 164.1, 139.2, 139.1, 128.39, 128.35, 128.2, 128.09, 128.08, 127.4, 127.3, 84.5, 79.0, 78.7, 71.8, 65.3, 29.9, 27.4, 26.6 ppm; IR (KBr) 2979, 1738, 1705, 1370, 1258, 954, 756, 700 cm^{-1}; HRMS (FAB) m/z: $[M+Na]^+$ Calcd for $C_{25}H_{26}O_5SNa$ 461.1399; found 461.1395. The enantioselectivity was determined by chiral HPLC analysis (DIACEL Chiralpak AD-H, hexane : 2-propanol = 80 : 20, flow rate = 1.0 mL/min, 23 °C, λ = 254 nm) retention time: major isomer 12.06 min, minor isomer 18.71 min, 61% ee, $[\alpha]^{20}_D = -3.47$ (*c* 1.0, $CHCl_3$).

(*R*)-1-Benzhydryl 3-(*tert*-butyl)-2-(acetylthio)-2-allylmalonate (10b)

Following the procedure **(B)** from the substrate **4** (30 mg, 0.075 mmol) using allyl bromide, the title molecule **10b** was obtained as a colorless oil (31.4 mg, 95% yield). ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.34 ~ 7.25 (m, 10H), 6.92 (s, 1H), 5.76 ~ 5.68 (m, 1H), 5.04 (s, 1H) 5.02 (d, *J* = 5.20 Hz, 1H), 3.10 ~ 3.02 (m, 2H), 2.18 (s, 3H), 1.26 (s, 9H) ppm; ^{13}C-NMR (125 MHz, $CDCl_3$) δ 193.6, 166.2, 165.3, 139.4, 139.3, 132.0, 128.4, 128.3, 128.1, 128.0, 127.5, 127.2, 119.6, 83.9, 78.6, 65.7, 39.0, 30.0, 27.5 ppm; IR (KBr) 2927, 1732, 1695, 1451, 1370, 1220, 1153, 953, 768 cm^{-1}; HRMS (FAB) m/z:

$[M+Na]^+$ Calcd for $C_{25}H_{28}O_5SNa$ 463.1555; found 463.1557. The enantioselectivity was determined by chiral HPLC analysis (DIACEL Chiralpak AD-H, hexane : 2-propanol = 80: 20, flow rate = 1.0 mL/min, 23 °C, λ = 254 nm) retention time: minor isomer 10.51 min, major isomer 15.96 min, 89% ee, $[\alpha]^{20}_D = -14.47$ (*c* 1.0, $CHCl_3$).

(*R*)-1-Benzhydryl 3-(*tert*-butyl)-2-(acetylthio)-2-(2-methylallyl)malonate (10c)

Following the procedure **(B)** from the substrate **4** (30 mg, 0.075 mmol) using 3-bromo-2-methylpropene, the title molecule **10c** was obtained as a pale yellow oil (31.0 mg, 91% yield). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.37 ~ 7.26 (m, 10H), 6.94 (s, 1H), 4.81 (s, 1H), 4.67 (s, 1H), 3.14 (s, 2H), 2.20 (s, 3H), 1.64 (s, 3H), 1.27 (s, 9H) ppm; ^{13}C-NMR (125 MHz, $CDCl_3$) δ 193.9, 166.6, 165.7, 140.4, 139.32, 139.30, 128.4, 128.3, 128.1, 128.0, 127.6, 127.3, 116.1, 83.9, 78.7, 65.7, 41.4, 29.9, 27.4, 23.4 ppm; IR (KBr) 2853, 1732, 1693, 1455, 1370, 1255, 1200, 950, 761 cm^{-1}; HRMS (FAB) m/z: $[M+Na]^+$ Calcd for $C_{26}H_{30}O_5SNa$ 477.1712; found 477.1726. The enantioselectivity was determined by chiral HPLC analysis (DIACEL Chiralpak AD-H, hexane : 2-propanol = 80: 20, flow rate = 1.0 mL/min, 23 °C, λ = 254 nm) retention time: minor isomer 8.44 min, major isomer 12.60 min, 94% ee, $[\alpha]^{20}_D = -23.78$ (*c* 1.0, $CHCl_3$).

(*R*)-1-Benzhydryl 3-(*tert*-butyl)-2-(acetylthio)-2-(2-bromoallyl)malonate (10d)

Following the procedure **(B)** from the substrate **4** (30 mg, 0.075 mmol) using 2,3-bromopropene, the title molecule **10d** was obtained as a yellow oil (33.5 mg, 86% yield). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.37 ~ 7.27 (s, 10H), 6.94 (s, 1H), 5.53 (s, 1H), 5.50 (d, J = 1.83 Hz, 1H), 3.63 (dd, J_1 = 22.40 Hz, J_2 = 15.83 Hz, 2H), 2.22 (s, 3H), 1.28 (s, 9H) ppm; ^{13}C-NMR (125 MHz, $CDCl_3$) δ 194.3, 165.7, 164.6, 139.1, 128.44, 128.36, 128.2, 128.1, 127.5, 127.3, 127.2, 121.9, 84.5, 79.1, 65.5, 44.0, 29.9, 27.4 ppm; IR (KBr) 2928, 1735, 1692, 1370, 1245, 1146, 1003, 953, 761 cm^{-1}; HRMS (FAB) m/z: $[M+Na]^+$ Calcd for $C_{25}H_{27}O_5BrSNa$ 541.0660; found 541.0655. The enantioselectivity was

determined by chiral HPLC analysis (DIACEL Chiralpak AD-H, hexane : 2-propanol = 80: 20, flow rate = 1.0 mL/min, 23 °C, λ = 254 nm) retention time: minor isomer 10.58 min, major isomer 15.07 min, 92% ee, $[\alpha]^{20}_{D} = -1.29$ (*c* 1.0, $CHCl_3$).

(*R*)-1-Benzhydryl 3-(*tert*-butyl)-2-(acetylthio)-2-benzylmalonate (10e)

Following the procedure **(B)** from the substrate **4** (30 mg, 0.075 mmol) using benzyl bromide, the title molecule **10e** was obtained as a colorless oil (36.4 mg, 99% yield). ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.36 ~ 7.31 (m, 4H), 7.30 ~ 7.25 (m, 6H), 7.20 ~ 7.13 (m, 3H), 7.02 (d, J = 6.90 Hz, 2H), 6.94 (s, 1H), 3.67 (dd, J_1 = 25.78 Hz, J_2 = 14.43 Hz, 2H), 2.17 (s, 3H), 1.25 (s, 9H) ppm; ^{13}C-NMR (125 MHz, $CDCl_3$) δ 194.0, 166.3, 165.2, 139.24, 139.23, 135.4, 130.6, 128.5, 128.3, 128.2, 127.95, 127.91, 127.7, 127.2, 127.1, 84.0, 78.8, 67.3, 39.5, 30.0, 27.5 ppm; IR (KBr) 3033, 2979, 1732, 1691, 1455, 1220, 1147, 951, 773 cm^{-1}; HRMS (FAB) m/z: $[M+Na]^+$ Calcd for $C_{29}H_{30}O_5SNa$ 513.1712; found 513.1722. The enantioselectivity was determined by chiral HPLC analysis (DIACEL Chiralpak AD-H, hexane : 2-propanol = 80: 20, flow rate = 1.0 mL/min, 23 °C, λ = 254 nm) retention time: minor isomer 11.94 min, major isomer 16.44 min, 95% ee, $[\alpha]^{20}_{D} = +74.53$ (*c* 1.0, $CHCl_3$).

(*R*)-1-Benzhydryl 3-(*tert*-butyl)-2-(acetylthio)-2-(4-methylbenzyl)malonate (10f)

Following the procedure **(B)** from the substrate **4** (30 mg, 0.075 mmol) using 4-methylbenzyl bromide, the title molecule **10f** was obtained as a pale yellow oil (36.4 mg, 96% yield). ^{1}H-NMR (500 MHz, CDCl3) δ 7.37 ~ 7.31 (m, 4H), 7.30 ~ 7.28 (m, 6H), 6.96 ~ 6.94 (m, 3H), 6.89 (d, J = 7.80 Hz, 2H), 3.62 (d, J = 3.70 Hz, 2H), 2.26 (s, 3H), 2.21 (s, 3H), 1.26 (s, 9H) ppm; ^{13}C-NMR (125 MHz, $CDCl_3$) δ 194.0, 166.4, 165.3, 139.3, 136.7, 132.2, 130.4, 128.6, 128.4, 128.3, 128.1, 127.9, 127.7, 127.2, 83.9, 78.7, 67.5, 39.1, 30.0, 27.5, 21.1 ppm; IR (KBr) 2927, 1733, 1692, 1455, 1370, 1257, 1182, 952, 746 cm^{-1}; HRMS (FAB) m/z: $[M+Na]^+$ Calcd for $C_{30}H_{32}O_5SNa$ 527.1868; found

527.1861. The enantioselectivity was determined by chiral HPLC analysis (DIACEL Chiralpak AD-H, hexane : 2-propanol = 80: 20, flow rate = 1.0 mL/min, 23 °C, λ = 254 nm) retention time: minor isomer 13.99 min, major isomer 16.66 min, 96% ee, $[\alpha]^{20}_{D}$ = +93.26 (*c* 1.0, $CHCl_3$).

(*R*)-1-Benzhydryl 3-(*tert*-butyl)-2-(acetylthio)-2-(4-fluorobenzyl)malonate (10g)

Following the procedure **(B)** from the substrate **4** (30 mg, 0.075 mmol) using 4-fluorobenzyl bromide, the title molecule **10g** was obtained as a pale yellow oil (37.8 mg, 99% yield). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.38 ~ 7.26 (m, 10H), 7.00 ~ 6.95 (m, 3H), 6.86 ~ 6.80 (m, 2H), 3.64 (dd, J_1 =16.11 Hz, J_2 =14.67 Hz, 2H), 2.23 (s, 3H), 1.26 (s, 9H) ppm; ^{13}C-NMR (125 MHz, $CDCl_3$) δ 193.9, 166.18, 165.17, 162.1 (d, *J* = 244.0 Hz), 139.14, 139.1, 132.1 (d, *J* = 7.80 Hz), 131.0 (d, *J* = 3.20 Hz), 128.5, 128.3, 128.2, 128.0, 127.6, 127.2, 114.7 (d, *J* = 21.10 Hz), 84.1, 78.8, 67.2, 38.8, 30.0, 27.5 ppm; IR (KBr) 2930, 1732, 1692, 1509, 1257, 1221, 1148, 772, 700 cm^{-1}; HRMS (FAB) m/z: $[M+Na]^+$ Calcd for $C_{29}H_{29}O_5FSNa$ 531.1617; found 531.1599. The enantioselectivity was determined by chiral HPLC analysis (DIACEL Chiralpak AD-H, hexane : 2-propanol = 80: 20, flow rate = 1.0 mL/min, 23 °C, λ = 254 nm) retention time: minor isomer 12.45 min, major isomer 14.55 min, 97% ee, $[\alpha]^{20}_{D}$ = +56.50 (*c* 1.0, $CHCl_3$).

(*R*)-1-Benzhydryl 3-(*tert*-butyl)-2-(acetylthio)-2-(4-chlorobenzyl)malonate (10h)

Following the procedure **(B)** from the substrate **4** (30 mg, 0.075 mmol), using 4-chlorobenzyl bromide, the title molecule **10h** was obtained as a pale yellow oil (39.0 mg, 99% yield). ^{1}H-NMR (300 MHz, CDCl3) δ 7.30 (*J* = 8.22 Hz, 2H), 6.94 ~ 6.92 (m, 3H), 3.63 (s, 2H), 2.23 (s, 3H), 1.27 (s, 9H) ppm; ^{13}C-NMR (125 MHz, $CDCl_3$) δ 193.9, 166.1, 165.1, 139.1, 139.0, 133.8, 133.1, 131.9, 128.5, 128.3, 128.2, 128.1, 127.6, 127.2, 84.2, 78.9, 67.0, 38.9, 30.0, 27.5 ppm; IR (KBr) 2926, 1733, 1692, 1493, 1256, 1181, 951, 772 cm^{-1}; HRMS (FAB) m/z: $[M+Na]^+$ Calcd for $C_{29}H_{29}O_5ClSNa$ 547.1322; found 547.1331. The enantioselectivity was determined by chiral HPLC analysis

(DIACEL Chiralpak AD-H, hexane : 2-propanol = 80: 20, flow rate = 1.0 mL/min, 23 °C, λ = 254 nm) retention time: minor isomer 15.51 min, major isomer 18.61 min, 98% ee, $[\alpha]^{20}_{D}$ = +96.64 (*c* 1.0, $CHCl_3$).

(*R*)-1-Benzhydryl 3-(*tert*-butyl)-2-(acetylthio)-2-(4-bromobenzyl)malonate (10i)

Following the procedure **(B)** from the substrate **4** (30 mg, 0.075 mmol) using 4-bromobenzyl bromide, the title molecule **10i** was obtained as a pale yellow oil (42.3 mg, 99% yield). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.36 ~ 7.25 (m, 12H), 6.94 (s, 1H), 6.87 (d, *J* = 8.43 Hz, 2H), 3.62 (s, 2H), 2.23 (s, 3H), 1.27 (s, 9H) ppm; ^{13}C-NMR (125 MHz, $CDCl_3$) δ 193.9, 166.1, 165.1, 139.1, 139.0, 134.4, 132.3, 131.0, 128.5, 128.4, 128.3, 128.1, 127.6, 127.2, 121.3, 84.2, 78.9, 67.0, 38.9, 30.0, 27.5 ppm; IR (KBr) 2979, 1733, 1693, 1489, 1256, 1148, 951, 759, 699 cm^{-1}; HRMS (FAB) m/z: $[M+Na]^+$ Calcd for $C_{29}H_{29}O_5BrSNa$ 591.0817; found 591.0828. The enantioselectivity was determined by chiral HPLC analysis (DIACEL Chiralpak AD-H, hexane : 2-propanol = 80: 20, flow rate = 1.0 mL/min, 23 °C, λ = 254 nm) retention time: minor isomer 18.44 min, major isomer 21.40 min, 97% ee, $[\alpha]^{20}_{D}$ = +111.17 (*c* 1.0, $CHCl_3$).

(*R*)-1-Benzhydryl 3-(*tert*-butyl)-2-(acetylthio)-2-(4-nitrobenzyl)malonate (10j)

Following the procedure **(B)** from the substrate **4** (30 mg, 0.075 mmol) using 4-nitrobenzyl bromide, the title molecule **10j** was obtained as a pale yellow oil (39.4 mg, 98% yield). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.96 (d, *J* = 8.43 Hz, 2H), 7.34 ~ 7.25 (m, 10H), 7.15 (d, *J* = 8.43 Hz, 2H), 6.94 (s, 1H), 3.76 (dd, J_1 = 16.65 Hz, J_2 = 14.28 Hz, 2H), 2.25 (s, 3H), 1.29 (s, 9H) ppm; ^{13}C-NMR (125 MHz, $CDCl_3$) δ 193.8, 165.8, 164.9, 147.1, 143.1, 138.9, 138.8, 131.4, 128.5, 128.4, 128.2, 127.5, 127.2, 123.0, 84.5, 79.1, 66.5, 39.3, 30.1, 27.5 ppm; IR (KBr) 2926, 1732, 1694, 1522, 1348, 1147, 951, 764, 699 cm^{-1}; HRMS (FAB) m/z: $[M+Na]^+$ Calcd for $C_{29}H_{29}O_7NSNa$ 558.1562; found 558.1591. The enantioselectivity was determined by chiral HPLC analysis (DIACEL Chiralpak AD-H, hexane :

2-propanol = 80: 20, flow rate = 1.0 mL/min, 23 °C, λ = 254 nm) retention time: minor isomer 24.01 min, major isomer 26.66 min, 95% ee, $[\alpha]^{20}_{D}$ = +79.89 (*c* 1.0, $CHCl_3$).

(*R*)-1-Benzhydryl 3-(*tert*-butyl)-2-(acetylthio)-2-(4-(*tert*-butyl)benzyl)malonate (10k)

Following the procedure **(B)** from the substrate **4** (30 mg, 0.075 mmol) using 4-(*tert*-butyl)benzyl bromide, the title molecule **10k** was obtained as a pale yellow oil (40.6 mg, 99% yield). ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.36 ~ 7.25 (m, 10H), 7.15 (d, *J* = 8.20 Hz, 2H), 6.97 (d, *J* = 8.15 Hz, 2H), 6.94 (s, 1H), 3.63 (dd, J_1 = 31.40 Hz, J_2 = 14.45 Hz, 2H), 2.21 (s, 3H), 1.25 (s, 9H), 1.23 (s, 9H) ppm; ^{13}C-NMR (125 MHz, $CDCl_3$) δ 194.0, 166.4, 165.3, 149.9, 139.3, 132.2, 130.3, 128.4, 128.3, 128.1, 127.9, 127.6, 127.3, 124.8, 83.9, 78.7, 67.3, 39.1, 34.4, 31.3, 30.0, 27.5 ppm; IR (KBr) 2963, 1733, 1692, 1456, 1257, 1182, 952, 759, 699 cm^{-1}; HRMS (FAB) m/z: $[M+Na]^+$ Calcd for $C_{33}H_{38}O_5SNa$ 569.2338; found 569.2325. The enantioselectivity was determined by chiral HPLC analysis (DIACEL Chiralpak AD-H, hexane : 2-propanol = 90: 10, flow rate = 1.0 mL/min, 23 °C, λ = 254 nm) retention time: minor isomer 14.78 min, major isomer 16.53 min, 96% ee, $[\alpha]^{20}_{D}$ = +53.64 (*c* 1.0, $CHCl_3$).

(*R*)-1-Benzhydryl 3-(*tert*-butyl)-2-(acetylthio)-2-(4-(trifluoromethyl)benzyl)malonate (10l)

Following the procedure **(B)** from the substrate **4** (30 mg, 0.075 mmol) using 4-(trifluoromethyl)benzyl bromide, the title molecule **10l** was obtained as a pale yellow oil (41.5 mg, 99% yield). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.40 ~ 7.25 (m, 12H), 7.11 (d, *J* = 7.86 Hz, 2H), 6.95 (s, 1H), 3.72 (s, 2H), 2.24 (s, 3H), 1.27 (s, 9H) ppm; ^{13}C-NMR (125 MHz, $CDCl_3$) δ 193.9, 166.0, 165.0, 139.5, 139.04, 138.99, 130.9, 129.4 (d, *J* = 32.10 Hz), 128.5, 128.3, 128.2, 128.1, 127.6, 127.2, 124.8 (d, *J* = 3.00 Hz), 124.1 (d, *J* = 270.50 Hz), 84.3, 78.9, 66.8, 39.3, 30.0, 27.5 ppm; IR (KBr) 2926, 1733, 1694, 1371, 1148, 1067, 761, 699 cm^{-1}; HRMS (FAB) m/z: $[M+Na]^+$ Calcd for $C_{30}H_{29}O_5F_3SNa$ 581.1586; found 581.1575. The enantioselectivity was determined by chiral HPLC

analysis (DIACEL Chiralpak AD-H, hexane : 2-propanol = 99: 1, flow rate = 1.0 mL/min, 23 °C, λ = 254 nm) retention time: minor isomer 78.77 min, major isomer 87.07 min, 96% ee, $[\alpha]^{20}_{D}$ = +36.16 (*c* 1.0, $CHCl_3$).

(*R*)-1-Benzhydryl 3-(*tert*-butyl)-2-(acetylthio)-2-(4-(trifluoromethoxy)benzyl)malonate (10m)

Following the procedure **(B)** from the substrate **4** (30 mg, 0.075 mmol) using 4-(trifluoromethoxy)benzyl bromide, the title molecule **10m** was obtained as a white solid (37.0 mg, 86% yield). mp 68 °C; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.37 ~ 7.26 (m, 9H), 7.06 ~ 6.95 (m, 6H), 3.67 (dd, J_1 = 20.16 Hz, J_2 = 14.46 Hz, 2H), 2.23 (s, 3H), 1.25 (s, 9H) ppm; ^{13}C-NMR (125 MHz, $CDCl_3$) δ 193.9, 166.1, 165.1, 148.4, 139.10, 139.06, 134.1, 132.0, 128.5, 128.3, 128.2, 128.1, 127.6, 127.2, 120.3, 84.3, 78.9, 66.9, 38.9, 30.0, 27.4 ppm; IR (KBr) 2981, 1733, 1693, 1508, 1371, 1149, 951, 743, 699 cm^{-1}; HRMS (FAB) m/z: $[M+Na]^+$ Calcd for $C_{30}H_{29}O_6F_3SNa$ 597.1535; found 597.1545. The enantioselectivity was determined by chiral HPLC analysis (DIACEL Chiralpak AD-H, hexane : 2-propanol = 99: 1, flow rate = 1.0 mL/min, 23 °C, λ = 254 nm) retention time: minor isomer 54.51 min, major isomer 56.66 min, 96% ee, $[\alpha]^{20}_{D}$ = +52.02 (*c* 1.0, $CHCl_3$).

(*R*)-1-Benzhydryl 3-(*tert*-butyl)-2-(acetylthio)-2-(4-(methoxycarbonyl)benzyl)malonate (10n)

Following the procedure **(B)** from the substrate **4** (30 mg, 0.075 mmol) using methyl 4-(bromomethyl)benzoate, the title molecule **10n** was obtained as a pale yellow oil (40.7 mg, 99% yield). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.82 (d, *J* = 8.22 Hz, 2H), 7.36 ~ 7.26 (m, 10H), 7.09 (d, *J* = 8.25 Hz, 2H), 6.95 (s, 1H), 3.88 (s, 3H), 3.71 (d, J_1 = 16.02 Hz, J_2 = 14.37 Hz, 2H), 2.23 (s, 3H), 1.27 (s, 9H) ppm; ^{13}C-NMR (125 MHz, $CDCl_3$) δ 193.9, 166.8, 166.0, 165.0, 140.8, 139.1, 139.0, 130.6, 129.2, 129.0, 128.5, 128.3, 128.2, 128.0, 127.6, 127.2, 84.3, 78.9, 66.9, 52.0, 39.4, 30.0, 27.5 ppm; IR (KBr) 2925, 1725, 1693, 1370, 1147, 1021, 952, 760, 700 cm^{-1}; HRMS (FAB) m/z: $[M+Na]^+$ Calcd for $C_{31}H_{32}O_7SNa$ 571.1766; found 571.1755. The enantioselectivity was determined

by chiral HPLC analysis (DIACEL Chiralpak AD-H, hexane : 2-propanol = 80: 20, flow rate = 1.0 mL/min, 23 °C, λ = 254 nm) retention time: minor isomer 16.98 min, major isomer 21.67 min, 96% ee, $[\alpha]^{20}_{D}$ = +110.02 (*c* 1.0, $CHCl_3$).

(*R*)-1-Benzhydryl 3-(*tert*-butyl)-2-(acetylthio)-2-(3-methoxybenzyl)malonate (10o)

Following the procedure **(B)** from the substrate **4** (30 mg, 0.075 mmol) using 3-methoxybenzyl bromide, the title molecule **10o** was obtained as a pale yellow oil (37.5 mg, 96% yield). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.39 ~ 7.23 (m, 10H), 7.11 ~ 7.05 (m, 1H), 6.96 (s, 1H), 6.76 ~ 6.72 (m, 1H), 6.64 ~ 6.61 (m, 2H), 3.66 (dd, J_1 = 18.03 Hz, J_2 = 14.58 Hz. 2H), 3.66 (s, 3H), 2.22 (s, 3H), 1.25 (s, 9H) ppm; ^{13}C-NMR (125 MHz, $CDCl_3$) δ 194.0, 166.3, 165.2, 159.1, 139.2, 136.9, 128.8, 128.5, 128.3, 128.1, 128.0, 127.5, 127.3, 122.9, 116.3, 112.6, 84.0, 78.7, 67.2, 55.0, 39.5, 30.0, 27.4 ppm; IR (KBr) 2931, 1733, 1692, 1455, 1370, 1148, 1052, 953, 771 cm^{-1}; HRMS (FAB) m/z: $[M+Na]^+$ Calcd for $C_{30}H_{32}O_6SNa$ 543.1817; found 543.1808. The enantioselectivity was determined by chiral HPLC analysis (DIACEL Chiralpak AD-H, hexane : 2-propanol = 80: 20, flow rate = 1.0 mL/min, 23 °C, λ = 254 nm) retention time: minor isomer 11.29 min, major isomer 14.08 min, 96% ee, $[\alpha]^{20}_{D}$ = +35.86 (*c* 1.0, $CHCl_3$).

(*R*)-1-Benzhydryl 3-(*tert*-butyl)-2-(acetylthio)-2-(naphthalen-2-ylmethyl)malonate (10p)

Following the procedure **(B)** from the substrate **4** (30 mg, 0.075 mmol) using 2-(bromomethyl) naphthalene, the title molecule **10p** was obtained as a pale yellow oil (37.0 mg, 91% yield). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.78 ~ 7.75 (m, 1H), 7.66 ~ 7.59 (m, 2H), 7.49 (s, 1H), 7.44 ~ 7.26 (m, 12H), 7.18 (d, *J* = 8.40 Hz, 1H), 6.97 (s, 1H), 3.90 ~ 3.80 (dd, J_1 = 17.10 Hz, J_2 = 14.37 Hz, 2H), 2.24 (s, 3H), 1.26 (s, 9H) ppm; ^{13}C-NMR (125 MHz, $CDCl_3$) δ 194.1, 166.3, 165.3, 139.22, 139.18, 133.04, 133.00, 132.5, 129.4, 128.6, 128.5, 128.3, 128.2, 128.0, 127.7, 127.6, 127.5, 127.4, 127.2, 125.8, 125.7, 84.1, 78.8, 67.5, 39.6, 30.0, 27.5 ppm; IR (KBr) 2928, 1732, 1691, 1370, 1216, 1147, 771,

700 cm^{-1}; HRMS (FAB) m/z: $[M+Na]^+$ Calcd for $C_{33}H_{32}O_5SNa$ 563.1868; found 563.1887. The enantioselectivity was determined by chiral HPLC analysis (DIACEL Chiralpak AD-H, hexane : 2-propanol = 80: 20, flow rate = 1.0 mL/min, 23 °C, λ = 254 nm) retention time: minor isomer 13.96 min, major isomer 19.34 min, 90% ee, $[\alpha]^{20}_D$ = +188.19 (*c* 1.0, $CHCl_3$).

(*R*)-1-Benzhydryl 3-*tert*-butyl 2-allyl-2-(benzylthio)malonate (11)

To a solution of acetylthio-allylmalonate, **10b** (27 mg, 62 μmol) and benzyl bromide (11 μL, 93 μmol) in dimethylformamide (1.5 mL) were added 1% aq. KOH (0.52 mL, 93 μmol) at room temperature. After completion of the reaction, the mixture was diluted with ethyl aceatate (10 mL) and the organic layer was separated and collected. Drying over anhydrous $MgSO_4$, filtration, and concentration were performed, and the residue was purified by flash column chromatography on silica gel eluting with Hexane-EtOAc solution (24:1) to afford the desired product, **11** (22.6 mg, 75% yield) as a colorless oil. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.44 ~ 7.15 (m, 15H), 6.97 (s, 1H), 3.69 (s, 2H), 5.87 ~ 5.73 (m, 1H), 5.10 ~ 5.04 (m, 2H), 2.88 (d, *J* = 7.2 Hz, 2H), 1.35 (s, 9H) ppm; ^{13}C-NMR (125 MHz, $CDCl_3$) δ 167.9, 167.0, 139.7, 139.6, 136.3, 131.7, 129.6, 128.72, 128.69, 128.66, 128.4, 128.3, 127.8, 127.5, 127.4, 119.6, 83.5, 78.6, 62.4, 38.5, 34.6, 27.9 ppm; IR (KBr) 2979, 1726, 1496, 1369, 1232, 1130, 1027, 841, 772 cm^{-1}; HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{30}H_{32}O_4SNa$ 511.1914; found 511.1917. $[\alpha]^{20}_D$ = −1.27 (*c* 1.0, $CHCl_3$).

(*R*)-1-Benzhydryl 3-*tert*-butyl 2-allyl-2-((3-(*tert*-butoxy)-3-oxopropyl)thio)malonate (12)

To a solution of acetylthio-allylmalonate, **10b** (44 mg, 0.10 mmol) in methanol (2.0 mL) were added K_2CO_3 (21 mg, 0.15 mmol) and *tert*-butyl acrylate (22 μL, 0.15 mmol) at room temperature. After completion of the reaction, the methanol was removed *in vacuo* and the residure was diluted with ethyl acetate (10 mL) and the organic layer was washed with brine and separated. Drying over anhydrous $MgSO_4$, filtration, and concentration were performed, and the residue was purified by

flash column chromatography on silica gel eluting with Hexane-EtOAc solution (20:1) to afford the desired product, **12** (43 mg, 82% yield) as a colorless oil. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.40 ~ 7.25 (m, 10H), 6.92 (s, 1H), 5.83 ~ 5.69 (m, 1H), 5.08 ~ 5.03 (m, 2H), 2.83 (d, *J*= 6.9 Hz, 2H), 2.75 ~ 2.60 (m, 2H), 2.35 (t, *J*= 7.5 Hz, 2H) 1.42 (s, 9H), 1.32 (s, 9H) ppm; ^{13}C-NMR (200 MHz, $CDCl_3$) δ 170.7, 167.7, 166.9, 139.40, 139.36, 131.4, 128.4, 128.1, 128.0, 127.5, 127.1, 119.3, 83.2, 80.8, 78.4, 77.2, 77.0, 76.8, 61.8, 38.2, 34.9, 28.0, 27.6, 24.5 ppm; IR (KBr) 2932, 1729, 1641, 1496, 1369, 1253, 1080, 843, 772 cm^{-1}; HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{30}H_{38}O_6SNa$ 549.2281; found 549.2285. $[\alpha]^{20}_D = -1.63$ (*c* 1.0, $CHCl_3$).

(*R*)-1-Benzhydryl 3-*tert*-butyl 2-(acetylthio)-2-(3-hydroxypropyl)malonate (13)

To a solution of the olefin, **10b** (45.5 mg, 0.103 mmol) in anhydrous THF (2 mL) was added borane dimethyl sulfide complex solution (1.0 M in DCM, 230 μL, 0.227 mmol) dropwise under argon at 0 ^{o}C, and stirred for 3 hours. After adding THF:MeOH (1:1) (1 ml) for quenching reaction, Aqueous phosphate buffer solution (1 mL) and aqueous H_2O_2 (30 % w/w, 25 μL) were added dropwise and the mixture was stirred for overnight at room temperature. After evaporating the mixture, the organic phase was extracted for two times (5 mL x 2), combined, dried over $MgSO_4$, filtered, and then concentrated. The residue was purified by column chromatography (silica gel, Hexane : EtOAc = 2:1) to afford the desired primary alcohol, **13** (26.0 mg, 55% yield) as a colorless oil.^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.37 ~ 7.26 (m, 10H), 6.94 (s, 1H), 3.57 (t, *J*= 6.45 Hz, 2H), 2.41 ~ 2.35 (m, 2H), 2.20 (s, 3H), 1.60 ~ 1.49 (m, 2H), 1.29 (s, 9H) ppm; ^{13}C-NMR (200 MHz, $CDCl_3$) δ 193.6, 166.6, 165.7, 139.4, 139.3, 128.4, 128.3, 128.1, 128.0, 127.5, 127.2, 83.9, 78.6, 66.1, 62.4, 31.0, 30.0, 28.3, 27.5 ppm; IR (KBr) 3566, 2934, 1729, 1497, 1370, 1150, 951, 839, 772 cm^{-1}; HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{25}H_{30}O_6SNa$ 481.1655; found 481.1651. $[\alpha]^{20}_D = -5.83$ (*c* 1.0, $CHCl_3$).

(*R*)-1-Benzhydryl 3-*tert*-butyl 2-(acetylthio)-2-(3-((methylsulfonyl)oxy)propyl)malonate (14)

The primary alcohol, **13** (13.5 mg, 29.4 μmol) in dichloromethane (2 mL) was treated with methanesulfonyl chloride (3 μL, 44.2 μmol) in the presence of trimethylamine (8 μL, 58.9 μmol) at room temperature under Ar atmosphere and stirred for 1 hour. After completion of the reaction, the reaction mixture was added with saturated sodium bicarbonate solution (5 mL), diluted with dichlromethane (10 mL), washed with brine (5 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated in *vacuo*. The residue was purified by flash column chromatography on silica gel eluting with Hexane-EtOAc solution (3:1) to afford the desired mesylate, **14** (15.3 mg, 97% yield) as a colorless oil. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.35 ~ 7.25 (m, 10H), 6.93 (s, 1H), 4.16 (td, J_1 = 6.3 Hz, J_2 = 1.8 Hz, 2H), 2.96 (s, 3H), 2.46 ~ 2.39 (m, 2H), 2.21 (s, 3H), 1.80 ~ 1.70 (m, 2H), 1.29 (s, 9H) ppm; ^{13}C-NMR (125 MHz, $CDCl_3$) δ 193.9, 166.4, 165.6, 139.5, 139.3, 128.7, 128.6, 128.4, 128.3, 127.7, 127.4, 84.5, 79.0, 69.4, 65.9, 37.6, 31.0, 30.2, 27.7, 25.2 ppm; IR (KBr) 2978, 1730, 1696, 1496, 1356, 1217, 1112, 949, 771 cm^{-1}; HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{26}H_{32}O_8S_2Na$ 559.1431; found 559.1440. $[\alpha]^{20}_D = -11.51$ (*c* 1.0, $CHCl_3$).

(*R*)-2-Benzhydryl 2-tert-butyl dihydrothiophene-2,2(3H)-dicarboxylate (15)

To a solution of the mesylate, **14** (16 mg, 0.03 mmol) in dimethylformamide (0.1 mL) was added 1% aq. KOH (2 μL, 35.3 μmol) at room temperature. After complete conversion of the starting material to the thiocycle compound, the mixture was diluted with Ethyl acetate (5 mL x 2) and the organic layer was separated and collected. Drying over anhydrous $MgSO_4$, filtration, and concentration were performed, and the residue was purified by flash column chromatography on silica gel eluting with Hexane-EtOAc solution (24:1) to afford the desired ring product, **15** (8.5 mg, 72% yield) as a colorless oil. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.40 ~ 7.26 (m, 10H), 6.92 (s, 1H), 3.04 ~ 2.92 (m, 2H), 2.43 ~ 2.32 (m, 2H), 2.22 ~ 2.08 (m, 2H), 1.26 (s, 9H) ppm; ^{13}C-NMR (150 MHz, $CDCl_3$) δ 169.4, 168.8, 139.6, 139.5, 128.5, 128.4, 128.1, 127.9, 127.4, 127.1, 82.7, 78.1, 67.2, 38.4, 34.0, 30.8, 27.5 ppm; IR (KBr) 2977, 1734, 1496, 1369, 1256, 1133, 1047, 993, 745 cm^{-1}; HRMS (ESI) m/z:

$[M+Na]^+$ Calcd for $C_{23}H_{26}O_4SNa$ 421.1444; found 421.1439. $[\alpha]^{20}_D = -3.33$ (*c* 1.0, $CHCl_3$).

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Supporting Information

Spectral data of all new compounds as well as an X-ray crystallographic analysis of (*R*)-**10m**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) Bijvoet method of anomalous X-ray scattering was used for the enantiomer assignment of **10m** and the molecular structure show the atomic numbering and 50% probability displacement ellipsoid. CCDC 1533604 contains the supplementary crystallographic data for compound **10m**. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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