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Note

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J. Org. Chem., **Just Accepted Manuscript** • DOI: 10.1021/acs.joc.7b00324 • Publication Date (Web): 17 Apr 2017

ACS Publications

The Journal of Organic Chemistry is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036

Enantioselective Synthesis of Chiral α-Azido and α-Aryloxy Quaternary Stereogenic Centers via the Phase-transfer Catalyzed α-Alkylation of α-Bromomalonates, Followed by S_N2 Substitution

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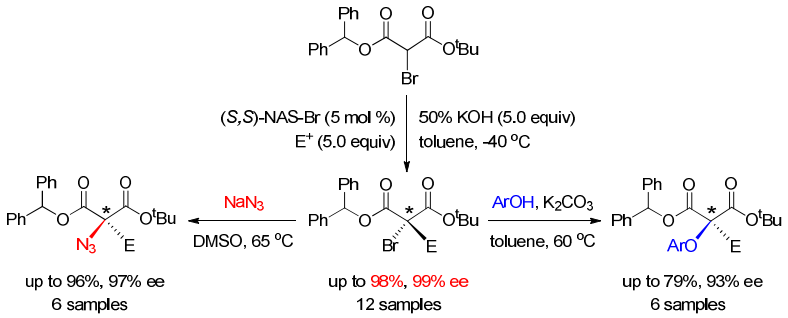
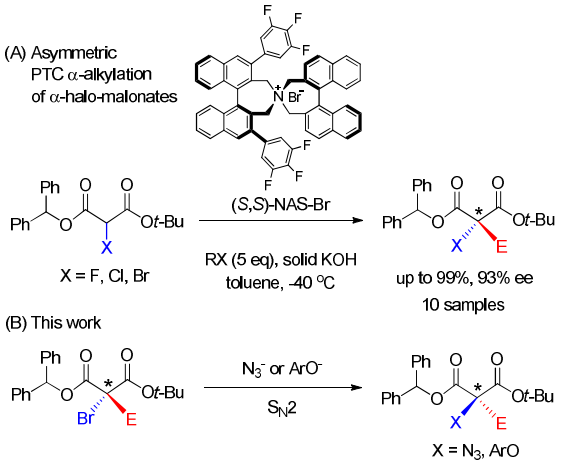


Abstract

A new efficient synthetic method for chiral α-azido-α-alkylmalonates and α-aryloxy-α-alkylmalonates were developed. The enantioselective α-alkylation of diphenylmethyl *tert*-butyl α-bromomalonate under phase-transfer catalytic conditions ((*S*,*S*)-3,4,5-trifluorophenyl-NAS bromide, 50% KOH, toluene, and –40 °C) provided the corresponding α-bromo-α-alkylmalonates in high chemical yields (up to 98%) and high optical yields (up to 99% ee). The resulting α-alkylated products were converted to α-azido-α-alkylmalonates (up to 96%, 97% ee) and α-aryloxy-α-alkylmalonates (up to 79%, 93% ee) by S_N2 substitution with sodium azide and aryloxides, respectively.

Optically active nitrogen- or oxygen-containing organic compounds are very important for natural product chemistry and medicinal chemistry due to their diverse biological activities.[1,2] Most pharmaceuticals contain nitrogen or oxygen that play important roles in binding to drug targets. Until a recent date, impressive levels of enantioselectivity have been achieved in the construction of α-amino quaternary stereogenic centers[3] and α-hydroxy quaternary stereogenic centers[4] via either organocatalysis or organometallic catalysis. Many enantioselective synthetic methods have been developed for α-amino-β-keto esters[5] and α-hydroxy-β-keto esters[6] via the electrophilic α-amination and the α-hydroxylation, respectively, of β-keto ester system. However, the enantioselective synthesis of α-amino-α-alkylmalonates and α-hydroxy-α-alkylmalonates have not been extensively studied, and there have been only a few reports as part of studies including each type of the aforementioned malonate.[7,8]

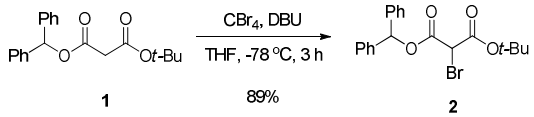


Scheme 1. Strategy for quaternary chiral α-azidomalonates and α-aryloxymalonates.

In 2012, the Shibatomi group reported an excellent enantioselective system for the α-chlorination of β-ketoesters using organometallic catalysis and successfully applied the resulting chiral α-chloro-β-ketoesters to prepare α-azido-β-ketoesters and α-alkylthio-β-ketoesters via an S_N2 substitution with sodium azide and alkylthiols, respectively.[9] Further application of S_N2 substitution to α-aryloxy-β-ketoesters with arylalcohols was reported in 2015.[10] However, only a few examples of S_N2 reactions with α-chloromalonate are included in their work.[9,10]

In recent years, we reported a new enantioselective synthetic method for the synthesis of quaternary α-fluorosubstituted malonates with high chemical yields and enantioselectivities via a phase-transfer catalytic (PTC[11]) α-alkylation of α-fluoromalonates in the presence of chiral quaternary ammonium salts, and its usefulness was successfully proved by the application to the synthesis of a precursor of Welch's (*R*,*R*)-HIV-1 protease inhibitor.[12] Additionally, each two samples of α-chloro-α-alkylmalonates and α-bromo-α-alkylmalonates were reported as supplementary data. Although we focused mainly on the synthesis of α-fluoro-substituted quaternary chiral malonates, the supplementary resulting chiral α-chloro-α-alkylmalonates and α-bromo-α-alkylmalonates are also potentially very useful intermediates for further chemical transformations. Herein, we report efficient enantioselective synthetic methods to produce α-azido-α-alkylmalonates and α-aryloxy-α-alkylmalonates via the S_N2 substitution of chiral α-bromo-α-alkylmalonates with azide and aryloxide, respectively (Scheme 1).

Our previously reported PTC reaction conditions for α-halo-α-alkylmalonates were optimized by the enantioselective α-benzylation of α-fluoromalonate.[12b] However, the optimized reaction conditions for α-chloromalonates or α-bromomalonate may be different. Therefore, we needed to re-optimize the enantioselective PTC α-benzylation of α-chloromalonate (93% ee) or α-bromomalonate (86% ee) for higher enantioselectivity. Among the two substrates, α-bromomalonate was chosen for re-optimization because it possessed a higher chemical yield of the substrate from malonate **1** and bromide is a more facile leaving group than chloride.



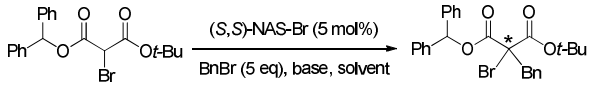
1 2

Scheme 2. Preparation of diphenylmethyl *tert*-butyl α-bromomalonate (**2**).

First, diphenylmethyl *tert*-butyl α-bromomalonate (**2**) was prepared from diphenylmethyl *tert*-butyl malonate (**1**) by a modified method (Scheme 2). Bromination of **1** using carbon

tetrabromide (CBr_4) in the presence of DBU under tetrahydrofuran at –78 °C afforded α-bromomalonate **2** (89%) without the corresponding α,α-dibromomalonate that was usually obtained as a side product by the previously reported method [NBS, $Mg(ClO_4)_2$].[12b]

Table 1. Optimization of the PTC α-benzylation of α-bromomalonate **2**.



2 **3d**

entry	base	Solvent	T (°C)	yield (%)[a]	ee (%)[b]
1	50% KOH	toluene	0	94	90
2	50% KOH	CH_2Cl_2	0	57	72
3	50% KOH	THF	0	87	65
4	50% CsOH	toluene	0	85	77
5	50% KOH	toluene	–20	97	93
6	50% KOH	toluene	–30	98	95
7	50% KOH	toluene	–40	96	98
8	Solid KOH	toluene	–40	99	86
9	Solid KOH	toluene	–78	48	89
10	Solid CsOH	toluene	–78	68	75

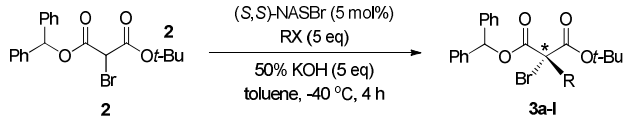
[a]Isolated yields. [b]Enantiopurity was determined by HPLC analysis using a chiral column (DAICEL Chiralcel OJ-H).

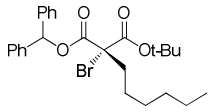
Next, the PTC reaction conditions were optimized using α-bromomalonate **2**. The PTC benzylation was carried out in the presence of the previously optimized catalyst, (*S*,*S*)-3,4,5-trifluorophenyl-NAS bromide[13] [(*S*,*S*)-NAS-Br], under variable base, solvent, and temperature conditions. The highest enantioselectivity was observed in toluene among the used solvent in the presence of 50% KOH at 0 °C (entries 1 – 3), as shown in Table 1. Aqueous bases generally afforded both higher chemical yield and enantioselectivities (entries 7 – 9). In case of temperature, the chemical yields did not significantly dependent on the reaction temperature under 50% KOH. However, the lower temperature conditions resulted in higher enantioselectivities (entries 1, 5 – 8), and the best enantioselectivity was obtained at –40 °C (entry 7, 98% ee). Consequentially, 50% KOH

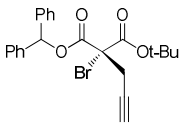
in toluene at –40 °C was chosen as the optimized reaction conditions based on the enantioselectivity, chemical yield, and reaction time.

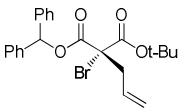
We then turned our attention to the scope and limitations of electrophiles in the optimized enantioselective PTC alkylation of **2**. As shown in Table 2, most of the alkylating agents showed very high enantioselectivities (**3d**–**l**, 91–99% ee) under the optimized reaction conditions (Table 1, entry 7). However, relatively low enantioselectivities were observed with unactivated n-hexyl iodide (**3a**) and propargyl bromide (**3b**) that is possibly due to low reactivity or small molecular size, respectively. Overall, the high enantioselectivities (up to 99% ee) were successfully achieved, and this established enantioselective PTC α-alkylation is a very efficient method for the synthesis of chiral α-bromo-α-alkylmalonates.

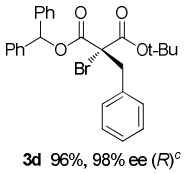
Table 2. Enantioselective synthesis of α-bromo-α-alkylmalonates via PTC α-alkylation

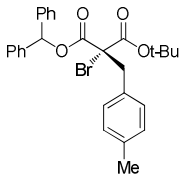


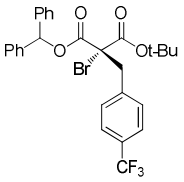

3a 70%[a] (96 h), 90% ee[b]

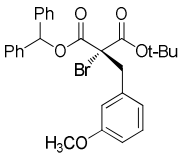

3b 79%, 52% ee

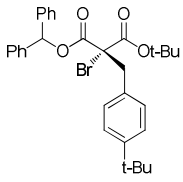

3c 63%, 93% ee

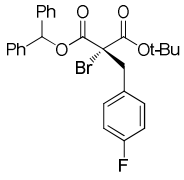

3d 96%, 98% ee (*R*)[c]

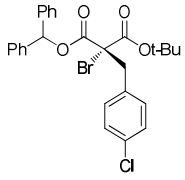

3e 75%, 99% ee

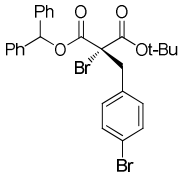

3f 81%, 98% ee

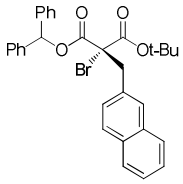

3g 93%, 98% ee


3h 98%, 96% ee


3i 91%, 98% ee


3j 82%, 97% ee

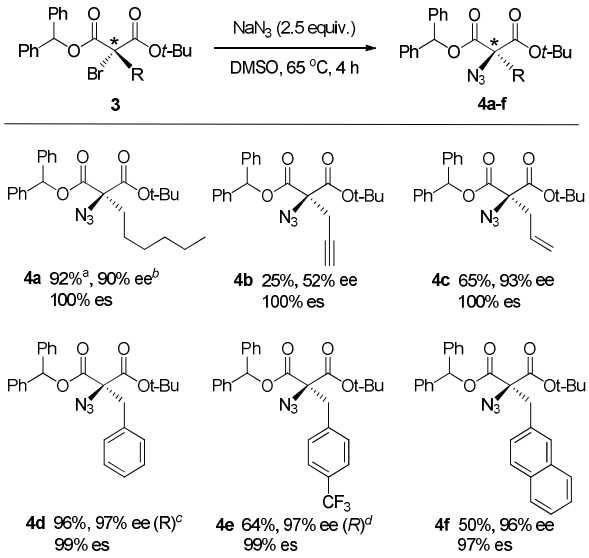

3k 62%, 99% ee


3l 98%, 99% ee

[a]Isolated yields. [b]Enantiopurity was determined by HPLC analysis using a chiral column (DAICEL Chiralpak AD-H or Chiralcel OJ-H) and the enantiopurity of **3a** and **3b** were determined by the enantiopurity of **4a** and **4b**, respectively. [c]Absolute configuration of **3d** was determined by the

comparison of the specific optical rotation values of **8** and α-benzylserine prepared from **3d** with reported values.[15]

Table 3. Preparation of α-azido-α-alkylmalonates from α-bromo-α-alkylmalonate

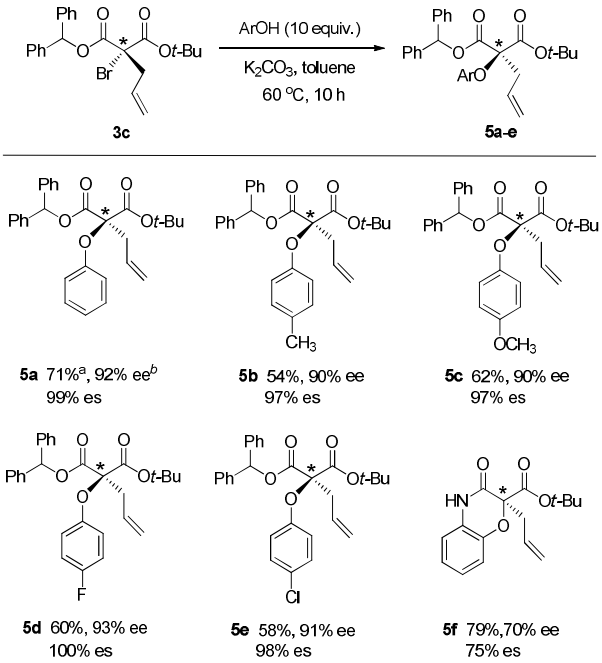


[a]Isolated yields. [b]Enantiopurity was determined by HPLC analysis using a chiral column (DAICEL Chiralpak AD-H). [c]Absolute configuration of **4d** was determined by the comparison of the specific optical rotation values of **8** and α-benzylserine prepared from **4d** with reported values.[15]

Encouraged by the high enantioselectivity, next, we focused on the S_N2 substitution of the resulting α-bromo-α-alkylmalonates with various nucleophiles. First, we attempted to use sodium azide. The S_N2 substitution of α-bromo-α-alkylmalonates (**3a** – **3e**) in the presence of sodium azide under dimethylsulfoxide at 65 °C successfully afforded the corresponding α-azido-α-alkylmalonates (**4a** – **4e**) in high chemical yields (Table 3). The enantioselectivities were preserved by complete inversion via S_N2 substitution except for **4f** due to its steric hindered β-naphthyl group. Additionally, α-aryloxymalonates were successfully prepared from α-bromo-α-allylmalonates by S_N2 substitution with phenolic alcohols (Table 4). The S_N2 substitution of α-bromo-α-allylmalonates (**3c**) with various aryl alcohols in the presence of potassium carbonate under toluene at 60 °C successfully resulted in the corresponding α-aryloxy-α-allylmalonates (**5a** – **5e**) in moderate chemical yields. However, some

of the enantioselectivities were slightly decreased (**5a** – **5c** and **5e**), and a moderate enantioselectivity was observed in the case of *o*-aminophenol producing the heterocycle product **5f**. Unfortunately, the nucleophilic substitutions with carboxylate, amines, thiols and aliphatic alcohols were not successful.

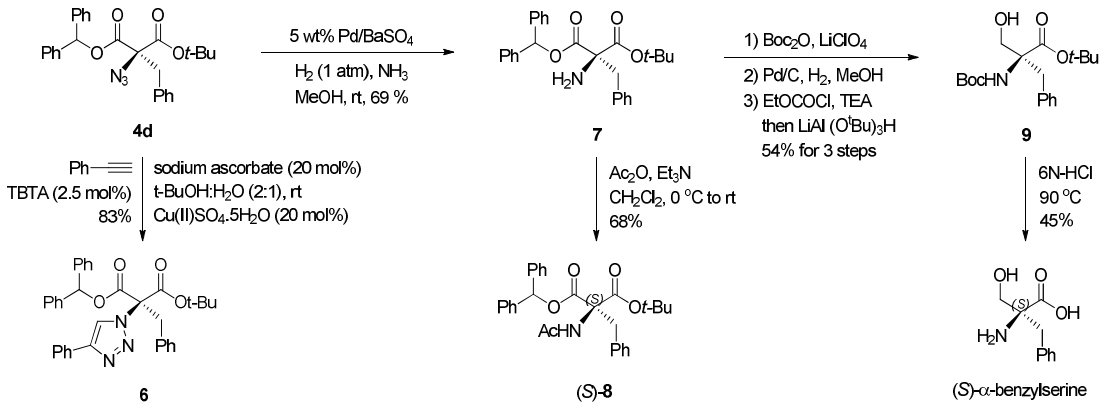
Table 4. Preparation of α-aryloxy-α-allylmalonates from α-bromo-α-allylmalonate



[a]Isolated yields. [b]Enantiopurity was determined by HPLC analysis using a chiral column (DAICEL Chiralpak AD-H).

The α-azido-α-benzylmalonate (**4d**) was converted to various valuable chiral building blocks as exemplified in Scheme 3. Triazole **6** was prepared from **4d** via click chemistry using phenylacetylene in the presence of a catalytic amount of TBTA, cupper (II) sulfate and sodium ascorbate (83%).[14] Catalytic hydrogenation of **4d** with $Pd/BaSO_4$-H_2 (1 atm) under ammonia saturated methanol afforded the corresponding amine **7** (69%). The following acetylation using acetic anhydride gave the corresponding acetamide (*S*)-**8** (68%) {$[\alpha]_D^{25} = -34.50$ (*c* 1.0, $CHCl_3$); lit[15] (*R*)-**8**, $[\alpha]_D^{25} = +23.06$ (*c* 1.0, $CHCl_3$), 95% ee}. Protection of **7** with N-Boc followed by catalytic hydrogenation with Pd/C-H_2 (1 atm) provided the corresponding mono acid. The activation of the

resulting acid via mixed anhydride followed by reduction with $LiAl(O^tBu)_3H$ gave the mono alcohol **9** (54%). Finally, the treatment of **9** with 6N-HCl at 90 °C successfully afforded (*S*)-α-benzylserine (85%) {$[\alpha]_D^{20}$ = +16.73 (*c* 1.0, H_2O); lit[15] (*R*)-α-benzylserine, $[\alpha]_D^{20}$ = –15.50 (*c* 1.0, H_2O), 95% ee}.



Scheme 3. Conversion of **4d** to **6** – **9** and (*S*)-α-benzylserine.

In conclusion, enantioselective PTC reaction conditions for α-bromo-α-alkylmalonates were optimized and successfully applied to synthesize α-azido-α-alkylmalonates and α-aryloxy-α-allylmalonates. The enantioselective PTC α-alkylation of diphenylmethyl-*tert*-butyl α-bromomalonates provided the corresponding α-bromo-α-alkylmalonates in high optical yields up to 99% ee and high chemical yields up to 98%. The resulting α-bromo-α-alkylmalonates were successfully applied to the synthesis of chiral α-azido-α-alkylmalonates and α-aryloxy-α-allylmalonates in high chemical yields and high enantioselectivities via S_N2 substitution with azide and aryloxide, respectively. Our newly established PTC catalytic reaction is an efficient asymmetric synthetic method to prepare useful versatile chiral molecules with α-bromo, α-amino or α-aryloxy quaternary stereogenic centers.

Experimental Section

General Methods

All reagents bought 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. (*S*,*S*)-3,4,5-Trifluorophenyl-NAS bromide were purchased from the commercial source. TLC analyses were performed using precoated 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 or Chiralcel OJ-H. Infrared analyses (KBr pellet) were performed by FT-IR. ^{1}H-NMR spectra was recorded at 300 MHz, 400 MHz, 500 MHz, or 800 MHz with reference to $CHCl_3$ (δ 7.26). ^{13}C-NMR spectra was obtained by 75 MHz, 100 MHz, 125 MHz, 150 MHz, or 200 MHz spectrometer relative to the central $CDCl_3$ (δ 77.0) 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. Optical rotations were measured on polarimeter and calibrated with pure solvent as blank.

Procedure for the preparation of diphenylmethyl *tert*-butyl α-bromomalonate (2)

DBU (1.37 mL, 9.19 mmol) was added to a stirred solution of benzhydryl *tert*-butyl malonate (**1**, 1.0 g, 3.06 mmol) in THF anhydrous at 0 °C under argon atmosphere and stirred the mixture for 1 h. Carbon tetrabromide (1.1 g, 3.31 mmol) solution in anhydrous THF was added slowly for 1 h at −78 °C and the reaction was stirred for 3 h at the same temperature. The mixture was quenched by a saturated ammonium chloride solution and diluted by *n*-Hexane. The reaction mixture was extracted by dichloromethane (50 mL x 2 times), dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography (silica gel, hexane : EtOAc = 30 : 1) to afford **2** (1.1 g, 89% yield) as a yellow oil.

Typical experimental procedure for enantioselective phase-transfer catalytic alkylation (Procedure A)

Benzyl bromide (44 μL, 0.37 mmol) was added to a solution of 1-benzhydryl 3-(*tert*-butyl) 2-bromomalonate (**2**, 30 mg, 0.074 mmol) and (*S*,*S*)-3,4,5-trifluorophenyl-NAS bromide (**10**, 3.6 mg, 0.004 mmol) in toluene (250 μL) at room temperature. At the designated low temperature, aqueous 50% w/v aqueous KOH (42 μL, 0.37 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 × 2), dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by flash column

chromatography (silica gel, hexane : EtOAc = 50 : 1) to afford **3d** (35.2 mg, 96%) as a colorless oil.

1-Benzylhydryl 3-(*tert*-butyl) 2-bromo-2-hexylmalonate (3a)

After compound **2** (30 mg, 74 μmol) was reacted with *n*-hexyl iodide by procedure A, the title compound **3a** was obtained as a colorless oil (25.4 mg, 70%). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.38 ~ 7.27 (m, 10H), 6.95 (s, 1H), 2.26 ~ 2.21 (m, 2H), 1.30 (s, 9H), 1.29 ~ 1.22 (m, 7H), 0.85 (t, 3H, *J* = 6.8 Hz) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 166.1, 165.4, 139.2, 139.0, 128.5, 128.4, 128.3, 128.1, 127.5, 127.1, 127.0, 83.8, 79.0, 65.2, 38.2, 31.4, 28.8, 27.4, 24.9, 22.4, 14.0 ppm; IR (KBr) 3064, 3032, 2956, 2929, 2857, 1736, 1495, 1455, 1394, 1369, 1252, 1215, 1182, 1154, 1127, 958, 842, 760, 743, 699, 647 cm^{-1}; Q-TOF (ESI) calcd for $[C_{26}H_{33}BrO_4Na]^+$ ($[M+Na]^+$) 511.1454, found: 511.1460; $[\alpha]^{20}_D$ = +2.77 (c 1.0, $CHCl_3$).

1-Benzylhydryl 3-(*tert*-butyl) 2-bromo-2-(prop-2yn-1-yl)malonate (3b)

After compound **2** (30 mg, 74 μmol) was reacted with propargyl bromide by procedure A, the title compound **3b** was obtained as a colorless oil (26 mg, 79%). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.36 ~ 7.29 (m, 10H), 6.96 (s, 1H), 3.25 (d, 2H, *J* = 3.0 Hz), 2.10 (t, 1H, 2.6 Hz), 1.32 (s, 9H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 165.1, 163.9, 138.9, 138.8, 128.5, 128.5, 128.3, 128.2, 127.5, 127.2, 84.7, 79.6, 77.6, 72.5, 61.1, 30.0, 27.4, ppm; IR (KBr) 3293, 2980, 2320, 1741, 1496, 1455, 1415, 1371, 1275, 1219, 1182, 1149, 1028, 984, 911, 838, 772, 699, 648 cm^{-1}; HRMS (FAB) calcd for $[C_{23}H_{24}BrO_4]^+$ ($[M+H]^+$) 443.0852, found: 443.0852; $[\alpha]^{20}_D$ = +12.43 (c 1.0, $CHCl_3$).

1-Benzyl 3-(*tert*-butyl) 2-bromo-2-allylmalonate (3c)

After compound **2** (30 mg, 74 μmol) was reacted with allyl bromide by procedure A, the title compound **3c** was obtained as a yellow oil (21 mg, 63%).; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.38 ~ 7.29 (m, 10H), 6.94 (s, 1H), 5.82 ~ 5.69 (m, 1H), 5.12 ~5.05 (m, 2H), 3.03 (d, 2H, *J* = 6.6 Hz), 1.29 (s, 9H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 165.8, 164.8, 139.1, 139.0, 131.2, 128.5, 128.5, 128.3, 128.1, 127.6, 127.0, 120.3, 84.2, 79.2, 63.4, 42.7, 27.4 ppm; IR (KBr) 3032, 2980, 1740, 1496, 1455, 1428, 1395, 1370, 1271,1234, 1185, 1154, 1130, 1080, 1028, 964, 840, 743, 699, 637 cm^{-1}; Q-TOF (ESI) calcd for $[C_{23}H_{25}BrNaO_4]^+$ ($[M+Na]^+$) 467.0828, found: 467.0836; The enantioselectivity was determined by chiral HPLC analysis (DAICEL Chiralpak AD-H, hexane : 2-propanol = 98 : 2, flow rate = 0.5 mL/min, 23 °C, λ = 254 nm), retention time; minor isomer 30.14 min, major isomer 31.43 min, 93% ee, $[\alpha]^{20}_D$ = +4.18 (c 1.0, $CHCl_3$).

1-Benzyl 3-(*tert*-butyl) 2-bromo-2-benzylmalonate (3d)

After compound **2** (30 mg, 74 μmol) was reacted with benzyl bromide by procedure A, the title compound **3d** was obtained as a colorless oil (35.2 mg, 96%). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.35 ~7.27 (m, 10H), 7.22 ~ 7.12 (m, 5H), 6.95 (s, 1H), 3.63 (s, 1H), 1.28 (s, 9H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 169.5, 165.1, 139.0, 138.9, 134.4, 130.5, 128.5, 128.4, 128.3, 128.0, 128.0, 127.7, 127.4, 127.1, 84.2, 79.4, 64.5, 43.5, 27.4, ppm; IR (KBr) 3032, 2980, 1740, 1496, 1455, 1429, 1394, 1370, 1259, 1148, 1082, 1020, 970, 911, 840, 743, 699, 639 cm^{-1}; HRMS (FAB) calcd for $[C_{27}H_{28}BrO_4]^+$ ($[M+H]^+$) 495.1171, found: 495.1164; The enantioselectivity was determined by chiral HPLC analysis (DAICEL Chiralcel OJ-H, hexane : 2-propanol = 98 : 2, flow rate = 1.0 mL/min, 23 °C, λ = 254 nm, retention time; minor isomer 10.29 min, major isomer 13.59 min, 98 % ee, $[\alpha]^{20}_D$ = +4.44 (c 1.0, $CHCl_3$).

1-Benzyl 3-(*tert*-butyl) 2-bromo-2-(*p*-methyl-benzyl)malonate (3e)

After compound **2** (30 mg, 74 μmol) was reacted with *p*-methyl-bromide by procedure A, the title compound **3e** was obtained as a yellow oil (28.3 mg, 75%). ^{1}H-NMR (300MHz, $CDCl_3$) δ 7.36 ~ 7.30 (m, 10H), 7.02 ~ 6.93 (m, 5H), 3.60 (d, 1H, *J* = 14.9 Hz), 3.54 (d, 1H, *J* = 14.9 Hz), 2.27 (s, 3H), 1.29 (s, 9H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 166.0, 165.2, 139.0, 139.0, 137.0, 131.3, 130.4, 128.7, 128.5, 128.4, 128.3, 128.0, 127.7, 127.1, 84.2, 79.4, 64.8, 43.1, 27.4, 21.1 ppm; IR (KBr) 3032, 2980, 1741, 1455, 1370, 1259, 1219, 1149, 1022, 962, 842, , 698 cm^{-1}; HRMS (FAB) calcd for $[C_{28}H_{30}BrO_4]^+$ ($[M+H]^+$) 509.1327, found: 509.1333; The enantioselectivity was determined by chiral HPLC analysis (DAICEL Chiralpak AD-H, hexane : 2-propanol = 200:1, flow rate = 1.0 mL/min, 23 °C, λ = 254 nm, retention time; minor isomer 24.21 min, major isomer 35.57 min, 99% ee, $[\alpha]^{20}_D$ = +9.65 (c 1.0, $CHCl_3$).

1-Benzyl 3-(*tert*-butyl) 2-bromo-2-(*p*-trifluoromethyl-benzyl)malonate (3f)

After compound **2** (30 mg, 74 μmol) was reacted with *p*-trifluoromethyl benzyl bromide by procedure A, the title compound **3f** was obtained as a yellow oil (33.7 mg, 81%). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.39 ~7.29 (m, 12H), 7.23 ~ 7.20 (m, 2H), 6.94 (s, 1H), 3.67 (d, 1H, *J* = 14.7 Hz), 3.63 (d, 1H, *J* = 14.7 Hz), 1.31 (s, 9H) ppm; ^{13}C-NMR (75 MHz, $CDCl_3$) δ 165.6, 165.0, 138.8, 138.7, 138.5, 130.8, 129.7 (q, *J* = 32.1 Hz), 128.5, 128.4, 128.4, 128.2, 127.6, 127.0, 125.9, 125.0 (q, *J* = 3.7 Hz), 124.1 (q, *J* = 270.2 Hz), 84.5, 79.6, 63.61, 43.17, 27.39 ppm; IR (KBr) 2929, 2127, 1744, 1619, 1496, 1455, 1372, 1325, 1244, 1165, 1126, 1021, 839, 772, 699 cm^{-1};

Q-TOF (ESI) calcd for $[C_{28}H_{26}BrF_3O_4Na]^+$ ($[M+Na]^+$) 585.0859, found: 585.0862; The enantioselectivity was determined by chiral HPLC analysis (DAICEL Chiralcel OJ-H, hexane : 2-propanol = 98 : 2, flow rate = 1.0 mL/min, 23 °C, λ = 254 nm, retention time; minor isomer 9.12 min, major isomer 11.83 min, 98% ee, $[\alpha]^{20}_D$ = +10.64 (c 1.0, $CHCl_3$).

1-Benzyl 3-(*tert*-butyl) 2-bromo-2-(*m*-methoxy-benzyl)malonate (3g)

After compound **2** (30 mg, 74 μmol) was reacted with *m*-methoxy-benzyl bromide by procedure A, the title compound **3g** was obtained as a yellow oil (36 mg, 93%).; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.35 ~ 7.31 (m, 10H), 7.10 ~ 7.05 (m, 1H), 6.34 (s, 1H), 6.76 ~ 6.70 (m, 3H), 3.66 (s, 3H), 3.61 (d, 2H, *J* = 2.7 Hz), 1.27 (s, 9H) ppm; ^{13}C-NMR (75 MHz, $CDCl_3$) δ 165.9, 165.0, 159.1, 139.0, 138.9, 135.8, 128.9, 128.5, 128.4, 128.2, 128.0, 127.5, 127.0, 122.8, 116.1, 113.1, 84.3, 79.4, 64.3, 55.0, 43.5, 27.4 ppm; IR (KBr) 2932, 2372, 2320, 1739, 1263, 772 2856, 1738, 1682, 1496, 1219, 1155, 772, 698 cm^{-1}; HRMS (FAB) calcd for $[C_{28}H_{29}BrO_5]^+$ ($[M]^+$) 524.1198, found: 524.1194; The enantioselectivity was determined by chiral HPLC analysis (DAICEL Chiralpak AD-H, hexane : 2-propanol = 98 : 2, flow rate = 1.0 mL/min, 23 °C, λ = 254 nm, retention time; minor isomer 13.13 min, major isomer 16.19 min, 98 % ee, $[\alpha]^{20}_D$ = +5.84 (c 1.0, $CHCl_3$).

1-Benzyl 3-(*tert*-butyl) 2-bromo-2-(*p*-*tert*-butyl-benzyl)malonate (3h)

After compound **2** (30 mg, 74 μmol) was reacted with *p*-*tert*-butyl benzyl bromide by procedure A, the title compound **3h** was obtained as a yellow oil (40 mg, 98%).; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.37 ~ 7.26 (m, 10H), 7.19 (d, 2H, *J* = 6.3 Hz), 7.07 (d, 2H, *J* = 8.4 Hz), 6.95 (s, 1H), 3.63 (d, 1H, *J* = 15.0 Hz), 3.57 (d, 1H, *J* = 15.0 Hz), 1.27 (s, 9H), 1.27 (s, 9H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 166.0, 165.1, 150.1, 139.0, 138.9, 131.3, 130.1, 128.5, 128.5, 128.4, 128.2, 128.0, 127.6, 127.2, 127.0, 124.9, 81.1, 79.5, 64.6, 43.0, 34,4, 31.3, 27.4 ppm; IR (KBr) 2963, 1741, 1514, 1369, 1259, 1149, 743, 699 cm^{-1}, Q-TOF (ESI) calcd for $[C_{31}H_{39}BrNO_4]^+$ ($[M+NH_4]^+$) 568.2057, found: 568.2041; The enantioselectivity was determined by chiral HPLC analysis (DAICEL Chiralpak AD-H, hexane : 2-propanol = 200 : 1, flow rate = 1.0 mL/min, 23 °C, λ = 254 nm, retention time; minor isomer 22.63 min, major isomer 24.85 min, 96% ee, $[\alpha]^{20}_D$ = +9.98 (c 1.0, $CHCl_3$).

1-Benzyl 3-(*tert*-butyl) 2-bromo-2-(*p*-fluoro-benzyl)malonate (3i)

After compound **2** (30 mg, 74 μmol) was reacted with *p*-fluoro benzyl bromide by procedure A, the title compound **3i** was obtained as a yellow oil (34.6 mg, 91%). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.36 ~ 7.30 (m, 10H),

7.09 ~ 7.04 (m, 2H), 6.93 (s, 1H), 6.82 (t, 2H, *J* = 8.4 Hz*)*, 3.61 (d, 1H, *J* = 14.9 Hz), 3.54 (d, 1H, *J* = 14.9 Hz), 1.30 (s. 9H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 165.8, 165.0, 162.3 (d, *J* = 325.7 Hz), 138.9, 138.8, 132.1 (d, *J* = 10.8 Hz), 130.2 (d, *J* = 4.1 Hz), 128.6, 128.5, 128.4, 128.1, 127.7, 127.1, 114.9 (d, *J* = 27.9 Hz), 84.4, 79.5, 64.4, 42.7, 27.4 ppm; IR (KBr) 2981, 2372, 2351, 2320, 1740, 1504, 1455, 1395, 1370, 1285, 1219, 1141, 1029, 956. 840, 772, 700, 673 cm^{-1}; Q-TOF (ESI) calcd for $[C_{27}H_{26}BrFNaO_4]^+$ ($[M+Na]^+$) 535.0891, found: 535.0887; The enantioselectivity was determined by chiral HPLC analysis (DAICEL Chiralcel OJ-H, hexane : 2-propanol = 98 : 2, flow rate = 1.0 mL/min, 23 °C, λ = 254 nm, retention time; minor isomer 9.12 min, major isomer 11.83 min, 98% ee, $[\alpha]^{20}_D$ = +13.34 (c 1.0, $CHCl_3$).

1-Benzyl 3-(*tert*-butyl) 2-bromo-2-(*p*-chloro-benzyl)malonate (3j)

After compound **2** (30 mg, 74 μmol) was reacted with *p*-chloro benzyl bromide by procedure A, the title compound **3j** was obtained as a yellow oil (32.2 mg, 82%).; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.34 ~ 7.29 (m, 10H), 7.06 (q, 4H, *J* = 6.6 Hz,), 6.93 (s, 1H), 3.61 (d, 1H, *J*= 15.0 Hz,), 3.54 (d, 1H, *J*= 15.0 Hz,), 1.30 (s, 9H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 165.7, 165.0, 138.9, 138.8, 133.4, 132.8, 131.8, 128.6, 128.5, 128.4, 128.2, 128.1 127.7, 127.0, 84.4, 79.5, 64.1, 42.8, 27.4 ppm; IR (KBr) 2979, 2348, 2309, 1740, 1682, 1493, 1219, 772, 699 cm^{-1}; HRMS(FAB) calcd for $[C_{27}H_{27}BrClO_4]^+$ ($[M+H]^+$) 529.0781, found: 529.0772; The enantioselectivity was determined by chiral HPLC analysis (DAICEL Chiralcel OJ-H, hexane : 2-propanol = 98 : 2, flow rate = 1.0 mL/min, 23 °C, λ = 254 nm, retention time; minor isomer 9.73 min, major isomer 13.91 min, 97% ee, $[\alpha]^{20}_D$ = +14.50 (c 1.0, $CHCl_3$).

1-Benzyl 3-(*tert*-butyl) 2-bromo-2-(*p*-bromo-benzyl)malonate (3k)

After compound **2** (30 mg, 74 μmol) was reacted with *p*-bromo-benzyl bromide by procedure A, the title compound **3k** was obtained as a yellow oil (26.3 mg, 62%). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.34 ~ 7.27 (m, 10H), 7.25 ~ 7.23 (m, 2H), 6.97 ~ 6.93 (m, 3H), 3.59 (d, 1H, *J* = 14.6 Hz), 3.52 (d, 1H, *J* = 14.6 Hz), 1.30 (s, 9H) ppm; ^{13}C-NMR (75 MHz, $CDCl_3$) δ 165.7, 165.0, 138.9, 138.7, 133.3, 132.2, 131.1, 128.6 128.5, 128.4, 128.4, 128.1, 127.6, 127.0, 121.6, 84.5, 79.5, 64.0, 42.8, 27.4 ppm; IR (KBr) 2978, 2373, 2323, 1741, 1586, 1489, 1450, 1370, 1260, 1219, 1150, 1075, 1013, 970, 771,692 cm^{-1}; HRMS(FAB) calcd for $[C_{27}H_{27}Br_2O_4]^+$ ($[M+H]^+$) 573.0276, found: 573.0272; The enantioselectivity was determined by chiral HPLC analysis (DAICEL Chiralpak AD-H, hexane : 2-propanol = 200 : 1, flow rate = 1.0 mL/min, 23 °C, λ = 254 nm, retention time; minor isomer 42.02 min, major isomer 44.90 min, 99% ee, $[\alpha]^{20}_D$ = +12.48 (c 1.0, $CHCl_3$).

1-Benzhydryl 3-(*tert*-butyl) 2-bromo-2-naphthylmalonate (3l)

After compound **2** (30 mg, 74 μmol) was reacted with 2-(Bromomethyl)naphthalene by procedure A, the title compound **3l** was obtained as a yellow oil (33.5 mg, 83%). mp 112.0 °C; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.75 (m, 1H), 7.66 ~ 7.59 (m, 4H), 7.44 ~ 7.41 (m, 3H), 7.36 ~ 7.33 (m, 9H), 6.95 (s, 1H), 3.80 (s, 2H), 1.29 (s, 9H) ppm; ^{13}C-NMR (75 MHz, $CDCl_3$) δ 165.9, 165.1, 139.0, 138.9, 133,1, 132.6, 132.0, 129.5, 128.6, 128.5, 128.5 128.4, 128.3, 128.0, 127.8, 127.6, 127.5, 127.0, 125.8, 125.7, 84.3, 79.4, 64.6, 43.5, 27.4 ppm; IR (KBr) 2979, 2372, 1739, 1600, 1370, 1271, 1220, 746, 699 cm^{-1}; HRMS (FAB) calcd for $[C_{31}H_{29}BrO_4]^+$ ($[M]^+$) 544.1249, found: 544.1243; The enantioselectivity was determined by chiral HPLC analysis (DAICEL Chiralpak AD-H, hexane : 2-propanol = 200 : 1, flow rate = 1.0 mL/min, 23 °C, λ = 254 nm, retention time; minor isomer 47.48 min, major isomer 65.97 min, 99% ee, $[\alpha]^{20}_D$ = +6.12 (c 1.0, $CHCl_3$).

Typical experimental procedure for the synthesis of azide compounds by S_N2 reaction (Procedure B)

Sodium azide (11.9 mg, 0.18 mmol) was added to 1-benzhydryl 3-(*tert*-butyl) 2-bromo-2-benzylmalonate (**3d,** 36 mg, 0.073 mmol) in DMSO (2.5 mL) at 65 °C. After 4 h, the reaction mixture was quenched by water, extracted by ethyl acetate (40 mL x 3 times), dried over anhydrous $MgSO_4$ and concentrated *in vacuo.* The residue was purified by flash column chromatography (silica gel, hexane : EtOAc = 30 : 1) to afford **4d** (32 mg, 96% yield) as a yellow oil.

1-Benzhydryl 3-(*tert*-butyl) 2-azido-2-hexylmalonate (4a)

After compound **3a** (25.5 mg, 52 μmol) was reacted sodium azide by procedure B, the title compound **4a** was obtained as a yellow oil (21.6 mg, 92%). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.36 ~ 7.29 (m, 10H), 7.00 (s, 1H), 1.95 ~ 1.81 (m, 2H), 1.34 (s, 9H), 1.29 ~ 1.20 (m, 8H), 0.85 (t, 3H, *J* = 3.0 Hz) ppm; ^{13}C-NMR (125 MHz, $CDCl_3$) δ 167.1, 166.1, 139.3, 139.2, 128.8, 128.8, 128.5, 128.5, 127.6, 127.4, 84.5, 79.2, 77.4, 72.6, 34.2, 31.6, 29.2, 27.9, 23.5, 22.6, 14.2 27. ppm; IR (KBr) 2924, 2854, 2348, 2310, 2121, 1745, 1456, 1371, 1252, 1218, 1183, 1152, 1030, 841, 772, 698 cm^{-1}; Q-TOF (ESI) calcd for $[C_{26}H_{33}N_3NaO_4]^+$ ($[M+Na]^+$) 474.2363, found: 474.2371; The enantioselectivity was determined by chiral HPLC analysis (DAICEL Chiralpak AD-H, hexane : 2-propanol = 200 : 1, flow rate = 1.0 mL/min, 23 °C, λ = 254 nm, retention time ; minor isomer 19.98 min, major isomer 22.94 min, 90% ee, $[\alpha]^{20}_D$ = +6.34 (c 1.0, $CHCl_3$).

1-Benzhydryl 3-(*tert*-butyl) 2-azido-2-(pro-2-yn-1-yl)malonate (4b)

After compound **3b** (28 mg, 63 μmol) was reacted sodium azide by procedure B, the title compound **4b** was obtained as a yellow oil (6.3 mg, 25%). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.37 ~7.33 (m, 10H), 7.00 (s, 1H), 2.84 (d, 2H, *J* = 2.4 Hz), 2.04 (t, 1H, *J* = 2.4 Hz), 1.35 (s, 9H) ppm; ^{13}C-NMR (150 MHz, $CDCl_3$) δ 165.8, 164.6, 139.0, 138.9, 131.4, 128.8, 128.8, 128.6, 128.6, 127.6, 127.5, 85.4, 79.8, 77.4, 72.4, 70.8, 27.8, 25.3 ppm; IR (KBr) 3295, 2982, 2359, 2129, 1745, 1745, 1455, 1396, 1371, 1292, 1248, 1219, 1149, 1046, 954, 837, 772, 699, 647 cm^{-1}; Q-TOF (ESI) calcd for $[C_{23}H_{23}N_3NaO_4]^+$ ($[M+Na]^+$) 428.1581, found: 428.1583; The enantioselectivity was determined by chiral HPLC analysis (DAICEL Chiralpak AD-H, hexane : 2-propanol = 98 : 2, flow rate = 1.0 mL/min, 23 °C, λ = 254 nm, retention time ; minor isomer 10.49 min, major isomer 12.52 min, 52% ee, $[\alpha]^{20}_D$ = +10.44 (c 1.0, $CHCl_3$).

1-Benzhydryl 3-(*tert*-butyl) 2-azido-2-allylmalonate (4c)

After compound **3c** (21 mg, 47 μmol) was reacted sodium azide by procedure B**,** the title compound **4c** was obtained as a yellow oil (12.4 mg, 65 %). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.36 ~ 7.27 (m, 10H), 7.00 (s, 1H), 5.72 ~5.61 (m, 1H), 5.08 ~5.01 (m, 2H), 2.67 (d, 2H, *J* = 6.9 Hz), 1.34 (s, 9H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 166.0, 164.9, 139.3, 139.2, 131.4, 128.7, 128.7, 128.5, 128.3, 127.8, 127.2, 120.5, 84.4, 79.4, 63.6, 42.9, 27.6 ppm; IR (KBr) 3735, 2981, 2348, 2309, 2126, 1743, 1455, 1395, 1371, 1248, 1218, 1144, 926, 838, 772, 699 cm^{-1}; HRMS (FAB) calcd for $[C_{23}H_{26}N_3O_4]^+$ ($[M+H]^+$) 408.1923, found: 408.1927; The enantioselectivity was determined by chiral HPLC analysis (DAICEL Chiralpak AD-H, hexane : 2-propanol = 200 : 1, flow rate = 1.0 mL/min, 23 °C, λ = 254 nm, retention time ; minor isomer 19.68 min, major isomer 25.31 min, 93% ee, $[\alpha]^{20}_D$ = +4.24 (c 1.0, $CHCl_3$).

1-Benzhydryl 3-(*tert*-butyl) 2-azido-2-benzylmalonate (4d)

After compound **3d** (36 mg, 73 μmol) was reacted sodium azide by procedure B, **t**he title compound **4d** was obtained as a yellow oil (31.9 mg, 96%). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.37 ~ 7.27 (m, 10H), 7.19 ~ 7.07 (m, 5H), 6.97 (s, 1H), 3.20 (s, 2H), 1.31 (s, 9H) ppm; ^{13}C-NMR (125 MHz, $CDCl_3$) δ 166.4, 165.4, 138.9, 138.9, 134.0, 130.4, 128.6, 128.5, 128.4, 128.2, 128.1, 127.7, 127.2, 127.1, 84.7, 79.3, 72.6, 39.6, 27.7 ppm; IR (KBr) 2979, 2372, 2351. 2320, 2125, 1744, 1541, 1455, 1371, 1218, 1149, 1018, 772, 699 cm^{-1}; HRMS (FAB) calcd for $[C_{27}H_{28}N_3O_4]^+$ ($[M+H]^+$) 458.2080, found: 458.2085; The enantioselectivity was determined by chiral HPLC

analysis (DAICEL Chiralpak AD-H, hexane : 2-propanol = 98 : 2, flow rate = 1.0 mL/min, 23 °C, λ = 254 nm, retention time ; minor isomer 13.01 min, major isomer 16.94 min, 97% ee, $[\alpha]^{20}_{D}$ = +5.44 (c 1.0, $CHCl_3$).

1-Benzhydryl 3-(*tert*-butyl) 2-azido-2-(4-(trifluoromethyl)benzyl)malonate (4e)

After compound **3f** (35 mg, 62 μmol) was reacted with sodium azide by procedure B**,** the title compound **4e** was obtained as a yellow oil (20.8 mg, 64 %). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.40 ~ 7.26 (m, 12H), 7.18 (d. 2H, *J* = 8.4 Hz), 6.97 (s, 1 H), 3.26 (d, 1H, *J* = 14.3 Hz), 3.19 (d, 1H, *J* = 14.3 Hz), 1.34 (s, 9H) ppm; ^{13}C-NMR (75 MHz, $CDCl_3$) δ 166.2, 165.2, 138.6 (d, *J* = 3.68 Hz), 138.1, 130.8, 129.5 (q, *J* = 20.9 Hz), 128.7, 128.5, 128.3, 127.8, 127.1, 125. 9, 124.9 (q, J_1 = 7.5 Hz, J_2 = 3.75 Hz), 85.1, 79.5, 77.2, 39.2, 27.4 ppm; IR (KBr) 2929, 2127, 1744, 1617, 1496, 1455, 1372, 1325, 1283, 1244 1218, 1165, 1150, 1126, 1067, 1021, 946, 839, 772, 699 cm^{-1} Q-TOF (ESI) calcd for $[C_{28}H_{26}F_3N_3O_4Na]^+$ ($[M+Na]^+$) 548.1768, found: 548.1771; The enantioselectivity was determined by chiral HPLC analysis (DAICEL Chiralpak AD-H, hexane : 2-propanol = 98 : 2, flow rate = 1.0 mL/min, 23 °C, λ = 254 nm, retention time ; minor isomer 7.10 min, major isomer 12.76 min, 97% ee, $[\alpha]^{20}_{D}$ = −3.26 (c 1.0, $CHCl_3$).

1-Benzhydryl 3-(*tert*-butyl) 2-azido-2-(naphthalene-2-ylmethyl)malonate (4f)

After compound **3l** (13 mg, 24 μmol) was reacted with sodium azide by procedure B, the title compound **4f** was obtained as a yellow oil (6.1 mg, 50 %). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.78 ~ 7.75 (m, 1H), 7.65 (d, 1H, *J* = 8.1 Hz), 7.60 ~ 7.57 (m, 1H), 7.54 (s, 1H), 7.43 ~ 7.40 (m, 2H), 7.38 ~ 7.34 (m, 5H), 7.29 (d, 1H, *J* = 1.8 Hz), 7.25 ~ 7.22 (m, 5H), 6.96 (s, 1H), 3.37 (s, 2H), 1.32 (s, 9H) ppm; ^{13}C-NMR (150 MHz, $CDCl_3$) δ 166.4, 165.4, 138.8, 133.1, 132.6, 131.6, 129.3, 128.7, 128.5, 128.5, 128.4, 128.2, 127.8, 127.6, 127.6, 127.5, 127.1, 125.8, 125.7, 133.1, 132.6, 131.6, 129.3, 84.8, 79.3, 72.8, 39.7, 27.7; IR (KBr) 2924, 2852, 2124, 1742, 1455, 1371, 1288, 1242 1219, 1149, 1032, 948, 838, 772, 699 cm^{-1} Q-TOF (ESI) calcd for $[C_{31}H_{29}N_3O_4Na]^+$ ($[M+Na]^+$) 530.2050, found: 530.2062; The enantioselectivity was determined by chiral HPLC analysis (DAICEL Chiralpak AD-H, hexane : 2-propanol = 98 : 2, flow rate = 1.0 mL/min, 23 °C, λ = 254 nm, retention time ; minor isomer 13.02 min, major isomer 21.05 min, 96% ee, $[\alpha]^{20}_{D}$ = −2.16 (c 1.0, $CHCl_3$).

Typical experimental procedure for the synthesis of aryloxy compounds by S_N2 reaction (Procedure C)

Phenol (54 mg, 575 μmol) was added to a toluene solution (1.5 mL) of 1-benzhydryl 3-(*tert*-butyl) 2-allyl-2-bromomalonate (**3c**, 25.6 mg, 57.5 μmol) and potassium carbonate (95 mg, 690 μmol) at room temperature and

raised temperature to 60 °C. The reaction mixture was turned to white heterogeneous solution. After 10 h, the solution was quenched by water (40 mL), extracted by ethyl acetate (50 mL x 2 times), dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash chromatography (silica gel, hexane : EtOAc = 10 : 1) to give the desired product **5a** (18.7 mg, 71%).

1-Benzhydryl 3-(*tert*-butyl) 2-allyl-2-phenoxymalonate (5a)

After compound **3c** (15 mg, 34 μmol) was reacted with phenol by procedure C, the title compound **5a** was obtained as a yellow oil (11 mg, 71%). ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.36 ~ 7.25 (s, 10H), 7.13 (td, 2H, J_1 = 7.3 Hz, J_2 = 0.75 Hz), 6.98 (s, 1H), 6.96 (t, 1H, J = 7.3 Hz), 6.89 (d, 2H, J = 8.5 Hz), 5.78 ~ 5.70 (m, 1H), 5.02 ~ 4.96 (m, 2H), 3.02 (d, 1H, J = 1.0 Hz), 3.00 (d, 1H, J = 1.0 Hz), 1.27 (s, 9H) ppm; ^{13}C-NMR (125 MHz, $CDCl_3$) δ 167.5, 166.2, 155.1, 139.4, 139.3, 130.6, 129.3, 128.6, 128.3, 128.2, 127.8, 127.6, 122.9, 119.9, 119.1, 85.2, 83.7, 78.6, 38.6, 27.8 ppm; IR (KBr) 3064, 2980, 2372, 2320, 1740, 1597, 1494, 1455, 1394, 1370, 1370, 1286, 1230, 1141, 1053, 1030, 955, 923, 840, 754, 698 cm^{-1}, HRMS (FAB) calcd for $[C_{29}H_{30}O_5]^+$($[M]^+$) 458.2093, found: 458.2086; The enantioselectivity was determined by chiral HPLC analysis (DAICEL Chiralpak AD-H, hexane : 2-propanol = 95 : 5, flow rate = 1.0 mL/min, 23 °C, λ = 254 nm, retention time ; minor isomer 12.41 min, major isomer 17.09 min, 92% ee, $[\alpha]^{20}_D$ = +14.84 (c 1.0, $CHCl_3$).

1-Benzhydryl 3-(*tert*-butyl) 2-allyl-2-(*p*-tolyloxy)malonate (5b)

After compound **3c** (24 mg, 54 μmol) was reacted with p-cresol by procedure C**,** the title compound **5b** was obtained as a yellow oil (13.8 mg, 54 %). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.29 ~ 7.27 (m, 10H), 6.98 (s, 1H), 6.92 (d, 2H, J = 8.6 Hz), 6.78 (d, 2H, J = 8.6 Hz), 5.82 ~ 5.68 (m, 1H), 5.03 ~ 4.93 (m, 2H), 2.98 (d, 2H, J = 7.2 Hz), 2.34 (s, 3H), 1.72 (s, 9H) ppm; ^{13}C-NMR (125 MHz, $CDCl_3$) 167.3, 166.2, 152.6, 139.2, 139.1, 132.2, 130.5, 129.6, 128.4, 128.3, 128.1, 128.0, 127.5, 127.4, 119.6, 119.2, 85.1, 83.3, 78.3, 38.2, 27.6, 20.5 ppm; IR (KBr) 3032, 2980, 2348, 2310, 1741, 1741, 1509, 1455, 1370, 1285, 1219, 1141, 1030, 841, 772, 699 cm^{-1}; HRMS (FAB) calcd for $[C_{30}H_{32}O_5]^+$($[M]^+$) 472.2250, found: 472.2251; The enantioselectivity was determined by chiral HPLC analysis (DAICEL Chiralpak AD-H, hexane : 2-propanol = 95 : 5, flow rate = 1.0 mL/min, 23 °C, λ = 254 nm, retention time ; minor isomer 8.68 min, major isomer 19.77 min, 90% ee, $[\alpha]^{20}_D$ = +3.44 (c 1.0, $CHCl_3$).

1-Benzhydryl 3-(*tert*-butyl) 2-allyl-2-(4-methoxylphenoxy)malonate (5c)

After compound **3c** (23 mg, 52 μmol) was reacted with 4-methoxyl-phenol by procedure C, the title compound **5c** was obtained as a yellow oil (15.7 mg, 62 %). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.32 ~ 7.29 (m, 10H), 6.98 (s, 1H), 6.85 (d, 2H, *J* = 6.8 Hz), 6.64 (d, 2H, *J* = 6.8 Hz), 5.84 ~ 5.70 (m, 1H), 5.06 ~ 4.95 (m, 2H), 3.72 (s, 3H), 2.94 (d, 2H, *J* = 7.8 Hz), 1.27 (s, 9H) ppm; ^{13}C-NMR (75 MHz, $CDCl_3$) 167.3, 166.1, 155.4, 148.3, 139.1, 139.0, 130.5, 128.4, 128.4, 128.1, 128.0, 127.5, 127.4, 121.1, 119.6, 114.0, 85.6, 83.3, 78.3, 55.46, 38.12, 27.60 ppm; IR (KBr) 2979, 2348, 2310, 1741, 1507, 1455, 1288, 1219, 1140, 1036, 923, 840, 772, 700 cm^{-1}; HRMS (FAB) calcd for $[C_{30}H_{32}O_6]^+$($[M]^+$) 488.2199, found: 488.2200; 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 ; minor isomer 11.47 min, major isomer 25.93 min, 90% ee, $[\alpha]^{20}_D$ = +14.30 (c 1.0, $CHCl_3$).

1-Benzhydryl 3-(*tert*-butyl) 2-allyl-2-(4-fluorophenoxy)malonate (5d)

After compound **3c** (23 mg, 52 μmol) was reacted with 4-fluoro-phenol by procedure C, the title compound **5d** was obtained as a yellow oil (15 mg, 60 %). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.30 ~ 7.28 (m, 10H), 6.98 (s, 1H), 6.87 ~6.76 (m, 4H), 5.82 ~ 5.68 (m, 1H), 5.07 ~ 4.96 (m, 2H), 2.97 (d, 2H, *J* = 9.0 Hz), 1.29 (s, 9H) ppm; ^{13}C-NMR (75 MHz, $CDCl_3$) 167.2, 166.0, 159.5 (d, *J* = 239.3 Hz), 150.9, 150.8, 139.0 (d, *J* = 8.6 Hz), 130.2, 128.4, 128.2, 128.1, 127.5, 127.4, 120.9 (d, *J* = 8.6 Hz) 119.8, 115.5 (d. *J* = 22.8 Hz), 85.6, 83.6, 78.5, 38.6, 27.6 ppm; IR (KBr) 3033, 2980, 2932, 1739, 1504, 1455, 1394, 1370, 1288, 1202, 1140, 1053, 1030, 924, 840, 757, 743, 699 cm^{-1}; HRMS (FAB) calcd for $[C_{29}H_{29}FO_5]^+$($[M]^+$) 476.1999, found: 476.1996; The enantioselectivity was determined by chiral HPLC analysis (DAICEL Chiralpak AD-H, hexane : 2-propanol = 95 : 5, flow rate = 1.0 mL/min, 23 °C, λ = 254 nm, retention time ; minor isomer 12.23 min, major isomer 17.05 min, 93% ee, $[\alpha]^{20}_D$ = +11.18 (c 1.0, $CHCl_3$).

1-Benzhydryl 3-(tert-butyl) 2-allyl-2-(4-chlorophenoxy)malonate (5e)

After compound **3c** (21 mg, 47 μmol) was reacted with 4-chloro-phenol by procedure C**,** the title compound **5e** was obtained as a yellow oil (13.4 mg, 58 %). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.32 ~ 7.23 (m, 10H), 7.05 (dt, 2H, J_1 = 9.0 Hz, J_2 = 3.3 Hz), 6.97 (s, 1H), 6.80 (dt, 2H, J_1 = 9.0 Hz, J_2 = 3.3 Hz), 5.80 ~ 5.66 (m, 1H), 5.07 ~ 4.97 (m, 2H), 2.98 (d, 2H, *J* = 6.6 Hz), 1.30 (s, 9H) ppm; ^{13}C-NMR (200 MHz, $CDCl_3$) δ 167.0, 165.8, 153.6, 139.0, 138.9, 130.1, 129.0, 128.4, 128.4, 128.2, 128.1, 127.7, 127.4, 127.3, 120.2, 120.0, 85.2, 83.7, 78.6, 38.7, 27.6

ppm; ; IR (KBr) 3680, 2980, 1740, 1489, 1455, 1370, 1232, 1140, 1052, 1032, 1017, 913, 835, 744, 700 cm^{-1}; Q-TOF (ESI) calcd for $[C_{29}H_{29}ClNaO_5]^+$([M+Na]$^+$) 515.1596, found: 515.1576; The enantioselectivity was determined by chiral HPLC analysis (DAICEL Chiralpak AD-H, hexane : 2-propanol = 90 : 10, flow rate = 1.0 mL/min, 23 °C, λ = 254 nm, retention time ; minor isomer 9.49 min, major isomer 16.25 min, 91% ee, $[\alpha]^{20}_D$ = +3.86 (c 1.0, $CHCl_3$).

***tert*-Butyl 2-allyl-3-oxo-3,4-dihydro-2*H*-benzo[b][1,4]oxazine-2-carboxylate (5f)**

After compound **3c** (20 mg, 45 μmol) was reacted with *o*-amino-phenol by procedure C, the title compound **5f** was obtained as a yellow oil (10.3 mg, 79 %). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.68 (bs, 1H), 7.08 ~ 6.91 (m, 3H), 6.75 (dd, 1 H, J_1 =7.2 Hz, J_2 = 1.8 Hz), 6.02 ~ 5.88 (m, 1H), 5.30 ~ 5.17 (m, 2H), 3.01 ~ 2.98 (m, 2H), 1.32 (s, 9H) ppm; ^{13}C-NMR (200 MHz, $CDCl_3$) 166.4, 163.5, 143.3, 130.8, 125.8, 124.2, 122.8, 119.9, 117.4, 115.2, 83.6, 77.2, 38.0, 27.7 ppm; IR (KBr) 3735, 2348, 2309, 1748, 1689, 1501, 1362, 1219, 772, 688, 671, 648 cm^{-1}; HRMS (FAB) calcd for $[C_{16}H_{19}NO_4]^+$([M]$^+$) 289.1314, found: 289.1313; The enantioselectivity was determined by chiral HPLC analysis (DAICEL Chiralpak AD-H, hexane : 2-propanol = 85 : 15, flow rate = 1.0 mL/min, 23 °C, λ = 254 nm, retention time ; minor isomer 6.37 min, major isomer 11.10 min, 70 % ee, $[\alpha]^{20}_D$ = +12.09 (c 1.0, $CHCl_3$).

1-Benzhydryl 3-(tert-butyl) 2-benzyl-2-(1H-1,2,3-triazol-1-yl)malonate (6)

Phenyl acetylene (7 μL, 62.7 μmol) was added to the *tert*-butanol (116 μL) and water (58 μL) solution of 1-benzhydryl 3-(*tert*-butyl) 2-azido-2-benzylmalonate (**4d**, 23.9 mg, 52.2 μmol), copper(II) sulfate penta-hydrate (2.6 mg 10.4 μmol), tris[(1-benzyl-1*H*-1,2,3-triazol-4-yl)methyl]amine (0.69 mg, 1.3 μmol) and sodium ascorbate (2.1 mg, 10.4 μmol). After stirring for 24 h at room temperature, the reaction was quenched by water, extracted by dichloromethane, dried over anhydrous $MgSO_4$ and concentrated *in vacuo.* The residue was purified by flash column chromatography (silica gel, hexane : EtOAc = 20 : 1) to afford **6** (24.3 mg, 83%) as a white amorphous solid. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.00 (s, 1H), 7.76 (dd, 2H, J_1 = 8.1 Hz, J_2 = 1.5 Hz), 7.44 ~7.34 (m, 7H), 7.34 ~ 7.26 (m, 6H), 7.14 (t, 1H, J = 7.5 Hz), 7.06 (s, 1H), 7.02 (t, 2H, J = 7.5 Hz), 6.56 (d, 2H, J = 6.9 Hz), 4.00 (d, 1H, J = 14.3 Hz), 3.89 (d, 1H, J = 14.3 Hz), 1.30 (s, 9H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 164.6, 163.4, 146.1, 138.6, 138.5, 133.2, 130.6, 130.0, 128.8, 128.7, 128.5, 128.3, 128.3, 128.0, 180.0, 127.6, 127.5, 127.0, 125.7, 122.3, 85.1, 79.5, 75.1, 42.0, 27.5 ppm; IR (KBr) 3021, 2978, 1735, 1586, 1496, 1455, 1369, 1180, 1142, 1080, 1029, 844, 747, 700 cm^{-1}, HRMS (FAB) calcd for $[C_{35}H_{34}N_3O_4]^+$([M+H]$^+$)

560.2549, found: 560.2553; $[\alpha]^{20}_{D} = -3.59$ (c 1.0, $CHCl_3$).

1-Benzhydryl 3-(tert-butyl) 2-amino-2-benzylmalonate (7)

To a methanol solution of 1-benzhydryl 3-(*tert*-butyl) 2-azido-2-benzylmalonate (**4d**, 671.9 mg, 1.469 mmol) and Pd/$BaSO_4$ (46.9 mg) was added 1 M ammonia solution in methanol (0.37 mL), and stirred under H_2 gas (1 atm). After 24 h, the reaction mixture was filtered through celite and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, hexane : EtOAc = 2 : 1) to give the desired product (**7**, 440 mg, 69%) as yellow oil. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.41 ~ 7.28 (m, 8H), 7.21 ~ 7.13 (m, 3H), 7.02 ~ 6.97 (m, 3H), 3.35 (d, 1H, *J* = 13.7 Hz), 3.29 (d, 1H, *J* = 13.7 Hz), 1.99 (bs, 2H), 1.33 (s, 9H) ppm; ^{13}C-NMR (75 MHz, $CDCl_3$) δ 170.7, 169.5, 139.4, 139.4, 135.0, 130.2, 128.6, 128.4, 128.3, 128.3, 128.0, 127.8, 127.1, 127.1, 82.8, 78.2, 66.7, 40.9, 27.7 ppm; IR (KBr) 3021, 2978, 1735, 1586, 1496, 1455, 1369, 1180, 1142, 1080, 1029, 844, 747, 700 cm^{-1}, HRMS (FAB) calcd for $[C_{27}H_{30}NO_4]^+$($[M+H]^+$) 432.2169, found: 432.2180; $[\alpha]^{20}_{D} = -20.26$ (c 1.0, $CHCl_3$).

1-Benzhydryl 3-(*tert*-butyl) 2-acetamino-2-benzylmalonate (8)

To a dichloromethane solution of 1-benzhydryl 3-(*tert*-butyl)-2-amino-2-benzylmalonate (**7**, 13.8 mg, 32 μmol) and trimethylamine (5.4 μL, 38 μmol) dropped acetic anhydride (3.6 μL, 38 μmol) at 0 °C and stirred at room temperature for 20 h. The reaction mixture was quenched by 1N HCl, extraction by ethyl acetate, washed sodium bicarbonate saturated solution, dried over anhydrous $MgSO_4$ and concentrated *in vacuo.* The residue was purified by column chromatography (silica gel, hexane : EtOAc = 7 : 1) to give the desired product (8, 10.3 mg, 68 %) as a colorless oil. ^{1}H-NMR (800 MHz, $CDCl_3$) δ 7.39 (d, 2H, *J* = 7.3 Hz), 7.36 (t, 2H, *J* = 7.3 Hz), 7.33 ~ 7.25 (m, 6H), 7.16 (t, 1H, *J* = 7.3 Hz), 7.13 (t, 2H, *J* = 7.2 Hz), 6.97 (s, 1H), 6.85 (d, 2H, *J* = 7.2 Hz), 6.52 (s, 1H), 3.70 (d, 1H, *J* = 14.2 Hz), 3.60 (d, 1H, *J* = 14.2 Hz), 1.96 (s, 3H), 1.27 (s, 9H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 168.9, 167.0, 166.1, 139.2, 139.1, 135.3, 130.0, 128.6, 128.4, 128.1, 128.0, 128.0, 127.2 , 127.0, 84.0, 78.7, 67.6, 37.6, 27.6, 23.0 ppm; IR (KBr) 3412, 3031, 2927, 1737, 1679, 1496, 1455, 1370, 1284, 1216, 1199, 1150, 1085, 1041, 957, 913, 840, 737, 700 cm^{-1}; HRMS (FAB) calcd for $[C_{29}H_{32}NO_5]^+$($[M+H]^+$) 474.2280, found: 474.2276; $[\alpha]^{20}_{D} = -34.49$ (c 1.0, $CHCl_3$).

1-Benzhydryl 3-(*tert*-butyl) (*R*)-2(N-Boc-amino)-2-benzyl malonate

Lithium perchlorate (20.3 mg, 0.19 mmol) was added to an ethanol solution of 1-benzhydryl 3-(*tert*-butyl)-2-amino-2-benzylmalonate (**7**, 164.9 mg, 0.38 mmol) and di-tert-butyl dicarbonate (416.9 mg, 1.91 mmol) in ethanol (2 mL) at room temperature. After stirring for 3 days, the solution was concentrated, diluted by ethyl acetate, washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, hexane : EtOAc = 10 : 1) afforded the desired product (152 mg, 75 %) as a white amorphous solid. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.39 ~ 7.27 (m, 8H), 7.25 ~ 7.14 (m, 4H), 7.00 (s, 1H), 6.90 ~ 6.88 (m , 2H), 5.76 (s, 1H), 3.70 ~ 3.55 (dd, 2H, *J* = 31.4 Hz, *J* = 14.4 Hz), 1.42 (s, 9H), 1.25 (s, 9H) ppm; ^{13}C-NMR (200 MHz, $CDCl_3$) δ 167.1, 166.2, 153.8, 139.2, 135.3, 130.1, 128.5, 128.3, 128.2, 128.0, 128.0, 127.9, 127.0, 126.9, 83.6, 79.9, 78.4, 67.2, 38.1, 28.2, 27.5 ppm; IR (KBr) 3432, 2979, 1737, 1716, 1487, 1369, 1285, 1219, 1152, 1013, 951, 839, 772, 699 cm^{-1}; Q-TOF (ESI) calcd for $[C_{32}H_{38}NO_6Na]^+$($[M+Na]^+$) 554.2513, found: 554.2489; $[\alpha]^{20}_D$ = −20.75 (c 1.0, $CHCl_3$).

***tert*-Butyl 2-benzyl-2-(N-Boc-amino)-3-hydroxypropanoate (9)**

To a methanol solution of 1-benzhydryl 3-(*tert*-butyl)-(*R*)-2(N-boc-amino)-2-benzylmalonate (43.5 mg, 81.8 μmol) was added Pd/C (50 mg) under H_2 (1 atm). After the reaction was stirred for 30 min, the solution was filtered over celite and evaporated *in vacuo*. After charging with argon gas, the crude residue was diluted by anhydrous THF and added triethylamine solution in THF (1.0M in THF) (0.1 mL, 98.2 μL) at room temperature. And then the reaction mixture was treated with ethyl chloroformate solution (1.0 M in THF) (0.1 mL, 98.2 μL) at −40 °C. After stirring for 1 h, the reaction mixture was filtered and concentrated *in vacuo*. To the residue in anhydrous THF solution under argon gas, lithium tri-*tert*-butoxyaluminum hydride solution (1.0 M in THF) (660 μL, 654 μmol) was added for 10 min at −78 °C and the mixture was stirred for 5 h at 65 °C. To the reaction solution, saturated ammonium chloride solution and an aqueous Rochelle salt solution was added at 0 °C, then the mixture was stirred for 1 h and extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous $MgSO_4$, then concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, hexane : EtOAc = 2 : 1) to afford the desired product as a colorless oil (9, 20.7 mg, 72%). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.31 ~ 7.14 (m, 5H), 5.41 (s, 1H), 4.25 ~ 4.20 (m, 1H), 3.89 ~ 3.83 (m, 1H), 3.39 (d, 1H *J* = 13.5 Hz), 3.24 (bs, 1H), 3.05 (d, 1H, *J*= 13.5 Hz), 1.47 (s, 9H), 1.46 (s, 9H) ppm; ^{13}C-NMR (125 MHz, $CDCl_3$) δ 171.2, 155.4, 135.7, 130.3, 128.5, 127.2, 83.3, 80.1, 66.6, 66.2, 37.6, 28.6, 28.1 ppm; IR (KBr) 3410, 3298, 2981, 1737, 1676, 1371, 1326, 1219, 1165, 772, 699 cm^{-1}; Q-TOF (ESI) calcd for $[C_{19}H_{29}NO_5Na]^+$ ($[M+Na]^+$) 374.1938, found: 374.1938, $[\alpha]^{20}_D$ = −32.05 (c 1.0, $CHCl_3$).

(*S*)-α-Benzylserine

tert-Butyl 2-benzyl-2-(N-Boc-amino)-3-hydroxypropanoate (**9**, 40 mg, 0.11 mmol) was added to 6 N-HCl (0.7 mL) and the reaction solution was heated at 90 °C for 5 h. The reaction solvent was removed *in vacuo* and the residue was purified by DOWEX 50WX8-100 ion exchange resin eluting with 10% NH_4OH solution to give (*S*)-α-benzylserine as a white solid (9.6 mg, 45 %). ^{1}H-NMR (300 MHz, D_2O) δ 7.34 ~7.31 (m, 3H), 7.22 ~ 7.19 (m, 2H), 3.98 (d, 1H, *J* = 12.0 Hz), 3.72 (d, 1H, *J* = 12.0 Hz), 3.20 (d, 1H, *J* = 14.3 Hz), 2.90 (d, 1H, *J* = 14.3 Hz). $[\alpha]_D^{20}$ = +16.73 (c 1.0, H_2O) {lit[15] (*R*)-α-benzylserine, $[\alpha]_D^{20}$ = −15.5 (c 1.0, H_2O), 95% ee}.

Acknowledgements

This work was supported by grants from the National Research Foundation of Korea (No. 2016R1A2B2008109) and BK21 Plus Program in 2016.

Supporting Information

Spectral data of all new compounds and HPLC analysis graph of optimized conditions. This material is available free of charge via the Internet at http://pubs.acs.org.

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