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Construction of Chiral α-Amino Quaternary Stereogenic Centers via Phase-Transfer Catalyzed Enantioselective α-Alkylation of α-Amidomalonates

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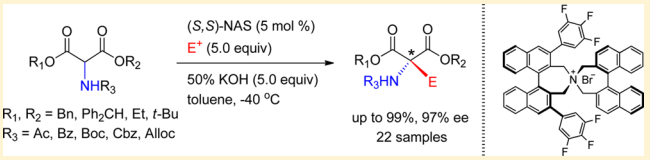
Supporting Information

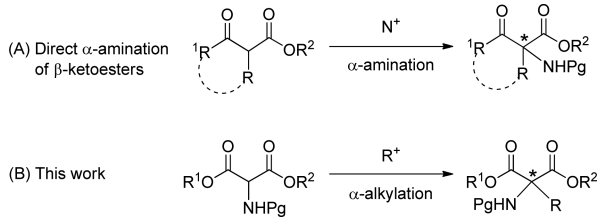
ABSTRACT: An efficient enantioselective synthetic method for α-amido-α-alkylmalonates via phase-transfer catalytic α-alkylation was successfully developed. The α-alkylation of α-amidomalonates under phase-transfer catalytic conditions (50% KOH, toluene, −40 °C) in the presence of (*S*,*S*)-3,4,5-trifluorophenyl-NAS bromide afforded the corresponding α-amido-α-alkylmalonates in high chemical yields (up to 99%) and optical yields (up to 97% ee), which could be readily converted to versatile chiral intermediates bearing α-amino quaternary stereogenic centers. The synthetic potential of this methodology was demonstrated via the synthesis of chiral azlactone, oxazoline, and unnatural α-amino acid.



The synthesis of optically active nitrogen-containing organic compounds is very important in organic chemistry and medicinal chemistry due to their versatile biological activities and pharmaceutical applications.[1] Alkaloids are a class of nitrogen-containing natural products, showing various biological activities, and also molecules of most pharmaceutics contain nitrogen. During the past decade, significant progress has enabled the construction of α-amino quaternary stereogenic centers with impressive levels of enantioselectivity, using either organometallic catalysis or organocatalysis.[2] There have been a lot of enantioselective synthetic methods developed for the α-amino-β-keto esters via electrophilic α-amination of β-keto esters (Scheme 1, A).[3] However, the enantioselective synthetic methods for the α-aminomalonates have mostly been achieved by the enzymatic desymmetrization[4] of prochiral α-amino-malonates, and there are only two cases as part of a study via chemical synthesis (each one malonate sample).[3u,5]

Recently, we reported new synthetic methods for producing α-monosubstituted chiral malonates or α,α-disubstituted chiral malonates with high chemical yields and enantioselectivities via phase-transfer catalytic (PTC)[6] α-alkylation of malonates in the presence of catalytic amounts of chiral quaternary ammonium salts, and successfully proved their usefulness by application to the synthesis of various chiral building blocks bearing quaternary stereogenic centers.[7] We planned to develop a new method for the synthesis of chiral quaternary α-aminomalonates via the well-established enantioselective phase-transfer catalytic α-alkylation of malonates. Incorporation of an amino group into the α-position of malonates, followed by enantioselective α-alkylation under phase-transfer catalysis conditions as the key step for asymmetric induction, would produce chiral α-aminomalonates (Scheme 1, B). This is an alternative strategy to the direct α-amination process (Scheme 1, A). Although the direct electrophilic α-aminations of carbonyl compounds can afford amines or protected amines directly in a single step, there is a limited availability of electrophilic nitrogen sources. In terms of diversity, the advantage of the alternative strategy compared to the direct electrophilic α-amination is that a variety of chiral compounds can be easily prepared simply by changing the alkylating reagent. Herein, we report a new and highly efficient enantioselective synthetic method for α-amino-α-alkylmalonates, which can be converted to valuable chiral building blocks bearing α-amino quaternary stereogenic centers (Scheme 2).

Scheme 1. Synthetic Strategy for Chiral α-Aminomalonates



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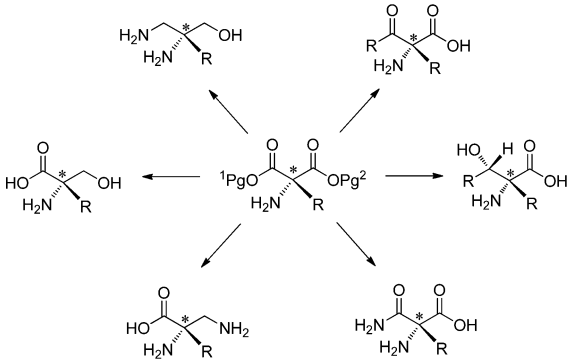
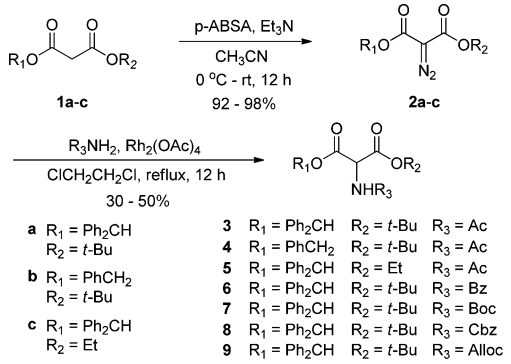
Scheme 2. Versatile Chiral Building Blocks from Chiral α-Amino-α-alkylmalonates[7b,8]



First, we needed to design enantiotopic unsymmetrical α-aminomalonates, possessing non-nucleophilic nitrogen as substrates for PTC α-alkylation. Seven α-amidomalonates (**3**–**9**) were prepared from various malonates **1a**–**c** in 2 steps (Scheme 3). Diazotization of **1a**–**c** by using *p*-acetamido-

Scheme 3. Preparation of α-Amidomalonates



benzenesulfonyl azide (p-ABSA) in the presence of triethylamine under acetonitrile afforded α-diazomalonates **2a**–**c**.[9] Subsequent N-H insertion of **2a**–**c** into acetamide, benzamide, or carbamates via carbenoid in the presence of rhodium(II) acetate [$Rh_2(OAc)_4$] successfully provided the corresponding α-amidomalonates **3**–**9** (30–50%).[10]

For preliminary study, the substrate efficiency of the prepared α-amidomalonates was examined by α-benzylation under typical PTC conditions, based on the previous reports.[7a] The enantioselective PTC benzylation of **3**–**9** was performed in the presence of the representative chiral quaternary ammonium salts (**10**–**14**)[11] (Figure 1), along with benzyl bromide (5.0 equiv) and 50% KOH (aq., 5.0 equiv) at room temperature in toluene (Table 1). As shown in Table 1, all substrates successfully gave the corresponding α-benzylated products in high chemical yields with variable enantioselectivities in the presence of Maruoka's catalyst, (*S*,*S*)-3,4,5-trifluorophenyl-NAS bromide (**10**) (entries 1–7). Diphenylmethyl ester and *tert*-butyl ester group (**3**) showed quite higher enantioselectivity than those of benzyl ester and ethyl ester group, respectively (**4** and **5**), which is in accord with the previous report for the synthesis of chiral quaternary α,α-disubstituted malonates.[7a] In the case of amide groups, acetyl group (**3**) gave better enantioselectivity than those of benzoyl (**6**), Boc (**7**). The Cbz (**8**) and Alloc (**9**) groups afforded the same enantioselectivity with a lower chemical yield than those

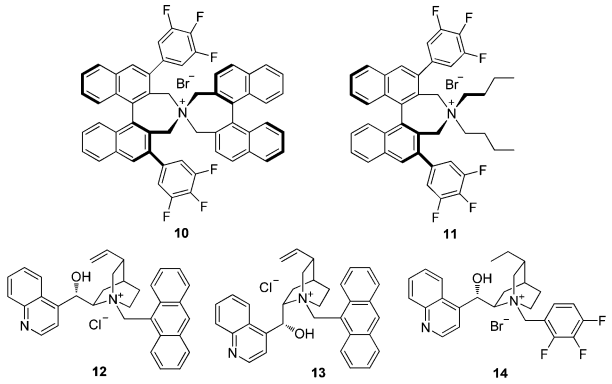
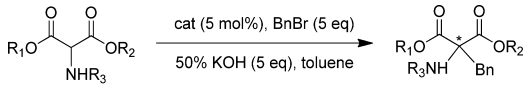


Figure 1. Representative chiral phase-transfer catalysts.

Table 1. Enantioselective PTC α-Benzylation of α-Amidomalonates (3–9).[a]



entry	sub.	cat.	*T* (°C)	time (h)	yield (%)[b]	ee (%)[c]
1	**3**	**10**	rt	0.5	99	87
2	**4**	**10**	rt	0.5	92	47
3	**5**	**10**	rt	0.5	95	59
4	**6**	**10**	rt	0.5	94	82
5	**7**	**10**	rt	0.5	98	80
6	**8**	**10**	rt	0.5	85	87
7	**9**	**10**	rt	0.5	93	87
8	**3**	**11**	rt	0.5	95	47
9	**3**	**12**	rt	0.5	91	23
10	**3**	**13**	rt	0.5	92	−19
11	**3**	**14**	rt	0.5	93	23
12	**3**	**10**	0	1	98	88
13	**3**	**10**	−20	2	96	91
14	**3**	**10**	−40	4	97	95
15	**3**	**10**	−60	23	92	94

[a]Reactions were performed with 5.0 equiv of benzyl 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 or DAICEL Chiralcel OD-H).

of acetyl group. Optimization of catalyst was then performed with substrate **3**.

Among the employed catalysts, Maruoka's catalyst, (*S*,*S*)-3,4,5-trifluorophenyl-NAS bromide (**10**), afforded the highest enantioselectivity in the PTC benzylation of **3** (entries 1 and 8–11). However, the other *N*,*N*-dibutylbinaphthyl derived catalyst **11** and the *cinchona* alkaloid derived catalysts (**12**–**14**) including Lygo's catalysts (**12**, **13**) resulted in lower enantioselectivities than the use of **10**. It is also notable that *N*-benzylation was not observed as a minor product, even in the presence of excess base and benzyl bromide under PTC conditions.

Next, the best substrate **3** was chosen to optimize the reaction conditions. The PTC benzylation of **3** was performed in the presence of the best catalyst, (*S*,*S*)-**10**, under variable base, solvent, and temperature conditions. Generally, the chemical yield and enantioseletivity were not significantly dependent on the base and solvent conditions at room temperature (data were not shown). In the case of temperature conditions, lower reaction temperatures clearly resulted in

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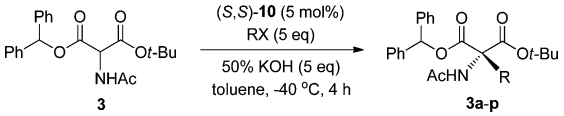
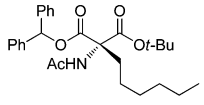
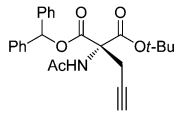
Table 2. Enantioselective Synthesis of α-Acetamido-α-alkylmalonates via PTC α-Alkylation

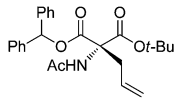




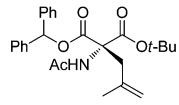
3a 26%[b] (75 h), 65% ee[c]



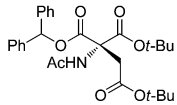
3b 99%, 54% ee



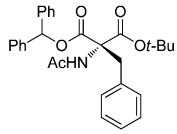
3c 99%, 76% ee



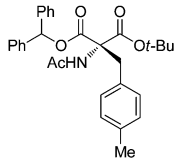
3d 98%, 91% ee



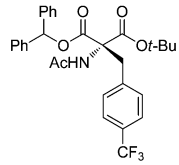
3e 67%, 63% ee



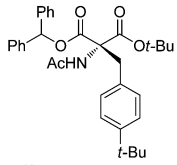
3f 97%, 95% ee (*R*)[d]



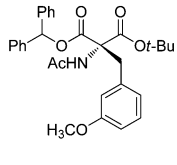
3g 99%, 97% ee



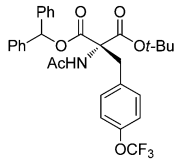
3h 95%, 95% ee



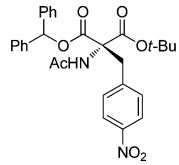
3i 99%, 95% ee



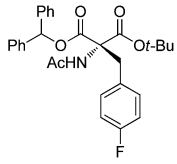
3j 96%, 94% ee



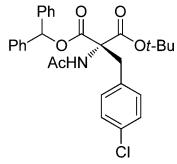
3k 91%, 95% ee



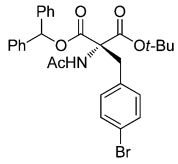
3l 99%, 96% ee



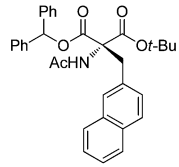
3m 99%, 96% ee



3n 86%, 97% ee



3o 98%, 97% ee



3p 98%, 91% ee

[a]Reactions were performed with 5.0 equiv of benzyl bromide and 5.0 equiv of 50% KOH (aq.) under the given conditions except **3a** (reaction time, 75 h). [b]Isolated yields. [c]Enantiopurity was determined by HPLC analysis using a chiral column (DAICEL Chiralpak AD-H). [d]Absolute configuration of **3f** was determined by the comparison of specific optical rotation value of α-benzylserine, prepared from **3f** with the reported (*S*)-α-benzylserine,[12] and by X-ray crystallography of **19** (Figure 2).[13]

higher enantioselectivity (entry 1, entries 12−15). However, the reaction time increased with a decrease in temperature, resulting in a quite longer reaction time at −60 °C (entry 15). Finally, 50% KOH base under toluene at −40 °C was chosen as the optimized reaction conditions, in consideration of enantioselectivity, chemical yield, and reaction time (entry 14; 97%, 95% ee).

The scope and limitations of enantioselective PTC alkylation of **3** with various electrophiles were performed under the optimized reaction conditions (Table 1, entry 14). As shown in Table 2, most of the alkylating agents showed very high enantioselectivities (**3d**, **3f**−**p**, 91−97% ee). However, unactivated alkylating reagent (**3a**, *n*-hexyl iodide) and three activated alkylating agents (**3b**−**c**, **3e**, propargyl bromide, allyl bromide, and *tert*-butyl bromoacetate) resulted in relatively lower enantioselectivities due to possibly low reaction rate or small molecular sizes, respectively. The very high enantioselectivities (up to 97% ee) indicate that this reaction system is a very efficient enantioselective synthetic method for α-amino-α-alkylmalonates.

The synthetic potential of this method was demonstrated via the synthesis of an unnatural amino acid, α-benzylserine, from optically active α-acetamido-α-benzylmalonate (**3e**), as exemplified in Scheme 4. Catalytic hydrogenation of **3e** with Pd/C-H_2 in methanol afforded the corresponding monoacid **15**. The activation of **15** via mixed anhydride by using ethyl chloroformate in the presence of *N*-methylmorphorine (NMM) gave azlactone **16** via intramolecular cyclization. The reduction of **16** using $NaBH_4$ provided the corresponding alcohol **17**. Finally, the acidic hydrolysis of **17** using 6 N HCl afforded (*R*)-α-benzylserine {$[\alpha]_D^{20}$ = −15.5 (*c* 1.0, H_2O); lit[12]

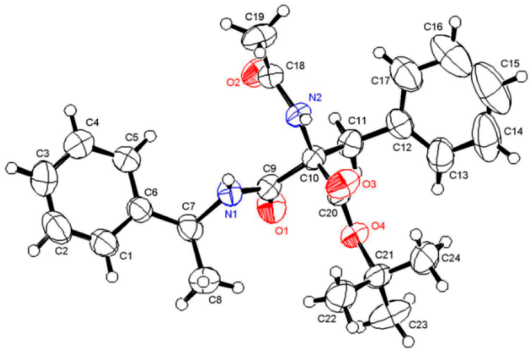


Figure 2. X-ray crystallographic structure of **19**.[13]

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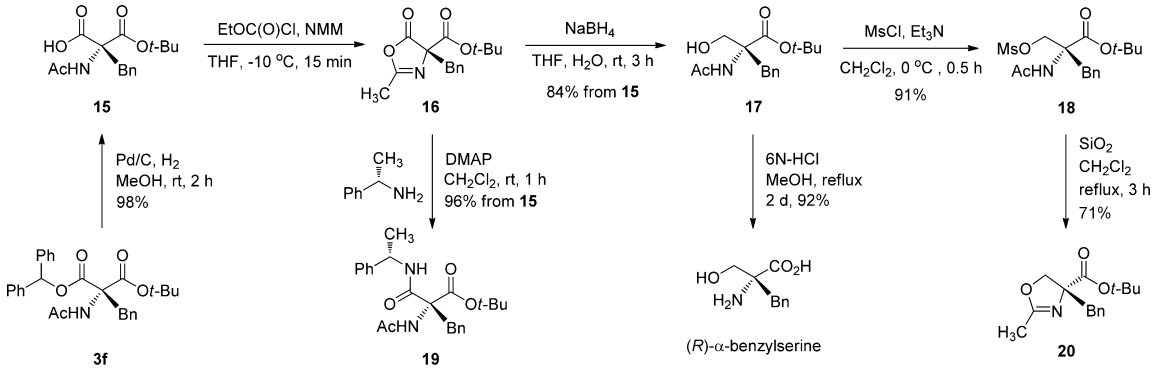
Scheme 4. Conversion of 3f to 19, 20, and (*R*)-α-Benzylserine



(*S*)-α-benzylserine, $[\alpha]_D^{20}$ = 16.4 (*c* 0.80, H_2O), 98% ee}. The mesylation of **17**, followed by intramolecular cyclization in the presence of triethylamine under methylene chloride, afforded oxazoline **20**. Also, opening of the ring of azlactone **16** was attempted via nucleophilic substitution of amine. The treatment of (*R*)-methylbenzylamine with azlactone **16** in the presence of DMAP under methylene chloride successfully afforded amide **19**.

In conclusion, an enantioselective synthetic method for α-amido-α-alkylmalonates via PTC α-alkylation was successfully developed. The asymmetric PTC α-alkylations of diphenylmethyl-*tert*-butyl α-acetamidomalonate afforded the corresponding α-acetamido-α-alkylmalonates in high chemical yields (up to 99%) and optical yields (up to 97% ee). Our new catalytic system provides an attractive synthetic method for versatile chiral building blocks, which could be readily converted to chiral target molecules involving α-amino quaternary stereogenic centers. We are now extending our synthetic method to the β-keto ester system.

■ 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. Phase-transfer catalyst (**12**, **14**) was prepared according to the reported procedure. Phase-transfer catalysts (**10**, **11**, **13**) were purchased from the commercial source. TLC analyses were performed using a 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. Infrared analyses (KBr pellet) were performed by FT-IR. ^{1}H NMR spectra were recorded at 300, 400, or 500 MHz with reference to $CHCl_3$ (δ 7.24) or CH_3OH (δ 3.31). ^{13}C NMR spectra were obtained by a 100, 125, or 150 MHz 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 a positive-ion FAB, CI, or Q-TOF (ESI) spectrometer. Melting points were measured on a melting point apparatus and were uncorrected. Optical rotations were measured on a polarimeter and calibrated with pure solvent as a blank.

Benzhydryl *tert*-Butyl Malonate (1a). Commercially available hydrogen *tert*-butyl malonate (1 g, 6.24 mmol) was dissolved in acetonitrile (20 mL) and heated to reflux. To this solution were added α-bromodiphenylmethane (1.7 g, 6.87 mmol) and triethylamine (960 μL, 6.87 mmol) in sequence. The reaction was stirred until the TLC analysis showed that the reaction was complete. Water mixable solvent was evaporated and diluted with dichloromethane. Quenching with ammonium chloride (200 mL), washing with brine (150 mL × 2), drying over anhydrous $MgSO_4$, filtration, and purifying by flash column chromatography (silica gel, hexane:EtOAc solution = 15:1) afforded **1a** (1.73 g, 85% yield) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34−7.18 (m, 10H), 6.89 (s, 1H), 3.33 (s, 2H), 1.36 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.8, 165.3, 139.6, 128.4, 127.9, 127.1, 82.0, 77.6, 43.2, 27.7 ppm; IR (KBr) 2960, 2924, 2853, 1732, 1680, 1462, 1377, 1021, 773 cm^{-1}; HRMS (ESI) calcd for $[C_{20}H_{22}O_4Na]^+$ ($[M + Na]^+$) 349.1410, found: 349.1422.

Benzyl *tert*-Butyl Malonate (1b). Commercially available hydrogen *tert*-butyl malonate (1 g, 6.24 mmol) was dissolved in acetonitrile (20 mL) and heated to reflux. To this solution were added benzyl bromide (816 mg, 6.87 mmol) and triethylamine (960 μL, 6.87 mmol) in sequence. The reaction was stirred until the TLC analysis showed that the reaction was complete. Water mixable solvent was evaporated and diluted with dichloromethane. Quenching with ammonium chloride (200 mL), washing with brine (150 mL × 2), drying over anhydrous $MgSO_4$, filtration, and purifying by flash column chromatography (silica gel, hexane:EtOAc solution = 20:1) afforded **1b** (1.27 g, 81% yield) as a pale yellow oil. ^{1}H NMR (300 MHz, CDCl3) δ 7.36−7.28 (m, 5H), 5.15 (s, 2H), 3.31 (s, 2H), 1.41 (s, 9H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.7, 165.5, 135.4, 128.5, 128.3, 128.3, 82.0, 66.9, 42.8, 27.8 ppm; IR (KBr) 2979, 1750, 1731, 1369, 1333, 1280, 1143, 1001, 772, 698 cm^{-1}; HRMS (FAB) calcd for $[C_{14}H_{19}O_4]^+$ ($[M + H]^+$) 251.1283, found: 251.1282.

Benzhydryl Ethyl Malonate (1c). Commercially available monoethyl malonate (1 g, 7.57 mmol) was dissolved in acetonitrile (25 mL) and heated to reflux. To this solution were added α-bromodiphenylmethane (2.06 g, 8.33 mmol) and triethylamine (1.16 mL, 8.33 mmol) in sequence. The reaction was stirred until the TLC analysis showed that the reaction was completed. Water mixable solvent was evaporated and diluted with dichloromethane. Quenching with ammonium chloride (200 mL), washing with brine (150 mL × 2), drying over anhydrous $MgSO_4$, filtration, and purifying by flash column chromatography (silica gel, hexane:EtOAc solution = 10:1) afforded **1c** (1.72 g, 76% yield) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34−7.24 (m, 10H), 6.93−6.92 (d, 1H, *J* = 1.65 Hz), 4.24−4.14 (p, 2H, *J* = 7.1 Hz), 3.46 (s, 2H), 1.25−1.19 (t, 3H, *J* = 7.1 Hz) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.3, 165.5, 165.3, 139.6, 139.5, 128.5, 128.0, 128.0, 127.1, 127.1, 127.0, 139.6, 139.5, 128.5, 128.0, 128.0, 127.1, 127.1, 127.0, 78.0, 61.6, 41.9, 14.0 ppm; IR (KBr) 3033, 1751, 1734, 1220, 1148, 1032, 772, 699 cm^{-1} ; HRMS (CI) calcd for $[C_{18}H_{17}O_4]^+$ ($[M - H]^+$) 297.1127, found: 297.1125.

Typical Experimental Procedure for the Preparation of Malonate Substrates (3−9) from 1a−c (Procedure A). Triethylamine (1.28 mL, 9.19 mmol) was added to a stirred solution of benzhydryl *tert*-butyl malonate (**1a**, 1.0 g, 3.06 mmol) and *p*-(acetamido)benzenesulfonyl azide (*p*-ABSA) (795 mg, 3.31 mmol) in acetonitrile (15 mL) at 0 °C under an argon atmosphere. The reaction was gradually warmed to room temperature overnight. Unexpectedly, the product spot had the same R_f value with the substrate spot on TLC. Therefore, the reaction was stirred during 12 h for complete conversion of the substrate into the product. The expected duration of the reaction might have been shorter than the actual reaction time. The reaction mixture was then filtered through a

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pad of Celite and washed with EtOAc, and the filtrate was purified by flash column chromatography on silica gel eluting with hexane−EtOAc (15:1) to afford **2a** (1.058 g, 98% yield) as a yellow solid. A solution of acetamide (101 mg, 1.70 mmol) and rhodium(II) acetate (2.5 mol %) in 1,2-dichloroethane (10 mL) was heated to reflux. To this solution was added a solution of the diazo compound **2a** (500 mg, 1.42 mmol) in 1,2-dichloroethane(5 mL) dropwise over 1 h. The reaction was stirred for a further 12 h until the reaction was complete. The mixture was evaporated and concentrated for loading on flash column chromatography without further workup procedure. Eluting with hexane−EtOAc (5:1) afforded purified α-acetamidomalonate **3** (272 mg, 50% yield) as a white solid.

1-Benzhydryl 3-(*tert*-Butyl) 2-Diazomalonate (2a). Following the procedure (A) from **1a**, **2a** was obtained quantitatively as a yellow solid (98% yield). mp 68.8 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37−7.20 (m, 10H), 7.03 (s, 1H), 1.50 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.3, 159.3, 139.5, 128.3, 127.8, 126.8, 82.8, 77.3, 65.9, 28.0 ppm; IR (KBr) 2979, 2139, 1954, 1755, 1727, 1687, 1325, 1276, 1166, 1097, 760, 700 cm^{-1}; HRMS (FAB) calcd for $[C_{20}H_{20}N_2NaO_4]^+$ ([M + Na]$^+$) 375.1321, found: 375.1316.

1-Benzyl 3-(*tert*-Butyl) 2-Diazomalonate (2b). Following the procedure (A) from **1b**, **2b** was obtained quantitatively as a pale yellow oil (95% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37−7.27 (m, 5H), 5.24 (s, 2H), 1.49 (s, 9H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.2, 159.7, 135.4, 128.5, 128.3, 128.2, 83.1, 66.7, 28.2 ppm; IR (KBr) 2979, 2137, 1757, 1731, 1687, 1370, 1328, 1276, 1165, 1095, 772, 697 cm^{-1}; HRMS (FAB) calcd for $[C_{14}H_{17}N_2O_4]^+$ ([M + H]$^+$) 277.1188, found: 277.1180.

1-Benzhydryl 3-Ethyl 2-Diazomalonate (2c). Following the procedure (A) from **1c**, **2c** was obtained quantitatively as a pale yellow oil (92% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40−7.24 (m, 10H), 7.01 (s, 1H), 4.37−4.28 (q, 2H, J = 7.1 Hz), 1.34−1.30(t, 3H, J = 7.1 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.8, 160.5, 139.7, 128.5, 128.0, 127.0, 77.9, 66.2, 61.7, 14.3 ppm; IR (KBr) 2941, 2143, 1759, 1733, 1692, 1372, 1320, 1307, 1269, 1098, 1076, 772, 701 cm^{-1}; HRMS (CI) calcd for $[C_{18}H_{15}N_2O_4]^+$ ([M-H]$^+$) 323.1032, found: 323.1036.

1-Benzhydryl 3-(*tert*-Butyl) 2-Acetamidomalonate (3). Following the procedure (A) on regitz-diazo transfer and N-H insertion via rhodium carbenoid, the title compound **3** was obtained as a white solid (50% yield). mp 120.3 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33−7.25 (m, 10H), 6.92 (s, 1H), 6.56−6.54 (d, 1H, J = 6.7 Hz), 5.20−5.18 (d, 1H, J = 7.0 Hz), 2.01 (s, 3H), 1.33 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.6, 165.9, 164.9, 139.2, 139.0, 128.5, 128.4, 128.2, 128.1, 127.3, 127.0, 83.8, 78.7, 57.2, 27.6, 22.6 ppm; IR (KBr) 3299, 2980, 1756, 1666, 1371, 772, 700 cm^{-1}; HRMS (FAB) calcd for $[C_{22}H_{26}NO_5]^+$ ([M + H]$^+$): 384.1811, found: 384.1803.

1-Benzyl 3-(*tert*-Butyl) 2-Acetamidomalonate (4). Following the procedure (A) from **2b** using acetamide, the title compound **4** was obtained as a colorless oil (49% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33−7.29 (m, 5H), 6.54−6.53 (d, 1H, J = 5.8 Hz), 5.28−5.26 (d,1H, J = 12.1 Hz), 5.13−5.10 (d, 1H, J = 12.1 Hz), 5.09−5.08 (d, 1H, J = 7.0 Hz), 2.03 (s, 3H), 1.33 (s, 9H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.7, 166.6, 165.0, 134.9, 128.5, 128.4, 83.8, 67.8, 57.0, 27.6, 22.7 ppm; IR (KBr) 3286, 2980, 2939, 1756, 1666, 1524, 1500, 1371, 1149, 1003, 770, 754, 699 cm^{-1}; HRMS (FAB) calcd for $[C_{16}H_{22}NO_5]^+$ ([M + H]$^+$) 308.1498, found: 308.1494.

1-Benzhydryl 3-Ethyl 2-Acetamidomalonate (5). Following the procedure (A) from **2c** using acetamide, the title compound **5** was obtained as a white solid (46% yield). mp 106.1 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36−7.24 (m, 10H), 6.90 (s, 1H), 6.60−6.57 (d, 1H, J = 7.0 Hz), 5.31−5.29 (d, 1H, J = 7.0 Hz), 4.21−4.14 (q, 2H, J = 7.2 Hz), 2.02 (s, 3H), 1.19−1.14 (t, 3H, J = 7.2 Hz) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.7, 166.1, 165.5, 139.1, 138.9, 128.5, 128.4, 128.2, 128.2, 127.0, 127.0, 79.0, 62.7, 56.6, 22.6, 13.8 ppm; IR (KBr) 3284, 3063, 3033, 2983, 1760, 1743, 1666, 1221, 1158, 1028, 771, 700 cm^{-1}; HRMS (FAB) calcd for $[C_{20}H_{22}NO_5]^+$ ([M + H]$^+$) 356.1498, found: 356.1489.

1-Benzhydryl 3-(*tert*-Butyl) 2-Benzamidomalonate (6). Following the procedure (A) from **2a** using benzamide, the title compound **6** was obtained as a colorless oil (37% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.84−7.81 (m, 2H), 7.55−7.20 (m, 13H), 7.13−7.11 (d, 1H, J = 6.6 Hz), 6.97 (s, 1H), 5.38−5.36 (d, 1H, J = 6.8 Hz), 1.37(s, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.8, 165.8, 164.9, 139.2, 139.0, 133.1, 132.0, 128.5, 128.5, 128.4, 128.2, 128.1, 127.3, 127.2, 127.0, 84.1, 78.9, 57.6, 27.6 ppm; IR (KBr) 3430, 2980, 1755, 1667, 1483, 1369, 1339, 1220, 1148, 772, 699 cm^{-1}; HRMS (FAB) calcd for $[C_{27}H_{28}NO_5]^+$ ([M + H]$^+$) 446.1967, found: 446.1967.

1-Benzhydryl 3-(*tert*-Butyl) 2-[(*tert*-Butoxycarbonyl)amino]-malonate (7). Following the procedure (A) from **2a** using *tert*-butyloxycarboxamide, the title compound **7** was isolated as a pale yellow oil (30% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30−7.21 (m, 10H), 6.89 (s, 1H), 5.52−5.49 (d, 1H, J = 7.3 Hz), 4.93−4.90 (d, 1H, J = 7.7 Hz), 1.39 (s, 9H), 1.29 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.1, 165.1, 154.7, 139.3, 139.2, 128.5, 128.4, 128.2, 128.1, 127.3, 127.1, 83.6, 80.4, 78.6, 58.4, 28.2, 27.6 ppm; IR (KBr) 3440, 2979, 2932, 1759, 1720, 1496, 1368, 1220, 1161, 772 cm^{-1}; HRMS (CI) calcd for $[C_{25}H_{32}NO_6]^+$ ([M + H]$^+$) 442.2230, found: 442.2229.

1-Benzhydryl 3-(*tert*-Butyl) 2-{[(Benzyloxy)carbonyl]amino}-malonate (8). Following the procedure (A) from **2a** using benzyl carbamate, the title compound **8** was isolated as a colorless oil (32% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33−7.24 (m, 15H), 6.93 (s, 1H), 5.81−5.78 (d, 1H, J = 7.5 Hz), 5.10 (s, 2H), 5.06−5.01 (d, 1H, J = 7.53 Hz), 1.33 (s, 9H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.8, 164.8, 155.3, 139.2, 139.1, 136.01, 128.5, 128.5, 128.5, 128.2, 128.2, 128.1, 127.3, 127.1, 83.9, 78.8, 67.3, 58.6, 27.6 ppm; IR (KBr) 1759, 1730, 1622, 1497, 1339, 1220, 1148, 840, 772 cm^{-1}; HRMS (CI) calcd for $[C_{28}H_{30}NO_6]^+$ ([M + H]$^+$) 476.2073, found: 476.2071.

1-Benzhydryl 3-(*tert*-Butyl) 2-{[(Allyloxy)carbonyl]amino}-malonate (9). Following the procedure (A) from **2a** using allylcarbamate, the title compound **9** was isolated as a colorless oil (33% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33−7.26 (m, 10H), 6.94 (s, 1H), 5.92−5.83 (m, 1H), 5.79−5.78 (d, 1H, J = 7.4 Hz), 5.31−5.28 (d, 1H, J = 17.2 Hz), 5.20−5.18(d, 1H, J = 10.4 Hz), 5.03−5.01(d, 1H, J = 7.7 Hz), 4.57−4.56(d, 2H, J = 5.4 Hz), 1.34(s, 9H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.8, 164.8, 155.2, 139.2, 139.0, 132.3, 128.5, 128.4, 128.2, 128.1, 127.3, 127.0, 83.9, 78.7, 66.1, 58.5, 27.6 ppm; IR (KBr) 2980, 1759, 1731, 1648, 1497, 1220, 1148, 1059, 772, 700 cm^{-1}; HRMS (FAB) calcd for $[C_{24}H_{28}NO_6]^+$ ([M + H]$^+$) 426.1917, found: 426.1931.

Typical Experimental Procedure for the Enantioselective Phase-Transfer Catalytic Alkylation (Procedure B). Benzyl bromide (46.5 μL, 0.39 mmol) was added to a solution of 1-benzhydryl 3-(*tert*-butyl) 2-acetamidomalonate (**3**, 30 mg, 0.078 mmol) and (*S*,*S*)-3,4,5-trifluorophenyl-NAS bromide (**10**, 3.6 mg, 0.004 mmol) in toluene (261 μL) at room temperature. At the designated low temperature, aqueous 50% w/v aqueous KOH (44 μL, 0.39 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 on silica gel eluting with hexane−EtOAc solution (7:1) to afford **3f** (36 mg, 97% yield) as a white solid.

1-Benzyl 3-(*tert*-Butyl) 2-Acetamido-2-benzylmalonate (4f). Following the procedure (B) from **4**, the title compound **4f** was obtained as a colorless oil (92% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40−7.30 (m, 5H), 7.21−7.18 (m, 3H), 7.00−6.94 (m, 2H), 6.50 (s, 1H), 5.29−5.25 (d,1H, J = 12.0 Hz), 5.17−5.13 (d, 1H, J = 12.0 Hz), 3.68−3.63 (d, 1H, J = 14.0 Hz), 3.58−3.53 (d, 1H, J = 14.0 Hz), 1.99 (s, 3H), 1.32 (s, 9H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.0, 167.6, 166.1, 135.3, 135.0, 123.0, 128.9, 128.5, 128.5, 128.1, 127.0, 83.9, 67.9, 67.4, 37.6, 27.6, 23.0 ppm; IR (KBr) 3412, 2979, 2933, 1739, 1681, 1496, 1370, 1217, 1198, 1150, 1048, 771, 701 cm^{-1}; HRMS (FAB) calcd for $[C_{23}H_{28}NO_5]^+$ ([M + H]$^+$) 398.1967, found: 398.1966; 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 6.99 min, major isomer 8.03 min, 47% ee, $[\alpha]_D^{25}$ = +6.92 (c 1.0, $CHCl_3$).

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1-Benzhydryl 3-Ethyl 2-Acetamido-2-benzylmalonate (5f). Following the procedure (B) from **5**, the title compound **5f** was obtained as a white solid (95% yield). mp 120.0 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39−7.21 (m, 10H), 7.21−7.10 (m, 3H), 6.96−6.92 (s, 1H), 6.82−6.79(d, 2H, J = 6.4 Hz), 6.53 (s, 1H), 4.16−4.08 (q, 2H, J = 7.1 Hz), 3.73−3.63 (m, 2H), 1.99 (s. 3H), 1.13−1.08 (t, 3H, J = 7.1 Hz) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.0, 167.3, 166.6, 139.1, 138.9, 135.0, 129.8, 128.6, 128.4, 128.4, 128.2, 128.1, 127.7, 127.1, 126.9, 78.9, 67.3, 62.7, 37.7, 22.9, 13.8 ppm; IR (KBr) 3411, 3032, 2983, 1742, 1680, 1496, 1281, 1218, 1196, 771, 701 cm^{-1}; HRMS (FAB) calcd for $[C_{27}H_{28}NO_5]^+$ ([M + H]$^+$) 446.1967, found: 446.1976; 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 16.38 min, major isomer 32.22 min, 59% ee, $[\alpha]_D^{25}$ = +16.8 (c 1.0, $CHCl_3$).

1-Benzhydryl 3-(*tert*-Butyl) 2-Benzamido-2-benzylmalonate (6f). Following the procedure (B) from **6**, the title compound **6f** was obtained as a white solid (94% yield). mp 101.9 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70−7.67 (m, 2H), 7.58−7.49 (m, 1H), 7.49−7.29 (m, 7H), 7.29−7.20 (m, 6H), 7.19−7.09 (m, 3H), 7.05 (s, 1H), 6.93−6.91 (d, 2H, J = 6.6 Hz), 3.88−3.83 (d,1H, J = 14.1 Hz), 3.76−3.71 (d, 1H, J = 14.1 Hz), 1.28 (s, 9H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.9, 166.2, 166.2, 139.2, 139.1, 135.2, 133.8, 131.8, 130.1, 128.5, 128.5, 128.3, 128.2, 128.2, 128.1, 128.0, 127.8, 127.0, 127.0, 84.2, 78.5, 67.7, 37.6, 27.6 ppm; IR (KBr) 3415, 3032, 3006, 2979, 1734, 1667, 1508, 1479, 1287, 1219, 1201, 1150, 839, 772, 700 cm^{-1}; HRMS (FAB) calcd for $[C_{34}H_{34}NO_5]^+$ ([M + H]$^+$) 536.2437, found: 536.2439; The enantioselectivity was determined by chiral HPLC analysis (DAICEL Chiralcel OD-H, hexane:2-propanol = 99:1, flow rate = 1.0 mL/min, 23 °C, λ = 254 nm, retention time; minor isomer 9.85 min, major isomer 11.26 min, 82% ee, $[\alpha]_D^{25}$ = +15.03 (c 1.0, $CHCl_3$).

1-Benzhydryl 3-(*tert*-Butyl) 2-Benzyl-2-((*tert*-butoxycarbonyl)amino)malonate (7f). Following the procedure (B) from **7**, the title compound **7f** was obtained as a white solid (98% yield). mp 104.0 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34−7.18 (m, 10H), 7.11−7.05 (m, 3H), 6.93 (s, 1H), 6.82−6.80 (m, 2H), 5.56 (s, 1H), 3.63−3.58 (d,1H, J = 14.0 Hz), 3.52−3.47 (d, 1H, J = 14.0 Hz), 1.35 (s, 9H), 1.19 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.2, 166.2, 153.8, 139.3, 135.4, 130.1, 128.6, 128.3, 128.1, 128.0, 127.1, 83.6, 80.0, 78.5, 67.3, 38.2, 28.36, 27.6 ppm; IR (KBr) 3410, 2927, 1736, 1682, 1370, 1219, 772, 700 cm^{-1}, HRMS (CI) calcd for $[C_{32}H_{38}NO_6]^+$ ([M + H]$^+$) 532.2699, found: 532.2703; 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 8.55 min, major isomer 10.16 min, 80% ee, $[\alpha]_D^{25}$ = +11.67 (c 1.0, $CHCl_3$).

1-Benzhydryl 3-(*tert*-Butyl) 2-Benzyl-2-(((benzyloxy)carbonyl)amino)malonate (8f). Following the procedure (B) from **8**, the title compound **8f** was obtained as a colorless oil (85% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37−7.24 (m, 15H), 7.17−7.04 (m, 3H), 6.98 (s, 1H), 6.81−6.79 (d, 2H, J = 6.96 Hz), 6.00 (s, 1H), 5.15−5.11 (d,1H, J = 12.3 Hz), 5.02−4.98 (d, 1H, J = 12.3 Hz), 3.68−3.63 (d,1H, J = 14.1 Hz), 3.60−3.55 (d, 1H, J = 14.1 Hz), 1.22 (s, 9H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.9, 165.9, 154.3, 139.2, 139.1, 136.4, 135.0, 130.0, 128.6, 128.5, 128.3, 128.1, 128.1, 128.0, 127.9, 127.1, 126.9, 83.9, 78.6, 67.7, 66.8, 38.0, 27.5 ppm; IR (KBr) 3421, 2979, 2932, 1727, 1496, 1286, 1261, 1219, 1150, 1023, 772, 699 cm^{-1}; HRMS (CI) calcd for $[C_{35}H_{36}NO_6]^+$ ([M + H]$^+$) 566.2543, found: 566.2548; The enantioselectivity was determined by chiral HPLC analysis (DAICEL Chiralcel AD-H, hexane:2-propanol = 80:20, flow rate = 1.0 mL/min, 23 °C, λ = 254 nm, retention time; minor isomer 13.42 min, major isomer 16.37 min, 87% ee, $[\alpha]_D^{25}$ = +15.63 (c 1.0, $CHCl_3$).

1-Benzhydryl 3-(*tert*-Butyl) 2-(((Allyloxy)carbonyl)amino)-2-benzylmalonate (9f). Following the procedure (B) from **9**, the title compound **9f** was obtained as a colorless oil (93% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37−7.26 (m, 10H), 7.20−7.10 (m, 3H), 6.98 (s, 1H), 6.92−6.89 (m, 2H), 6.00 (s, 1H), 5.94−5.81(m, 1H), 5.31−5.28 (d, 1H, J = 17.1 Hz), 5.22−5.18 (d, 1H, J = 11.0 Hz), 4.60−4.45 (m, 2H), 3.70−3.65 (d, 1H, J = 14.2 Hz), 3.61−3.56 (d, 1H, J = 14.2 Hz), 1.25 (s, 9H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.9, 165.9, 154.2, 139.2, 139.2, 135.0, 132.6, 130.1, 128.6, 128.3, 128.1, 128.0, 127.9, 127.6, 127.1, 127.0, 117.8, 84.0, 78.5, 67.6, 65.6, 38.0, 27.5 ppm; IR (KBr) 3421, 2925, 2854, 1728, 1495, 1258, 1219, 1150, 1095, 1027, 772 cm^{-1}; HRMS (FAB) calcd for $[C_{31}H_{34}NO_6]^+$ ([M + H]$^+$) 516.2386, found: 516.2396; The enantioselectivity was determined by chiral HPLC analysis (DAICEL Chiralcel AD-H, hexane:2-propanol = 80:20, flow rate = 1.0 mL/min, 23 °C, λ = 254 nm, retention time; minor isomer 8.83 min, major isomer 13.71 min, 87% ee, $[\alpha]_D^{25}$ = +16.16 (c 1.0, $CHCl_3$).

1-Benzhydryl 3-(*tert*-Butyl) 2-Acetamido-2-hexylmalonate (3a). Following the procedure (B), the title compound **3a** was obtained as a white solid (26% yield). mp 90.9 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27−7.17 (m, 10H), 6.87 (s, 1H), 6.70 (s, 1H), 2.38−2.15 (m, 2H), 1.92 (s, 3H), 1.20−1.11 (m, 15H), 0.95−0.90 (s, 2H), 0.79−0.74 (t, 3H, J = 6.9 Hz) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.7, 167.5, 167.0, 139.4, 139.3, 128.5, 128.3, 128.2, 128.0, 127.6, 127.3, 83.5, 78.3, 67.1, 32.1, 31.6, 28.9, 27.5, 23.4, 23.0, 22.5, 14.0 ppm; IR (KBr) 2956, 2926, 2856, 1738, 1682, 1496, 1219, 1155, 772 cm^{-1}; HRMS (FAB) calcd for $[C_{28}H_{38}NO_5]^+$ ([M + H]$^+$) 468.2750, found: 468.2764; 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 8.50 min, major isomer 17.66 min, 65% ee, $[\alpha]_D^{25}$ = +4.49 (c 1.0, $CHCl_3$).

1-Benzhydryl 3-(*tert*-Butyl) (*R*)-2-Acetamido-2-(prop-2-yn-1-yl)malonate (3b). Following the procedure (B), the title compound **3b** was obtained as a white solid (99% yield). mp 135.2 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31−7.18 (m, 10H), 6.91−6.88 (m, 2H), 3.37−3.30 (dd,1H, J_1 = 17.2 Hz, J_2 = 2.8 Hz), 3.21−3.15 (dd,1H, J_1 = 17.2 Hz, J_2 = 2.8 Hz) 1.96 (m, 3H), 1.87−1.85 (t, 1H, J = 2.66 Hz), 1.23 (s, 9H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.2, 165.9, 165.3, 139.0, 128.4, 128.3, 128.1, 128.1, 127.5, 127.4, 84.4, 78.8, 78.4, 71.3, 65.7, 27.4, 23.7, 22.8 ppm; IR (KBr) 3413, 3294, 2979, 2926, 2854, 2122, 1740, 1682, 1496, 1314, 1218, 1151, 963, 772, 699, 648 cm^{-1}; HRMS(FAB) calcd for $[C_{25}H_{28}NO_5]^+$ ([M + H]$^+$) 422.1967, found: 422.1977; 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 10.46 min, major isomer 25.78 min, 54% ee, $[\alpha]_D^{25}$ = +5.39 (c 1.0, $CHCl_3$).

1-Benzhydryl 3-(*tert*-Butyl) (*R*)-2-Acetamido-2-allylmalonate (3c). Following the procedure (B), the title compound **3c** was obtained as a white solid (99% yield). mp 71.9 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30−7.22 (m, 10H), 6.90 (s, 1H), 6.71 (s, 1H), 5.53−5.39 (m, 1H), 5.01−4.94 (m, 2H), 3.19−3.12 (m, 1H), 3.02−2.94 (m, 1H), 1.95 (s, 3H), 1.22 (m, 9H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.8, 166.9, 166.4, 139.2, 131.2, 128.5, 128.3, 128.2, 128.0, 127.6, 127.3, 119.7, 83.9, 78.5, 66.5, 36.8, 27.6, 22.9 ppm; IR (KBr) 3408, 2926, 1736, 1683, 1496, 1219, 1154, 959, 772, 699 cm^{-1}; HRMS(FAB) calcd for $[C_{25}H_{30}NO_5]^+$ ([M + H]$^+$) 424.2124, found: 424.2111; 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 9.42 min, major isomer 19.04 min, 76% ee, $[\alpha]_D^{25}$ = +6.02 (c 1.0, $CHCl_3$).

1-Benzhydryl 3-(*tert*-Butyl) (*R*)-2-Acetamido-2-(2-methylallyl)malonate (3d). Following the procedure (B), the title compound **3d** was obtained as a white solid (98% yield). mp 112.0 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32−7.20 (m, 10H), 6.90 (s, 1H), 6.76 (s, 1H), 4.74 (m, 1H), 4.56 (s, 1H), 3.19−3.14 (d, 1H, J = 14.2 Hz), 3.04−2.99 (d, 1H, J = 14.2 Hz), 1.93 (s, 3H), 1.55 (s, 3H), 1.20 (s, 9H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.8, 167.3, 166.7, 140.0, 139.3, 139.1, 128.4, 128.3, 128.2, 128.0, 127.7, 127.3, 115.8, 83.9, 78.5, 66.6, 39.6, 27.5, 23.3, 22.9 ppm; IR (KBr) 3413, 2979, 1736, 1682, 1370, 1277, 1219, 841, 772 cm^{-1}; HRMS (FAB) calcd for $[C_{26}H_{32}NO_5]^+$ ([M + H]$^+$) 438.2280, found: 438.2277; The enantioselectivity was determined by chiral HPLC analysis (DAICEL

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Chiralpak AD-H, hexane:2-propanol = 80:20, flow rate = 1.0 mL/min, 23 °C, λ = 254 nm, retention time; minor isomer 8.97 min, major isomer 17.43 min, 91% ee, $[\alpha]_D^{25}$ = +8.16 (*c* 1.0, $CHCl_3$).

1-Benzhydryl 1,2-Di-*tert*-butyl (*R*)-1-Acetamidoethane-1,1,2-tricarboxylate (3e). Following the procedure (**B**), the title compound **3e** was obtained as a white solid (67% yield). mp 120.5 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28−7.18 (m, 10H), 6.96 (s, 1H), 6.88 (s, 1H), 3.50−3.32 (dd, 2H, J_1 = 36.7 Hz, J_2 = 17.3 Hz), 1.91 (s, 3H), 1.29 (s, 9H), 1.19 (s, 9H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.4, 169.2, 166.3, 165.4, 139.2, 139.1, 128.4, 128.4, 128.1, 128.1, 127.4, 127.4, 83.9, 81.3, 78.7, 64.5, 38.7, 27.9, 27.4, 28.9 ppm; IR (KBr) 3413, 2979, 1682, 1153, 772, 2926, 1741, 1496, 1370, 1220, 961, 700 cm^{-1}; HRMS (FAB) calcd for $[C_{28}H_{36}NO_7]^+$ ($[M + H]^+$) 498.2492, found: 498.2483; The enantioselectivity was determined by chiral HPLC analysis (DAICEL Chiralcel AD-H, hexane:2-propanol = 80:20, flow rate = 1.0 mL/min, 23 °C, λ = 254 nm, retention time ; minor isomer 20.34 min, major isomer 41.45 min, 67% ee, $[\alpha]_D^{25}$ = −2.97 (*c* 1.0, $CHCl_3$).

1-Benzhydryl 3-(*tert*-Butyl) (*R*)-2-Acetamido-2-benzylmalonate (3f). Following the procedure (B), the title compound **3f** was obtained as a white solid (97% yield). mp 164.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41−7.26 (m, 10H), 7.17−7.11 (m, 3H), 6.98 (s, 1H), 6.87−6.85 (d, 2H, *J* = 6.4 Hz), 6.53 (s, 1H), 3.73−3.69 (d, 1H, *J* = 14.0 Hz), 3.63−3.59 (d, 1H, *J* = 14.0 Hz), 1.96 (s, 3H), 1.28 (s, 9H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.9, 167.0, 166.1, 139.2, 139.1, 135.3, 130.0, 128.6, 128.3, 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) 3410, 2927, 1736, 1682, 1370, 1219, 772, 700 cm^{-1}; HRMS (CI) calcd for $[C_{29}H_{32}NO_5]^+$ ($[M + H]^+$) 474.2280, found: 474.2277; 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 10.20 min, major isomer 17.04 min, 95% ee, $[\alpha]_D^{25}$ = +23.06 (*c* 1.0, $CHCl_3$).

1-Benzhydryl 3-(*tert*-Butyl) (*R*)-2-Acetamido-2-(4-methylbenzyl)malonate (3g). Following the procedure (B), the title compound **3g** was obtained as a white solid (99% yield). mp 165.6 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35−7.18 (m, 10H), 6.91−6.86 (m, 3H), 6.69−6.66 (m, 2H), 6.46 (s, 1H), 3.63−3.58 (d, 1H, *J* = 14.0 Hz), 3.52−3.47 (d, 1H, *J* = 14.0 Hz), 2.19 (s, 3H), 1.90 (s, 3H), 1.21(m, 9H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.9, 167.1, 168.2, 139.2, 139.1, 136.5, 132.1, 129.8, 128.8, 128.6, 128.3, 128.0, 127.9, 127.2, 83.9, 78.6, 67.6, 37.2, 27.6, 23.0, 21.0 ppm; IR (KBr) 3416, 2925, 1736, 1683, 1281, 1220, 1150, 772 cm^{-1}, HRMS (FAB) calcd for $[C_{30}H_{33}NO_5]^+$($[M + H]^+$) 488.2437, found: 488.2441; 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 11.53 min, major isomer 17.09 min, 97% ee, $[\alpha]_D^{25}$ = +22.59 (*c* 1.0, $CHCl_3$).

1-Benzhydryl 3-(*tert*-Butyl) (*R*)-2-Acetamido-2-(4-(trifluoromethyl)benzyl)malonate (3h). Following the procedure (B), the title compound **3h** was obtained as a white solid (95% yield). mp 158.5 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41−7.25 (m, 12H), 6.98 (s, 1H), 6.93−6.90 (d, 2H, *J* = 8.0 Hz), 6.53 (s, 1H), 3.77−3.65 (dd, 2H, J_1 = 22.2 Hz, J_2 = 14.0 Hz), 1.97 (s, 3H), 1.28 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.1, 166.8, 165.83 139.5, 138.9, 130.3, 129.3 (d, *J* = 32.4 Hz) 128.7, 128.4, 128.3 (d, *J* = 40.5 Hz), 128.0, 127.1, 125.0 (q, *J* = 3.5 Hz), 84.3, 78.9, 67.4, 37.4, 27.6, 22.9 ppm; IR (KBr) 3410, 3298, 2981, 1737, 1676, 1371, 1326, 1219, 1165, 772, 699 cm^{-1}; HRMS (FAB) calcd for $[C_{30}H_{31}F_3NO_5]^+$ ($[M + H]^+$) 542.2154, found: 542.2153; 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 8.26 min, major isomer 14.10 min, 95% ee, $[\alpha]_D^{25}$ = +25.74 (*c* 1.0, $CHCl_3$).

1-Benzhydryl 3-(*tert*-Butyl) (*R*)-2-Acetamido-2-(4-(*tert*-butyl)benzyl)malonate (3i). Following the procedure (B), the title compound **3i** was obtained as a white solid (99% yield). mp 156.5 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53−7.34 (m, 10H), 7.27−7.23 (m, 2H), 7.09 (s, 1H), 6.92−6.90 (m, 2H), 6.66 (s, 1H), 3.81−3.76 (d, 1H, *J* = 14.1 Hz), 3.71−3.66 (d, 1H, *J* = 14.1 Hz), 2.08 (s, 3H), 1.38−1.36 (m, 18H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.9, 167.1, 166.2, 149.7, 139.3, 139.1, 132.1, 129.7, 128.6, 128.3, 128.3, 128.0, 127.9, 127.3, 125.0, 83.9, 78.6, 67.6, 37.1, 34.3, 31.3, 27.6, 23.0 ppm; IR (KBr) 3410, 2963, 2927, 1736, 1676, 1496, 1369, 1219, 772 cm^{-1}; HRMS (FAB) calcd for $[C_{33}H_{40}NO_5]^+$ ($[M + H]^+$) 530.2906, found: 530.2902; 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 6.88 min, major isomer 11.26 min, 95% ee, $[\alpha]_D^{25}$ = +22.86 (*c* 1.0, $CHCl_3$).

1-Benzhydryl 3-(*tert*-Butyl) (*R*)-2-Acetamido-2-(3-methoxybenzyl)malonate (3j). Following the procedure (B), the title compound **3j** was obtained as a white solid (96% yield). mp 130.5 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41−7.29 (m, 10H), 7.07−7.02 (t, 1H, *J* = 7.9 Hz), 6.98 (s, 1H), 6.73−6.70 (m, 1H), 6.56 (s, 1H), 6.48−6.44 (m, 2H), 3.72−3.56 (m, 5H), 1.96 (s, 3H), 1.26 (s, 9H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.9, 167.0, 166.1, 159.3, 139.2, 139.1, 136.8, 129.0, 128.6, 128.3, 128.3, 128.0, 127.7, 127.3, 122.3, 115.6, 112.6, 84.0, 78.6, 67.5, 54.9, 37.7, 27.6, 23.0 ppm; IR (KBr) 2984, 1736, 1676, 1370, 1220, 1151, 1043, 772 cm^{-1}; HRMS (FAB) calcd for $[C_{30}H_{34}NO_6]^+$ ($[M + H]^+$) 504.2386, found: 504.2395; 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 11.56 min, major isomer 20.53 min, 94% ee, $[\alpha]_D^{25}$ = +15.05 (*c* 1.0, $CHCl_3$).

1-Benzhydryl 3-(*tert*-Butyl) (*R*)-2-Acetamido-2-(4-(trifluoromethoxy)benzyl)malonate (3k). Following the procedure (B), the title compound **3k** was obtained as a white solid (91% yield). mp 130.5 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40−7.22 (m, 10H), 6.97−6.94 (d, 3H, *J* = 9.2 Hz), 6.84−6.81 (d, 2H, *J* = 8.8 Hz), 6.55 (s, 1H), 3.71−3.59 (dd, 2H, J_1 = 22.4 Hz, J_2 = 14.1 Hz), 1.97 (s, 3H), 1.27 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.0, 166.8, 165.9, 148.3 (d, *J* = 1.6 Hz), 139.0, 134.0, 131.3, 128.6, 128.4, 128.3 (d, *J* = 38.5 Hz), 128.0, 127.1, 120.5, 84.2, 78.8, 67.5, 36.9, 27.6, 23.0 ppm; IR (KBr) 2925, 1739, 1508, 1262, 1153, 839, 3411, 1680, 1220, 699 cm^{-1}; HRMS (FAB) calcd for $[C_{30}H_{31}F_3NO_6]^+$ ($[M + H]^+$) 558.2103, found: 558.2093; 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 7.28 min, major isomer 11.90 min, 95% ee, $[\alpha]_D^{25}$ = +24.73 (*c* 1.0, $CHCl_3$).

1-Benzhydryl 3-(*tert*-Butyl) (*R*)-2-Acetamido-2-(4-nitrobenzyl)malonate (3l). Following the procedure (B), the title compound **3l** was obtained as a white solid (99% yield). mp 168.8 °C; ^{1}H NMR(300 MHz, $CDCl_3$) δ 7.92−7.89 (d, 2H, *J* = 8.6 Hz), 7.34−7.19 (m, 10H), 6.92−6.86 (t, 3H, *J* = 9.1 Hz), 6.47 (s, 1H), 3.75−3.65 (dd, 2H, J_1 = 18.3 Hz, J_2 = 14.1 Hz), 1.93 (s, 3H), 1.24 (s, 9H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.2, 166.6, 165.7, 147.1, 143.2, 138.8, 138.8, 130.8, 128.8, 128.7, 128.5, 128.2, 128.1, 127.7, 127.1, 123.8, 123.3, 84.5, 79.1, 67.3, 37.5, 31.9, 29.7, 29.4, 27.6, 23.0, 22.7, 14.1 ppm; IR (KBr) 2979, 2925, 1738, 1522, 1348, 1219, 1149 cm^{-1}; HRMS (FAB) calcd for $[C_{29}H_{31}N_2O_7]^+$ ($[M + H]^+$) 519.2131, found: 519.2131; 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 23.37 min, major isomer 37.80 min, 96% ee, $[\alpha]_D^{25}$ = +25.54 (*c* 1.0, $CHCl_3$).

1-Benzhydryl 3-(*tert*-Butyl) (*R*)-2-Acetamido-2-(4-fluorobenzyl)malonate (3m). Following the procedure (B), the title compound **3m** was obtained as a white solid (99% yield). mp 154.4 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40−7.24 (m, 10H), 6.96 (s, 1H), 6.84−6.74 (m, 4H), 6.52 (s, 1H), 3.69−3.56 (dd, 2H, J_1 = 25.3 Hz, J_2 = 14.3 Hz), 1.96 (s, 3H), 1.27 (m, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.0, 166.9, 166.0, 162.0 (d, *J* = 243.8 Hz), 139.1, 139.0, 131.4 (d, *J* = 7.9 Hz), 131.0 (d, *J* = 3.1 Hz), 128.6, 128.4, 128.4, 128.1, 128.0, 127.2, 115.0 (d, *J* = 21.0 Hz), 114.9, 84.1, 78.8, 67.6, 36.8, 27.6, 23.0 ppm; IR (KBr) 3408, 2926, 1736, 1676, 1510, 1220, 1150, 841, 772 cm^{-1}; HRMS (FAB) calcd for $[C_{29}H_{31}FNO_5]^+$ ($[M + H]^+$) 492.2186, found: 492.2195; The enantioselectivity was determined by

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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 10.77 min, major isomer 16.01 min, 96% ee, $[\alpha]_D^{25}$ = +23.41 (*c* 1.0, $CHCl_3$).

1-Benzhydryl 3-(*tert*-Butyl) (*R*)-2-Acetamido-2-(4-chlorobenzyl)malonate (3n). Following the procedure (B), the title compound **3n** was obtained as a white solid (86% yield). mp 158.9 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39−7.26 (m, 10H), 7.09−7.06 (m, 2H), 6.96 (s, 1H), 6.74−6.72 (m, 2H), 6.52 (s, 1H), 3.68−3.55 (dd, 2H, J_1 = 24.0 Hz, J_2 = 14.1 Hz), 1.96 (s, 3H), 1.27 (s, 9H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.0, 166.9, 165.9, 139.0, 139.0, 133.8, 133.0, 131.2, 128.6, 128.5, 128.4, 128.3, 128.1, 128.0, 127.1, 84.1, 78.8, 67.5, 37.0, 27.6, 23.0 ppm; IR (KBr) 3410, 2926, 1738, 1219, 1150, 1092, 2854, 1680, 1493, 772 cm^{-1} ; HRMS (FAB) calcd for $[C_{29}H_{31}ClNO_5]^+$ ([M + H]$^+$) 508.1891, found: 508.1901; 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 11.76 min, major isomer 18.48 min, 97% ee, $[\alpha]_D^{25}$ = +20.33 (*c* 1.0, $CHCl_3$).

1-Benzhydryl 3-(*tert*-Butyl) (*R*)-2-Acetamido-2-(4-bromobenzyl)malonate (3o). Following the procedure (B), the title compound **3o** was obtained as a white solid (98% yield). mp 182.5 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40−7.20 (m, 12H), 6.96 (s, 1H), 6.68−6.65 (m, 2H), 6.51 (s, 1H), 3.66−3.54 (dd, 2H, J_1 = 23.3 Hz, J_2 = 14.0 Hz), 1.95 (s, 3H), 1.27 (s, 9H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.0, 166.8, 165.9, 138.98, 138.96, 134.3, 131.6, 131.2, 128.6, 128.5, 128.4, 128.1, 128.0, 127.1, 121.1, 84.1, 78.8, 67.4, 37.0, 27.6, 23.0 ppm; IR (KBr) 3408, 2924, 1736, 1676, 1491, 1370, 1219, 1149, 1012, 772 cm^{-1}; HRMS (FAB) calcd for $[C_{29}H_{31}BrNO_5]^+$ ([M + H]$^+$) 552.1386, found: 552.1381; 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 11.86 min, major isomer 19.32 min, 97% ee, $[\alpha]_D^{25}$ = +29.97 (*c* 1.0, $CHCl_3$).

1-Benzhydryl 3-(*tert*-Butyl) (*R*)-2-Acetamido-2-(naphthalen-2-ylmethyl)malonate (3p). Following the procedure (B), the title compound **3p** was obtained as a white solid (98% yield). mp 162.4 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78−7.73 (m, 1H), 7.64−7.61 (d, 1H, *J* = 8.6 Hz), 7.56−7.52 (m, 1H), 7.46−7.24 (m, 13H), 7.01−6.98 (m, 2H), 6.53 (s, 1H), 3.91−3.86 (d, 1H, *J* = 14.1 Hz), 3.81−3.76 (d, 1H, *J* = 14.1 Hz), 1.98 (s, 3H), 1.30 (s, 9H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.1, 167.0, 166.1, 139.2, 139.2, 133.2, 132.9, 132.4, 128.8, 128.7, 128.4, 128.4, 128.1, 128.1, 127.9, 127.6, 127.5, 127.5, 127.2, 125.9, 125.6, 84.0, 78.7, 67.8, 37.7, 27.6, 23.0, ppm; IR (KBr) 3331, 2978, 1736, 1667, 1496, 1298, 1219, 1151, 772, 700 cm^{-1}, HRMS (FAB) calcd for $[C_{33}H_{34}NO_5]^+$ ([M + H]$^+$) 524.2437, found: 524.2424; 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 12.11 min, major isomer 19.45 min, 91% ee, $[\alpha]_D^{25}$ = +29.48 (*c* 1.0, $CHCl_3$).

(*R*)-2-Acetamido-2-benzyl-3-(*tert*-butoxy)-3-oxopropanoic Acid (15). Palladium carbon (5 mol %) was added to a stirred solution of 1-benzhydryl 3-(*tert*-butyl) (*R*)-2-acetamido-2-benzylmalonate (**3f**, 300 mg, 0.63 mmol) in methanol (20 mL) under hydrogen gas. After being stirred for 2−4 h, the substrate spot disappeared on TLC. The reaction mixture was filtered through a pad of Celite, and the filtrate was concentrated. The residue was purified by flash column chromatography on silica gel eluting with hexane/EtOAc (3:1 ∼ only EtOAc) to afford mono acid **15** as a white solid (98% yield). mp 135.7 °C; ^{1}H NMR (500 MHz, CD_3OD) 7.25−7.18 (m, 3H), 7.07−7.06 (d, 2H, *J* = 6.8 Hz), 3.57−3.49 (dd, 2H, J_1 = 26.4 Hz, J_2 = 13.9 Hz), 1.98 (s, 3H), 1.46 (s, 9H) ppm ; ^{13}C NMR (125 MHz, CD_3OD) δ 173.1, 171.0, 168. 8, 137.9, 131.9, 130.0, 128.8, 84.8, 70.0, 39.4, 28.8, 23.3 ppm; IR (KBr) 3378, 3351, 2979, 2490, 1738, 1370, 1216, 1152, 757 cm^{-1}; HRMS (FAB) calcd for $[C_{16}H_{22}NO_5]^+$ ([M + H]$^+$): 308.1498, found: 308.1497; $[\alpha]_D^{20}$ = −20.50 (*c* 1.0, MeOH).

***tert*-Butyl (*S*)-4-Benzyl-2-methyl-5-oxo-4,5-dihydrooxazole-4-carboxylate (16).** The mono acid **15** (660 mg, 2.15 mmol) was dissolved in dry THF (9 mL) under an argon atmosphere under −10 °C, which was maintained by an acetone/ice (1:1) mixture. Then, *N*-methylmorpholine (354 μL, 3.22 mmol) and ethyl chloroformate (307 μL, 3.22 mmol) were added sequentially. Formation of azlactone **16** took less than 15 min on TLC analysis. The reaction mixture was filtered for removal of NMM·HCl salt precipitate. All volatiles were also removed under reduced pressure to afford **16** as a colorless oil. The ^{1}H NMR spectroscopy and high-resolution mass spectrometry of the crude **16** could be obtained as soon as isolation. However, the ^{13}C NMR spectroscopy of **16** could not be obtained due to its low stability. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26−7.23 (m, 3H), 7.17−7.14 (m, 2H), 3.45−3.32 (dd, 2H, J_1 = 25.4 Hz, J_2 = 13.7 Hz), 2.02 (s, 3H), 1.48 (s, 9H) ppm; HRMS (FAB) calcd for $[C_{16}H_{20}NO_4]^+$ ([M + H]$^+$) 290.1392, found: 290.1392.

***tert*-Butyl (*R*)-2-Acetamido-2-benzyl-3-hydroxypropanoate (17).** The title compound **17** was prepared by two consecutive reaction steps from **15**. A solution of (*R*)-2-acetamido-2-benzyl-3-(*tert*-butoxy)-3-oxopropanoic acid (**15**, 500 mg, 1.63 mmol) in dry THF (7 mL) at −10 °C was stirred for 15 min with *N*-methylmorpholine (268 μL, 2.44 mmol) and ethyl chloroformate (232 μL, 2.44 mmol). *N*-methylmorpholine hydrochloride was removed by filtration, and the clear organic solution containing the intermediate **16** was added over a period of 10 min to a vigorously stirred suspension of sodium borohydride (215 mg, 5.70 mmol) in H_2O (2.5 mL) at 5 °C. The reaction was maintained for a further 3 h at room temperature until the TLC analysis showed that the reaction was completed. The mixture was then cooled to 0 °C, acidified to pH 2 with conc. HCl, diluted with water, and extracted with diethyl ether (100 mL × 2). The organic phase was collected, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel eluting hexane/EtOAc (1:2) to afford primary alcohol **17** as a white solid (398.8 mg, 84% yield). mp 142.7 °C; ^{1}H NMR (600 MHz, $CDCl_3$) 7.24−7.19 (m, 3H), 7.09−7.07 (m, 2H), 6.38 (s, 1H), 4.31−4.29 (d,1H, *J* = 11.2 Hz), 3.86−3.84 (d, 1H, *J* = 11.2 Hz), 3.50−3.47 (d,1H, *J* = 13.7 Hz), 3.03−3.01 (d, 1H, *J* = 13.7 Hz), 1.96 (s, 3H), 1.45 (s, 9H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.8, 135.6, 129.8, 128.2, 127.0, 83.4, 67.6, 66.1, 36.6, 27.8, 24.0 ppm; IR (KBr) 3400, 2978, 1731, 1659, 1514, 1370, 1248, 1157, 741 cm^{-1}; HRMS (FAB) calcd for $[C_{16}H_{24}NO_4]^+$ ([M + H]$^+$) 294.1705, found: 294.1706; $[\alpha]_D^{20}$ = +119.39 (*c* 1.0, $CHCl_3$).

***tert*-Butyl (*R*)-2-Acetamido-2-benzyl-3-((methylsulfonyl)-oxy)propanoate (18).** The title compound **18** was prepared by mesylation of primary alcohol **17**. A solution of *tert*-butyl (*R*)-2-acetamido-2-benzyl-3-hydroxypropanoate (**17**, 100 mg, 0.34 mmol) in dichloromethane (3 mL) at 0 °C was stirred for 30 min with triethylamine (119 μL, 0.85 mmol) and methanesulfonyl chloride (66 μL, 0.85 mmol). The mixture was then diluted with dichloromethane and washed with saturated NH_4Cl solution (25 mL) and brine (25 mL). The organic phase was collected, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel eluting hexane/EtOAc (2:1) to afford mesylated compound **18** as a white solid (115 mg, 91% yield). mp 117.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) 8.27 (bs, 1H), 7.30−7.27 (m, 5H), 4.57−4.48 (dd, 2H, J_1 = 22.2 Hz, J_2 = 11.8 Hz), 3.35−3.25 (dd, 2H, J_1 = 24.1 Hz, J_2 = 14.1 Hz), 2.69 (s, 3H), 2.10 (s, 3H), 1.36 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 166.7, 132.1, 130.5,. 128.8, 128.0, 85.1, 64.7, 63.7, 39.3, 38.5, 27.7, 20.6 ppm; IR (KBr) 3398, 3279, 2979, 2935, 1737, 1674, 1497, 1370, 1360, 1177, 1154, 989, 964, 838, 740, 704 cm^{-1}; LRMS (FAB) calcd for $[C_{17}H_{26}NO_6S]^+$ ([M + H]$^+$) 372, found: 372; $[\alpha]_D^{20}$ = +14.41 (*c* 1.0, $CHCl_3$).

***tert*-Butyl (*R*)-2-Acetamido-2-benzyl-3-oxo-3-{[(*S*)-1-phenylethyl]amino}propanoate (19).** To the crude *tert*-butyl (*S*)-4-benzyl-2-methyl-5-oxo-4,5-dihydrooxazole-4-carboxylate (**16**, 95 mg, 0.33 mmol) synthesized according to the method mentioned above were added a catalytic amount of 4-methylamino pyridine (10 mol %) and anhydrous dichloromethane (1 mL). An excess of (*S*)-(−)-α-methylbenzylamine (2 mL, 16 mmol) was added to open the azlactone ring structure. After being stirred for 1 h at room temperature, the reaction mixture was acidified with 6 N HCl in an ice bath. The crude residue was purified by column chromatography on silica gel (Hexane:EtOAc = 5:1 as eluent) and subsequent recrystallization

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(Hexane:EtOAc = 6:1 solvent system at room temperature) yielded stereochemically pure amide **19** as a white solid (129.6 mg, 96% yield). For your information: In the case of the reaction starting from a racemic mixture of **15**, the diastereomer bearing the different α-configuration appeared right below the title isomer **19** on TLC analysis. mp 122.5 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35−7.25 (m, 8H), 7.10−7.07 (m, 2H), 6.78 (s, 1H), 6.52−6.49 (d, 1H, J = 7.9 Hz), 5.14−5.04 (p, 1H, J = 7.2 Hz), 3.82−3.78 (d, 1H, J = 14.0 Hz), 3.51−3.46 (d, 1H, J = 14.0 Hz), 1.98 (s, 3H). 1.57−1.55 (d, 3H, J = 7.2 Hz), 1.37 (s, 9H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.0, 169.0, 165.4, 142.3, 135.3, 129.9, 128.6, 128.1, 127.5, 127.1, 125.9, 83.5, 67.4, 49.3, 38.6, 27.5, 23.1, 21.3 ppm; IR (KBr) 3353, 2978, 2927, 1731, 1496, 1155, 772 cm^{-1}; HRMS (FAB) calcd for $[C_{24}H_{31}N_2O_4]^+$ ($[M + H]^+$) 411.2284, found: 411.2285; $[\alpha]_D^{25}$ = −35.86 (c 1.0, $CHCl_3$).

(*R*)-α-Benzylserine. *tert*-Butyl (*R*)-2-acetamido-2-benzyl-3-hydroxypropanoate (**17**, 235 mg, 0.80 mmol) was dispersed in 6 N HCl (12 mL) and methanol (3 mL) and refluxed for 2 days. The mixture was diluted with water (50 mL) and washed with EtOAc (50 mL × 2). The aqueous layer was concentrated and purified by ion-exchange column chromatography through a DOWEX 50WX8-100 column eluting with 15% aqueous NH_4OH to afford (*R*)-α-benzylserine as a white solid (143.5 mg, 92% yield, decomposed around at 230 °C). ^{1}H NMR (500 MHz, D_2O) 7.34−7.27 (m, 3H), 7.20−7.18 (m, 2H), 3.98−3.95 (d, 1H, J = 12.0 Hz), 3.71−3.69 (d, 1H, J = 12.0 Hz), 3.19−3.16 (d, 1H, J = 14.3 Hz), 2.90−2.87 (d, 1H, J = 14.3 Hz) ppm; ^{13}C NMR (125 MHz, D_2O) δ 174.0, 133.9, 130.3, 129.4, 128.3, 67.4, 64.5, 38.2 ppm; IR (ATR) 3240, 3141, 2844, 2771, 1593, 1492, 1389, 1055, 697 cm^{-1}; HRMS (FAB) calcd for $[C_{10}H_{14}NO_3]^+$ ($[M + H]^+$) 196.0974, found: 196.0978. $[\alpha]_D^{20}$ = −15.50 (c 1.0, H_2O) {lit[12] (*S*)-α-benzylserine, $[\alpha]_D^{20}$ = +16.4 (c 0.80, H_2O), 98% ee}.

***tert*-Butyl (*R*)-4-Benzyl-2-methyl-4,5-dihydrooxazole-4-carboxylate (20).** The methanesulfonate **18** (100 mg, 0.27 mmol) was dissolved in dichloromethane (20 mL) and stirred for over 3 h with silica gel under reflux. The mixture was then evaporated and then yielded silica gel powder coated with organic compounds including the desired product **20**, which silica gel was loaded into column chromatography directly. Eluting solvent (Hexane:EtOAc = 1:1), the cyclized product from **18** was obtained successfully. (71% yield). ^{1}H NMR (300 MHz, $CDCl_3$) 7.30−7.19 (m, 5H), 4.50−4.47 (d, J = 9.0 Hz), 4.14−4.11 (d, J = 9.0 Hz), 3.11 (s, 2H), 1.92 (s, 3H), 1.46 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.5, 166.0, 135.6, 130.3, 128.1, 126.9, 82.1, 78.4, 72.7, 43.1, 27.9, 13.8 ppm; IR (KBr) 3433, 2979, 2931, 1726, 1670, 1369, 1256, 1163, 1096, 994, 915, 703, 618 cm^{-1}; HRMS (FAB) calcd for $[C_{16}H_{22}NO_3]^+$ ($[M + H]^+$) 276.1600, found: 276.1609; $[\alpha]_D^{20}$ = −47.28 (c 1.0, $CHCl_3$).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Spectral data of all new compounds as well as an X-ray crystallographic analysis of (*R*,*S*)-**19** and copies of NMR and HPLC analysis graphs of optimized conditions. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(13) CCDC 1045693 contains the supplementary crystallographic data for compound **19**. 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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