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Enantioselective Michael Addition of Malonates to Chalcone Derivatives Catalyzed by Dipeptide-derived Multifunctional Phosphonium Salts

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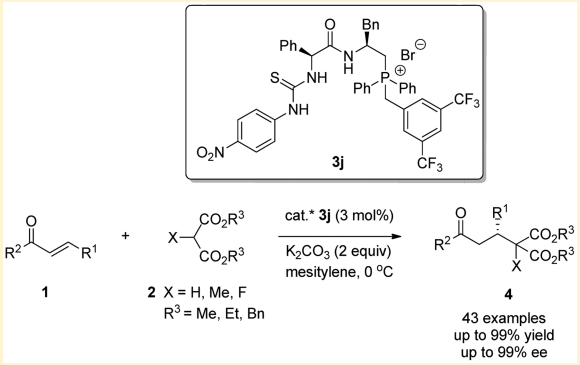
Supporting Information

ABSTRACT: Highly enantioselective Michael addition of malonates to enones catalyzed by dipeptide-derived multifunctional phosphonium salts has been developed. The newly established catalytic system was characterized with its wide substrate scope featured with aliphatic aldehyde-derived enones and substituted malonates. The gram scale-up synthesis of adducts can also be successfully achieved under optimal conditions with both excellent yield and enantioselectivity.



The development of highly effective, mild, and catalytic transformations for the construction of carbon−carbon bonds is an appealing and demanding topic in asymmetric synthesis. Among those well-established reactions, asymmetric Michael addition provides a powerful tool for the synthesis of numerous valuable enantioenriched compounds via the combination of different electrophiles and nucleophiles. Chalcone derivatives **1**, a challenging Michael addition acceptor with malonates **2** has been extensively studied for the resulting synthetically useful adducts highly functionalized with carbonyls and ester groups. A variety of highly efficient chiral catalysts such as L-proline derivatives,[1] phase-transfer catalysts,[2] metal−ligand complexes,[3] ionic liquid,[4] and other organocatalysts[5] have been developed to promote this reaction. In spite of these great achievements, limited success has been reported for aliphatic aldehyde-derived enones (e.g., R^1 = alkyl, CF_3, CO_2Et, R^2 = Ar), and 2-substituted malonates **2** (X = alkyl or Cl) were mostly restricted to react with cyclic enones,[6] yne-enones,[7] and 4-oxo-4-arybutenoates.[8] Specifically, the reported asymmetric Michael addition of fluoromalonates to acyclic enones only gave the moderate enantioselectivies.[2f,g]

Asymmetric phase-transfer catalysis has been recognized as a versatile and powerful tool for synthesis of the valuable enantioenriched compounds.[9] However, in the past few decades, tremendous efforts have focused on chiral quaternary ammonium salts catalysis. In contrast, the application of chiral quaternary phosphonium salts in asymmetric synthesis are rather limited.[9c,d,10] To our knowledge, related investigation on Michael addition of malonates to chalcone derivatives promoted by multifunctional chiral quaternary phosphonium salts has not been reported so far. Our group has been engaged in the design and synthesis of novel bifunctional quaternary ammonium and phosphonium salts and their application to asymmetric synthesis.[11] Recently, we have reported a new family of the dipeptide-derived multifunctional phosphonium salts in an asymmetric cyclization via Michael addition-S_N2 sequence[12] and synthesis of highly functionalized cyclopentane derivatives.[13] As further evaluation of versatility of these catalysts in carbon−carbon bond formation reactions, we reported herein highly enantioselective dipeptide-derived multifunctional phosphonium salts-catalyzed Michael addition of malonates to enones featured with wide substrate scope.

Asymmetric Michael addition of methyl malonate **2a** to chalcone **1a** was chosen as a model reaction to establish the optimal catalyst conditions (Table 1). L-Amino acids-derived bifunctional phosphonium salts **3a−3d**, which were previously developed in our laboratory for asymmetric aza-Henry reaction,[11b] were first introduced to catalyze this reaction. As shown in Table 1, good results were obtained with L-phenylalanine-derived bifunctional amide-phosphonium salt **3a** to give the product **4a** in 97% yield and with 53% ee (Table 1, entries 1−4). Enantioselectivity can then be further improved to 76% ee in the presence of catalyst **3e** which was synthesized from 3,5-bis(trifluoromethyl)benzyl bromide (entry 5). As only one N−H bond exists in the catalyst and actually two reactants need to be activated, we assumed that the inferior results might be attributed to the fact that the prochiral center is relatively far away from the chiral center of catalysts

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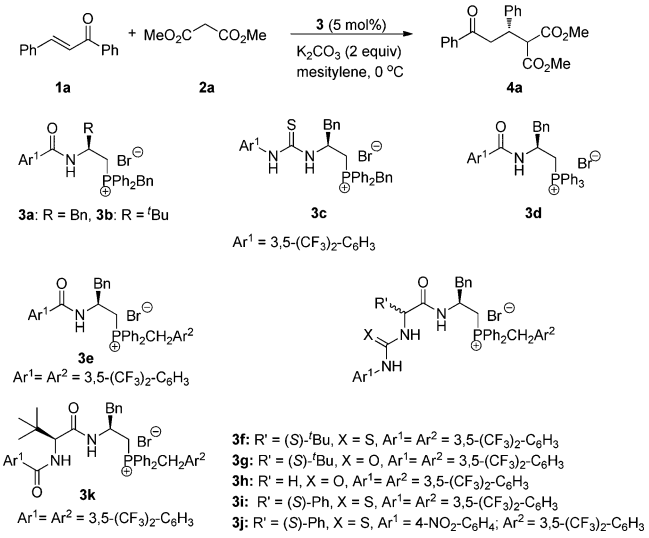
Table 1. Optimization of Catalysts[a]



entry	3	*t*/h	yield/%[b]	ee/%[c]
1	**3a**	24	97	53
2	**3b**	36	95	36
3	**3c**	24	97	−47
4	**3d**	24	96	24
5	**3e**	24	95	76
6	**3f**	9	97	92
7	**3g**	9	96	78
8	**3h**	9	96	69
9	**3i**	9	98	95
10	**3j**	9	99	99
11	**3k**	24	85	88
12[d]	**3j**	9	99	99
13[e]	**3j**	14	99	98

[a]Unless otherwised noted, the reaction was performed with 0.1 mmol of **1a**, 0.5 mmol of **2a**, and 2 equiv of K_2CO_3 in the presence of 5 mol % of **3** in mesitylene (1 mL) at 0 °C. [b]Isolated yield. [c]Determined by HPLC using chiral stationary phase. [d]3 mol% of **3j** was used. [e]1 mol% of **3j** was used.

(Figure 1a). To further improve the enantioselectivity, rational design of new chiral quaternary phosphonium salts is desirable. Of the fact that small synthetic peptides have proved to be efficient organocatalysts[14] and metal ligands[15] in asymmetric synthesis and (thio)urea is a versatile activator for the carbonyl compounds,[16] we envision that introduction of new stereocenter (R′) and (thio)urea moiety in the corresponding dipeptide-derived multifunctional phosphonium salts **3** can enhance the facial enantiodiscrimination of prochiral center (Figure 1b), which would provide the high stereoselectivity. Moreover, it is expected that stronger double hydrogen bond would be an advantage for the enantioselectivity. Based on these results, several novel dipeptide-derived multifunctional phosphonium salts **3f**−**3k** were synthesized.

To our delight, product **4a** can be obtained in 97% yield and 92% ee in a shorter reaction time by employing L-Phe-L-*tert*-Leu-derived multifunctional phosphonium salt **3f** and the thiourea moiety as hydrogen-bond donor proved to be better than urea (entries 6 and 7). Decreased enantioselectivity was also observed with L-Phe-Gly-derived catalyst **3h** which lacks the stereocenter of R′ (entry 8). Further screening of other phosphonium salts showed the L-Phe-L-Phg-derived multifunctional phosphonium salt **3j** with stronger double hydrogen-bond donor was the optimal catalyst of choice (entries 9−11). Reducing the catalyst loading amount to 3 mol% or 1 mol% almost had no effect on yield and enantioselectivity of the product (entries 12 and 13) albeit with a longer reaction time (entry 13). Other reaction parameters such as the structure of malonate, solvent, base, and temperature were also screened (see Supporting Information for details). Therefore, the optimal reaction conditions had been established as methyl malonate, 3 mol% of catalyst **3j**, mesitylene as a solvent, and 2 equiv of K_2CO_3 as a base (Table 1, entry 12) at 0 °C.

With the optimized reaction conditions for the asymmetric Michael addition of methyl malonate to enones in hand, we set out to investigate the scope of substrate. As shown in Table 2, when R^2 is fixed to phenyl group, both electronic nature and substituent effect on aromatic rings (when R^1 = Ar) have little influence on the results. The corresponding products were obtained with uniformly excellent yields (97−99%) and enantioselectivities (94−99%) (Table 2, entries 2−14). It is noteworthy that satisfactory enantioselectivity could be obtained at lower temperature for the enone bearing a strong electron-withdrawing group on aromatic ring (entry 7). Enones involving heteroaromatic or condensed ring also proved to be applicable (entries 15−17). To our delight, this catalytic system can be successfully applied to previously less-investigated aliphatic aldehydes-derived enones (R^1 = alkyl) in terms of

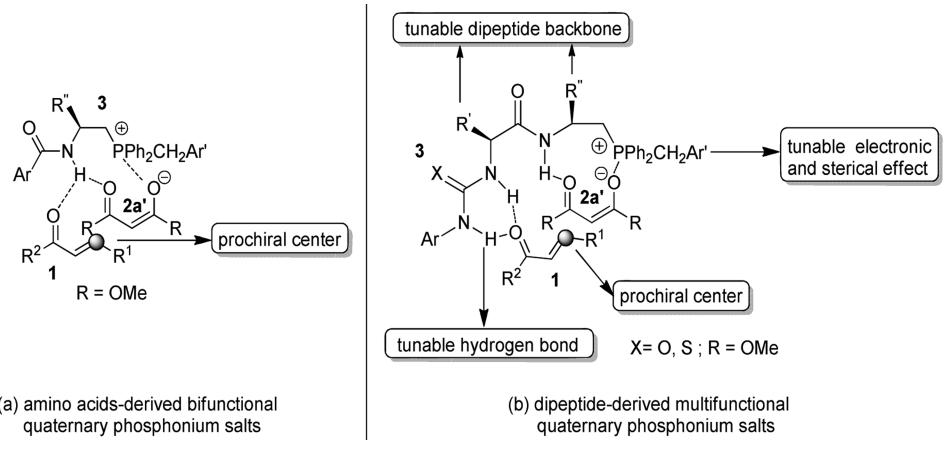


Figure 1. Rational design of dipeptide-derived multifunctional quaternary phosphonium salts **3**.

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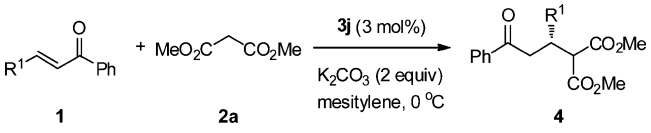
Table 2. Substrate Scope of Reaction[a]

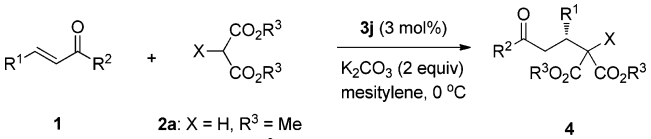


1 2a 4

entry	R^1/1	4	t/h	yield/%[b]	ee/%[c]
1	C_6H_5/**1a**	**4a**	9	99	99
2	4-FC_6H_4/**1b**	**4b**	12	97	96
3	4-ClC_6H_4/**1c**	**4c**	15	99	98
4	4-BrC_6H_4/**1d**	**4d**	5	99	96
5	4-MeC_6H_4/**1e**	**4e**	21	99	98
6	4-$MeOC_6H_4$/**1f**	**4f**	27	99	99
7[d]	4-$NO_2C_6H_4$/**1g**	**4g**	10	97	98
8	3-BrC_6H_4/**1h**	**4h**	8	99	96
9	2,4-$Cl_2C_6H_3$/**1i**	**4i**	8	99	97
10	4-$CF_3C_6H_4$/**1j**	**4j**	5	98	96
11	4-CNC_6H_4/**1k**	**4k**	5	99	94
12	4-PhC_6H_4/**1l**	**4l**	7	99	97
13	2-FC_6H_4/**1m**	**4m**	4	99	98
14	3-$MeOC_6H_4$/**1n**	**4n**	9	97	96
15	2-thienyl/**1o**	**4o**	5	99	97
16	1-naphthyl/**1p**	**4p**	5	98	96
17	2-naphthyl/**1q**	**4q**	36	99	96
18	(*E*)-PhCH = CH_2−/**1r**	**4r**	52	98	97
19	Me/**1s**	**4s**	6	98	95
20	pentyl/**1t**	**4t**	8	97	97
21[d]	CO_2Et/**1u**	**4u**	2	98	94
22[d]	CF_3/**1v**	**4v**	3	97	86
23	Cy/**1w**	**4w**	24	98	94
24[e]	Ph	**4a**	24	98	99

[a]Unless otherwised noted, all reactions were performed with 0.1 mmol of 1, 0.5 mmol of **2a**, and 2 equiv of K_2CO_3 in the presence of 3 mol% of **3j** in mesitylene (1 mL) at 0 °C. [b]Isolated yield. [c]Determined by HPLC using chiral stationary phase. [d]At −10 °C. [e]5 mmol scale-up.

Table 3. Substrate Scope of Reaction[a]



1 **2a**: X = H, R^3 = Me; **2a'**: X = Me, R^3 = Me; **2a"**: X = F, R^3 = Me; **2b**: X = H, R^3 = Et; **2c** : X= H, R^3 = Bn 4

entry	R^1/R^2/1	2/4	t/h	yield/%[b]	ee/%[c]
1	Ph/4-FC_6H_4/**1x**	**2a**/**4x**	7	98	98
2	Ph/4-ClC_6H_4/**1y**	**2a**/**4y**	7	94	99
3	Ph/4-BrC_6H_4/**1z**	**2a**/**4z**	5	99	97
4	Ph/4-MeC_6H_4/**1a'**	**2a**/**4a'**	20	98	99
5	Ph/4-$MeOC_6H_4$/**1b'**	**2a**/**4b'**	16	99	98
6	Ph/4-$NO_2C_6H_4$/**1c'**	**2a**/**4c'**	8	99	98
7	Ph/2-BrC_6H_4/**1d'**	**2a**/**4d'**	3	99	96
8	Ph/3-ClC_6H_4/**1e'**	**2a**/**4e'**	10	98	99
9	Ph/2-thienyl/**1f'**	**2a**/**4f'**	4	99	97
10	Ph/2-furyl/**1g'**	**2a**/**4g'**	4	97	96
11	Ph/1-naphthyl/**1h'**	**2a**/**4i'**	16	95	95
12	Ph/2-naphthyl/**1i'**	**2a**/**4i'**	4	99	99
13[d]	Ph/Me/**1j'**	**2a**/**4j'**	96	85	91
14[d]	$PhCH_2CH_2$/Me/**1k'**	**2a**/**4k'**	96	67	19
15	Ph/Ph/**1a**	**2b**/**4l'**	24	99	99
16	Ph/Ph/**1a**	**2c**/**4m'**	24	99	99
17	cyclopentenone/**1l'**	**2c**/**4n'**	41	98	17
18	cyclohexenone/**1m'**	**2c**/**4o'**	96	38	16
19	Ph/Ph/**1a**	**2a'**/**4p'**	120	95	98
20[e]	Ph/Ph/**1a**	**2a"**/**4q'**	30	89	98

[a]Unless otherwised noted, the reaction was performed with 0.1 mmol of **1**, 0.5 mmol of **2**, and 2 equiv of K_2CO_3 in the presence of 3 mol% of **3j** in mesitylene (1 mL) at 0 °C. [b]Isolated yield. [c]Determined by HPLC using chiral stationary phase. [d]10 equiv of **2a** was used. [e]**1a**:**2a"** = 5:1, and 5 equiv of K_2CO_3 was used.

the excellent yields (97−98%) and good to excellent enantioselectivities (86−97%) (entries 18−23). Generally, enones with electron-withdrawing groups on aromatic rings reacted faster than those with electron-donating groups due to the enhanced electrophilicity. When R^1 was stronger electron withdrawing group such as CF_3 or CO_2Et, the reaction still finished smoothly within 3 h at −10 °C. The gram scale-up synthesis of product **4a** can also be successfully achieved under optimal conditions with 98% yield and 99% ee (Table 2, entry 24).

Next, we fixed the R^1 as phenyl group and evaluated R^2 group on **1** as well as substituted malonates. The reaction also demonstrated a broad substrate scope (Table 3). Electronic nature and position of substitutes on aromatic rings (R^2 = Ar) had no influence on yield (94−99%) and enantioselectivity (96−99%) as before. Enones bearing heteroaromatic or condensed ring also proved to be competent candidates (Table 3, entries 1−12). Likewise, reaction of enones with electron-withdrawing groups on aromatic rings finished within a shorter time than those with electron-donating groups. To our delight, (*E*)-4-phenylbut-3-en-2-one, a challenging Michael acceptor in asymmetric phase-transfer catalysis,[2d] delivered the product in 85% yield and 91% ee albeit with a longer reaction time (entry 13) while (*E*)-6-phenylhex-3-en-2-one gave only 19% ee (entry 14). It is noteworthy that the sterically bulky diethyl and dibenzyl malonates had no inferior effect on the yield and enantioselectivity (entries 15 and 16). Cyclic enones, such as cyclopentenone and cyclohexeone, gave poor enantioselectivities (entries 17 and 18). Challenging 2-substituted malonates, such as 2-methyl or 2-fluoro methyl malonates, could also be applicable to this catalytic system in excellent yields and enantioselectivies (Table 3, entries 19 and 20) with a prolonged time. The absolute configuration of the product **4** was assigned as *S* by analogy to specific rotation of known compound.[3d,5c−f]

To gain some insights into the mechanism of the reaction, some control experiments were conducted as shown in Scheme 1. Both yields and enantioselectivities decreased dramatically when dipeptide-derived phosphine precursor **3l** or *N*-methyl protected dipeptide-derived phosphonium salt **3m** was employed (Figure 2a). The results showed that both hydrogen bonding and phosphonium moiety of the catalyst were indispensable for the reactivity and enantioselectivity of reaction.

Based on these results, a plausible transition state **TS-1** was proposed to explain the absolute configuration of the adduct (Figure 2b). We proposed that thiourea moiety of chiral phosphonium salt **3j** might activate the electrophilic enones **1** through double hydrogen-bond interactions while the amide and phosphonium salt cation of the catalyst **3j** might direct the nucleophilic malonate carbanion **2′** via hydrogen-bond interaction and electrostatic interaction, respectively to attack

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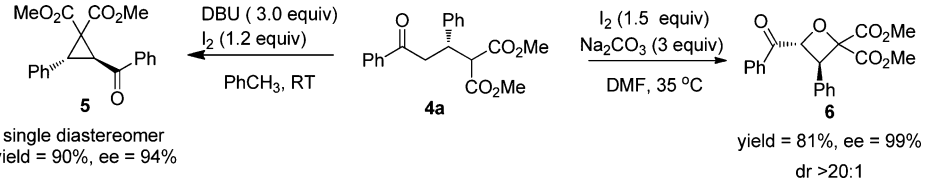
Scheme 1. Transformation of Product 4a



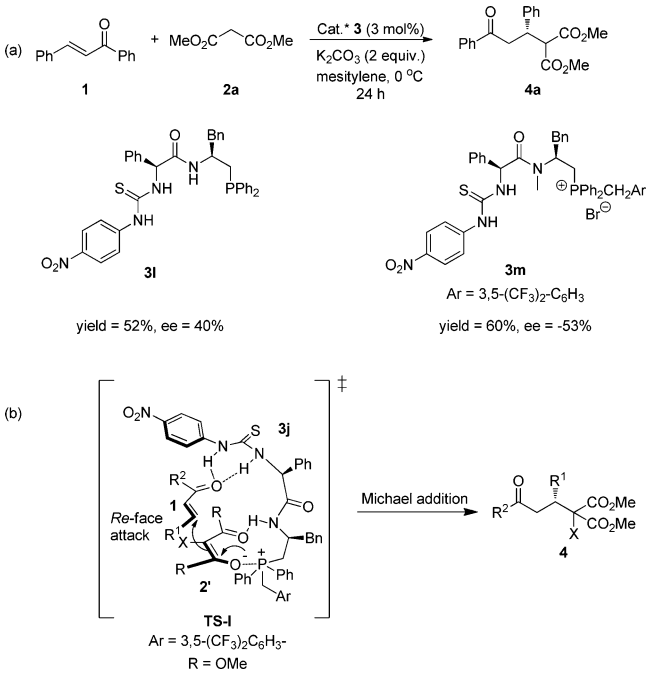


Figure 2. (a) Control experiment; (b) plausible transition state.

from the less sterically hindered *Re* face to afford the target product **4** with *S*-selectivity.

To demonstrate the synthetic utility of the product, compound **4a** was converted to *trans*-cyclopropane derivative **5** in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and iodine[17] in excellent yield as a single stereoisomer. With inorganic base in DMF,[18] chiral oxetane derivative **6** was also obtained in high yield (Scheme 1). As we know, chiral cyclopropane[19] and oxetane[20] derivatives are versatile building blocks in organic synthesis, and structural motif in some pharmaceuticals and biologically active natural compounds. This protocol provided an alternative method for the asymmetric cyclopropanation of chalcone derivatives.[21]

In conclusion, we have reported asymmetric Michael addition of malonates to enones catalyzed by dipeptide-derived multifunctional phosphonium salts with wide substrate scope under mild reaction conditions in terms of excellent yields and enantioselectivities. It is noteworthy that this catalytic system can be applied to alkyl enones (R^1 or R^2 = alkyl) in addition to aromatic ones. More challenging methyl enone and 2-substituted malonates were all applicable to deliver the corresponding products in excellent yields and enantioselectivities. Gram scale-up synthesis of product was also successfully achieved with excellent yield and enantioselectivity.

EXPERIMENTAL SECTION

The ^{1}H NMR spectra were recorded at 400 MHz in $CDCl_3$ using tetramethylsilane (TMS) as internal standard. All chemical shifts (δ) were given in ppm. Data were reported as follows: chemical shift, multiplicity (s = single, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), coupling constants (Hz), and integration. ^{13}C NMR spectra were recorded at 100 MHz in $CDCl_3$ and run with broadband decoupling. ^{19}F NMR and ^{31}P NMR spectra were recorded at 376 and 162 Hz, respectively. High-resolution mass spectra (HRMS) of compounds was reported for molecular ion (M+H) or $(M+Na)^+$ under TOF conditions. Analytical high-performance liquid chromatography (HPLC) was carried out on chiral stationary columns using *n*-hexane and isopropanol as mobile phase. Melting points were determined on a microscopic melting point meter without correction. Specific optical rotations were measured at λ = 589 nm. IR spectra were reported in wavenumber (cm^{-1}). Flash column chromatography was performed using H silica gel (300−400 mesh). For thin-layer chromatography (TLC), silica gel plates (HSGF 254) were used and compounds were visualized by irradiation with UV light. Phase-transfer catalysts **3a**−**3d**[11b] and **3f**−**3m**[12] have been described, and the catalyst **3e** was synthesized according to procedures reported previously.[11b] All reactions were carried out employing oven-dried glassware. All solvents and reagent were directly used as received without further manipulation.

Spectra Data of Catalyst 3e. (*S*)-(2-(3,5-Bis(trifluoromethyl)-benzamido)-3-phenylpropyl)(3,5-bis(trifluoromethyl)benzyl)-diphenylphosphonium bromide (**3e**): 217 mg, yield = 70%, white solid, mp = 137−138 °C, $[\alpha]_D^{24.0}$ = +48.6 (c = 1.0, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.35 (d, J = 8.4 Hz, 1H), 8.28 (s, 2H), 7.87−7.92 (m, 3H), 7.73 (s, 1H), 7.64 (t, J = 7.2 Hz, 1H), 7.24−7.45 (m, 12 H), 7.01 (dd, J = 7.8, 11.8 Hz, 2H), 5.22−5.30 (m, 1H), 5.10−5.20 (m, 1H), 4.58- 4.70 (m, 1H), 4.36−4.43 (m, 1H), 3.28−3.34 (m, 1H), 2.99 (dd, J = 11.0, 12.2 Hz, 1H), 2.68 (t, J = 13.6 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 163.9, 136.9, 135.0 (d, J_{C-P} = 5.9 Hz), 134.9 (d, J_{C-P} = 6.2 Hz), 134.5, 133.8 (d, J_{C-P} = 9.8 Hz), 133.3 (d, J_{C-P} = 9.3 Hz), 132.1 (q, J_{C-F} = 33.7 Hz), 132.0 (q, J_{C-F} = 33.7 Hz), 131.3 (q, J_{C-F} = 33.6 Hz), 130.5 (d, J_{C-P} = 8.5 Hz), 130.4 (brs), 130.1 (d, J_{C-P} = 12.5 Hz),129.9 (d, J_{C-P} = 12.7 Hz), 129.5, 128.9, 128.3 (d, J_{C-P} = 2.4 Hz), 127.1, 124.8 (brs), 123.0 (q, J_{C-F} = 271.4 Hz), 122.4 (q, J_{C-F} = 271.4 Hz), 122.1, 116.3 (d, J_{C-P} = 82.1 Hz), 115.4 (d, J_{C-P} = 83.2 Hz), 47.3 (d, J_{C-P} = 4.9 Hz), 42.5 (d, J_{C-P} = 14.1 Hz), 30.2 (d, J_{C-P} = 46.7 Hz), 22.9 (d, J_{C-P} = 50.2 Hz); ^{19}F NMR ($CDCl_3$, 376 MHz) δ −62.6, −63.1; ^{31}P NMR ($CDCl_3$, 162 MHz) δ 25.6; IR (KBr): ν 3327, 2963, 1662, 1539, 1439, 1374, 1337, 1279, 1182, 1136, 908, 846, 804, 743, 700 cm^{-1}; HRMS (MALDI-FT): calcd. for $[M-Br]^+$ $(C_{39}H_{29}F_{12}NOP)^+$ requires 786.1790; found 786.1795.

General Procedure for Asymmetric Michael Addition of Malonates to Enones. To a solution of **1** (0.1 mmol) and dipeptide-derived multifunctional phosphonium bromide **3j** (0.003 mmol, 2.8 mg) in mesitylene (1.0 mL) was added methyl malonate (5 equiv, 0.5 mmol, 66 mg, 57 μL). After cooling to 0 °C, anhydrous K_2CO_3 powder (2 equiv, 0.2 mmol, 28 mg) was added in one portion, and then the mixture continued to stir vigorously at 0 °C until the disappearance of the enones monitored by TLC. H_2O (5.0 mL) was added to quench the reaction, and then the aqueous solution was extracted with ethyl acetate (5.0 mL × 3). The combined organic phase was washed with brine, dried over anhydrous Na_2SO_4, and removed *in vacuo*. The resulting residue was purified by flash column chromatography (ethyl acetate/petroleum ether as eluent) to afford the desired products **4**.

Spectra Data of Product 4. *(S)-Dimethyl 2-(3-Oxo-1,3-diphenylpropyl)malonate (**4a**).*[3d] 34 mg, yield = 99%; white solid; mp = 95−96 °C; $[\alpha]_D^{26.9}$ = +21.0 (c = 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.89 (d, J = 7.6 Hz, 2H), 7.53 (t, J = 7.4 Hz, 1H), 7.41 (t,

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J = 7.6 Hz, 2H), 7.27−7.22 (m, 4H), 7.15−7.20 (m, 1H), 4.20 (dt, J = 5.2, 9.2 Hz, 1H), 3.86 (d, J = 9.2 Hz, 1H), 3.72 (s, 3H), 3.45−3.58 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 197.5, 168.7, 168.1, 140.4, 136.7, 133.0, 128.5, 128.4, 128.0, 127.2, 57.3, 52.6, 52.4, 42.3, 40.7 (one peak for aromatic carbon was not found probably due to overlapping); Enantiomeric excess: 99%, determined by HPLC (Phenomenex Cellulose-2, hexane/*i*-PrOH 80/20, flow rate 0.8 mL/min; t_{major} = 15.4 min, t_{minor} = 23.6 min, λ = 254 nm).

*(S)-Dimethyl 2-(1-(4-Fluorophenyl)-3-oxo-3-phenylpropyl)-malonate (**4b**).*[3d] 35 mg, yield = 97%; white solid; mp = 82−84 °C; $[\alpha]_D^{25.8}$ = +18.7 (c = 0.90, CHCl3); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.89 (d, J = 7.6 Hz, 2H), 7.54 (t, J = 7.2 Hz, 1H), 7.43 (t, J = 7.4 Hz, 2H), 7.22−7.26 (m, 2H), 6.94 (t, J = 8.4 Hz, 2H), 4.15−4.21 (m, 1H), 3.82 (d, J = 9.2 Hz, 1H), 3.74 (s, 3H), 3.41−3.56 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 197.3, 168.5, 168.0, 161.7 (d, J_{C-F} = 244.5 Hz), 136.6, 136.0 (d, J_{C-F} = 3.2 Hz), 133.1, 129.7 (d, J_{C-F} = 8.0 Hz), 128.6, 128.0, 115.3 (d, J_{C-F} = 21.2 Hz), 57.2, 52.7, 52.4, 42.3, 40.0; Enantiomeric excess: 96%, determined by HPLC (Phenomenex Cellulose-2, hexane/*i*-PrOH 80/20, flow rate 0.8 mL/min; t_{major} = 12.6 min, t_{minor} = 17.7 min, λ = 254 nm).

*(S)-Dimethyl 2-(1-(4-Chlorophenyl)-3-oxo-3-phenylpropyl)-malonate (**4c**).*[3d] 37 mg, yield = 99%; white solid; mp = 84−86 °C; $[\alpha]_D^{26.5}$ = +23.9 (c = 0.93, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.89 (d, J = 7.2 Hz, 2H), 7.54 (t, J = 7.4 Hz, 1H), 7.43 (t, J = 7.6 Hz, 2H), 7.19−7.24 (m, 4H), 4.17 (dt, J = 4.8, 9.2 Hz, 1H), 3.83 (d, J = 9.6 Hz, 1H), 3.73 (s, 3H), 3.42−3.56 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 197.1, 168.5, 167.9, 138.9, 136.5, 133.2, 132.9, 129.5, 128.6, 128.5, 128.0, 57.0, 52.7, 52.5, 42.1, 40.5; Enantiomeric excess: 98%, determined by HPLC (Phenomenex Cellulose-2, hexane/*i*-PrOH 80/20, flow rate 0.8 mL/min; t_{major} = 12.7 min, t_{minor} = 16.6 min, λ = 254 nm).

*(S)-Dimethyl 2-(1-(4-Bromophenyl)-3-oxo-3-phenylpropyl)-malonate (**4d**).*[5e] 41 mg, yield = 99%; white solid; mp = 89−91 °C; $[\alpha]_D^{25.5}$ = +19.5 (c = 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.89 (d, J = 7.2 Hz, 2H), 7.54 (t, J = 7.4 Hz, 1H), 7.43 (t, J = 7.8 Hz, 2H), 7.37 (d, J = 8.4 Hz, 2H), 7.16 (d, J = 8.4 Hz, 2H), 4.13−4.19 (m, 1H), 3.83 (d, J = 9.2 Hz, 1H), 3.73 (s, 3H), 3.42−3.56 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 197.1, 168.4, 167.9, 139.5, 136.6, 133.2, 131.6 129.9, 128.6, 128.0, 121.1, 56.9, 52.7, 52.5, 42.0, 40.1 ; Enantiomeric excess: 96%, determined by HPLC (Phenomenex Cellulose-2, hexane/*i*-PrOH 80/20, flow rate 0.8 mL/min; t_{major} = 13.2 min, t_{minor} = 16.9 min, λ = 254 nm).

*(S)-Dimethyl 2-(3-Oxo-3-phenyl-1-(p-tolyl)propyl)malonate (**4e**).*[5e] 35 mg, yield = 99%; white solid; mp = 72−73 °C; $[\alpha]_D^{26.7}$ = +15.1 (c = 0.89, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.90 (d, J = 7.2 Hz, 2H), 7.52 (t, J = 7.2 Hz, 1H), 7.41 (t, J = 7.6 Hz, 2H), 7.14 (d, J = 8.0 Hz, 2H), 7.05 (d, J = 8.0 Hz, 2H), 4.13−4.18 (m, 1H), 3.84 (d, J = 9.2 Hz, 1H), 3.72 (s, 3H), 3.42−3.56 (m, 5H), 2.26 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 197.5, 168.7, 168.1, 137.3, 136.8, 136.7, 133.0, 129.1, 128.5, 128.0, 127.8, 57.3, 52.6, 52.3, 42.4, 40.4, 21.0; Enantiomeric excess: 98%, determined by HPLC (Phenomenex Cellulose-2, hexane/*i*-PrOH 80/20, flow rate 0.8 mL/min; t_{major} = 16.5 min, t_{minor} = 23.9 min, λ = 254 nm).

*(S)-Dimethyl 2-(1-(4-Methoxyphenyl)-3-oxo-3-phenylpropyl)-malonate (**4f**).*[3d] 37 mg, yield = 99%, white solid; mp = 75−76 °C; $[\alpha]_D^{25.1}$ = +18.1 (c = 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.89 (d, J = 6.8 Hz, 2H), 7.52 (t, J = 7.4 Hz, 1H), 7.42 (t, J = 7.6 Hz, 2H), 7.17 (d, J = 8.8 Hz, 2H), 6.78 (d, J = 8.8 Hz, 2H), 4.11−4.17 (m, 1H), 3.82 (d, J = 9.6 Hz, 1H), 3,74 (s, 3H), 3.73 (s, 3H), 3.39−3.54 (m, 5H). ^{13} C NMR ($CDCl_3$, 100 MHz) δ 197.6, 168.7, 168.2, 158.5, 136.8, 133.0, 132.2, 129.1, 128.5, 128.1, 113.8, 57.4, 55.1, 52.6, 42.5, 40.1; Enantiomeric excess: 99%, determined by HPLC (Phenomenex Cellulose-2, hexane/*i*-PrOH 80/20, flow rate 0.8 mL/min; t_{major} = 23.5 min, t_{minor} = 32.2 min, λ = 254 nm).

*(S)-Dimethyl 2-(1-(4-Nitrophenyl)-3-oxo-3-phenylpropyl)-malonate (**4g**).*[3d] 37 mg, yield = 97%; white solid; mp = 74−76 °C; $[\alpha]_D^{26.8}$ = +33.5 (c = 0.96, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.13 (d, J = 8.4 Hz, 2H), 7.89 (d, J = 7.2 Hz, 2H), 7.56 (t, J = 7.6 Hz, 1H), 7.42−7.49 (m, 4H), 4.28- 4.34 (m, 1H), 3.89 (d, J = 9.6 Hz, 1H), 3.75 (s, 3H), 3.51−3.63 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 196.6, 168.1, 167.6, 148.2, 147.0, 136.3, 133.5, 129.2, 128.7, 128.0, 123.6, 56.5, 52.9 52.6, 41.7, 40.3; Enantiomeric excess: 98%, determined by HPLC (Chiralpak column AD, hexane/*i*-PrOH 50/50, flow rate 0.8 mL/min; t_{major} = 30.9 min, t_{minor} = 16.0 min, λ = 254 nm).

*(S)-Dimethyl 2-(1-(3-Bromophenyl)-3-oxo-3-phenylpropyl)-malonate (**4h**).* 41 mg, yield = 99%; colorless oil; $[\alpha]_D^{26.7}$ = +24.9 (c = 0.84, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.90 (d, J = 7.2 Hz, 2H), 7.54 (t, J = 7.4 Hz, 1H), 7.41−7.45 (m, 3H), 7.32 (d, J = 8.4 Hz, 1H), 7.23 (d, J = 8.0 Hz, 1H), 7.13 (t, J = 7.8 Hz, 1H), 4.14- 4.20 (m, 1H), 3.83 (d, J = 8.8 Hz, 1H), 3.72 (s, 3H), 3.44−3.58 (m, 5H), ^{13}C NMR ($CDCl_3$, 100 MHz) δ 197.0, 168.4, 167.9, 142.9, 136.5, 133.2, 131.0, 130.3, 130.0, 128.6, 128.0, 126.9, 122.4, 56.9, 52.7, 52.5, 41.9, 40.1; IR (Neat): ν 3073, 3012, 2953, 2924, 2862, 1736, 1687, 1596, 1568, 1448, 1434, 1257, 1157, 1075, 1021, 785, 754, 693 cm^{-1}; HRMS (ESI): calcd. for $[M+H]^+$ $(C_{20}H_{20}BrO_5)^+$ requires 419.0494; found 419.0494; Enantiomeric excess: 96%, determined by HPLC (Phenomenex Cellulose-2, hexane/*i*-PrOH 80/20, flow rate 0.8 mL/min; t_{major} = 12.6 min, t_{minor} = 18.0 min, λ = 254 nm).

*(S)-Dimethyl 2-(1-(2,4-Dichlorophenyl)-3-oxo-3-phenylpropyl)-malonate (**4i**).* 40 mg, yield = 99%; colorless oil; $[\alpha]_D^{26.7}$ = +36.3 (c = 0.82, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.92 (d, J = 7.2 Hz, 2H), 7.55 (t, J = 7.4 Hz, 1H), 7.43 (t, J = 7.8 Hz, 2H), 7.36 (d, J = 2.0 Hz, 1H), 7.24−7.26 (m, 1H), 7.14 (dd, J = 2.4, 8.4 Hz 1H), 4.58−4.64 (m, 1H), 4.06 (d, J = 8.4 Hz, 1H), 3.67−3.74 (m, 4H), 3.58−3.64 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 197.1, 168.4, 168.0, 136.5, 136.4, 134.8, 133.4, 133.3, 129.9, 128.6, 128.0, 127.1, 54.6, 52.7, 52.6, 39.9, 36.8 (one peak for aromatic carbon was not found probably due to overlapping); IR (Neat) ν 2954, 2917, 2849, 1737, 1687, 1589, 1475, 1449, 1435, 1232, 1157, 1106, 1023, 869, 826, 754, 733, 691 cm^{-1}; HRMS (ESI): calcd. for $[M+H]^+$ $(C_{20}H_{19}Cl_2O_5)^+$ requires 409.0610; found 409.0600; Enantiomeric excess: 97%, determined by HPLC (Chiralpak column AD, hexane/*i*-PrOH 80/20, flow rate 0.8 mL/min; t_{major} = 13.9 min, t_{minor} = 11.0 min, λ = 254 nm).

*(S)-2-(3-Oxo-3-phenyl-1-(4-(trifluoromethyl)phenyl)propyl)-malonate (**4j**).* 40 mg, yield = 98%; white solid; mp = 107−109 °C; $[\alpha]_D^{26.6}$ = +22.3 (c = 0.82, CHCl3); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.89 (d, J = 7.2 Hz, 2H), 7.51−7.57 (m, 3H), 7.44 (d, J = 11.6 Hz, 2H), 7.42 (d, J = 12.0 Hz, 2H), 4.24−4.30 (m, 1H), 3.88 (d, J = 9.2 Hz, 1H), 3.74 (s, 3H), 3.48−3.60 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 196.9, 168.4, 167.9, 144.7, 136.5, 133.3, 129.4(q, J_{C-F} = 32.3 Hz), 128.6, 128.5, 128.0, 125.4 (q, J_{C-F} = 3.8 Hz), 124.1 (q, J_{C-F} = 270.6 Hz), 56.8, 52.8, 52.5, 41.9, 40.3; ^{19}F NMR ($CDCl_3$, 282 MHz) δ −62.6; IR (KBr) ν 2955, 1731, 1680, 1334, 1240, 1165, 1122, 843, 686 cm^{-1}; HRMS (ESI): calcd. for $[M+H]^+$ $(C_{21}H_{20}F_3O_5)^+$ requires 409.1263; found 409.1251; Enantiomeric excess: 96%, determined by HPLC (Chiralpak column AD, hexane/*i*-PrOH 50/50, flow rate 0.8 mL/min; t_{major} = 13.7 min, t_{minor} = 9.0 min, λ = 254 nm).

*(S)-Dimethyl 2-(1-(4-cyanophenyl)-3-oxo-3-phenylpropyl)-malonate (**4k**).* 36 mg, yield = 99%, colorless oil; $[\alpha]_D^{25.6}$ = +31.3 (c = 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.89 (d, J = 7.2 Hz, 2H), 7.55−7.57 (m, 3H), 7.44 (d, J = 12.4 Hz, 2H), 7.43 (d, J = 12.8 Hz, 2H), 4.22−4.27 (m, 1H), 3.86 (d, J = 9.2 Hz, 1H), 3.74 (s, 3H), 3.48−3.60 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 196.7, 168.2, 167.7, 146.1, 136.3, 133.4, 132.2, 129.1, 128.7, 128.0, 118.6, 111.1, 56.5, 52.8, 52.6, 41.7, 40.5; IR (Neat) ν 2955, 2917, 1749, 1734, 1680, 1508, 1449, 1317, 1262, 1156, 1016, 977, 841, 755, 726, 687 cm^{-1}; HRMS (ESI): calcd. for $[M+H]^+$ $(C_{21}H_{20}NO_5)^+$ requires 366.1341; found 366.1333; Enantiomeric excess: 94%, determined by HPLC (Chiralpak column, hexane/*i*-PrOH, flow rate 0.8 mL/min; t_{major} = 26.2 min, t_{minor} = 15.8 min, λ = 254 nm).

*(S)-Dimethyl 2-(1-([1,1′-biphenyl]-4-yl)-3-oxo-3-phenylpropyl)-malonate (**4l**).* 41 mg, yield = 99%, white solid. mp = 146−147 °C; $[\alpha]_D^{26.4}$ = +24.6 (c = 0.99, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.97 (d, J = 8.4 Hz, 2H), 7.64 (d, J = 8.4 Hz, 2H), 7.60 (d, J = 7.2 Hz, 2H), 7.45 (t, J = 7.4 Hz, 2H), 7.38 (t, J = 7.4 Hz, 1H), 7.23−7.30 (m, 4H), 7.16−7.20 (m, 1H), 4.19- 4.25 (m, 1H), 3.88 (d, J = 9.6 Hz, 1H), 3.73 (s, 3H), 3.47−3.61 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 197.1, 168.7, 168.1, 145.7, 140.4, 139.8, 135.4, 128.9, 128.7, 128.5, 128.2, 128.0, 127.2, 127.1, 57.3, 52.7, 52.4, 42.3, 40.8 (one peak for

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aromatic carbon was not found probably due to overlapping); IR (KBr) ν 2956, 2910, 1732, 1676, 1604, 1431, 1296, 1237, 1156, 1024, 759, 701, 691 cm^{-1}; HRMS (ESI): calcd. for $[M+H]^+$ $(C_{26}H_{25}O_5)^+$ requires 417.1702; found 417.1690; Enantiomeric excess: 97%, determined by HPLC (Phenomenex Cellulose-2, hexane/*i*-PrOH 50/50, flow rate 0.8 mL/min; t_{major} = 14.6 min, t_{minor} = 18.0 min, λ = 254 nm).

*(S)-Dimethyl 2-(1-(2-Fluorophenyl)-3-oxo-3-phenylpropyl)-malonate (**4m**).*[5e] 35 mg, yield = 99%; colorless oil; $[\alpha]_D^{25.7}$ = +31.1 (*c* = 0.99, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.90 (d, *J* = 7.2 Hz, 2H), 7.53 (t, *J* = 7.4 Hz, 1H), 7.42 (t, *J* = 7.8 Hz, 2H), 7.26–7.30 (m, 1H), 7.15–7.20 (m, 1H), 6.96–7.04 (m, 2H), 4.34–4.40 (m, 1H), 4.04 (d, *J* = 10.0 Hz, 1H), 3.73 (s, 3H), 3..49–3.65 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 197.3, 168.5, 168.0, 161.0 (d, J_{C-F} = 245.0 Hz), 136.6, 133.1, 130.9 (d, J_{C-F} = 4.9 Hz), 128.9 (d, J_{C-F} = 8.6 Hz), 128.5, 128.0, 126.9 (d, J_{C-F} = 13.1 Hz), 124.0 (d, J_{C-F} = 3.3 Hz), 115.7 (d, J_{C-F} = 22.3 Hz), 55.3 (d, J_{C-F} = 2.2 Hz), 52.7, 52.4, 40.7 (d, J_{C-F} = 2.1 Hz), 36.4; Enantiomeric excess: 98%, determined by HPLC (Phenomenex Cellulose-2, hexane/*i*-PrOH 80/20, flow rate 0.8 mL/min; t_{major} = 13.9 min, t_{minor} = 18.8 min, λ = 254 nm).

*(S)-Dimethyl 2-(1-(3-Methoxyphenyl)-3-oxo-3-phenylpropyl)-malonate (**4n**).*[5e] 36 mg, yield = 97%, colorless oil; $[\alpha]_D^{26.4}$ = +21.4 (*c* = 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.90 (d, *J* = 7.6 Hz, 2H), 7.52 (t, *J* = 7.4 Hz, 1H), 7.42 (t, *J* = 7.6 Hz, 2H), 7.16 (t, *J* = 7.8 Hz, 1H), 6.84 (d, *J* = 7.6 Hz, 1H), 6.80 (t, *J* = 1.8 Hz, 1H), 6.72 (dd, *J* = 2.2, 8.2 Hz 1H), 4.15- 4.20 (m, 1H), 3.86 (d, *J* = 9.2 Hz, 1H), 3.74 (s, 3H), 3.72 (s, 3H), 3.44–3.56 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 197.4, 168.6, 168.1, 159.4, 142.1, 136.7, 133.0, 129.4, 128.5, 128.0, 120.2, 113.9, 112.4, 57.1, 55.1, 52.6, 52.4, 42.2, 40.6; Enantiomeric excess: 96%, determined by HPLC (Chiralpak column AS-H, hexane/*i*-PrOH 80/20, flow rate 0.8 mL/min; t_{major} = 20.3 min, t_{minor} = 15.5 min, λ = 254 nm).

*(S)-Dimethyl 2-(3-Oxo-3-phenyl-1-(thiophen-2-yl)propyl)-malonate (**4o**).* 34 mg, yield = 99%; colorless oil; $[\alpha]_D^{24.0}$ = +30.5 (*c* = 0.87, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.93 (d, *J* = 7.6 Hz, 2H), 7.55 (t, *J* = 7.4 Hz, 1H), 7.44 (t, *J* = 7.6 Hz, 2H), 7.12 (d, *J* = 5.2 Hz, 1H), 6.92 (d, *J* = 2.8 Hz, 1H), 6.87 (dd, *J* = 3.6, 5.2 Hz, 1H), 4.51–4.57 (m, 1H), 3.92 (d, *J* = 8.4 Hz, 1H), 3.73 (s, 3H), 3.62 (s, 3H), 3.58 (d, *J* = 6.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 197.1, 168.4, 168.0, 143.5, 136.6, 133.2, 128.6, 128.1, 126.6, 125.7, 124.2, 57.5, 52.7, 52.6, 42.9, 35.9; IR (Neat) ν 2960, 1748, 1721, 1682, 1449, 1296, 1264, 1173, 851, 753, 686 cm^{-1}; HRMS (ESI): calcd. for $[M+H]^+$ $(C_{18}H_{19}O_5S)^+$ requires 347.0953; found 347.0943; Enantiomeric excess: 97%, determined by HPLC (Phenomenex Cellulose-2, hexane/*i*-PrOH 80/20, flow rate 0.8 mL/min; t_{major} = 15.6 min, t_{minor} = 20.9 min, λ = 254 nm).

*(S)-Dimethyl 2-(1-(Naphthalen-1-yl)-3-oxo-3-phenylpropyl)-malonate (**4p**).*[5e] 37 mg, yield = 95%; colorless oil; $[\alpha]_D^{26.7}$ = +63.1 (*c* = 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 8.30 (d, *J* = 8.4 Hz, 1H), 7.88 (d, *J* = 7.2 Hz, 2H), 7.81 (d, *J* = 8.4 Hz, 1H), 7.69 (d, *J* = 7.6 Hz, 1H), 7.45–7.57 (m, 3H), 7.34–7.41 (m, 4H), 5.15–5.20 (m, 1H), 4.07 (d, *J* = 8.4 Hz, 1H), 3.74 (d, *J* = 6.0 Hz, 2H), 3.65 (s, 3H), 3.44 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 197.5, 168.8, 168.3, 137.1, 137.0, 136.7, 134.0, 133.0, 131.3, 128.9, 128.5, 128.0, 127.8, 126.4, 125.6, 125.1, 123.2, 56.5, 52.5, 52.4, 41.8 ; Enant-iomeric excess: 96%, determined by HPLC (Phenomenex Cellulose-2, hexane/*i*-PrOH 80/20, flow rate 0.8 mL/min; t_{major} = 18.4 min, t_{minor} = 29.7 min, λ = 254 nm).

*(S)-Dimethyl 2-(1-(Naphthalen-2-yl)-3-oxo-3-phenylpropyl)-malonate (**4q**).* 38 mg, yield = 98%, white solid. mp = 112–114 °C. $[\alpha]_D^{25.9}$ = +25.2 (*c* = 0.98, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.89 (d, *J* = 7.2 Hz, 2H), 7.74–7.76 (m, 3H), 7.70 (s, 1H), 7.50 (t, *J* = 7.4 Hz, 1H), 7.38–7.44 (m, 5H), 4.35- 4.41 (m, 1H), 3.98 (d, *J* = 9.6 Hz, 1H), 3.72 (s, 3H), 3.60–3.62 (m, 2H), 3.46 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 197.4, 168.7, 168.1, 138.0, 136.7, 133.3, 133.1, 132.5, 128.5, 128.2, 128.0, 127.8, 127.5, 126.9, 126.1, 126.0, 125.7, 57.2, 52.7, 52.4, 42.3, 40.7; IR (KBr) ν 3056, 2952, 2853, 1736, 1686, 1598, 1577, 1508, 1448, 1434, 1340, 1261, 1219, 1156, 1019, 859, 820, 750, 690 cm^{-1}; HRMS (ESI) calcd. for $[M+Na]^+$ $(C_{24}H_{22}NaO_5)^+$ requires 413.1365; found 413.1369. Enantiomeric excess: 96%, determined by HPLC (Phenomenex Cellulose-2, hexane/*i*-PrOH 80/20, flow rate 0.8 mL/min; t_{major} = 20.5 min, t_{minor} = 30.6 min, λ = 254 nm).

*(R,E)-Dimethyl 2-(5-Oxo-1,5-diphenylpent-1-en-3-yl)malonate (**4r**).* 36 mg, yield = 98%, white solid. mp = 109–110 °C; $[\alpha]_D^{24.3}$ = +8.2 (*c* = 1.22, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.96 (d, *J* = 7.2 Hz, 2H), 7.55 (t, *J* = 7.2 Hz, 1H), 7.45 (t, *J* = 7.6 Hz, 2H), 7.17–7.30 (m, 5H), 6.47 (d, *J* = 16.0 Hz, 1H), 6.24 (dd, *J* = 9.0, 15.8 Hz, 1H), 3.81 (d, *J* = 7.2 Hz, 1H), 3.65–3.74 (m, 7H), 3.39 (dd, *J* = 5.2, 16.8 Hz, 1H), 3.26 (dd, *J* = 8.0, 16.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 197.9, 168.7, 168.5, 136.8, 136.7, 133.1, 132.6, 128.6, 128.4, 128.3, 128.1, 127.5, 126.3, 55.3, 5 2.5, 52.4, 41.1, 38.8; IR (KBr) ν 2953, 2916, 2848, 1732, 1678, 1596, 1449, 1438, 1356, 1294, 1233, 164, 1025, 980, 755, 691 cm^{-1}; HRMS (ESI): calcd. for $[M+H]^+$ $(C_{22}H_{23}O_5)^+$ requires 367.1545; found 367.1536; Enantiomeric excess: 97%, determined by HPLC (Phenomenex Cellulose-2, hexane/*i*-PrOH 80/20, flow rate 0.8 mL/min; t_{major} = 11.2 min, t_{minor} = 13.7 min, λ = 254 nm).

*(S)-Dimethyl 2-(4-Oxo-4-phenylbutan-2-yl)malonate (**4s**).*[22] 27 mg, yield = 98%, colorless oil; $[\alpha]_D^{25.3}$ = +4.8 (*c* = 0.93, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.98 (d, *J* = 7.2 Hz, 2H), 7.57 (t, *J* = 7.2 Hz, 1H), 7.47 (t, *J* = 7.6 Hz, 2H), 3.75 (s, 3H), 3.74 (s, 3H), 3.54 (d, *J* = 6.4 Hz, 1H), 3.27 (dd, *J* = 4.0, 16.0 Hz, 1H), 2.90–3.04 (m, 2H), 1.09 (d, *J* = 6.4 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 198.6, 169.1, 169.0, 136.8, 133.1, 128.6, 128.1, 56.1, 52.4, 52.3, 42.6, 29.5, 17.7. Enanti- omeric excess: 95%, determined by HPLC (Chiralpak column AD-H, hexane/*i*-PrOH 90/10, flow rate 0.7 mL/min; t_{major} = 11.4 min, t_{minor} = 12.6 min, λ = 254 nm).

*(S)-Dimethyl 2-(1-Oxo-1-phenyloctan-3-yl)malonate (**4t**).* 32 mg, yield = 97%, colorless oil; $[\alpha]_D^{26.4}$ = +8.9 (*c* = 0.84, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.98 (d, *J* = 7.6 Hz, 2H), 7.56 (t, *J* = 7.4 Hz, 1H), 7.46 (t, *J* = 7.6 Hz, 2H), 3.73 (s, 3H), 3.69–3.71 (m, 4H), 3.30 (dd, *J* = 5.4, 17.4 Hz, 1H), 3.05 (dd, *J* = 7.0, 17.4 Hz, 1H), 2.85–2.93 (m, 1H), 1.61–1.65 (m, 1H), 1.43–1.46 (m, 2H), 1.27–1.40 (m, 5H), 0.86 (t, *J* = 6.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 199.0, 169.4, 169.2, 137.0, 133.0, 128.5, 128.1, 53.8, 52.4, 52.3, 40.1, 34.0, 32.0, 31.6, 26.7, 22.4, 14.0; IR (Neat) ν 2955, 2931, 2859, 1736, 1687, 1598, 1581, 1449, 1436, 1219, 1158, 1024, 751, 738, 691 cm^{-1}; HRMS (ESI): calcd. for $[M+H]^+$ $(C_{19}H_{27}O_5)^+$ requires 335.1858; found 335.1849. Enantiomeric excess: 97%, determined by HPLC (Phenomenex Cellulose-2, hexane/*i*-PrOH 90/10, flow rate 0.8 mL/min; t_{major} = 9.8 min, t_{minor} = 12.0 min, λ = 254 nm).

*(S)-2-Ethyl 1,1-Dimethyl 4-oxo-4-phenylbutane-1,1,2-tricarboxy-late (**4u**).* 33 mg, yield = 98%,colorless oil; $[\alpha]_D^{26.6}$ = −1.9 (*c* = 0.84, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.97 (d, *J* = 7.2 Hz, 2H), 7.57 (t, *J* = 7.4 Hz, 1H), 7.47 (t, *J* = 7.6 Hz, 2H), 4.15 (q, *J* = 7.2 Hz, 2H), 4.04 (d, *J* = 6.4 Hz, 1H), 3.83–3.87 (m, 1H), 3.75 (s, 3H), 3.73 (s, 3H), 3.63 (dd, *J* = 6.8, 18.0 Hz 1H), 3.34 (dd, *J* = 4.8, 18.0 Hz, 1H), 1.20 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 197.1, 172.0, 168.4, 168.3, 136.3, 133.3, 128.6, 128.0, 61.4, 52.7, 52.6, 51.9, 39.6, 37.3, 13.9; IR (Neat) ν 3060, 2983, 2955, 2928, 2850, 1736, 1686, 1597, 1581, 1438, 1025, 860, 755 cm^{-1}; HRMS (ESI): calcd. for $[M+H]^+$ $(C_{17}H_{21}O_7)^+$ requires 337.1287; found 337.1278. Enantiomeric excess: 94%, determined by HPLC (Phenomenex Cellulose-2, hexane/*i*-PrOH 50/50, flow rate 0.8 mL/min; t_{major} = 18.3 min, t_{minor} = 15.5 min, λ = 254 nm).

*(S)-Dimethyl 2-(1,1,1-Trifluoro-4-oxo-4-phenylbutan-2-yl)-malonate (**4v**).* 32 mg, yield = 97%, white solid. mp = 84–86 °C; $[\alpha]_D^{26.2}$ = −1.9 (*c* = 0.83, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.99 (d, *J* = 8.0 Hz, 2H), 7.60 (t, *J* = 8.0 Hz, 1H), 7.49 (t, *J* = 8.0 Hz, 2H), 4.00–4.11 (m, 1H), 3.88 (d, *J* = 8.0 Hz, 1H), 3.76 (s, 3H), 3.74 (s, 3H), 3.65 (dd, *J* = 6.0, 18.0 Hz, 1H), 3.37 (dd, *J* = 6.0, 18.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 195.2, 167.5, 167.3, 136.0, 133.5, 128.7, 128.1, 126.6 (q, J_{C-F} = 278.6 Hz), 53.2, 52.9, 49.1 (q, J_{C-F} = 2.2 Hz), 38.2 (q, J_{C-F} = 27.4 Hz), 34.4 (q, J_{C-F} = 1.7 Hz); ^{19}F NMR ($CDCl_3$, 282 MHz) δ −70.2 (d, J_{C-F} = 5.6 Hz); IR (KBr) ν 2960, 1745, 1686, 1441, 1366, 1331, 1293, 1225, 1162, 1117, 1070, 1026, 1000, 982, 957, 932, 756, 688 cm^{-1}; HRMS (ESI): calcd. for $[M+H]^+$ $(C_{15}H_{16}F_3O_5)^+$ requires: 333.0950; found 333.0940. Enantiomeric excess: 86%, determined by HPLC (Phenomenex Cellulose-2,

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hexane/*i*-PrOH 90/10, flow rate 0.5 mL/min; t_{major} = 12.2 min, t_{minor} = 11.5 min, λ = 254 nm).

*(R)-Dimethyl 2-(1-Cyclohexyl-3-oxo-3-phenylpropyl)malonate (**4w**).* 35 mg, yield = 98%, colorless oil; $[\alpha]_D^{26.5}$ = +16.3 (*c* = 0.87, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.98 (d, *J* = 7.6 Hz, 2H), 7.55 (t, *J* = 7.4 Hz, 1H), 7.46 (t, *J* = 7.6 Hz, 2H), 3.72 (d, *J* = 6.0 Hz, 1H), 3.69 (s, 6H), 3.29 (dd, *J* = 5.2, 18.0 Hz, 1H), 3.15(dd, *J* = 5.8, 18.2 Hz, 1H), 2.92−2.98 (m, 1H), 1.58−1.75 (m, 4H), 1.38−1.45 (m, 1H), 0.94−1.26 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 198.7, 169.9, 169.4, 136.9, 132.9, 128.5, 128.0, 52.7, 52.5, 52.3, 40.6, 38.5, 38.2, 30.9, 29.9, 26. 5, 26.4, 26.3;IR (Neat) ν 2927, 2852, 1732, 1687, 1598, 1581, 1448, 1435, 1220, 1156, 1021, 981, 751, 691 cm^{-1}; HRMS (ESI): calcd. for $[M+H]^+$ $(C_{20}H_{27}O_5)^+$ requires 347.1858; found 347.1848. Enantiomeric excess: 94%, determined by HPLC (Chiralpak column AD, hexane/*i*-PrOH 80/20, flow rate 0.8 mL/min; t_{major} = 8.8 min, t_{minor} = 9.5 min, λ = 254 nm).

*(S)-Dimethyl 2-(3-(4-Fluorophenyl)-3-oxo-1-phenylpropyl)-malonate (**4x**).* 34 mg, yield = 98%, colorless oil; $[\alpha]_D^{24.9}$ = +21.6 (*c* = 0.90, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.90−7.95 (m, 2H), 7.23−7.27 (m, 4H), 7.16−7.21 (m, 1H), 7.06−7.11 (m, 2H), 4.14- 4.20 (m, 1H), 3.85 (d, *J* = 9.2 Hz, 1H), 3.73 (s, 3H), 3.40−3.56 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 196.0, 168.7, 168.1, 165.7 (d, J_{C-F} = 253.5 Hz), 140.2, 133.1 (d, J_{C-F} = 2.8 Hz), 130.7 (d, J_{C-F} = 9.3 Hz), 128.5, 128.0, 127.3, 115.6 (d, J_{C-F} = 21.8 Hz), 57.2, 52.7, 52.4, 42.2, 40.8; ^{19}F NMR ($CDCl_3$, 376 MHz) δ −105.2 (m); IR (Neat): ν 3065, 3031, 3005, 2954, 2924, 2852, 1738, 1688, 1597, 1506, 1455, 1435, 1410, 1232, 1157, 1024, 841, 767 cm^{-1}; HRMS (ESI): calcd. for $[M+H]^+$ $(C_{20}H_{20}FO_5)^+$ requires 359.1295; found 359.1284. Enantiomeric excess: 98%, determined by HPLC (Phenomenex Cellulose-2, hexane/*i*-PrOH 80/20, flow rate 0.8 mL/min; t_{major} = 14.1 min, t_{minor} = 17.6 min, λ = 254 nm).

*(S)-Dimethyl 2-(3-(4-Chlorophenyl)-3-oxo-1-phenylpropyl)-malonate (**4y**).*[5e] 35 mg, yield = 94%, white solid. mp = 67−68 °C; $[\alpha]_D^{26.5}$ = +20.9 (*c* = 0.94, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.83 (d, *J* = 8.8 Hz, 2H), 7.39 (d, *J* = 8.8 Hz, 2H), 7.21−7.27 (m, 4H), 7.16−7.20 (m, 1H), 4.13−4.19 (m, 1H), 3.84 (d, *J* = 9.2 Hz, 1H), 3.72 (s, 3H), 3.40−3.56 (m, 5H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 196.3, 168.6, 168.0, 140.1, 139.5, 135.0, 129.5, 128.8, 128.5, 127.9, 127.3, 57.1, 52.6, 52.4, 42.2, 40.8. Enantiomeric excess: 99%, determined by HPLC (Phenomenex Cellulose-2, hexane/*i*-PrOH 80/20, flow rate 0.8 mL/min; t_{major} = 15.1 min, t_{minor} = 18.1 min, λ = 254 nm).

*(S)-Dimethyl 2-(3-(4-Bromophenyl)-3-oxo-1-phenylpropyl)-malonate (**4z**).* 41 mg, yield = 99%, white solid. mp = 87−88 °C; $[\alpha]_D^{23.6}$ = +19.7 (*c* = 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.76 (d, *J* = 8.4 Hz, 2H), 7.56 (d, *J* = 8.4 Hz, 2H), 7.17−7.27 (m, 5H), 4.13−4.19 (m, 1H), 3.84 (d, *J* = 9.2 Hz, 1H), 3.73 (s, 3H), 3.50−3.55 (m, 4H), 3.42 (dd, *J* = 8.8, 16.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 196.5, 168.7, 168.0, 140.1, 135.4, 131.8, 129.6, 128.5, 128.2, 127.9, 127.3, 57.1, 52.7, 52.4, 42.2, 40.8; IR (KBr) ν 2955, 1733, 1682, 1587, 1499, 1457, 1435, 1330, 1296, 1238, 1155, 1089, 1072, 1025, 1011, 980, 823, 786, 765, 703 cm^{-1}; HRMS (ESI): calcd. for $[M+H]^+$ $(C_{20}H_{20}BrO_5)^+$ requires 419.0494; found 419.0483. Enantiomeric excess: 97%, determined by HPLC (Phenomenex Cellulose-2, hexane/*i*-PrOH 80/20, flow rate 0.8 mL/min; t_{major} = 18.4 min, t_{minor} = 22.1 min, λ = 254 nm).

*(S)-Dimethyl 2-(3-Oxo-1-phenyl-3-(p-tolyl)propyl)malonate (**4a′**).* 35 mg, yield = 98%, white solid. mp = 76−77 °C; $[\alpha]_D^{25.4}$ = +21.2 (*c* = 0.89, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.79 (d, *J* = 8.0 Hz, 2H), 7.14−7.27 (m, 7H), 4.16−4.22 (m, 1H), 3.85 (d, *J* = 9.2 Hz, 1H), 3.71 (s, 3H), 3.41−3.54 (m, 5H), 2.38 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 197.0, 168.7, 168.1, 143.8, 140.4, 134.2, 129.2, 128.4, 128.1, 128.0, 127.1, 57.3, 52.6, 52.3, 42.1, 40.7, 21.6; IR (KBr): ν 3031, 2953, 2918, 2848, 1737, 1682, 1607, 1496, 1454, 1435, 1259, 1155, 1026, 813, 771 cm^{-1}; HRMS (ESI) calcd. for $[M+H]^+$ $(C_{21}H_{23}O_5)^+$ requires 355.1545; found 355.1540. Enantiomeric excess: 99%, determined by HPLC (Phenomenex Cellulose-2, hexane/*i*-PrOH 80/20, flow rate 0.8 mL/min; t_{major} = 18.9 min, t_{minor} = 27.8 min, λ = 254 nm).

*(S)-Dimethyl 2-(3-(4-Methoxyphenyl)-3-oxo-1-phenylpropyl)-malonate (**4b′**).* 39 mg, yield = 99%, white solid. mp = 60−62 °C; $[\alpha]_D^{25.9}$ = +20.5 (*c* = 0.93, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.88 (d, *J* = 8.8 Hz, 2H), 7.22−7.26 (m, 4H), 7.14−7.20 (m, 1H), 6.89 (d, *J* = 8.8 Hz, 2H), 4.15- 4.21 (m, 1H), 3.86 (d, *J* = 9.6 Hz, 1H), 3.84 (s, 3H), 3.72 (s, 3H), 3.38−3.51 (m, 5H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 195.9, 168.7, 168.1, 163.4, 140.4, 130.3, 129.8, 128.4, 128.0, 127.1, 113.6, 57.3, 55.4, 52.6, 52.3; IR (KBr): ν 3006, 2953, 2842, 1736, 1677, 1600, 1511, 1434, 1257, 1170, 1025, 838, 775 cm^{-1}. HRMS (ESI): calcd. for $[M+Na]^+$ $(C_{21}H_{21}NaO_6)^+$ requires 393.1314; found 393.1316. Enantiomeric excess: 98%, determined by HPLC (Chiralpak column AD, hexane/*i*-PrOH 50/50, flow rate 0.8 mL/min; t_{major} = 22.4 min, t_{minor} = 15.5 min, λ = 254 nm).

*(S)-Dimethyl 2-(3-(4-Nitrophenyl)-3-oxo-1-phenylpropyl)-malonate (**4c′**).* 38 mg, Yield = 99%, colorless oil; $[\alpha]_D^{24.6}$ = +19.5 (*c* = 0.96, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.27 (d, *J* = 8.8 Hz, 2H), 8.04 (d, *J* = 8.8 Hz, 2H), 7.17−7.28 (m, 5H), 4.13−4.19 (m, 1H), 3.86 (d, *J* = 9.2 Hz, 1H), 3.74 (s, 3H), 3.64 (dd, *J* = 4.8, 16.8 Hz, 1H), 3.47−3.53 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 196.3, 168.7, 168.0, 150.2, 141.1, 139.8, 129.1, 128.6, 127.9, 127.5, 123.8, 57.0, 52.7, 52.5, 42.8, 40.7; IR (Neat) ν 2955, 1759, 1728, 1694, 1603, 1522, 1455, 1431, 1406, 1350, 1313, 1260, 1200, 1169, 1139, 1012, 855, 744, 699 cm^{-1}; HRMS (ESI): calcd. for $[M+H]^+$ $(C_{20}H_{20}NO_7)^+$ requires 386.1240; found 386.1229. Enantiomeric excess: 98%, determined by HPLC (Chiralpak column AD, hexane/*i*-PrOH 50/50, flow rate 0.8 mL/min; t_{major} = 19.6 min, t_{minor} = 17.2 min, λ = 254 nm).

*(S)-Dimethyl 2-(3-(2-Bromophenyl)-3-oxo-1-phenylpropyl)-malonate (**4d′**).* 41 mg, yield = 99%, white solid. mp = 98−99 °C; $[\alpha]_D^{26.6}$ = +1.8 (*c* = 0.84, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.53 (d, *J* = 7.6 Hz, 1H), 7.18−7.26 (m, 7H), 7.10 (d, *J* = 5.6 Hz, 1H), 4.06−4.12 (m, 1H), 3.81 (d, *J* = 8.0 Hz, 1H), 3.75 (s, 3H), 3.51−3,56 (m, 4H), 3.43 (dd, *J* = 9.4, 17.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 201.4, 168.5, 168.0, 141.3, 139.8, 133.5, 128.5, 128.4, 128.2, 127.3, 127.2, 118.5, 57.1, 52.7, 52.4, 46.2, 40.8 (one peak for aromatic carbon was not found probably due to overlapping). IR (KBr) ν 2951, 1749, 1725, 1695, 1586, 1468, 1456, 1435, 1401, 1368, 1303, 1260, 1166, 1049, 1018, 754, 702 cm^{-1}; HRMS (ESI): calcd. for $[M+H]^+$ $(C_{20}H_{20}BrO_5)^+$ requires 419.0494; found 419.0483. Enantiomeric excess: 96%, determined by HPLC (Phenomenex Cellulose-2, hexane/*i*-PrOH 80/20, flow rate 0.8 mL/min; t_{major} = 16.3 min, t_{minor} = 20.3 min, λ = 254 nm).

*(S)-Dimethyl 2-(3-(3-Chlorophenyl)-3-oxo-1-phenylpropyl)-malonate (**4e′**).* 39 mg, yield = 98%. colorless oil.$[\alpha]_D^{28.6}$ = +24.1 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (s, 1H), 7.71 (d, *J* = 8.0 Hz, 1H), 7.43 (d, *J* = 8.0 Hz, 1H), 7.30 (t, *J* = 8.0 Hz, 1H), 7.16−7.21 (m, 4H), 7.09−7.15 (m. 1H), 4.07−4.13 (m, 1H), 3.78 (d, *J* = 9.6 Hz, 1H), 3.66 (s, 3H), 3.43−3.49 (m, 4H), 3.38 (dd, *J* = 8.8, 17.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.2, 168.6, 168.0, 140.2, 138.2, 134.9, 133.0, 129.9, 128.5, 128.1, 128.0, 127.3, 126.2, 57.1, 52.7, 52.4, 42.4, 40.6; IR (Neat): ν 3065, 3031, 2953, 2920, 2849, 1737, 1691, 1571, 1496, 1454, 1434, 1323, 1286, 1257, 1221, 1157, 1077, 1026, 780, 701, 682 cm^{-1}. HRMS (ESI): calcd. for $[M+Na]^+$ $(C_{20}H_{19}ClNaO_5)^+$ requires 397.0819; found 397.0820. Enantiomeric excess: 99%, determined by HPLC (Phenomenex Cellulose-2, hexane/*i*-PrOH 90/10, flow rate 0.8 mL/min; t_{major} = 22.8 min, t_{minor} = 30.0 min, λ = 254 nm).

*(S)-Dimethyl 2-(3-Oxo-1-phenyl-3-(thiophen-2-yl)propyl)-malonate (**4f′**).* 34 mg, yield = 99%, white solid. mp = 82−83 °C; $[\alpha]_D^{26.5}$ = +15.5 (*c* = 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.72 (d, *J* = 3.6 Hz, 1H), 7.58 (d, *J* = 4.8 Hz, 1H), 7.23−7.26 (m, 4H), 7.15−7.21 (m, 1H), 7.09 (t, *J* = 4.2 Hz, 1H), 4.14−4.20 (m, 1H), 3.87 (d, *J* = 9.6 Hz, 1H), 3.73 (s, 3H), 3.50 (s, 3H), 3.47 (dd, *J* = 5.2, 16.4 Hz, 1H), 3.39 (dd, *J* = 8.8, 16.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 190.3, 168.6, 168.0, 144.0, 140.0, 133.7, 132.0, 128.5, 128.0, 127.9, 127.3, 57.1, 52.6, 52.4, 43.0, 41.1; IR (KBr) ν2955, 1732, 1659, 1516, 1434, 1418, 1358, 1239, 1163, 1070, 1013, 957, 854, 730 cm-1; HRMS (ESI): calcd. for $[M+H]^+$ $(C_{18}H_{19}O_5S)^+$ requires 347.0953; found 347.0944. Enantiomeric excess: 97%, determined by HPLC (Phenomenex Cellulose-2, hexane/*i*-PrOH 80/20, flow rate 0.8 mL/min; t_{major} = 21.9 min, t_{minor} = 28.9 min, λ = 254 nm).

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*(S)-Dimethyl 2-(3-(Furan-2-yl)-3-oxo-1-phenylpropyl)malonate (**4g′**).* 32 mg, yield = 97%, white solid. mp = 106−108 °C; $[\alpha]_D^{25.6}$ = +29.0 (*c* = 0.83, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) *δ* 7.53 (s, 1H), 7.14−7.25 (m, 6H), 6.48 (s, 1H), 4.13−4.19 (m, 1H), 3.86 (d, *J* = 9.6 Hz, 1H), 3.73 (s, 3H), 3.50 (s, 3H), 3.29−3.41 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) *δ* 186.5, 168.6, 168.0, 152.5, 146.3, 140.1, 128.4, 128.0, 127.2, 117.2, 112.2, 57.2, 52.6, 52.4, 42.1, 40.6; IR (KBr) *ν* 3126, 3098, 2958, 1727, 1666, 1474, 1404, 1296, 1239, 1160, 1095, 1072, 1018, 980, 951, 919, 771, 700 cm^{-1}; HRMS (ESI): calcd. for $[M+H]^+$ $(C_{18}H_{19}O_6)^+$ requires 331.1182; found 331.1172. Enantiomeric excess: 96%, determined by HPLC (Phenomenex Cellulose-2, hexane/*i*-PrOH 80/20, flow rate 0.8 mL/min; t_{major} = 28.7 min, t_{minor} = 39.9 min, *λ* = 254 nm).

*(S)-Dimethyl 2-(3-(Naphthalen-1-yl)-3-oxo-1-phenylpropyl)-malonate (**4h′**).* 37 mg, yield = 95%, white solid. mp = 98−99 °C; $[\alpha]_D^{25.8}$ = −16.8 (*c* = 0.88, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) *δ* 8.11 (d, *J* = 8.0 Hz, 1H), 7.93 (d, *J* = 8.0 Hz, 1H), 7.80 (d, *J* = 7.6 Hz, 1H), 7.77 (d, *J* = 7.2 Hz, 1H), 7.40−7.48 (m, 3H), 7.14−7.22 (m, 5H), 4.18−4.24 (m, 1H), 3.87 (d, *J* = 9.6 Hz, 1H), 3.74 (s, 3H), 3.67 (dd, *J* = 4.6, 16.6 Hz, 1H), 3.45−3.52 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) *δ* 201.8, 168.7, 168.1, 140.0, 135.9, 133.8, 132.4, 129.9, 128.5, 128.2, 127.6, 127.3, 127.2, 126.3, 125.6, 124.3, 57.3, 52.7, 52.4, 45.8, 41.3; IR (KBr) *ν* 2951, 1728, 1676, 1507, 1433, 1305, 1238, 1163, 1083, 774, 707 cm^{-1}; HRMS (ESI): calcd. for $[M+H]^+$ $(C_{24}H_{23}O_5)^+$ requires 391.1545; found 391.1533. Enantiomeric excess: 95%, determined by HPLC (Chiralpak column AD-H, hexane/*i*-PrOH 80/20, flow rate 0.8 mL/min; t_{major} = 15.8 min, t_{minor} = 14.4 min, *λ* = 254 nm).

*(S)-Dimethyl 2-(3-(Naphthalen-2-yl)-3-oxo-1-phenylpropyl)-malonate (**4i′**).* 39 mg, yield = 99%, white solid. mp = 98−99 °C; $[\alpha]_D^{26.5}$ = +46.6 (*c* = 0.98, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) *δ* 8.44 (s, 1H), 7.93−7.96 (m, 2H), 7.84 (d, *J* = 8.4 Hz, 2H), 7.52−7.60 (m, 2H), 7.23−7.30 (m, 4H), 7.14−7.20 (m, 1H), 4.24−4.29 (m, 1H), 3.91 (d, *J* = 9.6 Hz, 1H), 3.74 (s, 3H), 3.68 (dd, *J* = 5.0, 17.2 Hz, 1H), 3.61 (dd, *J* = 8.8, 16.8 Hz, 1H), 3.52 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) *δ* 197.4, 168.7, 168.1, 140.4, 135.5, 134.0, 132.4, 129.8, 129.5, 128.5, 128.4, 128.3, 128.0, 127.7, 127.2, 126.7, 123.8, 57.3, 52.7, 52.4, 42.3, 40.9. IR (KBr) *ν* 3065, 3034, 2952, 2849, 1735, 1681, 1627, 1498, 1454, 1434, 1357, 1261, 1155, 1124, 1025, 862, 823, 750, 701 cm^{-1}; HRMS (ESI) calcd. for $[M+Na]^+$ $(C_{24}H_{22}NaO_5)^+$ requires 413.1365; found 413.1367. Enantiomeric excess: 99%, determined by HPLC (Phenomenex Cellulose-2, hexane/*i*-PrOH 50/50, flow rate 0.8 mL/min; t_{major} = 14.1 min, t_{minor} = 18.6 min, *λ* = 254 nm).

*(S)-Dimethyl 2-(3-Oxo-1-phenylbutyl)malonate (**4j′**).*[23] 24 mg, yield = 85%. colorless oil. $[\alpha]_D^{28.4}$ = +11.0 (*c* = 1.0, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) *δ* 7.11−7.23 (m, 5H), 3.88−3.94 (m, 1H), 3.66 (d, *J* = 9.6 Hz, 1H), 3.65 (s, 3H), 3.43 (s, 3H), 2.91 (dd, *J* = 5.4, 17.0 Hz 1H), 2.84 (dd, *J* = 8.6, 17.0 Hz, 1H), 1.96 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) *δ* 206.0, 168.6, 168.0, 140.4, 128.5, 128.0, 127.3, 57.1, 52.6, 52.4, 47.1, 40.4, 30.3. Enantiomeric excess: 91%, determined by HPLC (Chiralpak AD-H column, hexane/*i*-PrOH 80/20, flow rate 0.8 mL/min; t_{major} = 8.8 min, t_{minor} = 8.0 min, *λ* = 214 nm).

*(S)-Dimethyl 2-(5-Oxo-1-phenylhexan-3-yl)malonate (**4k′**).*[24] 21 mg, Yield = 67%. Colorless oil. $[\alpha]_D^{23.8}$ = +2.0 (*c* = 1.02, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) *δ* 7.25−7.29 (m, 2H), 7.14−7.19 (m, 3H), 3.72 (s, 3H), 3.71 (s, 3H), 3.63 (d, *J* = 5.6 Hz, 1H), 2.72−2.83 (m, 2H), 2.53−2.67 (m, 3H), 2.12 (s, 3H), 1.63−1.78 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) *δ* 207.2, 169.2, 169.0, 141.4, 128.4, 128.3, 125.9, 53.6, 52.4, 52.3, 45.1, 34.1, 33.4, 30.2. Enantiomeric excess: 19%, determined by HPLC (Phenomenex Cellulose-2 column, hexane/*i*-PrOH 85/15, flow rate 0.8 mL/min; t_{major} = 10.0 min, t_{minor} = 11.4 min, *λ* = 220 nm).

*(S)-Diethyl 2-(3-Oxo-1,3-diphenylpropyl)malonate(**4l′**).*[2d] 49 mg, Yield = 99%. White solid. mp = 65−68 °C; $[\alpha]_D^{28.0}$ = +18.5 (*c* = 1.0, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) *δ* 7.89 (d, *J* = 7.2 Hz, 2H), 7.52 (t, *J* = 7.2 Hz, 1H), 7.41 (t, *J* = 7.6 Hz, 2H), 7.21−7.27 (m, 4H), 7.14−7.18 (m, 1H), 4.14−4.26 (m, 3H), 3.95 (q, *J* = 7.2 Hz, 2H), 3.82 (d, *J* = 10.0 Hz, 1H), 3.54 (dd, *J* = 4.6, 16.6 Hz, 1H), 3.46 (dd, *J* = 9.2, 16.8 Hz, 1H), 1.24 (t, *J* = 7.2 Hz, 3H), 1.00 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) *δ* 197.5, 168.3, 167.7, 140.4, 136.7, 133.0, 128.5, 128.3, 128.2, 128.0, 127.1, 61.6, 61.3, 57.5, 42.6, 40.7, 14.0, 13.7. Enantiomeric excess: 99%, determined by HPLC (Phenomenex Cellulose-2 column, hexane/*i*-PrOH 80/20, flow rate 1.0 mL/min; t_{major} = 10.3 min, t_{minor} = 16.4 min, *λ* = 254 nm).

*(S)-Dibenzyl 2-(3-Oxo-1,3-diphenylpropyl)malonate(**4m′**).*[5b] 36 mg, Yield = 99%. White solid. mp = 90−91 °C; $[\alpha]_D^{27.9}$ = +12.5 (*c* = 0.97, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) *δ* 7.80 (d, *J* = 7.6 Hz, 2H), 7.50 (t, *J* = 7.4 Hz, 1H), 7.37 (t, *J* = 7.6 Hz, 2H), 7.13−7.27 (m, 13 H), 7.05−7.06 (m, 2H), 5.16 (d, *J* = 12.0 Hz, 1H), 5.11 (d, *J* = 12.4 Hz, 1H), 4.90 (s, 2H), 4.20−4.25 (m, 1H), 3.95 (d, *J* = 9.6 Hz, 1H), 3.44 (d, *J* = 6.8 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) *δ* 197.3, 167.9, 167.4, 140.2, 136.6, 135.1, 135.0, 132.9, 128.5, 128.4 (×2), 128.3 (×2), 128.2, 128.1 (×3), 128.0, 127.1, 67.3, 67.1, 57.5, 42.2, 40.7. Enantiomeric excess: 99%, determined by HPLC (Phenomenex Cellulose-2, hexane/*i*-PrOH 70/30, flow rate 1.0 mL/min; t_{major} = 13.4 min, t_{minor} = 28.1 min, *λ* = 254 nm).

*(S)-Dibenzyl 2-(3-Oxocyclopentyl)malonate(**4n′**).*[25] 36 mg, Yield = 98%. Colorless oil; $[\alpha]_D^{28.0}$ = −6.9 (*c* = 0.97, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) *δ* 7.28−7.32 (m, 10 H), 5.13−5.16 (m, 4H), 3.45 (d, *J* = 9.2 Hz, 1H), 2.81−2.92 (m, 1H), 2.42−2.48 (m, 1H), 2.25−2.33 (m, 1H), 2.10−2.22 (m, 2H), 1.95−202 (m, 1H), 1.55−1.67 (m, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) *δ* 216.9, 167.7, 167.6, 135.0, 134.9, 128.5 (×2), 128.4 (×2), 128.2 (×2), 67.3, 67.2, 56.4, 42.7, 38.1, 36.3, 27.3. Enantiomeric excess: 17%, determined by HPLC (Phenomenex Cellulose-2, hexane/*i*-PrOH 88/12, flow rate 0.8 mL/min; t_{major} = 49.3 min, t_{minor} = 44.2 min, *λ* = 220 nm).

*(S)-Dibenzyl 2-(3-Oxocyclohexyl)malonate(**4o′**).*[25] 14 mg, Yield = 38%. White solid. mp = 55−57 °C. $[\alpha]_D^{26.5}$ = +1.4 (*c* = 0.73, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) *δ* 7.27−7.34 (m, 10H), 5.15 (s, 2H), 5.14 (s, 2H), 5.41 (d, *J* = 7.6 Hz, 1H), 2.51−2.60 (m, 1H), 2.35−2.46 (m, 2H), 2.15−2.27 (m, 2H), 1.98−2.05 (m, 1H), 1.88−1.91 (m, 1H), 1.57−1.69 (m, 1H), 1.41−1.51 (m, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) *δ* 209.4, 167.5, 167.4, 135.0 (×2), 128.5, 128.4 (×2), 128.2, 67.2 (×2), 56.7, 45.0, 40.9, 38.1, 28.6, 24.4 (two peaks for aromatic carbon were not found probably due to overlapping). Enantiomeric excess: 16%, determined by HPLC (Chiralpak AS-H column, hexane/*i*-PrOH 90/10, flow rate 0.5 mL/min; t_{major} = 75.9 min, t_{minor} = 62.9 min, *λ* = 220 nm).

*(R)-Dimethyl 2-Methyl-2-(3-oxo-1,3-diphenylpropyl)malonate (**4p′**).* 35 mg, Yield = 98%. White solid. mp = 135−136 °C. $[\alpha]_D^{25.8}$ = +53.1 (*c* = 0.50, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) *δ* 7.84 (d, *J* = 7.2 Hz, 2H), 7.43 (t, *J* = 7.4 Hz, 1H), 7.33 (t, *J* = 7.6 Hz, 2H), 7.07−7.18 (m, 5H), 4.12 (dd, *J* = 2.8, 10.8 Hz, 1H), 3.65−3.72 (m, 4H), 3.57 (s, 3H), 3.49 (dd, *J* = 2.8, 17.2 Hz, 1H), 1.36 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 197.7, 171.9, 171.7, 138.8, 136.9, 132.9, 129.2, 128.4, 128.1, 128.0, 127.3, 57.9, 52.5, 52.4, 45.5, 41.0, 19.4 ; IR (KBr): *ν* 3008, 2994, 2952, 1739, 1716, 1672, 1447, 1374, 1301, 1254, 1231, 1124, 1107, 750, 703, 689 cm^{-1}; HRMS (ESI): calcd. for $[M+Na]^+$ $(C_{21}H_{22}NaO_5)^+$ requires 377.1365; found 377.1364. Enantiomeric excess: 98%, determined by HPLC (Chiralpak AD-H column, hexane/*i*-PrOH 90/10, flow rate 0.7 mL/min; t_{major} = 24.2 min, t_{minor} = 15.9 min, *λ* = 254 nm).

*(R)-Dimethyl 2-Fluoro-2-(3-oxo-1,3-diphenylpropyl)malonate (**4q′**).* 32 mg, yield = 89%. White solid. mp = 122−123 °C. $[\alpha]_D^{25.5}$ = +60.2 (*c* = 0.5, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) *δ* 7.81−7.83 (m, 2H), 7.46 (t, *J* = 7.4 Hz, 1H), 7.35 (t, *J* = 7.6 Hz, 2H), 7.29 (d, *J* = 8.0 Hz, 2H), 7.12−7.21 (m, 3H), 4.46 (ddd, *J* = 3.8, 9.4 Hz, J_{H-F} = 32.6 Hz, 1H), 3.78 (s, 3H), 3.59 (dd, *J* = 9.4, 17.4 Hz, 1H), 3.48 (s, 3H), 3.33 (dd, *J* = 4.0, 17.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 196.2, 165.9 (d, J_{C-F} = 25.8 Hz), 165.2 (d, J_{C-F} = 26.4 Hz), 137.0, 136.4, 133.3, 129.2 (d, J_{C-F} = 1.9 Hz), 128.6, 128.4, 128.0, 127.8, 97.4 (d, J_{C-F} = 204.6 Hz), 53.7, 53.1, 44.9 (d, J_{C-F} = 18.6 Hz), 39.3 (d, J_{C-F} = 3.4 Hz). ^{19}F NMR (376 MHz, CDCl3) *δ* −173.4 (d, J_{C-F} = 32.7 Hz). IR (KBr): *ν* 3064, 3032, 2960, 2921, 2890, 1758, 1736, 1682, 1448, 1431, 1300, 1267, 1240, 1145, 1092, 1049, 1039, 959, 940, 788, 755, 702, 687 cm^{-1}; HRMS (ESI): calcd. for $[M+Na]^+$ $(C_{20}H_{19}FNaO_5)^+$ requires 381.1114; found 381.1103. Enantiomeric excess: 98%, determined by HPLC (Chiralpak AS-H column, hexane/

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i-PrOH 80/20, flow rate 0.7 mL/min; t_{major} = 13.0 min, t_{minor} = 15.5 min, λ = 254 nm).

Procedure for Synthesis of Compound **5**.[17] To a solution of product **4a** (0.1 mmol, 34 mg) and iodine (1.2 equiv, 0.12 mmol, 31 mg) in toluene (1 mL) under argon was added 1,8-diazabicyclo[5.4.0]-undec-7-ene (DBU) (3 equiv, 0.3 mmol, 46 mg, 44 μL), and then the solution was stirred at ambient temperature for 0.5 h before being quenched by 10% $Na_2S_2O_3$ aqueous solution (5.0 mL). The aqueous phase was extracted with ethyl acetate three times (5 mL × 3). The combined organic phase was washed with saturated brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (petroleum ether/ethyl acetate = 6:1) to deliver the desired single diastereomer *trans*-cyclopropane derivative **5**.

(2S,3R)-Dimethyl 2-Benzoyl-3-phenylcyclopropane-1,1-dicarboxylate (5).[21] 30 mg, yield = 90%. colorless oil. $[\alpha]_D^{28.4}$ = +28.1 (c = 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, J = 7.2 Hz, 2H), 7.62 (t, J = 7.4 Hz, 1H), 7.52 (t, J = 7.6 Hz, 2H), 7.27−7.34 (m, 5H), 4.14 (d, J = 7.6 Hz, 1H), 3.88 (d, J = 7.6 Hz, 1H), 3.71 (s, 3H), 3.54 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.8, 166.5, 166.1, 136.7, 133.7, 133.3, 128.8, 128.5, 128.4, 127.7, 53.0, 52.9, 46.0, 36.6, 35.0. (one peak for aromatic carbon was not found probably due to overlapping). Enantiomeric excess: 94%, determined by HPLC (Phenomenex Cellulose-2, hexane/*i*-PrOH 80/20, flow rate 0.8 mL/min; t_{major} = 9.5 min, t_{minor} = 11.6 min, λ = 254 nm).

Procedure for Synthesis of Compound **6**.[18] To a solution of product **4a** (0.1 mmol, 34 mg) and iodine (1.5 equiv, 0.15 mmol, 38 mg) in DMF (1 mL) was added Na_2CO_3 (3 equiv, 0.3 mmol, 32 mg). Then the mixture was stirred under air at 35 °C for 16 h. After cooling to room temperature, the mixture was diluted with ethyl acetate (20 mL). The resulting mixture was washed with H_2O (5 mL) and brine, respectively, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (petroleum ether/ethyl acetate = 10:1) to give the product **6**.

Dimethyl (3S,4R)-4-Benzoyl-3-phenyloxetane-2,2-dicarboxylate (6).[18b] 29 mg, yield = 81%; colorless oil. $[\alpha]_D^{27.0}$ = −15.4 (c = 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, J = 7.2 Hz, 2H), 7.50 (t, J = 7.6 Hz, 1H), 7.38−7.26 (m, 7H), 6.07 (d, J = 7.6 Hz, 1H), 4.92 (d, J = 7.2 Hz, 1H), 3.78 (s, 3H), 3.32 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.8, 167.6, 166.9, 134.1, 133.7, 133.1, 128.8, 128.7, 128.5, 128.0, 87.3, 82.3, 53.4, 52.5, 49.0 (one peak for aromatic carbon was not found probably due to overlapping); Enantiomeric excess: 99%, determined by HPLC (Chiralpak AD-H column, hexane/*i*-PrOH 90/10, flow rate 1 mL/min; t_{major} = 18.7 min, t_{minor} = 24.5 min, λ = 254 nm).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b01752.

^{1}H and ^{13}C NMR spectra and HPLC traces (PDF)

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Notes

The authors declare no competing financial interest.

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