Regular Article

Lithium Binaphtholate-Catalyzed Michael Reaction of Malonates with Maleates and Its Application to the Enantioselective Synthesis of Tricarboxylic Acid Derivatives

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The Michael reaction of malonates with maleates afforded the corresponding adducts in high yields with high enantioselectivities (up to 98% enantiomeric excess (ee)) by using dilithium 3,3′-dichlorobinaphtholate as a catalyst. The obtained Michael adducts could be converted to optically active tricarboxylic acid (TCA) derivatives *via* the Krapcho reaction.

Key words Michael reaction; lithium binaphtholate; tricarboxylic acid ester; Krapcho reaction; stereoselectivity

Introduction

The Michael reaction of various nucleophiles with acceptors is one of the most versatile tools for the carbon–carbon bond formation reaction.[1–7] Enantioselective Michael reaction has emerged as a key step in the construction of complex natural products. Therefore, an elegant and economical Michael reactions have still attracted considerable attentions. To date, numerous catalytic enantioselective Michael reactions have been demonstrated. Generally, enones,[8–20] maleimides[21,22] and others have been used as Michael acceptors. In contrast, maleates have been used as acceptors to a lesser extent as acceptors. The Michael reaction of malonates to maleates is a typical example of this conjugate addition, which has been previously described even in an early volume of the famous 'Organic Syntheses.'[23] However, to the best of our knowledge, no reports are available on the enantioselective Michael reactions of malonates to maleates. Our group has reported enantioselective reactions catalyzed by metal binaphtholates.[24–33] Metal binaphtholates,[34–45] which are easily prepared from 2,2′-binaphthols (BINOLs) and metal bases, such as ^{n}BuLi or Grignard reagents, act as Brønsted bases to promote asymmetric reactions. Recently, we also reported the first example of the enantioselective Michael reaction of malonates to maleates,[46] affording tetracarboxylic acid esters as Michael adducts in high yields with high enantioselectivities. Herein, we describe the details of this reaction, including the extension of substrates and the mechanism of lithium binaphtholate-catalyzed Michael reaction of maleates as acceptors. Furthermore, we demonstrate the transformation of obtained product to the tricarboxylic acid (TCA) derivatives, which are often found in biologically active compounds, through decarboxylation.[47,48]

The initial experiment was started with the addition of dibenzyl malonate (**1a**) to diethyl maleate (**2a**) in diethyl ether using lithium binaphtholate catalyst (**4a**), which was prepared from (*R*)-3,3′-Cl_2-BINOL and ^{n}BuLi. The reaction proceeded smoothly,[49] resulting in the corresponding product **3aa** in high yield with moderate selectivity within 0.5 h (Table 1, entry 1). Enantioselectivity decreased using toluene as a solvent, probably owing to the lack of coordination of lithium atom in the solvent (entry 2). Changing the solvent to *tert*-butyl methyl ether (TBME) and lowering catalyst concentration (0.01 mmol/mL) dramatically improved the enantioselectivity for **3aa** to 90% enantiomeric excess (ee) (entry 5). Neither lowering the catalyst concentration below 0.01 mmol/mL nor lowering the temperature (0°C) increased the enantioselectivity of **3aa** (entries 6 and 7). When cyclopentyl methyl ether (CPME) was used as an ether solvent, the same effect as TBME was obtained (entry 8). In the case of l,2-dimethoxyethane (DME) (entry 9), the Michael reaction did not proceed at all owing to its high chelation ability.

Next, we investigated the effect of the substitution on the 3,3′-position of binaphthols in more detail. The catalyst **4b**, prepared from (*R*)-3,3′-Br_2-BINOL and ^{n}BuLi, afforded the Michael adduct in high yield with high enantioselectivity (entry 10), whereas unsubstituted (*R*)-BINOL-Li_2 (**4c**), (*R*)-3,3′-Me_2-BINOL-Li_2 (**4d**), and (*R*)-3,3′-Ph_2-BINOL-Li_2 (**4e**) were ineffective in this Michael reaction (entries 11–13). From these results, it is suggested that the electron deficiency might increase catalytic activity.

Next, the Michael reactions between various malonates and maleates were carried out under optimized reaction conditions (Table 2). As for the Michael acceptors, reduced stereoselectivities were obtained with dimethyl maleate (**2b**) or dibenzyl maleate (**2c**), or substituted dibenzyl maleates (**2d** and **2e**) were found to be decreased (entries 2–4). These results indicate that the electronic and steric effects affect for the reaction rate of this reaction. Di-*n*-propyl maleate (**2f**) reacted with malonate **1a** to give the corresponding Michael adduct **3af**, albeit in low enantioselectivity, but diallyl maleate (**2g**) gave a result similar to that of diethyl maleate (**2a**). Among the other Michael donors, no alkyl malonate performed better than dibenzyl malonate (**1a**) (entries 9–11). As the general Michael acceptors, the enantioselectivities of *N*-phenylmaleimide (**2h**) and chalcone (**2i**) were decreased (entries 12, 13). Interestingly, fumarate **2j**, the *trans*-isomer of maleate **2a**, gave an almost racemic product **3aa** (entry 14), suggesting that the *cis* geometry of the C–C double bond of **2a** allows both carbonyl groups to coordinate with lithium metals. A ketone with a *cis*

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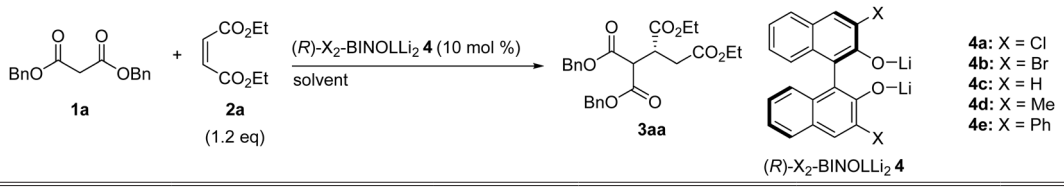
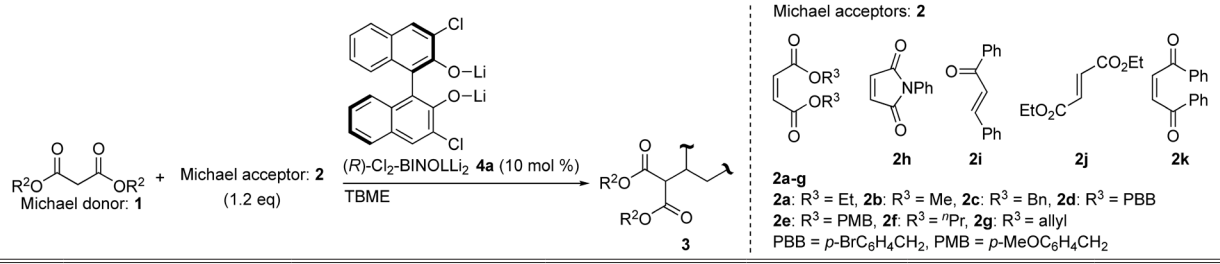
Table 1. Optimization of Enantioselective Michael Reaction of Malonate **1a** with Maleate **2a**



Entry	Solvent	*c* (mol/L) (%)[a]	Cat.: X	Conditions	Yield (%)[b]	ee (%)[c,d]
1	Et_2O	0.1	**4a**: Cl	r.t., 0.5 h	93	45 (*R*)
2	Toluene	0.1	**4a**: Cl	r.t., 0.5 h	92	20 (*R*)
3	THF	0.1	**4a**: Cl	r.t., 4 h	85	57 (*R*)
4	TBME	0.1	**4a**: Cl	r.t., 0.5 h	94	58 (*R*)
5	TBME	0.01	**4a**: Cl	r.t., 1 h	94	90 (*R*)
6	TBME	0.003	**4a**: Cl	r.t., 1 h	92	90 (*R*)
7	TBME	0.1	**4a**: Cl	0°C, 3 h	88	91 (*R*)
8	CPME	0.01	**4a**: Cl	r.t., 1 h	87	91 (*R*)
9	DME	0.01	**4a**: Cl	r.t., 15 h	N. R.	—
10	TBME	0.01	**4b**: Br	r.t., 1 h	94	87 (*R*)
11	TBME	0.01	**4c**: H	r.t., 24 h	65	20 (*R*)
12	TBME	0.01	**4d**: Me	r.t., 24 h	99	25 (*R*)
13	TBME	0.01	**4e**: Ph	r.t., 3 h	79	18 (*R*)

a) Catalyst concentration. *b*) Isolated yield. *c*) Determined by HPLC. *d*) The absolute configuration was determined by the comparison to literature value and authentic sample **3ca** prepared from Michael adduct **3aa**.

Table 2. Michael Reaction of Malonates with Various Acceptors



Entry	Donor	Acceptor	Conditions	Product	Yield (%)[a]	ee (%)[b]
1	**1a**: R^2 = Bn	**2a** (R^3 = Et)	r.t., 1 h	**3aa**	94	90 (*R*)[c]
2	**1a**: R^2 = Bn	**2b** (R^3 = Me)	r.t., 1 h	**3ab**	94	85 (*R*)[c]
3	**1a**: R^2 = Bn	**2c** (R^3 = Bn)	r.t., 1 h	**3ac**	75	83
4	**1a**: R^2 = Bn	**2d** (R^3 = PBB)	r.t., 4 h	**3ad**	94	78
5[d]	**1a**: R^2 = Bn	**2e** (R^3 = PMB)	50°C, 24 h	**3ae**	80	72
6	**1a**: R^2 = Bn	**2f** (R^3 = nPr)	r.t., 3 h	**3af**	66	74
7[d]	**1a**: R^2 = Bn	**2g** (R^3 = allyl)	r.t., 5 h	**3ag**	90	91
8	**1b**: R^2 = Me	**2b** (R^3 = Me)	r.t., 1 h	**3bb**	93	85 (*R*)[e]
9	**1b**: R^2 = Me	**2a** (R^3 = Et)	r.t., 1 h	**3ba**	92	77
10	**1c**: R^2 = Et	**2a** (R^3 = Et)	r.t., 1 h	**3ca**	82	88 (*R*)[c]
11	**1d**: R^2 = tBu	**2a** (R^3 = Et)	r.t., 1 h	**3da**	99	55
12	**1a**: R^2 = Bn	**2h**	r.t., 2 h	**3ah**	69	18
13	**1a**: R^2 = Bn	**2i**	r.t., 1 h	**3ai**	78	20
14	**1a**: R^2 = Bn	**2j**	r.t., 24 h	**3aa**	83	−8
15	**1a**: R^2 = Bn	**2k**	50°C, 1 h	**3ak**	79	4

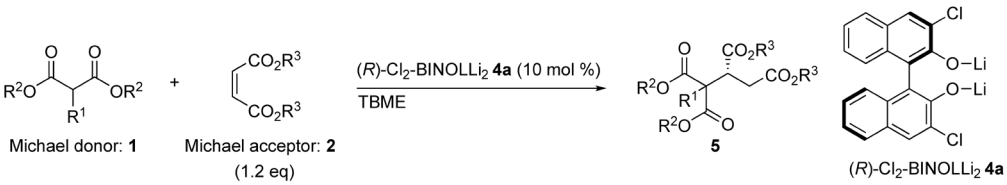
a) Isolated yield. *b*) Determined by HPLC. *c*) The absolute configuration was determined by the comparison to literature value and authentic sample **3ca** prepared from each Michael adduct. *d*) (*R*)-3,3′-Cl_2-BINOL (20 mol%), ^{n}BuLi (40 mol%). *e*) The absolute configuration was determined to be *R* by the comparison with the literature values of the HPLC retention time [CHIRALPAK AD-H, hexane–2-PrOH (9 : 1), 0.5 mL/min; 23.4 min (*S*), 24.32 min (*R*)].[8]

geometry (**2k**)[50] yielded very low selectivity (entry 15).

Introduction of an additional substituent, such as a methyl, ethyl, benzyl, isopropyl, and halogen groups on the 2-position of malonates afforded adducts containing quaternary carbon (Table 3).

2-Alkyl malonate donors prepared the adducts **5ea**, **fa**, **fd**, **ga**, **ha**, **ic**, **ja**, and **kc** with a sterically congested carbons in good yields with high enantioselectivities (entries 1–8), although 2-isopropyl malonates (**1h** and **1i**) required 20 mol% catalyst and heating to 50°C to achieve a smooth reaction. This Michael reaction is not limited to 2-alkylmalonates. In the case of malonate bearing a chlorine atom (**1l**), the elimina-

Table 3. Michael Reaction of Substituted Malonates with Maleates



Entry	Donor	Acceptor	Conditions	Product	Yield (%)[a]	ee (%)[b]
1	**1e**: R^1 = Me, R^2 = Me	**2a** (R^3 = Et)	r.t., 1 h	**5ea**	91	94
2	**1f**: R^1 = Me, R^2 = Bn	**2a** (R^3 = Et)	r.t., 1 h	**5fa**	93	98 (*R*)[c]
3	**1f**: R^1 = Me, R^2 = Bn	**2d** (R^3 = PBB)	r.t., 1 h	**5fd**	92	93
4	**1g**: R^1 = Et, R^2 = Bn	**2a** (R^3 = Et)	r.t., 3 h	**5ga**	88	92 (*R*)[c]
5[d]	**1h**: R^1 = ^{i}Pr, R^2 = Bn	**2a** (R^3 = Et)	50°C, 17 h	**5ha**	91	95 (*R*)[c]
6	**1i**: R^1 = ^{i}Pr, R^2 = Et	**2c** (R^3 = Bn)	50°C, 17 h	**5ic**	79	90
7	**1j**: R^1 = Bn, R^2 = Bn	**2a** (R^3 = Et)	r.t., 3 h	**5ja**	36	86
8	**1k**: R^1 = Bn, R^2 = Et	**2c** (R^3 = Bn)	r.t., 87 h	**5kc**	44	79
9	**1l**: R^1 = Cl, R^2 = Et	**2a** (R^3 = Et)	r.t., 17 h	**5la**	79	74
10	**1m**: R^1 = F, R^2 = Bn	**2a** (R^3 = Et)	r.t., 15 h	**5ma**	91	91 (*S*)[c]
11	**1n**: R^1 = F, R^2 = Et	**2a** (R^3 = Et)	r.t., 2 h	**5na**	74	98

a) Isolated yield. *b*) Determined by HPLC. *c*) The absolute configuration was determined by the comparison with authentic samples prepared from the known compound **3aa**. *d*) (*R*)-Cl_2-BINOL (20 mol%), ^{n}BuLi (40 mol%).

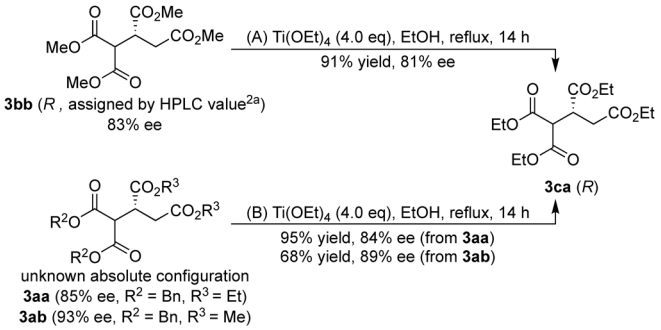


Chart 1. Determination of the Absolute Configurations of Compounds by Their Introduction into a Known Compound Using Transesterification

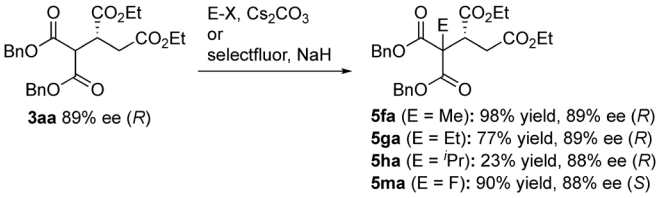


Chart 2. Determination of the Absolute Configurations of Compounds Bearing Quaternary Carbon Center

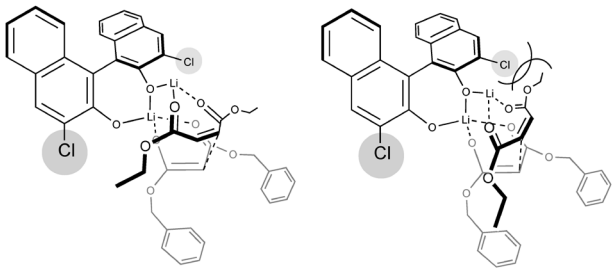


Fig. 1. Proposed Transition State in the Asymmetric Michael Reaction

tion reaction proceeded from the adduct, resulting in a low yield of Michael adduct with moderate enantioselectivity (entry 9). However, 2-fluoro malonates **1m** and **1n** afforded the corresponding adducts in high yields with high enantioselectivities (entries 10, 11).

The absolute configuration of the Michael adduct **3bb** prepared from **1b** and **2b** (Table 2, entry 8) was found to be *R*, which was assigned *via* the comparison with the HPLC data to the literature value.[8] Furthermore, methyl ester **3bb** was converted to ethyl ester **3ca** by the transesterification reaction using $Ti(OEt)_4$ (Chart 1A). The values of HPLC retention time from the two methods, transesterification product and Michael adduct prepared from **1c** and **2a** were identical. From these experiments, the absolute configuration of the obtained **3ca** was determined to be *R*. Similarly, the absolute configuration of other adducts **3aa** and **3ab** were found to be *R*, after conversion to **3ca** by transesterification (Chart 1B). As a result, it was found that the adducts **3bb**, **3aa**, and **3ab**, respectively, have the same absolute configuration. It is suggested that the other Michael adducts possess the same configuration. Next, to determine the absolute configuration of compounds **5fa**, **5ga**, **5ha**, and **5ma**, we conducted the functionalization for the known compound **3aa**, which was prepared from **1a** and **2a** (Table 1, entry 1). As shown in Chart 2, compound **5fa** could be prepared from the obtained adduct **3aa** by reacting with methyl iodide in the presence of base.[51,52] Comparing the HPLC value of this methylated product and Michael adduct from **1f** and **2a**, the absolute configuration of **5fa** was found to be *R*. Therefore, these results indicate that the adduct synthesized from 2-methyl benzyl malonate (**1f**) have the same absolute configuration as the adducts from unsubstituted malonate (**1a**). In addition, the absolute configurations of **5ga** and **5ha** were determined to be *R* by the comparison with the values of the HPLC retention time after substitution reactions with appropriate alkyl halides in the presence of bases. Similarly, that of **5ma** was determined to be *S* after fluorination reaction using the Selectfluor.

Considering of the absolute configuration of products, the proposed transition state of this reaction is shown in Fig. 1.

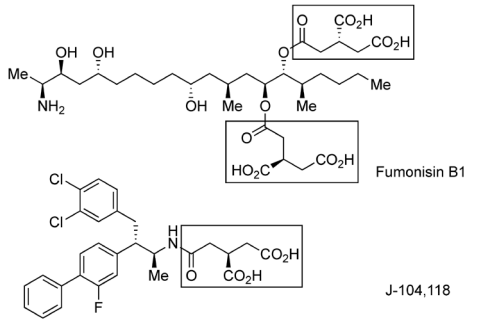


Fig. 2. Examples of Tricarboxylic Acid in Natural and Bioactive Compounds

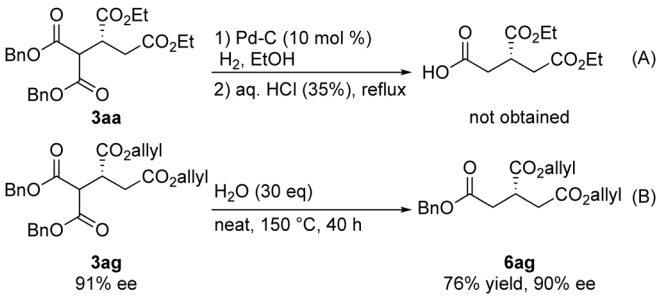


Chart 3. Decarboxylation of Tetracarboxylic Acid Ester

It is presumed that maleate ester approaches to the catalyst-binding malonates while avoiding steric hindrance caused by the substitution of a catalyst, leading an enantioselective carbon–carbon bond formation.

Next, to demonstrate the utility of this reaction, the transformation of tetracarboxylic acid ester is accomplished. Optically active tricarboxylic acids (TCA) are widely found in biologically and pharmaceutically active compounds. Important natural compounds such as Fumonisin Bl[53–63] or pharmaceutical compounds such as J-104, 118[64–67] contain tricarboxylic acid moiety and possess bioactivities (Fig. 2).

For instance, in the reported methods for the synthesis of tricarboxylic acid moiety of Fumonisins or J-104, 118, enantioselective syntheses were achieved by using chiral auxiliary[47,48,58,62] or optical resolution of racemic compound using stoichiometric amount of chiral amines.[64–66] In order to improve the efficiency of the synthesis of such compounds, we envisioned that Michael reaction of malonates to maleates and subsequent decarboxylation would afford the desired tricarboxylic acid derivatives.

Our study for decarboxylation commenced with reaction under acidic media,[68] but the decarboxylation product was not obtained by heating with aqueous HCl after deprotection of benzyl group (Chart 3A). To improve this transformation, we performed the Krapcho reaction of **3ag** in the presence of lithium salt,[69–73] but enantioselectivity of the product **6ag** decreased. Finally, we discovered that on heating with water in a sealed tube in the absence of alkali bases[74] caused the decarboxylation reaction to proceed well, without the loss of remarkable enantioselectivity (Chart 3B). As mentioned above, these tricarboxylic acids and its derivatives are common and versatile structures in biologically active natural products. Our method allows facile access to the optically active tricarboxylic acid derivatives from commercially available materials through base-catalyzed Michael reaction.

In conclusion, we report the first example of enantioselective Michael reaction of malonates to maleates, catalyzed by dilithium 3,3′-dichlorobinaphtholate, affording the tetracarboxylic acid esters with high enantioselectivities. This Michael reaction can accommodate a wide range of donors and acceptors, even producing adducts with quaternary carbon. Furthermore, the resulting adduct can successfully be functionalized to biologically important compounds. Further investigation including the application to other substrates is ongoing in our laboratory.

Experimental

General All reactions were performed under argon atmosphere using dried glasswares equipped with a rubber septum and a magnetic stirring bar. The column chromatography purifications were performed using Kanto Chemical Silica Gel 60N (spherical, neutral, 63–210 μm). The IR spectra were recorded using a PerkinElmer, Inc. Frontier MIR/NIR. The ^{1}H- and ^{13}C-NMR spectra were recorded in $CDCl_3$ using a JEOL JNM-ECX-400 spectrometer. The chemical shifts are reported in ppm relative to the internal tetramethylsilane (TMS) standard (δ 0.00 ppm) for the ^{1}H-NMR spectra and solvent signals (δ 77.0 ppm) for the ^{13}C-NMR spectra. The mass spectra were recorded using a JEOL JMS-700MStation mass spectrometer. The HPLC analyses were performed using JASCO P-2080 and UV-2075.

Typical Procedure of Michael Reaction (Table 1, Entry 5) Under argon atmosphere, *n*-butyllithium (0.10 mmol, 20 mol%) in hexane (0.15 M, 0.67 mL) was added to a solution of (*R*)-3,3′-Cl_2-BINOL (17.8 mg, 0.05 mmol, 10 mol%) in TBME (5.0 mL) at 0°C. After stirring for 1 min, dibenzyl malonate (**1a**) (0.125 mL, 0.5 mmol, 1.0 eq) and diethyl maleate (**2a**) (0.096 mL, 0.6 mmol, 1.2 eq) was successively added to the mixture at room temperature (r.t.). After 1 h, the reaction was quenched with sat. NH_4Cl aq. (2 mL) and stirred for 0.5 h. The aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (20 mL), and dried over Na_2SO_4. After filtration and concentration, the crude product was purified by column chromatography (hexane–EtOAc = 9 : 1, SiO_2: 10 g) to give product **3aa** as a colorless oil (214 mg, 94% yield, 90% ee).

(*R*)-1,1-Dibenzyl 2,3-Diethyl Propane-1,1,2,3-tetracarboxylate (3aa)[46] Colorless oil. 214 mg. 94% yield. TLC: *Rf* 0.52 (hexane–EtOAc = 4 : 1, stained white with anisaldehyde). $[\alpha]_{435}^{27}$ +11.5 (c = 1.03, $CHCl_3$) for 90% ee. ^{1}H-NMR ($CDCl_3$) δ: 1.15 (3H, t, J = 7.2 Hz), 1.23 (3H, t, J = 7.6 Hz), 2.66 (1H, dd, J = 17.0, 5.2 Hz), 2.79 (1H, dd, J = 17.0, 7.6 Hz), 3.60–3.62 (1H, m), 4.04–4.12 (5H, m), 5.14 (2H, s), 5.15 (2H, s), 7.28–7.37 (10H, m). The enantiomeric excess was determined to be 90% ee by chiral HPLC with Daicel Chiralpak AD-H column [eluent: hexane–IPA = 9 : 1; flow rate: 1.0 mL/min; detection: 254 nm; t_R: 22.0 min (*R*), 23.7 min (*S*)].

(*R*)-1,1-Dibenzyl 2,3-Dimethyl Propane-1,1,2,3-tetracarboxylate (3ab)[46] Colorless oil. 201 mg. 94% yield. TLC: *Rf* 0.41 (hexane–EtOAc = 4 : 1, stained blue with phosphomolybdic acid). $[\alpha]_{435}^{29}$ +7.5 (c = 0.88, $CHCl_3$) for 85% ee. ^{1}H-NMR ($CDCl_3$) δ: 2.67 (1H, dd, J = 17.0, 4.8 Hz), 2.80 (1H, dd, J = 17.0, 8.0 Hz), 3.58 (3H, s), 3.60–3.64 (1H, m), 3.65 (3H, s), 4.03 (1H, d, J = 6.8 Hz), 5.15 (2H, s), 5.16 (2H, s), 7.26–7.37 (10H, m). The enantiomeric excess was determined to be

85% ee by chiral HPLC with Daicel Chiralpak AD-3 column [eluent: hexane–IPA = 19 : 1; flow rate: 1.0 mL/min; detection: 254 nm; t_R: 54.0 min (*R*), 56.9 min (*S*)].

(+)-Tetrabenzyl Propane-1,1,2,3-tetracarboxylate (3ac)[46] Colorless oil. 217 mg. 75% yield. TLC: *Rf* 0.33 (hexane–EtOAc = 4 : 1, stained blue with phosphomolybdic acid). $[\alpha]_{435}^{31}$ +11.4 (c = 1.15, $CHCl_3$) for 83% ee. ^{1}H-NMR ($CDCl_3$) δ: 2.72 (1H, dd, J = 17.0, 5.2 Hz), 2.88 (1H, dd, J = 17.0, 7.6 Hz), 3.67–3.70 (1H, m), 4.05 (1H, d, J = 6.8 Hz), 5.00–5.08 (8H, m), 7.21–7.34 (20H, m). The enantiomeric excess was determined to be 83% ee by chiral HPLC with Daicel Chiralpak AS-H column [eluent: hexane–IPA = 4 : 1; flow rate: 1.0 mL/min; detection: 254 nm; t_R: 11.5 min (*minor*), 15.0 min (*major*)].

(+)-1,1-Dibenzyl 2,3-Bis(4-bromobenzyl) Propane-1,1,2,3-tetracarboxylate (3ad) Pale yellow oil. 346 mg. 94% yield. TLC: *Rf* 0.47 (hexane–EtOAc = 4 : 1, stained white with anisaldehyde). $[\alpha]_{435}^{19}$ +5.8 (c = 1.2, $CHCl_3$) for 78% ee. IR (ATR) cm^{-1}: 3035, 1729, 1153. ^{1}H-NMR ($CDCl_3$) δ: 2.71 (1H, dd, J = 16.9, 4.6 Hz), 2.86 (1H, dd, J = 16.9, 7.8 Hz), 3.65–3.70 (1H, m), 4.00–4.03 (1H, m), 4.94 (2H, s), 4.98 (2H, s), 5.04 (2H, s), 5.09 (2H, s), 7.07 (2H, d, J = 8.2 Hz), 7.14 (2H, d, J = 8.2 Hz), 7.22–7.31 (10H, m), 7.41 (2H, d, J = 8.2 Hz), 7.45 (2H, d, J = 7.8 Hz). ^{13}C-NMR ($CDCl_3$) δ: 33.2, 40.3, 52.1, 66.4, 65.8, 67.5, 67.6, 122.3, 122.3, 128.2, 128.4, 128.4, 128.5, 129.8, 129.9, 131.6, 131.6, 134.1, 134.5, 134.7, 134.8, 167.1, 167.3, 170.7, 171.1 (two carbons overlapped). FAB-MS *m/z*: 759.0211 (Calcd for $C_{35}H_{30}Br_2O_8Na$: 761.0188). MS *m/z*: 759, 761, 763 ($M + Na^+$), 91. The enantiomeric excess was determined to be 78% ee by chiral HPLC with Daicel Chiralcel AS-H column [eluent: hexane–IPA = 4 : 1; flow rate: 1.0 mL/min; detection: 254 nm; t_R: 24.3 min (*minor*), 32.2 min (*major*)].

(+)-1,1-Dibenzyl 2,3-Bis(4-methoxybenzyl) Propane-1,1,2,3-tetracarboxylate (3ae) Colorless oil. 256 mg. 80% yield. TLC: *Rf* 0.44 (hexane–EtOAc = 4 : 1, stained white with anisaldehyde). $[\alpha]_{435}^{19}$ +9.5 (c = 0.92, $CHCl_3$) for 72% ee. IR (ATR) cm^{-1}: 3034, 1732, 1153. ^{1}H-NMR ($CDCl_3$) δ: 2.68 (1H, dd, J = 16.9, 5.0 Hz), 2.83 (1H, dd, J = 16.9, 8.2 Hz), 3.63–3.68 (1H, m), 3.77 (3H, s), 3.80 (3H, s), 4.02 (1H, d, J = 6.9 Hz), 4.93–4.98 (4H, m), 5.02 (2H, s), 5.07 (2H, s), 6.81(2H, d, J = 8.7 Hz), 6.85 (2H, d, J = 8.2 Hz), 7.16 (2H, d, J = 8.7 Hz), 7.21–7.31 (12H, m). ^{13}C-NMR ($CDCl_3$) δ: 33.4, 40.5, 52.2, 55.3, 66.5, 67.1, 67.5, 67.5, 113.8, 113.9, 127.3, 127.7, 128.2, 128.4, 128.5, 130.1, 130.2, 134.9, 135.0, 159.6, 159.6, 167.3, 167.4, 171.0, 171.3 (four carbons overlapped). FAB-MS *m/z*: 663.2218 (Calcd for $C_{37}H_{36}O_{10}Na$: 663.2206). MS *m/z*: 663 ($M + Na^+$), 91. The enantiomeric excess was determined to be 72% ee by chiral HPLC with Daicel Chiralcel AD-3 column [eluent: hexane–IPA = 4 : 1; flow rate: 1.0 mL/min; detection: 254 nm; t_R: 47.6 min (*major*), 51.4 min (*minor*)].

(+)-1,1-Dibenzyl 2,3-Dipropyl Propane-1,1,2,3-tetracarboxylate (3af) Colorless oil. 160 mg. 66% yield. TLC: *Rf* 0.26 (hexane–EtOAc = 4 : 1, stained blue with phosphomolybdic acid). $[\alpha]_{435}^{27}$ +11.5 (c = 1.07, $CHCl_3$) for 74% ee. IR (ATR) cm^{-1}: 3035, 2967, 1730, 1151. ^{1}H-NMR ($CDCl_3$) δ: 0.86 (3H, t, J = 7.4 Hz), 0.91 (3H, t, J = 7.3 Hz), 1.50–1.66 (4H, m), 2.67 (1H, dd, J = 17.0, 4.6 Hz), 2.81 (1H, dd, J = 17.0, 7.8 Hz), 3.60–3.62 (1H, m), 4.04–4.12 (5H, m), 5.14 (2H, s), 5.15 (2H, s), 7.28–7.37 (10H, m) ^{13}C-NMR ($CDCl_3$) δ: 10.2, 10.3, 21.7, 21.8, 33.4, 40.5, 52.3, 66.4, 67.0, 67.5, 128.2, 128.4, 128.4, 128.5, 135.0, 135.0, 167.3, 167.5, 171.1, 171.5 (three carbons overlapped). FAB-MS *m/z*: 485.2173 (Calcd for $C_{27}H_{33}O_8$: 485.2175). MS *m/z*: 485 ($M + H^+$), 91. The enantiomeric excess was determined to be 74% ee by chiral HPLC with Daicel Chiralpak AD-H column [eluent: hexane–IPA = 9 : 1; flow rate: 1.0 mL/min; detection: 254 nm; t_R: 15.9 min (*major*), 17.4 min (*minor*)].

(+)-2,3-Diallyl 1,1-Dibenzyl Propane-1,1,2,3-tetracarboxylate (3ag) Colorless oil. 216 mg. 90% yield. TLC: *Rf* 0.47 (hexane–EtOAc = 4 : 1, stained purple with anisaldehyde). $[\alpha]_{435}^{19}$ +7.8 (c = 0.98, $CHCl_3$) for 91% ee. IR (ATR) cm^{-1}: 3034, 1731, 1649, 1153. ^{1}H-NMR ($CDCl_3$) δ: 2.72 (1H, dd, J = 17.2, 4.6 Hz), 2.85 (1H, dd, J = 17.2, 7.8 Hz), 3.64–3.69 (1H, m), 4.05 (1H, d, J = 6.9 Hz), 4.51 (2H, d, J = 6.0 Hz), 4.55 (2H, d, J = 6.0 Hz), 5.14 (2H, s), 5.15 (2H, s), 5.17–5.32 (4H, m), 5.74–5.91 (2H, m), 7.26–7.32 (10H, m). ^{13}C-NMR ($CDCl_3$) δ: 33.2, 40.4, 52.2, 65.5, 66.1, 67.6, 118.4, 118.6, 128.3, 128.4, 128.4, 128.5, 131.5, 131.8, 134.9, 135.0, 167.3, 167.4, 170.7, 171.1 (three carbons overlapped). FAB-MS *m/z*: 481.1892 (Calcd for $C_{27}H_{29}O_8$: 481.1862). MS *m/z*: 481 ($M + H^+$). The enantiomeric excess was determined to be 91% ee by chiral HPLC with Daicel Chiralpak AS-H column [eluent: hexane–IPA = 9 : 1; flow rate: 1.0 mL/min; detection: 254 nm; t_R: 16.6 min (*minor*), 21.7 min (*major*)].

(*R*)-Tetramethyl Propane-1,1,2,3-tetracarboxylate (3bb)[8] Colorless oil. 127 mg. 93% yield. TLC: *Rf* 0.26 (hexane–EtOAc = 4 : 1, stained blue with phosphomolybdic acid). $[\alpha]_D^{29}$ +13.4 (c = 0.2, $CHCl_3$) for 85% ee (*R*). [(lit[8]: $[\alpha]_D^{25}$ +5.3, c = 0.2, $CHCl_3$) for 93% ee (*R*)]. ^{1}H-NMR ($CDCl_3$) δ: 2.72 (1H, dd, J = 17.2, 4.8 Hz), 2.84 (1H, dd, J = 17.2, 7.0 Hz), 3.58–3.63 (1H, m), 3.70 (3H, s), 3.72 (3H, s), 3.76 (3H, s), 3.78 (3H, s), 3.94 (1H, d, J = 6.8 Hz). The enantiomeric excess was determined to be 85% ee by chiral HPLC with Daicel Chiralpak AD-H column [eluent: hexane–IPA = 9 : 1; flow rate: 0.5 mL/min; detection: 220 nm; t_R: 23.4 min (*S*), 24.3 min (*R*)].

(+)-2,3-Diethyl 1,1-Dimethyl Propane-1,1,2,3-tetracarboxylate (3ba)[46] Pale yellow oil. 140 mg. 92% yield. TLC: *Rf* 0.71 (hexane–EtOAc = 1 : 1, stained blue with phosphomolybdic acid). $[\alpha]_{435}^{28}$ +29.6 (c = 1.02, $CHCl_3$) for 77% ee. ^{1}H-NMR ($CDCl_3$) δ: 1.24 (3H, t, J = 7.4 Hz), 1.32 (3H, t, J = 7.4 Hz), 2.69 (1H, dd, J = 16.8, 5.2 Hz), 2.81 (1H, dd, J = 16.8, 8.0 Hz), 3.56–3.61 (1H, m), 3.75 (3H, s), 3.76 (3H, s), 3.94 (1H, d, J = 7.6 Hz), 4.15 (2H, q, J = 7.4 Hz), 4.17 (2H, q, J = 7.4 Hz). The enantiomeric excess was determined to be 77% ee by chiral HPLC with Daicel Chiralpak AD-3 column [eluent: hexane–IPA = 29 : 1; flow rate: 1.0 mL/min; detection: 220 nm; t_R: 27.6 min (*minor*), 28.6 min (*major*)].

(+)-Tetraethyl Propane-1,1,2,3-tetracarboxylate (3ca) Pale yellow oil. 136 mg. 82% yield. TLC: *Rf* 0.26 (hexane–EtOAc = 4 : 1, stained blue with phosphomolybdic acid). $[\alpha]_{435}^{29}$ +23.2 (c = 1.01, $CHCl_3$) for 88% ee. IR (film on NaCl) cm^{-1}: 2983, 1731, 1164. ^{1}H-NMR ($CDCl_3$) δ: 1.24–1.29 (12H, m), 2.69 (1H, dd, J = 16.8, 5.2 Hz), 2.81 (1H, dd, J = 16.8, 8.0 Hz), 3.55–3.60 (1H, m), 3.89 (1H, d, J = 7.2 Hz), 4.12–4.25 (8H, m). ^{13}C-NMR ($CDCl_3$) δ: 14.0, 14.1, 33.5, 40.5, 52.4, 60.8, 61.4, 61.8, 167.7, 167.8, 171.2, 171.7 (three carbons overlapped). FAB-MS *m/z*: 333.1559 (Calcd for $C_{15}H_{25}O_8$: 333.1549). MS *m/z*: 333 ($M + H^+$), 259. The enantiomeric excess was determined to be 88% ee by chiral HPLC with Daicel Chiralpak AS-H column [eluent: hexane–IPA = 49 : 1; flow rate: 1.0 mL/min; detection: 220 nm; t_R: 17.1 min (*minor*), 18.7 min (*major*)].

(+)-1,1-Di-*tert*-butyl 2,3-Diethyl Propane-1,1,2,3-tetra-

carboxylate (3da)[46] Colorless oil. 192 mg. 99% yield. TLC: *Rf* 0.29 (hexane–EtOAc = 4 : 1, stained blue with phosphomolybdic acid). $[\alpha]_{435}^{29}$ +11.5 (c = 1.13, $CHCl_3$) for 55% ee. ^{1}H-NMR ($CDCl_3$) δ: 1.23–1.28 (6H, m), 1.46 (18H, s, 18H), 2.69 (1H, dd, J = 16.8, 4.4 Hz), 2.78 (1H, dd, J = 16.8, 8.4 Hz), 3.45–3.50 (1H, m), 3.71 (1H, d, J = 7.2 Hz), 4.14 (2H, q, J = 7.6 Hz), 4.18 (2H, q, J = 7.2 Hz). The enantiomeric excess was determined to be 55% ee by chiral HPLC with Daicel Chiralpak AD-H column [eluent: hexane–IPA = 29 : 1; flow rate: 1.0 mL/min; detection: 220 nm; t_R: 9.7 min (*minor*), 11.4 min (*major*)].

(−)-Dibenzyl 2-(2,5-Dioxo-1-phenylpyrrolidin-3-yl)malonate (3ah)[46] Colorless prisms. mp: 90.0–92.0°C. 158 mg. 69% yield. TLC: *Rf* 0.66 (hexane–EtOAc = 1 : 1, stained blue with phosphomolybdic acid). $[\alpha]_{435}^{30}$ −5.8 (c = 0.94, $CHCl_3$) for 18% ee. ^{1}H-NMR ($CDCl_3$) δ: 2.88–3.00 (2H, m), 3.45–3.51 (1H, m), 4.31 (1H, d, J = 4.0 Hz), 5.18 (2H, s), 5.21 (2H, s), 7.19 (2H, d, J = 7.6 Hz), 7.26–7.45 (13H, m). The enantiomeric excess was determined to be 18% ee by chiral HPLC with Daicel Chiralcel OZ-H column [eluent: hexane–IPA = 1 : 1; flow rate: 1.0 mL/min; detection: 254 nm; t_R: 19.5 min (*minor*), 40.0 min (*major*)].

(*S*)-Dibenzyl 2-(3-Oxo-1,3-diphenylpropyl)malonate (3ai)[10] Colorless oil. 192 mg. 78% yield. TLC: *Rf* 0.51 (hexane–EtOAc = 4 : 1, stained blue with anisaldehyde). $[\alpha]_D^{25}$ +1.6 (c = 1.0, $CHCl_3$) for 20% ee. [(lit[10]: $[\alpha]_D^{25}$ +18.4 (c = 1.0, $CHCl_3$) for 91% ee (*S*)]. ^{1}H-NMR ($CDCl_3$) δ: 3.44 (2H, d, J = 6.8 Hz), 3.94 (1H, d, J = 9.8 Hz), 4.19–4.25 (1H, m), 4.90 (2H, s), 5.12 (1H, d, J = 12.4 Hz), 5.17 (1H, d, J = 12.4 Hz), 7.05–7.07 (2H, m), 7.15–7.34 (13H, m), 7.36–7.43 (2H, m), 7.46–7.55 (1H, m), 7.80 (2H, d, J = 8.2 Hz). The ee was determined to be 20% ee by chiral HPLC with Daicel Chiralpak AS-H column [eluent: hexane–IPA = 9 : 1; flow rate: 1.0 mL/min; detection: 254 nm; t_R: 19.9 min (*R*), 23.0 min (*S*)].

(*S*)-1,1-Dibenzyl 2,3-Diethyl Propane-1,1,2,3-tetracarboxylate (3aa)[46] Colorless oil. 189 mg. 83% yield. TLC: *Rf* 0.52 (hexane–EtOAc = 4 : 1, stained white with anisaldehyde). $[\alpha]_{435}^{29}$ −1.1 (c = 1.1, $CHCl_3$) for −8% ee. The enantiomeric excess was determined to be −8% ee by chiral HPLC with Daicel Chiralpak AD-H column [eluent: hexane–IPA = 9 : 1; flow rate: 1.0 mL/min; detection: 254 nm; t_R: 20.8 min (*R*), 22.2 min (*S*)].

(*S*)-Dibenzyl 2-(1,4-Dioxo-1,4-diphenylbutan-2-yl)malonate (3ak)[50] White prisms. mp: 66.0–68.0°C. 205 mg. 79% yield. TLC: *Rf* 0.50 (hexane–EtOAc = 4 : 1, stained blue with anisaldehyde). $[\alpha]_D^{24}$ +1.1 (c = 1.1, $CHCl_3$) for 4% ee. [(lit[50]: $[\alpha]_D^{23}$ −23.4 (c = 0.25, $CHCl_3$) for 88% ee (*R*)]; ^{1}H-NMR ($CDCl_3$) δ: 3.38 (1H, dd, J = 18.3, 6.3 Hz), 3.54 (1H, dd, J = 18.3, 5.9 Hz), 4.04 (1H, d, J = 8.4 Hz), 4.9–5.13 (5H, m), 7.14–7.28 (10H, m), 7.35–7.44 (4H, m), 7.52–7.58 (2H, m), 7.13 (2H, d, J = 7.6 Hz), 7.32 (2H, d, J = 6.8 Hz). The enantiomeric excess was determined to be 4% ee by chiral HPLC with Daicel Chiralpak AD-3 column [eluent: hexane–IPA = 4 : 1; flow rate: 1.0 mL/min; detection: 254 nm; t_R: 51.6 min (*R*), 54.3 min (*S*)].

(−)-1,2-Diethyl 3,3-Dimethyl Butane-1,2,3,3-tetracarboxylate (5ea)[46] Colorless oil. 144 mg. 91% yield. TLC: *Rf* 0.20 (hexane–EtOAc = 4 : 1, stained blue with phosphomolybdic acid). $[\alpha]_D^{24}$ −22.3 (c = 1.01, $CHCl_3$) for 94% ee. ^{1}H-NMR ($CDCl_3$) δ: 1.24 (3H, t, J = 6.8 Hz), 1.26 (3H, t, J = 7.2 Hz), 1.47 (3H, s), 2.57 (1H, dd, J = 16.4, 3.2 Hz), 2.82 (1H, dd, J = 16.4, 10.4 Hz), 3.69–3.72 (1H, m), 3.75 (6H, s), 4.14 (2H, q, J = 6.8 Hz), 4.15 (2H, q, J = 7.2 Hz). The enantiomeric excess was determined to be 94% ee by chiral HPLC with Daicel Chiralpak AD-H column [eluent: hexane–IPA = 19 : 1; flow rate: 1.0 mL/min; detection: 220 nm; t_R: 13.6 min (*major*), 15.0 min (*minor*)].

(*R*)-3,3-Dibenzyl 1,2-Diethyl Butane-1,2,3,3-tetracarboxylate (5fa)[46] Pale yellow oil. 219 mg. 93% yield. TLC: *Rf* 0.34 (hexane–EtOAc = 4 : 1, stained white with anisaldehyde). $[\alpha]_D^{29}$ −11.4 (c = 1.0, $CHCl_3$) for 98% ee. ^{1}H-NMR ($CDCl_3$) δ: 1.16 (3H, t, J = 7.2 Hz), 1.24 (3H, t, J = 7.6 Hz), 1.50 (3H, s), 2.56 (1H, dd, J = 16.6, 3.2 Hz), 2.77 (1H, dd, J = 16.6, 10.4 Hz), 3.76 (1H, dd, J = 10.4, 3.2 Hz), 4.03 (2H, q, J = 7.2 Hz), 4.10 (2H, q, J = 7.6 Hz), 5.08 (1H, d, J = 12.4 Hz), 5.12 (2H, s), 5.14 (1H, d, J = 12.4 Hz), 7.22–7.25 (4H, m), 7.30–7.32 (6H, m). The enantiomeric excess was determined to be 98% ee by chiral HPLC with Daicel Chiralpak AD-3 column [eluent: hexane–IPA = 19 : 1; flow rate: 1.0 mL/min; detection: 254 nm; t_R: 29.6 min (*S*), 30.8 min (*R*)].

(−)-3,3-Dibenzyl 1,2-Bis(4-bromobenzyl)butane-1,2,3,3-tetracarboxylate (5fd)[46] Pale yellow oil. 345 mg. 92% yield. TLC: *Rf* 0.41 (hexane–EtOAc = 4 : 1, stained white with anisaldehyde). $[\alpha]_D^{27}$ −12.8 (c = 0.69, $CHCl_3$) for 93% ee. ^{1}H-NMR ($CDCl_3$) δ: 1.49 (3H, s), 2.62 (1H, dd, J = 16.6, 3.2 Hz), 2.86 (1H, dd, J = 16.6, 11.0 Hz), 3.81 (1H, dd, J = 11.0, 3.2 Hz), 4.83–5.02 (8H, m), 7.08 (2H, d, J = 8.0 Hz), 7.14–7.20 (6H, m), 7.26–7.30 (6H, m), 7.41 (2H, d, J = 8.4 Hz), 7.45 (2H, d, J = 8.0 Hz). The enantiomeric excess was determined to be 93% ee by chiral HPLC with Daicel Chiralpak AD-3 column [eluent: hexane–IPA = 4 : 1; flow rate: 1.0 mL/min; detection: 254 nm; t_R: 31.9 min (*minor*), 40.0 min (*major*)].

(*R*)-3,3-Dibenzyl-1,2-diethylpentane-1,2,3,3-tetracarboxylate (5ga)[46] Colorless oil. 212 mg. 88% yield. TLC: *Rf* 0.31 (hexane–EtOAc = 4 : 1, stained white with anisaldehyde). $[\alpha]_D^{28}$ +19.5 (c = 0.99, $CHCl_3$) for 92% ee. ^{1}H-NMR ($CDCl_3$) δ: 0.92 (3H, t, J = 7.6 Hz), 1.15 (3H, t, J = 7.6 Hz), 1.24 (3H, t, J = 7.2 Hz), 1.93–2.03 (2H, m), 2.64 (1H, dd, J = 16.6, 2.8 Hz), 2.82 (1H, dd, J = 16.6, 10.8 Hz), 3.62 (1H, dd, J = 10.8, 2.8 Hz), 4.01 (2H, q, J = 7.6 Hz), 4.11 (2H, q, J = 7.2 Hz), 5.07 (2H, d, J = 12.0 Hz), 5.17 (2H, d, J = 12.0 Hz), 7.24–7.27 (2H, m), 7.29–7.32 (8H, m). The ee was determined to be 92% ee by chiral HPLC with Daicel Chiralpak AS-H column [eluent: hexane–IPA = 19/1; flow rate: 1.0 mL/min; detection: 254 nm; t_R: 7.7 min (*S*), 9.6 min (*R*)].

(*R*)-3,3-Dibenzyl 1,2-Diethyl 4-Methylpentane-1,2,3,3-tetracarboxylate (5ha)[46] Pale yellow oil. 226 mg. 91% yield. TLC: *Rf* 0.37 (hexane–EtOAc = 4 : 1, stained blue with phosphomolybdic acid). $[\alpha]_D^{26}$ +23.7 (c = 0.7, $CHCl_3$) for 95% ee. ^{1}H-NMR ($CDCl_3$) δ: 1.01 (3H, d, J = 6.4 Hz), 1.02 (3H, d, J = 6.4 Hz), 1.09 (3H, t, J = 6.8 Hz), 1.24 (3H, t, J = 6.8 Hz), 2.43–2.51 (2H, m), 2.67 (1H, dd, J = 16.4, 11.6 Hz), 3.75 (1H, dd, J = 11.6, 2.0 Hz), 3.91 (2H, q, J = 6.8 Hz), 4.12 (2H, q, J = 6.8 Hz), 5.07 (1H, d, J = 12.4 Hz), 5.13 (1H, d, J = 12.4 Hz), 5.19 (2H, d, J = 12.4 Hz), 7.29–7.32 (10H, m). The ee was determined to be 95% ee by chiral HPLC with Daicel Chiralpak AD-3 column [eluent: hexane–IPA = 19 : 1; flow rate: 1.0 mL/min; detection: 254 nm; t_R: 20.1 min (*R*), 22.8 min (*S*)].

(+)-1,2-Dibenzyl 3,3-Diethyl 4-Methylpentane-1,2,3,3-tetracarboxylate (5ic)[46] Pale yellow oil. 196 mg. 79% yield. TLC: *Rf* 0.37 (hexane–EtOAc = 4 : 1, stained blue with phosphomolybdic acid). $[\alpha]_{435}^{24}$ +11.5 (c = 0.7, $CHCl_3$) for 90%

ee. ^{1}H-NMR ($CDCl_3$) δ: 1.01 (3H, d, J = 7.6 Hz), 1.03 (3H, d, J = 7.6 Hz), 1.16 (3H, t, J = 7.6 Hz), 1.22 (3H, t, J = 7.2 Hz), 2.38 (1H, sept, J = 7.6 Hz), 2.58 (1H, dd, J = 17.0, 2.0 Hz), 2.80 (1H, dd, J = 17.0, 11.2 Hz), 3.82 (1H, dd, J = 11.2, 2.0 Hz), 3.95–4.17 (4H, m), 5.01–5.13 (4H, m), 7.26–7.32 (10H, m). The ee was determined to be 90% ee by chiral HPLC with Daicel Chiralcel OD-H column [eluent: hexane–IPA = 19 : 1; flow rate: 1.0 mL/min; detection: 254 nm; t_R: 10.7 min (*minor*), 13.4 min (*major*)].

(+)-3,3-Dibenzyl 1,2-Diethyl 4-Phenylbutane-1,2,3,3-tetracarboxylate (5ja) Pale yellow oil. 98 mg. 36% yield. TLC: *Rf* 0.39 (hexane–EtOAc = 4 : 1, stained blue with phosphomolybdic acid). $[\alpha]_{435}^{26}$ +5.6 (c = 1.3, EtOH) for 86% ee. IR (ATR) cm^{-1}: 3065, 3033, 2981, 1727, 1173. ^{1}H-NMR ($CDCl_3$) δ: 1.20 (3H, t, J = 7.6 Hz), 1.21 (3H, t, J = 7.2 Hz), 2.75 (1H, dd, J = 16.8, 2.8 Hz), 2.88 (1H, dd, J = 16.8, 10.8 Hz), 3.33 (2H, s), 3.65 (1H, dd, J = 10.8, 2.8 Hz), 4.06–4.12 (4H, m), 4.96 (2H, s), 5.09 (2H, s), 7.12–7.14 (2H, m), 7.21–7.31 (13H, m). ^{13}C-NMR ($CDCl_3$) δ: 13.7, 14.1, 33.8, 39.6, 45.4, 60.6, 60.8, 61.3, 67.4, 67.5, 127.2, 128.2, 128.3, 128.3, 128.4, 128.4, 128.4, 128.4, 130.5, 134.6, 134.9, 135.4, 168.7, 169.0, 171.8 (one carbon overlapped). FAB-MS *m/z*: 547.2333 (Calcd for $C_{32}H_{35}O_8$: 547.2332). MS *m/z*: 547 ($M + H^+$), 455, 91. The ee was determined to be 86% ee by chiral HPLC with Daicel Chiralpak AD-3 column [eluent: hexane–IPA = 19 : 1; flow rate: 1.0 mL/min; detection: 254 nm; t_R: 33.7 min (*major*), 38.7 min (*minor*)].

(−)-1,2-Dibenzyl 3,3-Diethyl 4-Phenylbutane-1,2,3,3-tetracarboxylate (5kc) Colorless oil. 120 mg. 44% yield. TLC: *Rf* 0.42 (hexane–EtOAc = 4 : 1, stained blue with phosphomolybdic acid). $[\alpha]_{435}^{24}$ −5.9 (c = 1.3, MeOH) for 79% ee. IR (ATR) cm^{-1}: 3033, 1728, 1155. ^{1}H-NMR ($CDCl_3$) δ: 1.09 (3H, t, J = 6.8 Hz), 1.14 (3H, t, J = 7.2 Hz), 2.84 (1H, dd, J = 16.8, 3.2 Hz), 2.97 (1H, dd, J = 16.8, 11.2 Hz), 3.28 (2H, s) 3.71 (1H, dd, J = 11.2, 3.2 Hz), 3.95–4.08 (4H, m), 4.99–5.15 (4H, m), 7.18–7.22 (5H, m), 7.27–7.37 (10H, m). ^{13}C-NMR ($CDCl_3$) δ: 13.7, 13.8, 25.3, 33.9, 39.5, 45.3, 60.6, 61.6, 66.5, 67.3, 127.0, 128.0, 128.2, 128.3, 128.4, 128.5, 128.6, 130.5, 135.2, 135.6, 135.7, 169.0, 169.1, 171.6 (two carbons overlapped). FAB-MS *m/z*: 547.2335 (Calcd for $C_{32}H_{35}O_8$: 547.2332). MS *m/z*: 547($M + H^+$), 455, 91. The ee was determined to be 79% ee by chiral HPLC with Daicel Chiralpak AD-H column [eluent: hexane–IPA = 9 : 1; flow rate: 1.0 mL/min; detection: 254 nm; t_R: 17.2 min (*minor*), 18.9 min (*major*)].

(−)-Tetraethyl 1-Chloropropane-1,1,2,3-tetracarboxylate (5la) Pale yellow oil. 144 mg. 79% yield. TLC: *Rf* 0.53 (hexane–EtOAc = 4 : 1, stained yellow with phosphomolybdic acid). $[\alpha]_{435}^{27}$ −8.1 (c = 1.07, $CHCl_3$) for 74% ee. IR (ATR) cm^{-1}: 2984, 1732, 1239, 1199, 1175, 1023. ^{1}H-NMR ($CDCl_3$) δ: 1.21–1.33 (12H, m), 2.83 (1H, dd, J = 16.9, 3.2 Hz), 2.94 (1H, dd, J = 16.9, 9.6 Hz), 4.09–4.11 (1H, m), 4.14–4.21 (4H, m), 4.28–4.32 (4H, m). ^{13}C-NMR ($CDCl_3$) δ: 13.7, 13.8, 14.1, 29.7, 33.0, 47.9, 61.0, 61.8, 63.4, 63.5, 71.1, 165.1, 165.6, 169.3, 171.3. FAB-MS *m/z*: 367.1181 (Calcd for $C_{15}H_{24}O_8Cl$: 367.1160). MS *m/z*: 367 ($M + H^+$). The ee was determined to be 74% ee by chiral HPLC with Daicel Chiralpak AD-3 column [eluent: hexane–IPA = 9 : 1; flow rate: 1.0 mL/min; detection: 220 nm; t_R: 12.0 min (*major*), 13.9 min (*minor*)].

(*S*)-1,1-Dibenzyl 2,3-Diethyl 1-Fluoropropane-1,1,2,3-tetracarboxylate (5ma) Pale yellow oil. 215 mg. 91% yield. TLC: *Rf* 0.53 (hexane–EtOAc = 4 : 1, stained blue with phosphomolybdic acid). $[\alpha]_D^{29}$ −9.1 (c = 1.0, $CHCl_3$) for 91% ee. IR (ATR) cm^{-1}: 3067, 1734, 1215, 1024. ^{1}H-NMR ($CDCl_3$) δ: 1.14 (3H, t, J = 7.3 Hz), 1.24 (3H, t, J = 6.9 Hz), 2.47 (1H, dd, J = 16.9, 3.7 Hz), 2.83 (1H, dd, J = 16.9, 10.1 Hz), 4.02–4.17 (5H, m), 5.21 (4H, s), 7.28–7.37 (10H, m). ^{13}C-NMR ($CDCl_3$) δ: 13.7, 14.0, 31.1, 31.1, 45.8 (d), 61.5 (d), 68.4 (d), 68.6 (d), 94.3 (d), 128.3, 128.4, 128.6, 128.6, 128.7, 134.1, 134.3, 134.4, 164.2 (d), 164.6 (d), 168.7 (d), 170.6. FAB-MS *m/z*: 475.1738 (Calcd for $C_{25}H_{28}O_8F$: 475.1768). MS *m/z*: 475 ($M + H^+$), 91. The ee was determined to be 91% ee by chiral HPLC with Daicel Chiralpak AD-3 column [eluent: hexane–IPA = 9 : 1; flow rate: 1.0 mL/min; detection: 254 nm; t_R: 22.9 min (*S*), 27.8 min (*R*)].

(−)-Tetraethyl 1-Fluoropropane-1,1,2,3-tetracarboxylate (5na) Pale yellow oil. 129 mg. 74% yield. TLC: *Rf* 0.26 (hexane–EtOAc = 4 : 1, stained white with anisaldehyde). $[\alpha]_D^{29}$ −10.3 (c = 0.88, $CHCl_3$) for 98% ee. IR (ATR) cm^{-1}: 2985, 1735, 1231. ^{1}H-NMR ($CDCl_3$) δ: 1.24 (3H, t, J = 7.3 Hz), 1.27 (3H, t, J = 7.3 Hz), 1.33 (3H, t, J = 7.3 Hz), 1.33 (3H, t, J = 7.3 Hz), 2.57 (1H, dd, J = 16.5, 3.7 Hz), 2.88 (1H, dd, J = 16.5, 10.1 Hz), 4.04 (1H, ddd, J = 26.8, 10.1, 3.7 Hz), 4.14–4.20 (4H, m), 4.29–4.35 (4H, m). ^{13}C-NMR ($CDCl_3$) δ: 13.7, 14.0, 29.5, 31.1, 45.6 (d), 61.4 (d), 63.0 (d), 93.0 (d), 164.4 (d), 164.7 (d), 168.7, 170.7 (three carbons overlapped). FAB-MS *m/z*: 351.1463 (Calcd for $C_{15}H_{24}O_8F$: 351.1455). MS *m/z*: 351 ($M + H^+$). The ee was determined to be 98% ee by chiral HPLC with Daicel Chiralpak AD-H column [eluent: hexane–IPA = 19 : 1; flow rate: 1.0 mL/min; detection: 220 nm; t_R: 14.5 min (*major*), 15.5 min (*minor*)].

Typical Procedure of Transesterification (Chart 1) Under argon atmosphere, $Ti(OEt)_4$ (0.21 mL, 1.0 mmol, 4.0 eq) in EtOH (2 mL) was added Michael adduct **3bb** (69.0 mg, 0.25 mmol) in EtOH (1 mL). After refluxing for 14 h, the reaction was quenched with sat. NH_4Cl aq. (2 mL) and stirred for 0.5 h. The aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (20 mL), and dried over Na_2SO_4. After filtration and concentration, the crude product was purified by column chromatography (hexane–EtOAc = 9 : 1, SiO_2: 5 g) to give product **3ca** as a pale yellow oil (76 mg, 91% yield, 81% ee).

Typical Procedure of Alkylation of Michael Adduct 3aa (Chart 2) Under argon atmosphere, methyl iodide (0.024 mL, 0.4 mmol, 4.0 eq) was added to a solution of Cs_2CO_3 (45.6 mg, 0.14 mmol, 1.4 eq) and Michael adduct **3aa** (45.6 mg, 0.1 mmol, 1.0 eq) in DMF (1 mL) at r.t. After 14 h, the reaction was quenched with water (2 mL) and stirred for 0.5 h. The aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (20 mL), and dried over Na_2SO_4. After filtration and concentration, the crude product was purified by column chromatography (hexane–EtOAc = 9 : 1, SiO_2: 5 g) to give product **5fa** as a pale yellow oil (24 mg, 50% yield, 89% ee).

Procedure of Fluorination of Michael Adduct 3aa (Chart 2) Under argon atmosphere, solution of Michael adduct **3aa** (68.4 mg, 0.15 mmol, 1.0 eq) in DMF (3 mL) was added NaH (7.2 mg, 0.18 mmol, 1.2 eq content; 60% by weight in oil) at 0°C and stirred for 0.5 h. Then Selectfluor® (69.1 mg, 0.20 mmol, 1.3 eq) was added to the reaction mixture and stirred 14 h at r.t. The reaction solution was poured into ice water (5 mL). The aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with brine (20 mL), and dried over Na_2SO_4. After filtration and

concentration, the crude product was purified by column chromatography (hexane–EtOAc = 9 : 1, SiO_2: 5 g) to give product **5ma** as a yellow oil (64 mg, 90% yield, 88% ee).

Procedure of Krapcho Reaction (Chart 3) Michael adduct **3ag** (160 mg, 0.3 mmol) and H_2O (0.16 mL, 9.0 mmol, 30 eq were stirred at 150°C. After 40 h, the crude product was loaded directly onto column chromatography and purified (hexane–EtOAc = 12 : 1, SiO_2: 10 g) to give product **6ag** as a colorless oil (78.9 mg, 76% yield, 90% ee).

(−)-1,2-Diallyl 3-Benzyl-propane-1,2,3-tricarboxylate (6ag) Colorless oil. 78.9 mg. 76% yield. TLC: *Rf* 0.47 (hexane–EtOAc = 4 : 1, stained blue with phosphomolybdic acid). $[\alpha]_{435}^{20}$ −5.2 (c = 1.05, $CHCl_3$) for 90% ee. IR (ATR) cm^{-1}: 3034, 1729, 1649, 1152. ^{1}H-NMR ($CDCl_3$) δ: 2.62–2.71 (2H, m), 2.79–2.88 (2H, m), 3.30–3.35 (1H, m), 4.57 (4H, t, J = 5.5 Hz), 5.13 (2H, s), 5.20–5.33 (4H, m), 5.80–5.93 (2H, m), 7.33–7.39 (5H, m). ^{13}C-NMR ($CDCl_3$) δ: 35.2, 35.2, 37.4, 65.5, 65.7, 66.6, 118.4, 118.5, 128.3, 128.3, 128.5, 131.8, 131.8, 135.6, 170.9, 171.1, 172.7. FAB-MS *m*/*z*: 347.1533 (Calcd for $C_{19}H_{23}O_6$: 347.1495). MS *m*/*z*: 347 ($M + H^+$). The ee was determined to be 90% ee by chiral HPLC with Daicel Chiralpak AD-3 column [eluent: hexane–IPA = 19 : 1; flow rate: 1.0 mL/min; detection: 254 nm; t_R: 18.5 min (*major*), 19.7 min (*minor*)].

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Conflict of Interest The authors declare no conflict of interest.

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68) The procedure of acidic condition: Under H_2 atmosphere, Pd-C (31.9 mg, 0.03 mmol, 10% of the weight of the substrate) in EtOH (1.0 mL) was added Michael product **3aa** (160 mg, 0.3 mmol) in EtOH (3.0 mL). After stirring for 0.5 h, the reaction mixture was filtered using a celite cake and the filtrate was concentrated *in vacuo*. The crude product 2-(1,4-diethoxy-1,4-dioxobutan-2-yl)malonic acid was used without further purification. A solution of obtained dicarboxylic acid in HCl (5.0 mL, 35% in weight) was refluxed for 5 h.
69) The procedure of standard Krapcho reaction: Michael adduct **3ag** (160 mg, 0.3 mmol), H_2O (0.05 mL. 3.0 mmol, 10 eq and LiCl (0.6 mmol, 2.0 eq were stirred at 150°C in DMSO. After 11 h, the crude product was loaded directly onto column chromatography and purified (hexane–EtOAc = 12 : 1, SiO_2: 10 g) to give product **6ag** as a colorless oil (27.0 mg, 26% yield, 87% ee).
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