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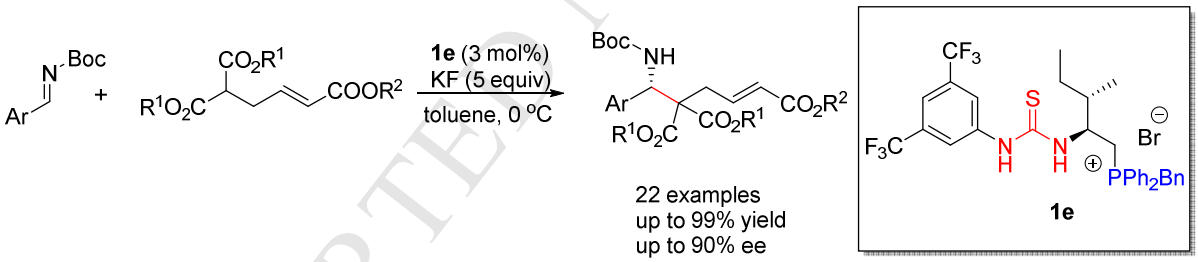

Enantioselective Mannich reaction of γ-malonate-substituted α,β-unsaturated esters with N-Boc imines catalyzed by chiral bifunctional thiourea-phosphonium salts

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Abstract: A novel enantioselective Mannich reaction of *γ*-malonate-substituted *α*, *β*-unsaturated esters with *N*-protected arylaldimines was realized by using asymmetric phase-transfer catalysis (APTC). With amino acid-derived bifunctional thiourea-phosphonium salts as a catalyst, a series of enantio-enriched Mannich products could be synthesized under very mild and simple reaction conditions with high yields and enantioselectivities.

Keywords: Bifunctional thioureas; phosphonium salts; Mannich reaction; asymmetric catalysis; phase-transfer catalysis

1. Introduction

Chiral *β*-amino carbonyl compounds are very useful building blocks in the synthesis of numerous biologically and pharmaceutically active substances.[1] Being one of the most convenient way to these useful compounds, the enantioselective Mannich reaction has received much research attention and impressive advances have been achieved by using both metal catalysis [2] and organocatalysis.[3] In this regard, over the past decade, asymmetric organocatalytic Mannich reaction of various malonates to imines or imine surrogates has made significant advances. [4] Various chiral organocatalysts including cinchona alkaloid-derived phase-transfer catalysts [5] and thioureas, bifunctional tertiary amine-thiourea catalysts, [6] and guanidine-bisthiourea catalysts [7] have all been successfully applied in this reaction. Particularly, Enders and co-workers have recently utilized *γ*-malonate-substituted α, β-unsaturated esters to react with *N*-protected arylaldimines, which involes a novel domino Mannich/aza-Michael process. [8] Such a process provided a highly useful

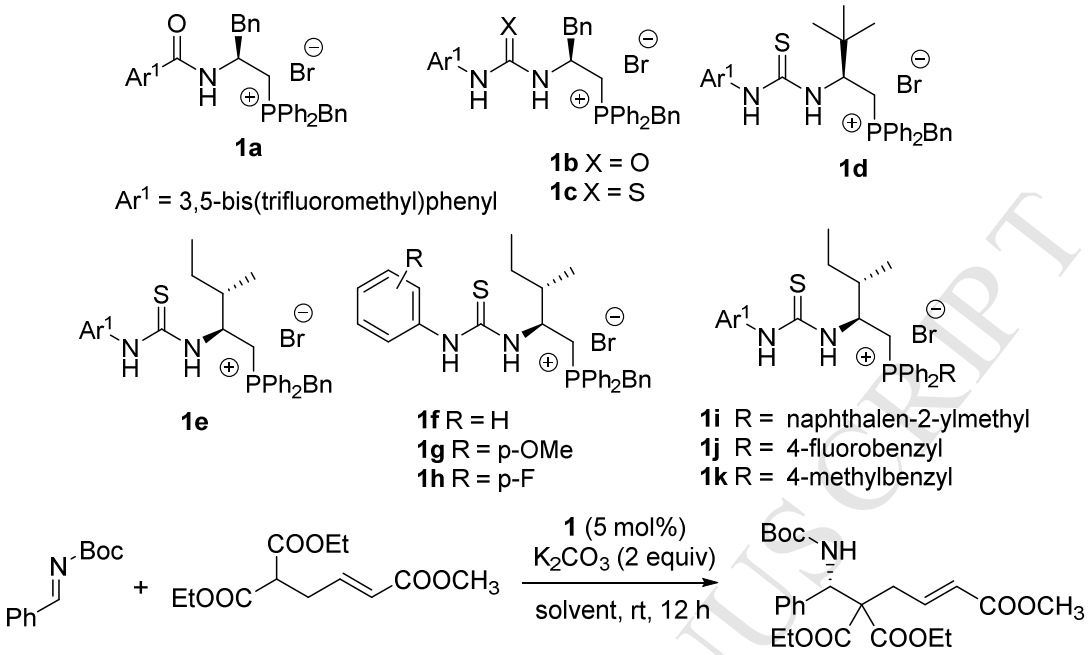
new way to enantio-enriched polysubstituted pyrrolidines. However, with bifunctional tertiary amine-thiourea catalysts, the practicality of this process was somewhat impaired by the long reaction time (3-11 days), relatively high catalyst loading and not-so-satisfactory enantioselectivities.

On the other hand, our group has developed chiral amino acid-derived phase-transfer catalysts. [9] In the field of asymmetric PTC, quaternary ammonium salt-based catalysts have been utilized in the Mannich-type reaction of malonates [4] while the compatibility of quaternary phosphonium salt-based catalysts with this reaction remains unknown. Our group has very recently reported novel bifunctional thiourea-phosphonium salts as highly efficient catalysts in asymmetric aza-Henry reactions and Mannich reactions.[10] We report herein that these bifunctional thiourea-phosphonium salts are also highly effective for the catalytic enantioselective Mannich reaction of aldimines with *γ*-malonated-substituted *α,β*-unsaturated esters, which is highly complementary to current methods.

2. Results and discussion

Using the reaction between *N*-Boc imine **2a** and *γ*-malonate-substituted *α, β*-unsaturated ester **3a** as the model reaction, we first tested the catalytic efficiency of different bifunctional phosphonium salts (Table 1, entries 1-8). In general, these catalysts showed high efficiency in this Mannich reaction, which could proceed to completion to give almost quantitative yields within 12 h at room temperature with a catalyst loading of 5 mol%. Both the thiourea moiety and the amino acid skeletons have significant influence on the reaction. The catalyst **1c** derived from *L*-phenylalanine with the thiourea structure gave better enantioselectivity than the acetyl amine and the urea structure (entries 1-3). Then catalyst **1e** derived from *L*-isoleucine with the 3, 5-bis(trifluoromethyl)phenyl thiourea moiety was found to be better to give 61% ee (entry 5). Further structural modification in the thiourea moiety or the substitution types of the phosphonium center is failed to improve the enantioselectivity (entries 6-11). Next, solvent effect was explored with catalyst **1e**, but the enantioselectivity was also not improved (entries 12-15).

Table 1 Screening of catalysts and solvents.[a]



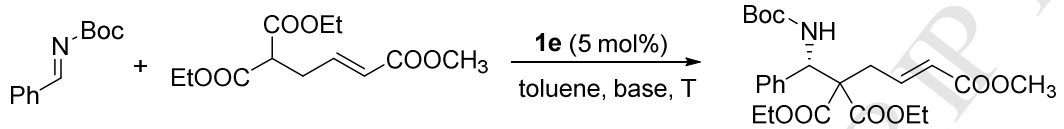
Entry	Catalyst	Solvent	Yield [%][b]	ee [%][c]
1	**1a**	Toluene	97	2
2	**1b**	Toluene	98	35
3	**1c**	Toluene	95	50
4	**1d**	Toluene	99	59
5	**1e**	Toluene	99	61
6	**1f**	Toluene	99	55
7	**1g**	Toluene	99	55
8	**1h**	Toluene	99	59
9[d]	**1i**	Toluene	96	33
10[d]	**1j**	Toluene	94	43
11[d]	**1k**	Toluene	99	59
12	**1e**	CH_2Cl_2	95	19
13	**1e**	THF	99	9
14	**1e**	TBME	99	27
15	**1e**	$PhCF_3$	99	56

[a] Reaction conditions: **2a** (0.15 mmol), **3a** (0.1 mmol) and base (0.2 mmol) in the presence of **1** (5 mol%) in solvents (1.0 mL).
[b] Isolated yields.
[c] Determined by chiral stationary phase HPLC.
[d] Reaction time was 8 h and 0.5 mmol K_2CO_3 was used.

To further improve the enantioselectivity, we then screened different bases (Table 2). Pleasingly, when a milder base KF was used, a significantly improved enantioselectivity of 81% ee at 0 ^oC (entry 8). Moreover, the catalyst loading amount

could be decreased to 3 mol% while maintain the same high chemical yield and enantioselectivity (entry 10), while a reduction in the amount of KF to inferior results (entry 11). Thus, the optimum reaction conditions were identified as follows: 3 mol% of **1e** and 5 equiv. of KF in toluene at 0 ^{o}C.

Table 2 Screening of bases. [a]



2a **3a** **4a**

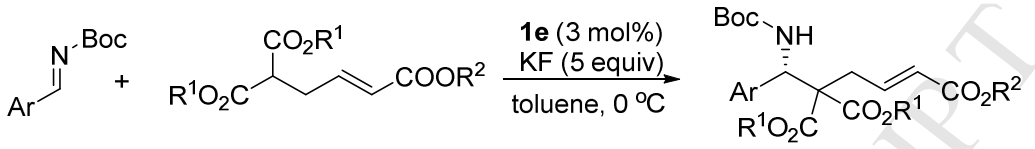
Entry	Base	Time [h]	T [^{o}C]	Yield [%][b]	ee [%][c]
1	KOH	8	rt	complicated	nd
2	Na_2CO_3	15	rt	99	68
3	K_2CO_3	15	rt	99	60
4	K_2HPO_4	15	rt	99	75
5	KF	15	rt	99	74
6	CsF	15	rt	98	70
7	K_2HPO_4	24	0	96	76
8	KF	24	0	97	81
9	KF	32	-10	92	80
10[d]	KF	24	0	97	82
11[e]	KF	50	0	90	57

[a] Reaction conditions: **2a** (0.15 mmol), **3a** (0.1 mmol) and base (0.5 mmol) in the presence of **1e** (5 mol%) in toluene (1.0 mL).
[b] Isolated yields.
[c] Determined by chiral stationary phase HPLC.
[d] 3 mol% of catalyst **1e** was used.
[e] 0.05 mmol KF was used.

Next, a series of *N*-Boc-protected aryl aldimines **2a-2p** and different substituted γ-malonate-substituted α,β-unsaturated esters **3a-3f** were investigated under the optimized conditions (Table 3). In general, excellent yields and high enantioselectivities were obtained within a relatively short reaction time (12-30 h). For different **3**, increasing the steric hindrance of the ester moieties seemed slightly favored in terms of enantioselectivity (entries 1-5). As to different aldimines **1**, when Ar was a substituted benzene ring, good to excellent yields and high ee values were generally obtained, irrespective of the electronic nature of the substituents on the benzene ring. Notably, an apparent *meta* effect was observed: the more sterically

demanding *m*-substituted aryl imines gave higher ee values (entries 6-17). Moreover, heteroaryl imines **2n** and **2o** also took part in the reaction to give excellent yields, albeit with relatively lower ees (65% and 70%) (entries 18 and 19).

Table 3 Substrate scope study. [a]



2 **3** **4**

Entry	**2** (Ar)	**3** (R^1/ R^2)	Time (h)	**4**	Yield (%)[b]	ee (%)[c]
1	**2a** (Ph)	**3b** (Me/Me)	24	**4b**	99	77
2	**2a** (Ph)	**3c** (Bn/Me)	24	**4c**	99	83
3	**2a** (Ph)	**3d** (Ph/ Me)	24	**4d**	96	78
4	**2a** (Ph)	**3e** (Me/Et)	24	**4e**	99	81
5	**2a** (Ph)	**3f** (Et/ Et)	24	**4f**	99	81
6	**2b** (*o*-ClC_6H_4)	**3a** (Et/ Me)	20	**4g**	99	85
7	**2c** (*m*-ClC_6H_4)	**3a** (Et/ Me)	20	**4h**	85	87
8	**2d** (*p*-ClC_6H_4)	**3a** (Et/ Me)	20	**4i**	98	81
9	**2e** (*p*-FC_6H_4)	**3a** (Et/ Me)	20	**4j**	97	79
10	**2f** (*p*-BrC_6H_4)	**3a** (Et/ Me)	20	**4k**	84	81
11	**2g** (*p*-MeC_6H_4)	**3a** (Et/ Me)	24	**4l**	95	81
12	**2h** (*p*-$MeOC_6H_4$)	**3a** (Et/ Me)	20	**4m**	98	80
13	**2i** (*p*-$NO_2C_6H_4$)	**3a** (Et/ Me)	24	**4n**	83	83
14	**2j** (*m*-FC_6H_4)	**3a** (Et/ Me)	24	**4o**	93	81
15	**2k** (*m*-MeC_6H_4)	**3a** (Et/ Me)	20	**4p**	99	85
16	**2l** (*m*-$MeOC_6H_4$)	**3a** (Et/ Me)	20	**4q**	99	86
17	**2m** (*m*-BrC_6H_4)	**3a** (Et/ Me)	20	**4r**	80	86
18	**2n** (2-Thienyl)	**3a** (Et/ Me)	24	**4s**	95	70
19	**2o** (α-Naphthyl)	**3a** (Et/ Me)	30	**4t**	60	87
20	**2c** (*m*-ClC_6H_4)	**3c** (Bn/Me)	12	**4u**	99	88
21	**2k** (*m*-MeC_6H_4)	**3c** (Bn/Me)	12	**4v**	99	90

[a] Reaction conditions: **2a** (0.15 mmol), **3a** (0.1 mmol) and base (0.5 mmol) in the presence of **1e** (3 mol%) in toluene (1.0 mL).
[b] Isolated yields.
[c] Determined by chiral stationary phase HPLC.

In order to get more insight into the role of the cooperative action between the thiourea moiety and the phosphonium center in these bifunctional thiourea-phosphonium salts in this reaction, control experiments were performed with two variants of the catalyst **1c** under the optimized reaction conditions as in Table 3

(Figure 1a). The use of catalyst **1m** with a blocked hydrogen bonding site or catalyst **1n** without the quaternary phosphonium center all led to much inferior results in terms of yield, enantioselectivity and reaction time compared to their parent catalyst **1c**. This result indicates the importance of cooperative catalysis of the two functionalities in the catalytic process. Moreover, allyl-substituted and methyl-substituted malonates were investigated under the optimized conditions (Figure 1b), furnishing the desired products with good enantioselectivities. The absolute configuration of **4y** was assigned to be *S* by comparison of the optical rotation values with the literature data [10c] and those of others were determined by analogy. The product **4p** was treatment with TBAB (tetrabutylammonium bromide) and Cs_2CO_3 gave the pyrrolidine product **5** with 96% yield and 61% ee (Figure 1c) [13].

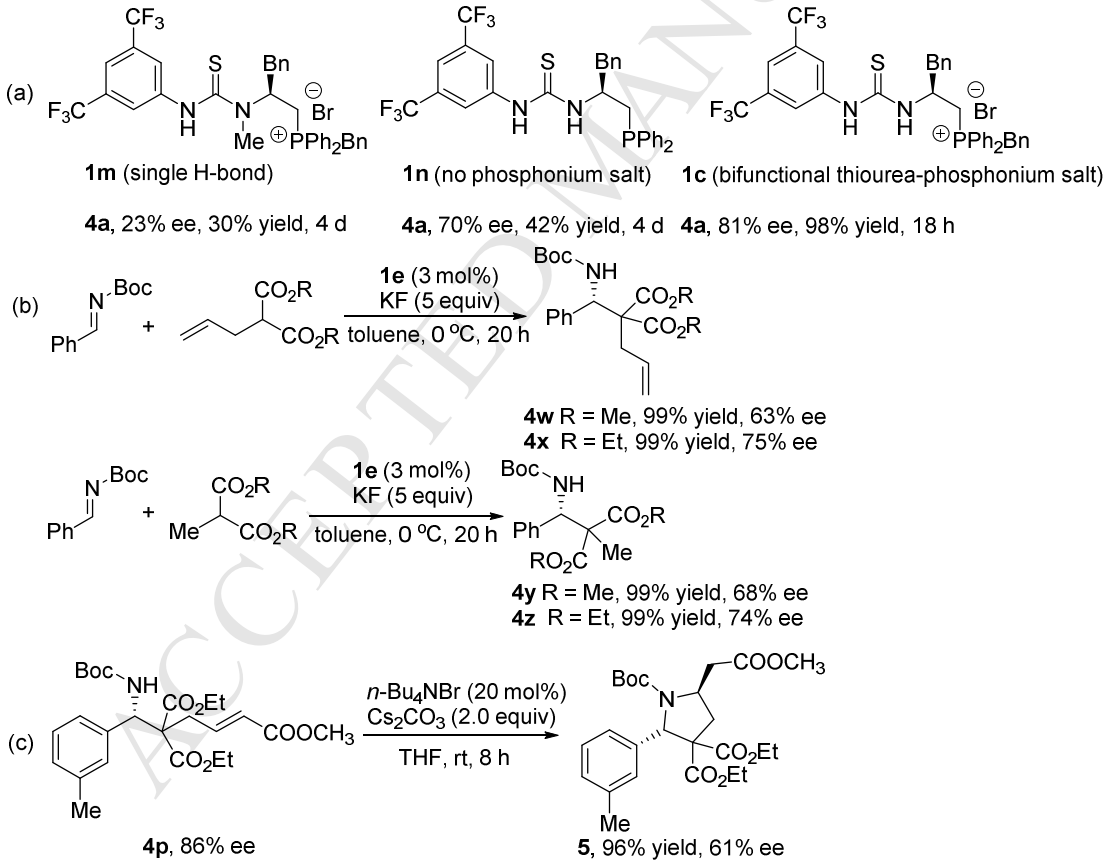


Figure 1. Control experiments and product transformatiom.

3. Conclusion

In conclusion, we have successfully applied amino acid-derived bifunctional

thiourea-phosphonium salts to catalyze asymmetric Mannich reaction between γ-malonate-substituted α, β-unsaturated esters and N-Boc aryl aldimines. These phase-transfer catalysts demonstrated high efficiency in the reaction, providing the desired products in excellent yields and high enantioselectivities within much shortened reaction time compared to previously used organocatalysts. Further applications of this kind of phase-transfer catalysts to other reactions as well as synthetically useful conversions of the chiral β-amino carbonyl products are underway in our laboratory.

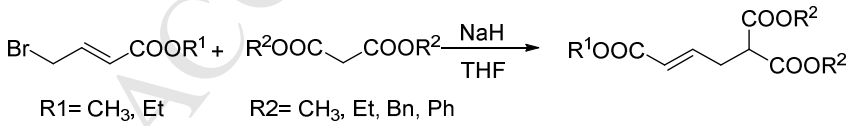
4. Experimental

4.1 General information

The ^{1}H NMR spectra were recorded on a Bruker (400 MHz) spectrometer. All chemical shifts (δ) were given in ppm. Data were reported as follows: chemical shift, integration, multiplicity (s = single, d = doublet, t = triplet, q = quartet, br = broad, m = multiple) and coupling constants (Hz). ^{13}C NMR spectra were recorded on a DPX-400 (400 MHz). Flash column chromatography was performed using H silica gel. For thin-layer chromatography (TLC), silica gel plates (HSGF 254) were used and compounds were visualized by irradiation with UV light. Analytical high performance liquid chromatography (HPLC) was carried out on SHIMADZU equipment using chiral columns. Melting points were determined on a SGW X-4 melting point apparatus and were uncorrected. Optical rotations were measured on a JASCO P-1010 Polarimeter at λ = 589 nm. IR spectra were recorded on a Perkin-Elmer 983G instrument. Mass spectra analysis was performed on API 200 LC/MS system (Applied Biosystems Co. Ltd.).

All starting imines were synthesized according to reported methods. [11, 3c] All bifunctional phosphonium salt catalysts were synthesized according to procedures reported previously. [10a] **3a-3c**, **3e-3f** [12] were prepared by literature procedure.

4.2 Preparation of catalysts 3



In a flame dried, one-necked round-bottom flask NaH (60% in oil, 1.0 equiv.) was suspended in anhydrous THF (0.15 M) and the reaction was cooled to 0 °C. Malonic ester (1.0 equiv.) was added in small portions over a period of 30 minutes and the reaction was stirred for 1 h at 0 °C. After the addition of alkyl 4-bromocrotonate (1.3 eq.) the reaction was stirred for further 60 minutes at 0 °C. The mixture was quenched by the addition of aqueous HCl (1.0 N) and extracted three times with dichloromethane. The combined organic layers were dried over sodium sulfate, filtered and concentrated *in vacuo*. Column chromatography (petroleum ether: ethyl

acetate = 10:1 to 5:1) afforded the pure products as colorless oils.

*4.2.1 (E)-4-methyl 1, 1-diphenyl but-3-ene-1, 1, 4-tricarboxylate (**3d**)*

3d was synthesized according to the general procedure using NaH (360 mg, 9 mmol), THF (70 mL), diphenylmalonate (2.3 g, 9 mmol) and (*E*)-methyl-4-bromocrotonate (1.97 g, 1.3 mL, 11 mmol).

1.6 g yield (50%, white solid), m.p. = 52-53^{o}C. ^{1}**H-NMR** (400 MHz, $CDCl_3$): δ 3.03-3.06 (m, 2H), 3.75 (s, 3H), 4.00 (t, *J* = 8.0 Hz, 1H), 6.06 (d, *J* = 16.0 Hz, 1H), 7.02-7.08 (m, 1H), 7.10-7.13 (m, 4H), 7.24-7.28 (m, 2H), 7.37-7.41 (m, 4H) ppm. ^{13}**C-NMR** (100 MHz, $CDCl_3$): δ 31.1, 50.7, 51.7, 121.2, 124.2, 126.4, 129.6, 143.2, 150.3, 166.3, 166.6 ppm; **IR (Neat)** 2951, 1753, 1724, 1591, 1492, 1273, 1190, 1162, 1134, 747, 689; **HRMS(MALDI)**: calcd. for $[M+Na]^+$ ($C_{20}H_{18}O_6$) requires 377.1001, found 377.0993.

4.3 Preparation of catalysts 1j and 1k

To a solution of the corresponding amino acid-derived bifunctional phosphine (1.0 equiv.) in anhydrous toluene was added the corresponding benzylic halide (1.2 equiv.), and the resulting mixture was stirred at 110^{o}C for 8h. Then the mixture was allowed to cool to ambient temperature and concentrated under reduced pressure. The crude mixture was purified by flash column chromatography to afford the desired phase transfer catalyst (CH_2Cl_2/MeOH = 20:1).

*4.3.1 ((2S,3S)-2-(3-(3,5-bis(trifluoromethyl)phenyl)thioureido)-3-methylpentyl)(4-fluorobenzyl)diphenylphosphonium bromide (**1j**)*

Yield: 72%; White solid. m.p. = 108-110^{o}C; $[\alpha]_D^{25}$ = -50.1 (*c* = 1.2, $CHCl_3$); ^{1}**H-NMR** (400 MHz, $CDCl_3$): δ 9.81 (bs, 2H), 8.13 (s, 2H), 7.82 (m, 1H), 7.69-7.72 (m, 6H), 7.55-7.59 (m, 3H), 6.86-6.90 (m, 5H), 5.15 (m, 1H), 4.66-4.83 (m, 2H), 3.68-3.72 (m, 1H), 3.51 (d, *J* = 16.0 Hz, 1H), 1.81 (m, 1H), 1.26-1.28 (m, 1H), 1.18-1.20 (m, 1H), 1.01 (d, *J* = 8.0 Hz, 3H), 0.80 (t, *J* = 8.0 Hz, 3H); ^{13}**C-NMR** (100 MHz, $CDCl_3$): δ 180.9, 164.4 (d, $J_{C\text{-}P}$ = 4 Hz), 161.9 (d, $J_{C\text{-}P}$ = 4 Hz), 141.2, 135.7 (d, $J_{C\text{-}P}$ = 2.9 Hz), 135.3 (d, $J_{C\text{-}P}$ = 3 Hz), 133.8 (d, $J_{C\text{-}P}$ = 1.4 Hz), 133.7 (d, $J_{C\text{-}P}$ = 1.4 Hz), 132.6 (d, $J_{C\text{-}P}$ = 5.6 Hz), 132.5 (d, $J_{C\text{-}P}$ = 5.6 Hz), 131.6 (q, $J_{C\text{-}F}$ = 24 Hz), 130.8 (d, $J_{C\text{-}P}$ = 12.2 Hz), 130.6 (d, $J_{C\text{-}P}$ = 12.4), 123.7 (q, $J_{C\text{-}F}$ = 271.4 Hz), 123.0, 122.9-123.0 (m), 117.8, 117.7, 117.0 (d, $J_{C\text{-}P}$ = 3.1 Hz), 116.9, 116.7 (d, $J_{C\text{-}P}$ = 3.1 Hz), 52.1 (d, $J_{C\text{-}P}$ = 4.4 Hz), 41.3 (d, $J_{C\text{-}P}$ = 12.0 Hz), 28.9 (d, $J_{C\text{-}P}$ = 45.3 Hz), 26.0, 24.9 (d, $J_{C\text{-}P}$ = 51.2 Hz), 15.2, 11.9; ^{31}**P-NMR** (163 MHz, $CDCl_3$): δ 25.2; ^{19}**F-NMR** (282 MHz, $CDCl_3$): δ -62.9, -111.7; **IR (Neat)** 3048, 2963, 2962, 2878, 1549, 1510, 1473, 1438, 1284, 1177, 1134, 846, 739, 681; **HRMS(MALDI)**: calcd. for $[M-Br]^+$ ($C_{34}H_{33}N_2F_7PS$) requires 665.1985, found 665.1980.

*4.3.2 ((2S,3S)-2-(3-(3,5-bis(trifluoromethyl)phenyl)thioureido)-3-methylpentyl)-diphenyl(4-methylbenzyl)phosphonium bromide (**1k**)*

Yield: 70%; White solid. m.p. = 204-206°C; $[\alpha]_D^{25}$ = -70.7 (*c* = 1.6, $CHCl_3$); **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 9.77-9.80 (m, 2H), 8.10 (s, 2H), 7.75-7.78 (m, 3H), 7.53-7.61 (m, 8H), 7.01 (d, *J* = 7.6 Hz, 2H), 6.80 (d, *J* = 7.2 Hz, 2H), 5.21 (m, 1H), 4.73-4.80 (t, *J* = 16.0 Hz, 1H), 4.48-4.55 (t, *J* = 16.0 Hz, 1H), 3.49-3.58 (m, 1H), 2.51-2.58 (t, *J* = 14.4 Hz, 1H), 2.28 (s, 3H), 1.82 (m, 1H), 1.02 (d, *J* = 6.8 Hz, 3H), 0.84 (t, *J* = 7.2 Hz, 3H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 180.8, 141.2, 139.5 (d, J_{C-P} = 4 Hz), 135.5 (d, J_{C-P} = 3 Hz), 135.1 (d, J_{C-P} = 3 Hz), 133.8 (d, J_{C-P} = 9.3 Hz), 133.6 (d, J_{C-P} = 9.1 Hz), 131.5 (q, J_{C-F} = 34 Hz), 130.7, 130.6, 130.5, 130.5, 130.4, 123.8 (q, J_{C-P} = 272 Hz), 123.5 (d, J_{C-P} = 9 Hz), 122.9, 119.7, 119.4, 118.6, 117.9, 117.5, 117.1, 52.1 (d, J_{C-P} = 5 Hz), 41.5 (d, J_{C-P} = 12 Hz), 29.3 (d, J_{C-P} = 45 Hz), 25.9, 24.8 (d, J_{C-P} = 52 Hz), 21.5, 15.4, 12.0; **^{31}P-NMR** (163 MHz, $CDCl_3$): δ 23.5; **^{19}F-NMR** (282 MHz, $CDCl_3$): δ -62.8; **IR (Neat)** 3047, 2965, 2877, 1549, 1457, 1386, 1277, 1177, 1134, 738, 681; **HRMS(MALDI)**: calcd. for $[M-Br]^+$ ($C_{35}H_{36}N_2F_6PS$) requires 661.2236, found 661.2240.

4.4 General procedure for the enantioselective Mannich reaction

To a suspension of the corresponding γ-malonate substituted α, β-unsaturated ester **3** (0.1 mmol) in toluene (1.0 ml) was added catalyst **1e** (3 mol%) and aryl aldimine (0.15 mmol) sequentially, and the resulting mixture was stirred at 0°C for 5 min. Then KF (28 mg, 0.5 mmol) was added. The resulting suspension was vigorously stirred at 0 °C for 12-30 h, and then purified by column chromatography (petroleum ether/ethyl acetate = 10/1 – 4/1) on silica get to afford the product.

4.4.1
*4,4-diethyl-1-methyl-(S,E)-5-((tert-butoxycarbonyl)amino)-5-phenylpent-1-ene-1,4,4-tricarboxylate (**4a**)*

Yield: 97%; colorless oil. Enantiomeric excess: 82%, $[\alpha]_D^{25}$ = -20.2 (*c* = 2.70, $CHCl_3$), determined by HPLC (Chiralpak AD-H column hexane/*i*-PrOH 9:1, flow rate 1.0 ml/min, t_{minor} = 11.4 min, t_{major} = 14.4 min, λ = 254 nm); **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 7.27-7.29 (m, 5H), 6.84-6.92 (m, 1H), 6.57 (d, *J* = 13.2 Hz, 1H), 5.81 (d, *J* = 15.6 Hz, 1H), 5.20 (d, *J* = 9.6 Hz, 1H), 4,16-4.25 (m, 4H), 3.70 (s, 3H), 2.59-2.62 (m, 2H), 1.37 (s, 9H), 1.27 (t, *J* = 7.2 Hz, 3H), 1.20 (t, *J* = 7.2 Hz, 3H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 169.5, 169.1, 166.2, 154.6, 143.2, 137.7, 128.4, 128.2, 128.0, 124.3, 79.6, 62.0, 58.9, 51.5, 37.3, 29.6, 28.2, 14.0, 13.8; **IR (Neat)** 3431, 2980, 1724, 1658, 1494, 1367, 1275, 1169; **HRMS(MALDI)**: calcd. for $[M+Na]^+$ ($C_{24}H_{33}NO_8Na$) requires 486.2098, found 486.2095.

4.4.2 trimethyl-(S,
*E)-5-((tert-butoxycarbonyl)amino)-5-phenylpent-1-ene-1,4,4-tricarboxylate (**4b**)*

Yield: 99%; colorless oil. Enantiomeric excess: 77%, $[\alpha]_D^{25}$ = -25.2 (*c* = 2.85, $CHCl_3$), determined by HPLC (Chiralpak AS-H column hexane/*i*-PrOH 95:5, flow rate 1.0 ml/min, t_{minor} = 9.4 min, t_{major} = 12.8 min, λ = 254 nm); **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 7.22-7.31 (m, 5H), 6.81-6.88 (m, 1H), 6.44 (d, *J* = 8.8 Hz, 1H), 5.81 (d, *J* = 15.6 Hz, 1H), 5.21 (d, *J* = 9.2 Hz, 1H), 3.75 (s, 3H), 3.73 (s, 3H), 3.71 (s, 3H), 2.60-2.64

(m, 2H), 1.38 (s, 9H); ^{13}**C-NMR** (100 MHz, $CDCl_3$): δ 169.7, 169.5, 166.2, 154.6, 142.9, 137.5, 128.5, 128.3, 127.8, 124.4, 79.7, 63.1, 58.8, 52.8, 51.5, 37.3, 29.6, 28.2; **IR (Neat)** 3434, 2977, 2954, 1723, 1658, 1495, 1436, 1366, 1276, 1169; **HRMS(MALDI)**: calcd. for $[M+Na]^+$ ($C_{22}H_{29}NO_8Na$) requires 458.1785, found 458.1793.

4.4.3

*4,4-dibenzyl-1-methyl-(S,E)-5-((tert-butoxycarbonyl)amino)-5-phenylpent-1-ene-1,4,4-tricarboxylate (**4c**)*

Yield: 99%; colorless oil. Enantiomeric excess: 83%, $[\alpha]_D^{25}$ = -19.1 (*c* = 2.45, $CHCl_3$), determined by HPLC (Chiralpak AD-H column hexane/*i*-PrOH 9:1, flow rate 1.0 ml/min, t_{minor} = 27.6 min, t_{major} = 17.1 min, λ = 254 nm); ^{1}**H-NMR** (400 MHz, $CDCl_3$): δ 7.29-7.32 (m, 15H), 6.77-6.85 (m, 1H), 6.50 (d, *J* = 8.0 Hz, 1H), 5.67 (d, *J* = 15.6 Hz, 1H), 5.18-5.25 (m, 2H), 5.11 (s, 2H), 3.65 (s, 3H), 2.55-2.68 (m, 2H), 1.36 (s, 9H); ^{13}**C-NMR** (100 MHz, $CDCl_3$): δ 169.7, 169.5, 166.6, 155.1, 143.1, 138.0, 135.3, 134.9, 129.15, 129.13, 129.11, 129.07, 129.0, 128.7, 128.5, 125.2, 80.2, 68.4, 68.3, 63.4, 59.4, 52.0, 37.9, 30.2, 28.8; **IR (Neat)** 3446, 2977, 1723, 1655, 1496, 1275, 1246, 1168, 753, 699; **HRMS(MALDI)**: calcd. for $[M+Na]^+$ ($C_{34}H_{37}NO_8$) requires 610.2417, found 610.2428.

4.4.4

*1-methyl-4,4-diphenyl-(S,E)-5-((tert-butoxycarbonyl)amino)-5-phenylpent-1-ene-1,4,4-tricarboxylate (**4d**)*

Yield: 96%; colorless oil. Enantiomeric excess: 78%, $[\alpha]_D^{24}$ = +5.1 (*c* = 2.60, $CHCl_3$), determined by HPLC (Chiralpak AD-H column hexane/*i*-PrOH 9:1, flow rate 1.0 ml/min, t_{minor} = 48.3 min, t_{major} = 24.0 min, λ = 254 nm); ^{1}**H-NMR** (400 MHz, $CDCl_3$): δ 7.25-7.44 (m, 15H), 6.97-6.99 (m, 1H), 6.56 (m, 1H), 6.02 (d, *J* = 15.6 Hz, 1H), 5.52 (d, *J* = 8.8 Hz, 1H), 3.71 (s, 3H), 2.98-2.99 (m, 2H), 1.39 (s, 9H); ^{13}**C-NMR** (100 MHz, $CDCl_3$): δ 167.8, 166.1, 154.7, 150.1, 149.9, 142.2, 137.3, 129.8, 129.7, 129.6, 128.7, 128.6, 128.4, 128.3, 126.6, 126.5, 125.3, 121.3, 121.1, 121.0, 115. 4, 80.1, 63.3, 59.3, 51.6, 37.8, 28.3, 28.2; **IR (Neat)** 3447, 2977, 1756, 1724, 1655, 1492, 1367, 1163, 748, 688; **HRMS(MALDI)**: calcd. for $[M+Na]^+$ ($C_{34}H_{32}NO_8$) requires 582.2104, found 582.2103.

4.4.5

*1-ethyl-4,4-dimethyl-(S,E)-5-((tert-butoxycarbonyl)amino)-5-phenylpent-1-ene-1,4,4-tricarboxylate (**4e**)*

Yield: 99%; colorless oil. Enantiomeric excess: 81%, $[\alpha]_D^{26}$ = -23.0 (*c* = 2.80, $CHCl_3$), determined by HPLC (Chiralpak AD-H column hexane/*i*-PrOH 95:5, flow rate 1.0 ml/min, t_{minor} = 32.1 min, t_{major} = 27.8 min, λ = 254 nm); ^{1}**H-NMR** (400 MHz, $CDCl_3$): δ 7.23-7.31 (m, 5H), 6.78-6.84 (m, 1H), 6.46 (d, *J* = 9.2 Hz, 1H), 5.80 (d, *J* = 15.6 Hz, 1H), 5.22 (d, *J* = 9.2 Hz, 1H), 4.16 (q, *J* = 7.2 Hz, 2H), 3.75 (s, 3H), 3.73 (s, 3H), 2.60-2.64 (m, 2H), 1.38 (s, 9H), 1.27 (t, *J* = 7.2 Hz, 3H); ^{13}**C-NMR** (100 MHz, $CDCl_3$): δ 169.8, 169.5, 166.8, 154.6, 142.5, 137.5, 128.4, 128.3, 127.9, 124.9, 79.7, 63.1, 58.7, 52.8, 37.3, 28.2, 18.3, 14.2; **IR (Neat)** 3448, 2979, 1719, 1654,

1492, 1367, 1247, 1169, 1044; **HRMS(MALDI)**: calcd. for $[M+Na]^+$ ($C_{23}H_{31}NO_8Na$) requires 472.1942, found 472.1940.

4.4.6

*triethyl-(S,E)-5-((tert-butoxycarbonyl)amino)-5-phenylpent-1-ene-1,4,4-tricarboxylate (**4f**)*

Yield: 99%; colorless oil. Enantiomeric excess: 81%, $[\alpha]_D^{25}$ = -20.2 (*c* = 2.70, $CHCl_3$), determined by HPLC (Chiralpak AD-H column hexane/*i*-PrOH 9:1, flow rate 1.0 ml/min, t_{minor} = 11.3 min, t_{major} = 13.9 min, λ = 254 nm); **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 7.27-7.29 (m, 5H), 6.82-6.86 (m, 1H), 6.57 (d, *J* = 9.2 Hz, 1H), 5.80 (d, *J* = 15.6 Hz, 1H), 5.20 (d, *J* = 9.6 Hz, 1H), 4.13-4.25 (m, 6H), 2.59-2.62 (m, 2H), 1.37 (s, 9H), 1.18-1.29 (m, 9H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 168.7, 168.3, 165.9, 143.7, 143.5, 123.9, 123.8, 110.0, 61.7, 60.4, 52.7, 50.6, 50.3, 31.1, 14.2, 14.0; **IR (Neat)** 3446, 2980, 1719, 1540, 1490, 1367, 1244, 1173, 756, 703; **HRMS(MALDI)**: calcd. for $[M+Na]^+$ ($C_{25}H_{35}NO_8$) requires 500.2260, found 500.2248.

4.4.7

*4,4-diethyl-1-methyl-(S,E)-5-((tert-butoxycarbonyl)amino)-5-(2-chloro-phenyl)pent-1-ene-1,4,4-tricarboxylate (**4g**)*

Yield: 99%; colorless oil. Enantiomeric excess: 85%, $[\alpha]_D^{26}$ = -36.6 (*c* = 2.80, $CHCl_3$), determined by HPLC (Chiralpak AD-H column hexane/*i*-PrOH 95:5, flow rate 1.0 ml/min, t_{minor} = 16.3 min, t_{major} = 37.0 min, λ = 254 nm); **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 7.28-7.30 (m, 2H), 7.13-7.20 (m, 2H), 6.71-6.75 (m, 1H), 6.59 (d, *J* = 8.8 Hz, 1H), 5.87 (d, *J* = 9.2 Hz, 1H), 5.73 (d, *J* = 15.6 Hz, 1H), 4.15-4.20 (m, 4H), 3.61 (s, 3H), 2.80-2.86 (m, 1H), 2.48-2.53 (m, 1H), 1.30 (s, 9H), 1.21 (t, *J* = 7.2 Hz, 3H), 1.15 (t, *J* = 7.2 Hz, 3H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 169.4, 169.0, 166.2, 154.4, 143.3, 136.3, 129.8, 129.2, 128.7, 127.1, 124.0, 79.6, 63.3, 62.2, 62.1, 54.2, 51.4, 35.8, 30.9, 28.2, 14.0, 13.7; **IR (Neat)** 3428, 2979, 2926, 1724, 1491, 1391, 1260, 1170, 1097, 801, 758; **HRMS(MALDI)**: calcd. for $[M+Na]^+$ ($C_{24}H_{32}NO_8Cl$) requires 520.1714, found 520.1715.

4.4.8

*4,4-diethyl-1-methyl-(S,E)-5-((tert-butoxycarbonyl)amino)-5-(3-chloro-phenyl)pent-1-ene-1,4,4-tricarboxylate (**4h**)*

Yield: 85%; colorless oil. Enantiomeric excess: 87%, $[\alpha]_D^{25}$ = -34.5 (*c* = 2.25, $CHCl_3$), determined by HPLC (Chiralpak AD-H column hexane/*i*-PrOH 9:1, flow rate 1.0 ml/min, t_{minor} = 10.2 min, t_{major} = 13.3 min, λ = 254 nm); **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 7.17-7.27 (m, 5H), 6.83-6.90 (m, 1H), 6.52 (d, *J* = 8.8 Hz, 1H), 5.82 (d, *J* = 15.6 Hz, 1H), 5.16 (d, *J* = 9,2 Hz, 1H), 4.18-4.25 (m, 4H), 3.71 (s, 3H), 2.49-2.65 (m, 2H), 1.38 (s, 9H), 1.20-1.29 (m, 9H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 169.3, 168.9, 166.1, 154.5, 142.8, 139.8, 134.3, 129.6, 128.4, 128.1, 126.5, 124.5, 79.9, 63.3, 62.5, 62.2, 62.1, 58.4, 58.3, 51.5, 37.2, 28.2, 18.4, 14.0, 13.8; **IR (Neat)** 3433, 2980, 1724, 1493, 1367, 1244, 1167, 1097, 870, 783, 699; **HRMS(MALDI)**: calcd. for $[M+Na]^+$ ($C_{24}H_{32}NO_8Cl$) requires 520.1714, found 520.1709.

4.4.9

*4,4-diethyl-1-methyl-(S,E)-5-((tert-butoxycarbonyl)amino)-5-(4-chloro-phenyl)pent-1-ene-1,4,4-tricarboxylate (**4i**)*

Yield: 98%; colorless oil. Enantiomeric excess: 81%, $[\alpha]_D^{24}$ = -19.0 (*c* = 3.20, $CHCl_3$), determined by HPLC (Chiralpak AD-H column hexane/*i*-PrOH 9:1, flow rate 1.0 ml/min, t_{minor} = 17.1 min, t_{major} = 22.1 min, λ = 254 nm); ^{1}**H-NMR** (400 MHz, $CDCl_3$): δ 7.27-7.29 (m, 2H), 7.21-7.23 (m, 2H), 6.82-6.90 (m, 1H), 6.53 (d, *J* = 9.2 Hz, 1H), 5.80 (d, *J* = 15.6 Hz, 1H), 5.16 (d, *J* = 9.2 Hz, 1H), 4.17-4.25 (m, 4H), 3.71 (s, 3H), 2.58-2.62 (m, 2H), 1.37 (s, 9H), 1.27 (t, *J* = 7.2 Hz, 3H), 1.21 (t, *J* = 7.2 Hz, 3H); ^{13}**C-NMR** (100 MHz, $CDCl_3$): δ 169.4, 168.9, 166.1, 154.5, 142.8, 136.4, 134.1, 129.5, 128.5, 124.4, 79.8, 62.4, 62.2, 58.3, 51.5, 37.2, 28.2, 14.0, 13.8; **IR (Neat)** 3433, 2980, 1724, 1493, 1368, 1273, 1245, 1169, 1093, 1015, 848, 756; **HRMS(MALDI)**: calcd. for $[M+Na]^+$ ($C_{24}H_{32}NO_8Cl$) requires 520.1714, found 520.1710.

4.4.10

*4,4-diethyl-1-methyl-(S,E)-5-((tert-butoxycarbonyl)amino)-5-(4-fluoro-phenyl)pent-1-ene-1,4,4-tricarboxylate (**4j**)*

Yield: 97%; colorless oil. Enantiomeric excess: 79%, $[\alpha]_D^{26}$ = -17.9 (*c* = 2.50, $CHCl_3$), determined by HPLC (Chiralpak AD-H column hexane/*i*-PrOH 9:1, flow rate 1.0 ml/min, t_{minor} = 14.0 min, t_{major} = 18.5 min, λ = 254 nm); ^{1}**H-NMR** (400 MHz, $CDCl_3$): δ 7.26-7.27 (m, 2H), 6.97-7.01 (m, 2H), 6.82-6.90 (m, 1H), 6.53 (d, *J* = 8.0 Hz, 1H), 5.81 (d, *J* = 15.2 Hz, 1H), 5.17 (d, *J* = 8.8 Hz, 1H), 4.16-4.26 (m, 4H), 3.70 (s, 3H), 2.59-2.62 (m, 2H), 1.37 (s, 9H), 1.27 (t, *J* = 7.2 Hz, 3H), 1.21 (t, *J* = 7.2 Hz, 3H); ^{13}**C-NMR** (100 MHz, $CDCl_3$): δ 169.4, 169.0, 166.2, 163.7, 161.2, 154.5, 142.9, 133.7, 127.5, 124.4, 115.4, 115.2, 79.7, 62.6, 62.1, 58.3, 51.5, 37.3, 28.3, 28.2, 28.1, 18.4, 14.0, 13.8; **IR (Neat)** 2980, 1733, 1508, 1489, 1226, 1165, 1097, 838, 802; **HRMS(MALDI)**: calcd. for $[M+Na]^+$ ($C_{24}H_{32}NO_8F$) requires 504.2010, found 504.2005.

4.4.11

*4,4-diethyl-1-methyl-(S,E)-5-(4-bromophenyl)-5-((tert-butoxy-carbonyl)-amino)pent-1-ene-1,4,4-tricarboxylate (**4k**)*

Yield: 84%; colorless oil. Enantiomeric excess: 81%, $[\alpha]_D^{25}$ = -21.7 (*c* = 2.0, $CHCl_3$), determined by HPLC (Chiralpak AD-H column hexane/*i*-PrOH 9:1, flow rate 1.0 ml/min, t_{minor} = 16.3 min, t_{major} = 20.0 min, λ = 254 nm); ^{1}**H-NMR** (400 MHz, $CDCl_3$): δ 7.43 (d, *J* = 8 Hz, 2H), 7.16 (d, *J* = 7.6 Hz, 2H), 6.81-6.87 (m, 1H), 6.53 (d, *J* = 8.4 Hz, 1H), 5.80 (d, *J* = 15.6 Hz, 1H), 5.14 (d, *J* = 9,2 Hz, 1H), 4.18-4.25 (m, 4H), 3.71 (s, 3H), 2.58-2.62 (m, 2H), 1.37 (s, 9H), 1.27 (t, *J* = 7.2 Hz, 3H), 1.22 (t, *J* = 7.2 Hz, 3H); ^{13}**C-NMR** (100 MHz, $CDCl_3$): δ 169.3, 168.9, 166.1, 154.5, 142.8, 136.9, 132.4,131.5, 130.9, 129.8, 127.7, 127.6, 124.4, 122.3, 79.8, 62.4, 62.2, 58.4, 51.5, 37.2, 28.2, 28.1, 18.4, 15.1, 14.0, 13.8; **IR (Neat)** 3431, 2980, 1723, 1489, 1367, 1245, 1168, 1011, 847, 804; **HRMS(MALDI)**: calcd. for $[M+Na]^+$ ($C_{24}H_{32}NO_8Br$) requires 564.1209, found 564.1212.

4.4.12

4,4-diethyl-1-methyl-(S,E)-5-((tert-butoxycarbonyl)amino)-5-(p-tolyl)pent-1-ene-1,4,4

*-tricarboxylate (**4l**)*

Yield: 95%; colorless oil. Enantiomeric excess: 81%, $[\alpha]_D^{25}$ = -20.6 (*c* = 2.40, $CHCl_3$), determined by HPLC (Chiralpak AD-H column hexane/*i*-PrOH 9:1, flow rate 1.0 ml/min, t_{minor} = 11.1 min, t_{major} = 14.4 min, λ = 254 nm); **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 7.01-7.15 (m, 4H), 6.84-6.88 (m, 1H), 6.54 (d, *J* = 9.2 Hz, 1H), 5.80 (d, *J* = 15.6 Hz, 1H), 5.16 (d, *J* = 9,2 Hz, 1H), 4.18-4.24 (m, 4H), 3.70 (s, 3H), 2.53-2.65 (m, 2H), 2.31 (s, 3H), 1.37 (s, 9H), 1.27 (t, *J* = 7.2 Hz, 3H), 1.22 (t, *J* = 7.2 Hz, 3H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 169.5, 169.2, 166.2, 154.5, 143.3, 137.9, 134.7, 129.1, 127.9, 124.3, 79.5, 62.7, 62.0, 58.7, 51.5, 37.3, 30.9, 28.3, 21.1, 14.0, 13.8; **IR (Neat)** 3433, 2980, 1724, 1492, 1366, 1244, 1168, 1098, 1044; **HRMS(MALDI)**: calcd. for $[M+Na]^+$ ($C_{25}H_{35}NO_8$) requires 500.2260, found 500.2261.

4.4.13

*4,4-diethyl-1-methyl-(S,E)-5-((tert-butoxycarbonyl)amino)-5-(4-methoxy-phenyl)pent-1-ene-1,4,4-tricarboxylate (**4m**)*

Yield: 98%; colorless oil. Enantiomeric excess: 80%, $[\alpha]_D^{25}$ = -36.3 (*c* = 1.50, $CHCl_3$), determined by HPLC (Chiralpak AD-H column hexane/*i*-PrOH 9:1, flow rate 1.0 ml/min, t_{minor} = 19.3 min, t_{major} = 25.3 min, λ = 254 nm); **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 7.18 (d, *J* = 8.0 Hz, 2H), 6.85-6.91 (m, 1H), 6.82 (d, *J* = 8.0 Hz, 2H), 6.52 (d, *J* = 8.8 Hz, 1H), 5.80 (d, *J* = 15.6 Hz, 1H), 5.14 (d, *J* = 8.8 Hz, 1H), 4.18-4.24 (m, 4H), 3.78 (s, 3H), 3,70 (s, 3H), 2.53-2.65 (m, 2H), 1.37 (s, 9H), 1.21-1.29 (m, 6H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 169.6, 169.2, 166.2, 159.5, 154.5, 143.3, 132.0, 129.8, 129.2, 124.2, 114.3, 113.7, 79.5, 62.8, 62.0, 58.4, 55.6, 55.2, 51.5, 37.3, 28.3, 28.2, 14.0, 13.8; **IR (Neat)** 3436, 2980, 1724, 1515, 1495, 1368, 1250, 1169, 1098, 1034, 838, 766; **HRMS(MALDI)**: calcd. for $[M+Na]^+$ ($C_{25}H_{35}NO_9$) requires 516.2210, found 516.2215.

4.4.14

*4,4-diethyl-1-methyl-(S,E)-5-((tert-butoxycarbonyl)amino)-5-(4-nitro-phenyl)-pent-1-ene-1,4,4-tricarboxylate (**4n**)*

Yield: 83%; pale yellow oil. Enantiomeric excess: 83%, $[\alpha]_D^{25}$ = -30.8 (*c* = 1.90, $CHCl_3$), determined by HPLC (Chiralpak AD-H column hexane/*i*-PrOH 7:3, flow rate 1.0 ml/min, t_{minor} = 15.2 min, t_{major} = 11.1 min, λ = 254 nm); **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 8.17 (d, *J* = 8.4 Hz, 2H), 7.50 (d, *J* = 8.4 Hz, 2H), 6.81-6.87 (m, 1H), 6.56 (d, *J* = 9.2 Hz, 1H), 5.83 (d, *J* = 15.6 Hz, 1H), 5.29 (d, *J* = 11.6 Hz, 1H), 4.16-4.27 (m, 4H), 3.71 (s, 3H), 3,70 (s, 3H), 2.66 (d, *J* = 7.2 Hz, 2H), 1.38 (s, 9H), 1.27 (t, *J* = 7.2 Hz, 3H), 1.20 (t, *J* = 7.2 Hz, 3H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 169.1, 168.7, 166.0, 154.5, 147.7, 145.3, 142.1, 129.3, 124.7, 123.5, 80.3, 62.4, 62.1, 58.4, 51.6, 37.2, 30.9, 28.2, 14.0, 13.8; **IR (Neat)** 3429, 2981, 1724, 1525, 1491, 1316, 1247, 1169, 1108, 1014, 859, 752, 701; **HRMS(MALDI)**: calcd. for $[M+Na]^+$ ($C_{25}H_{35}NO_9$) requires 531.1955, found 531.1966.

4.4.15

*4,4-diethyl-1-methyl-(S,E)-5-((tert-butoxycarbonyl)amino)-5-(3-fluoro-phenyl)pent-1-ene-1,4,4-tricarboxylate (**4o**)*

Yield: 93%; colorless oil. Enantiomeric excess: 81%, $[\alpha]_D^{23}$ = -26.8 (*c* = 2.10, $CHCl_3$),

determined by HPLC (Chiralpak AD-H column hexane/*i*-PrOH 95:5, flow rate 1.0 ml/min, t_{minor} = 17.7 min, t_{major} = 23.7 min, λ = 254 nm); ^{1}**H-NMR** (400 MHz, $CDCl_3$): δ 7.25-7.30 (m, 1H), 6.99-7.07 (m, 3H), 6.83-6.91 (m, 1H), 6.54 (d, *J* = 8.8 Hz, 1H), 5.82 (d, *J* = 15.6 Hz, 1H), 5.19 (d, *J* = 9.2 Hz, 1H), 4.18-4.28 (m, 4H), 3.71 (s, 3H), 2.56-2.68 (m, 2H), 1.38 (s, 9H), 1.27 (t, *J* = 7.2 Hz, 3H), 1.21 (t, *J* = 7.2 Hz, 3H); ^{13}**C-NMR** (100 MHz, $CDCl_3$): δ 169.3, 168.9, 166.1, 163.9, 161.4, 154.5, 142.8, 140.3, 129.9, 129.8, 124.5, 124.0, 115.3, 115.1, 114.8, 79.8, 62.4, 62.2, 62.1, 58.5, 51.5, 37.2, 28.2, 14.0, 13.8; **IR (Neat)** 3431, 2981, 1727, 1489, 1367, 1252, 1169, 868, 785, 700; **HRMS(MALDI)**: calcd. for $[M+Na]^+$ ($C_{24}H_{32}NO_8F$) requires 504.2010, found 504.2005.

4.4.16

*4,4-diethyl-1-methyl-(S,E)-5-((tert-butoxycarbonyl)amino)-5-(m-tolyl)pent-1-ene-1,4,4-tricarboxylate (**4p**)*

Yield: 99%; colorless oil. Enantiomeric excess: 85%, $[\alpha]_D^{23}$ = -32.1 (*c* = 2.70, $CHCl_3$), determined by HPLC (Chiralpak AD-H column hexane/*i*Pro 9:1, flow rate 1.0 ml/min, m_{inor} = 8.2 min, m_{ajor} = 10.3 min, λ = 254 nm); ^{1}**H-NMR** (400 MHz, $CDCl_3$): δ 7.16-7.20 (m, 1H), 7.05-7.09 (m, 3H), 6.84-6.92 (m, 1H), 6.56 (d, *J* = 9.6 Hz, 1H), 5.80 (d, *J* = 15.6 Hz, 1H), 5.16 (d, *J* = 9.2 Hz, 1H), 4.20-4.24 (m, 4H), 3.70 (s, 3H), 2.56-2.61 (m, 2H), 2.32 (s, 3H), 1.38 (s, 9H), 1.27 (t, *J* = 7.2 Hz, 3H), 1.22 (t, *J* = 7.2 Hz, 3H); ^{13}**C-NMR** (100 MHz, $CDCl_3$): δ 169.5, 169.1, 166.2, 154.6, 143.3, 137.9, 137.6, 129.0, 128.8, 128.3, 125.0, 124.3, 79.5, 62.7, 62.0, 61.9, 58.9, 51.5, 37.3, 29.7, 28.3, 28.2, 21.4, 14.0, 13.8; **IR (Neat)** 3434, 2980, 1725, 1492, 1367, 1242, 1167, 1098, 1045, 874, 781, 707; **HRMS(MALDI)**: clad. for $[M+Na]^+$ ($C_{25}H_{35}NO_8$) requires 500.2260, found 500.2255.

4.4.17

*4,4-diethyl-1-methyl-(S,E)-5-((tert-butoxycarbonyl)amino)-5-(3-methoxy-phenyl)pent-1-ene-1,4,4-tricarboxylate (**4q**)*

Yield: 99%; colorless oil. Enantiomeric excess: 86%, $[\alpha]_D^{26}$ = -28.8 (*c* = 2.50, $CHCl_3$), determined by HPLC (Chiralpak AD-H column hexane/*i*-PrOH 9:1, flow rate 1.0 ml/min, t_{minor} = 11.7 min, t_{major} = 17.9 min, λ = 254 nm); ^{1}**H-NMR** (400 MHz, $CDCl_3$): δ 7.19-7.24 (m, 1H), 6.86-6.92 (m, 1H), 6.81-6.85 (m, 3H), 6.55 (d, *J* = 9.2 Hz, 1H), 5.81 (d, *J* = 15.2 Hz, 1H), 5.17 (d, *J* = 9.2 Hz, 1H), 4.19-4.24 (m, 4H), 3.78 (s, 3H), 3.70 (s, 3H), 2.54-2.67 (m, 2H), 1.38 (s, 9H), 1.27 (t, *J* = 7.2 Hz, 3H), 1.23 (t, *J* = 7.2 Hz, 3H); ^{13}**C-NMR** (100 MHz, $CDCl_3$): δ 169.5, 169.1, 166.2, 159.5, 154.6, 143.2, 139.2, 129.4, 124.3, 120.3, 114.0, 113.4, 79.6, 62.6, 62.0, 58.8, 55.2, 51.5, 37.3, 28.3, 28.2, 14.0, 13.8; **IR (Neat)** 3430, 2980, 1724, 1491, 1368, 1263, 1168, 1098, 1044, 866, 783, 703; **HRMS(MALDI)**: calcd. for $[M+Na]^+$ ($C_{25}H_{35}NO_9$) requires 516.2210, found 516.2203.

4.4.18

*4,4-diethyl-1-methyl-(S,E)-5-(3-bromophenyl)-5-((tert-butoxycarbonyl)-amino)pent-1-ene-1,4,4-tricarboxylate (**4r**)*

Yield: 99%; colorless oil. Enantiomeric excess: 86%, $[\alpha]_D^{22}$ = -16.8 (*c* = 0.20, $CHCl_3$),

determined by HPLC (Chiralpak AD-H column hexane/*i*-PrOH 9:1, flow rate 1.0 ml/min, t_{minor} = 9.7 min, t_{major} = 11.9 min, λ = 254 nm); **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 7.34-7.35 (m, 2H), 7.09-7.16 (m, 1H), 6.75-6.83 (m, 1H), 6.45 (d, *J* = 9.6 Hz, 1H), 5.75 (d, *J* = 15.6 Hz, 1H), 5.08 (d, *J* = 9.6Hz, 1H), 4.11-4.18 (m, 4H), 3.63 (s, 3H), 2.48-2.60 (m, 2H), 1.31 (s, 9H), 1.20 (t, *J* = 7.2 Hz, 3H), 1.15 (t, *J* = 7.2 Hz, 3H);; **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 169.3, 168.8, 166.1, 154.5, 142.7, 140.1, 131.3, 130.9, 129.9, 127.0, 124.5, 122.5, 79.9, 62.5, 62.3, 62.2, 58.4, 51.5, 37.2, 28.2, 14.0, 13.8; **IR (Neat)** 3433, 2959, 2924, 2853, 1725, 1493, 1367, 1260, 1167, 1097, 1018, 869, 800, 699; **HRMS(MALDI)**: calcd. for $[M+Na]^+$ ($C_{24}H_{32}NO_8Br$) requires 564.1209, found 564.1208.

4.4.19

*4,4-diethyl-1-methyl--(S,E)-5-((tert-butoxycarbonyl)amino)-5-(thiophen-2-yl)pent-1-ene-1,4,4-tricarboxylate (**4s**)*

Yield: 95%; colorless oil. Enantiomeric excess: 70%, $[\alpha]_D^{25}$ = +1.5 (*c* = 2.80, $CHCl_3$), determined by HPLC (Chiralpak AD-H column hexane/*i*-PrOH 9:1, flow rate 1.0 ml/min, t_{minor} = 12.5 min, t_{major} = 14.1 min, λ = 254 nm); **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 7.22 (d, *J* = 5.2 Hz, 1H), 6.95-7.00 (m, 1H), 6.87-6.93 (m, 2H), 6.35 (d, *J* = 9.6 Hz, 1H), 5.80 (d, *J* = 15.2 Hz, 1H), 5.51 (d, *J* = 10.0 Hz, 1H), 4.19-4.29 (m, 4H), 3.70 (s, 3H), 2.72-2.78 (m, 1H), 2.58-2.62 (m, 1H), 1.39 (s, 9H), 1.26-1.30 (m, 6H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 169.6, 169.0, 166.2, 154.4, 143.0, 140.7, 127.4, 126.5, 125.6, 124.3, 79.8, 62.8, 62.3, 62.2, 55.0, 51.5, 37.2, 28.3, 14.0, 13.8; **IR (Neat)** 3448, 2981, 1724, 1490, 1368, 1247, 1168, 1097, 1043, 855, 706; **HRMS(MALDI)**: calcd. for $[M+Na]^+$ ($C_{25}H_{35}NSO_8$) requires 492.1668, found 492.1658.

4.4.20

*4,4-diethyl-1-methyl-(S,E)-5-((tert-butoxycarbonyl)amino)-5-(naphthalen-1-yl)pent-1-ene-1,4,4-tricarboxylate (**4t**)*

Yield: 60%; colorless oil. Enantiomeric excess: 70%, $[\alpha]_D^{25}$ = +1.5 (*c* = 2.80, $CHCl_3$), determined by HPLC (Chiralpak AD column hexane/*i*-PrOH 95:5, flow rate 0.5 ml/min, t_{minor} = 28.3 min, t_{major} = 37.8 min, λ = 254 nm); **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 8.38 (d, *J* = 8.4 Hz, 1H), 7.84 (d, *J* = 8.0 Hz, 1H), 7.78 (d, *J* = 8.0 Hz, 1H), 7.40-7.60 (m, 4H), 6.72-6.78 (m, 2H), 6.28 (d, *J* = 9.2 Hz, 1H), 5.61 (d, *J* = 15.6 Hz, 1H), 4.12-4.30 (m, 4H), 3.65 (s, 3H), 2.64-2.70 (m, 1H), 2.34-2.43 (m, 1H), 1.36 (s, 9H), 1.11-1.34 (m, 6H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 169.7, 169.4, 166.2, 154.7, 143.2, 135.0, 133.6, 132.0, 128.8, 128.7, 126.7, 125.7, 125.1, 124.9, 123.9, 123.2, 79.6, 62.1, 62.0, 52.6, 51.4, 37.1, 28.3, 14.1, 13.7; **IR (Neat)** 3428, 2980, 1724, 1490, 1367, 1243, 1167, 1097, 1045, 884, 860, 779; **HRMS(MALDI)**: calcd. for $[M+Na]^+$ ($C_{28}H_{35}NO_8$) requires 536.2260, found 536.2245.

4.4.21

*4,4-dibenzyl-1-methyl-(S,E)-5-((tert-butoxycarbonyl)amino)-5-(3-chloro-phenyl)pent-1-ene-1,4,4-tricarboxylate (**4u**)*

Yield: 99%; colorless oil. Enantiomeric excess: 90%, $[\alpha]_D^{24}$ = -24.3 (*c* = 3.10, $CHCl_3$),

determined by HPLC (Chiralpak AD-H column hexane/*i*-PrOH 9:1, flow rate 1.0 ml/min, t_{minor} = 18.5 min, t_{major} = 14.5 min, λ = 254 nm); **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 7.30-7.32 (m, 8H), 7.05-7.24 (m, 6H), 6.76-6.84 (m, 1H), 6.46 (d, *J* = 8.8 Hz, 1H), 5.69 (d, *J* = 15.6 Hz, 1H), 5.17-5.20 (m, 2H), 5.11 (s, 2H), 5.02-5.08 (m, 1H), 3.66 (s, 3H), 2.56-2.69 (m, 2H), 1.36 (s, 9H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 169.0, 168.7, 166.0, 154.5, 142.2, 139.7, 134.6, 134.4, 134.2, 129.7, 128.7, 128.63, 128.60, 128.52, 128.5, 128.45, 128.41, 128.1, 126.3, 124.8, 80.0, 68.03, 67.95, 62.6, 58.5, 51.5, 37.3, 28.2; **IR (Neat)** 3446, 2977, 1724, 1496, 1272, 1168, 1102, 1044, 783, 750, 698; **HRMS(MALDI)**: calcd. for $[M+Na]^+$ ($C_{34}H_{36}NClO_8$) requires 644.2027, found 644.2019.

*4.4.22 4,4-dibenzyl-1-methyl-(S,E)-5-((tert-butoxycarbonyl)amino)-5-(m-tolyl)pent-1-ene-1,4,4-tricarboxylate (**4v**)*

Yield: 99%; colorless oil. Enantiomeric excess: 88%, $[\alpha]_D^{24}$ = -21.1 (*c* = 3.90, $CHCl_3$), determined by HPLC (Chiralpak AD-H column hexane/*i*-PrOH 9:1, flow rate 1.0 ml/min, t_{minor} = 17.2 min, t_{major} = 12.9 min, λ = 254 nm); **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 7.31-7.32 (m, 8H), 7.17-7.22 (m, 2H), 6.94-7.12 (m, 4H), 6.77-6.85 (m, 1H), 6.50 (d, *J* = 8.8 Hz, 1H), 5.66 (d, *J* = 15.6 Hz, 1H), 5.16-5.22 (m, 2H), 5.12 (s, 2H), 5.07-5.10 (m, 1H), 3.65 (s, 3H), 3,70 (s, 3H), 2.58-2.67 (m, 2H), 1.36 (s, 9H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 169.2, 169.0, 166.0, 142.7, 138.0, 137.4, 134.8, 134.4, 128.9, 128.8, 128.6, 128.56, 128.51, 128.49, 128.42, 128.37, 128.31, 124.8, 124.6, 79.6, 67.8, 62.9, 58.9, 51.4, 37.3, 28.3, 21.4; **IR (Neat)** 3446, 2976, 1724, 1490, 1274, 1167, 1044, 750, 689; **HRMS(MALDI)**: calcd. for $[M+Na]^+$ ($C_{35}H_{39}NO_8$) requires 624.2573, found 624.2566.

*4.4.23 dimethyl (S)-2-allyl-2-(((tert-butoxycarbonyl)amino)(phenyl)methyl)malonate (**4w**)*

Yield: 99%; colorless oil. Enantiomeric excess: 68%, $[\alpha]_D^{25}$ = -8.83 (*c* = 2.63, $CHCl_3$), determined by HPLC (Chiral Pak AD-H column hexane/*i*Pro 9:1, flow rate 1.0 ml/min, m_{inor} = 6.6 min, m_{ajor} = 5.9 min, λ = 220 nm); **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 7.22-7.31 (m, 5H), 6.46 (d, *J* = 9.6 Hz, 1H), 5.75-5.85 (m, 1H), 5.24 (d, *J* = 9.6 Hz, 1H), 5.05-5.10 (m, 2H), 3.73 (s, 3H), 3,72 (s, 3H), 2.53-2.58 (m, 1H), 2.41-2.46 (m, 1H), 1.39 (s, 9H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 165.5, 165.2, 149.9, 133.1, 128.1, 123.6, 123.3, 123.0, 114.3, 74.8, 59.0, 53.6, 47.7, 47.6, 34.3, 23.5; **IR (Neat)** 3431, 2978, 1720, 1494, 1366, 1225, 1169; **HRMS(ESI)**: clad. for $[M+H]^+$ ($C_{20}H_{28}NO_6$) requires 378.1911, found 378.1915.

*4.4.24 diethyl (S)-2-allyl-2-(((tert-butoxycarbonyl)amino)(phenyl)methyl)malonate (**4x**)*

Yield: 99%; colorless oil. Enantiomeric excess: 74%, $[\alpha]_D^{25}$ = -11.3 (*c* = 1.88, $CHCl_3$), determined by HPLC (Chiralpak AD-H column hexane/*i*-PrOH 95:5, flow rate 0.7 ml/min, t_{minor} = 11.4 min, t_{major} = 10.3 min, λ = 254 nm); **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 7.27-7.28 (m, 5H), 6.59 (d, *J* = 9.6 Hz, 1H), 5.77-5.87 (m, 1H), 5.22 (d, *J* = 9.6 Hz, 1H), 5.04-5.10 (m, 2H), 4.15-4.24 (m, 4H), 2.52-2.58 (m, 1H), 2.39-2.45

(m, 1H), 1.37 (s, 9H), 1.27 (t, *J* = 7.6 Hz, 3H), 1.21 (t, *J* = 7.6 Hz, 3H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 165.3, 164.8, 149.8, 133.3, 128.3, 124.9, 124.2, 123.5, 123.3, 123.2, 123.1, 114.1, 74.5, 58.4, 56.9, 56.8, 53.8, 34.3, 23.5, 9.3, 9.1; **IR (Neat)** 3431, 2980, 1720, 1494, 1367, 1275, 1170; **HRMS(ESI)**: calcd. for $[M+H]^+$ ($C_{23}H_{32}NO_6$) requires 406.2224, found 406.2225.

*4.4.25 dimethyl (S)-2-(((tert-butoxycarbonyl)amino)(phenyl)methyl)-2-methyl-malonate (**4y**)*

Yield: 99%; white solid. Enantiomeric excess: 63% (91% after recrystallization), $[\alpha]_D^{24}$ = +3.37 (*c* = 0.60, $CHCl_3$), determined by HPLC (Chiralpak AD-H column hexane/*i*-PrOH 9:1, flow rate 1.0 ml/min, t_{minor} = 8.3 min, t_{major} = 7.5 min, λ = 220 nm); **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 7.29-7.33 (m, 5H), 6.52 (d, *J* = 10.0 Hz, 1H), 5.18 (d, *J* = 10.0 Hz, 1H), 3.80 (s, 3H), 3.74 (s, 3H), 1.42 (s, 12H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 171.9, 171.3, 154.9, 137.9, 128.4, 128.3, 128.0, 79.6, 59.1, 53.0, 52.7, 28.4; **IR (Neat)** 3438, 2956, 1724, 1495, 1456, 1369, 1321, 1017; **HRMS(ESI)**: calcd. for $[M+Na]^+$ ($C_{18}H_{25}NO_6Na$) requires 374.1583, found 374.1574.

*4.4.26 diethyl (S)-2-(((tert-butoxycarbonyl)amino)(phenyl)methyl)-2-methylmalonate (**4z**)*

Yield: 99%; white solid. Enantiomeric excess: 75%, $[\alpha]_D^{25}$ = +2.86 (*c* = 1.37, $CHCl_3$), determined by HPLC (Chiralpak OD-H column hexane/*i*-PrOH 99:1, flow rate 1.0 ml/min, t_{minor} = 7.0 min, t_{major} = 7.9 min, λ = 220 nm); **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 7.27-7.30 (m, 5H), 6.58 (d, *J* = 10.0 Hz, 1H), 5.14 (d, *J* = 10.0 Hz, 1H), 4.14-4.26 (m, 4H), 1.37 (s, 9H), 1.29 (t, *J* = 7.6 Hz, 3H), 1.20 (t, *J* = 7.6 Hz, 3H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 171.3, 170.8, 154.8, 138.1, 134.4, 129.7, 129.0, 128.4, 128.1, 127.8, 79.3, 61.8, 61.6, 59.1, 58.9, 28.3, 20.3, 14.0, 13.8; **IR (Neat)** 3437, 2979, 1721, 1494, 1366, 1249, 1170, 1105; **HRMS(ESI)**: calcd. for $[M+H]^+$ ($C_{20}H_{30}NO_6$) requires 380.2068, found 380.2068.

*4.4.27 1-(tert-butyl) 3,3-diethyl (2S,5R)-5-(2-methoxy-2-oxoethyl)-2-(m-tolyl)-pyrrolidine-1,3,3-tricarboxylate (**5**)*

Yield: 99%; colorless oil. Enantiomeric excess: 61%, $[\alpha]_D^{25}$ = -7.66 (*c* = 1.37, $CHCl_3$), determined by HPLC (Chiralpak IC column hexane/*i*-PrOH 95:5, flow rate 1.0 ml/min, t_{minor} = 21.5 min, t_{major} = 46.0 min, λ = 220 nm); **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 7.07-7.11 (m, 1H), 6.90-6.98 (m, 3H), 5.52 (s, 1H), 4.42-4.27 (m, 1H), 4.10-4.18 (m, 1H), 4.00-4.08 (m, 1H), 3.74-3.78 (m, 1H), 3.64 (s, 3H), 3.58-3.67 (m, 2H), 253-2.63 (m, 3H), 2.24 (s, 3H), 1.19-1.26 (m, 12H), 0.89 (t, *J* = 7.2 Hz, 3H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 171.7, 170.1, 167.2, 154.7, 137.4, 128.4, 128.3, 127.9, 124.4, 110.0, 80.0, 66.5, 65.5, 65.4, 62.1, 61.5, 53.4, 51.7, 28.2, 27.9, 21.4, 14.0, 13.5; **IR (Neat)** 2979, 1736, 1699, 1439, 1367, 1263, 1174, 1138; **HRMS(ESI)**: calcd. for $[M+H]^+$ ($C_{25}H_{36}NO_8$) requires 478.2435, found 478.2434.

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Supplementary data

Supplementary data associated with this article can be found in the online version at doi:

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[13] The relative stereochemistry of **5** was determined by NOE experiments and its absolute configuration was assigned to be (2*S*, 5*R*) (for detail, see the Supplementary data).