

Enantioselective Synthesis of 1,2,4-Triazolines Catalyzed by a Cinchona Alkaloid-Derived Organocatalyst

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Supporting Information

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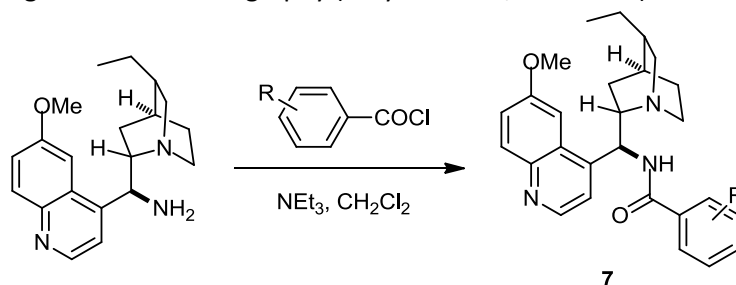
General Methods and Materials:

All reactions were carried out under air using anhydrous solvents. Catalyst **5**,¹ catalyst **6**²⁻⁵, and catalyst **7a-d**⁶ were prepared according to literature procedures. Azlactones were prepared according to reported procedures.⁷ All other reagents were purchased and used without further purification unless specified otherwise. Solvents for chromatography were technical grade and distilled prior to use. Flash chromatography was performed using 200-300 mesh silica gel (Qingdao Haiyang Chemical HG/T2354-92) with the indicated solvent system according to standard techniques. Analytical thin-layer chromatography (TLC) was performed using Huanghai silica gel plates with HSGF 254. Visualization of the developed chromatogram was performed by UV absorbance (254 nm) or appropriate stains. ¹H NMR and ¹³C NMR data were recorded on Bruker 400M or 500M nuclear resonance spectrometers unless otherwise specified. Chemical shifts (δ) in ppm are reported as quoted relative to the residual signals of chloroform (¹H 7.26 ppm or ¹³C 77.16 ppm). Multiplicities are described as: s (singlet), bs (broad singlet), d (doublet), t (triplet), q (quartet), m (multiplet); and coupling constants (J) are reported in Hertz (Hz). ¹³C NMR spectra were recorded with total proton decoupling. Chiral HPLC was recorded on a Shimadzu LC-20A spectrometer using Daicel Chiralpak OD-H, OJ-H, AD-H, AS-H, IA, or IB columns (250 x 4.6 mm). HRMS (ESI) analysis was performed by The Analytical Instrumentation Center at Peking University; Shenzhen Graduate School and the data were reported with ion mass/charge (m/z) ratios as values in atomic mass units.

Preparation of cinchona alkaloid-derived catalysts

General procedure for the synthesis of catalyst **7** from Carboxylic Acid Chlorides and (*S*)-((1*S*,2*S*,4*S*,5*R*)-5-ethylquinuclidin-2-yl)(6-methoxyquinolin-4-yl)-methanamine:⁶

A solution of (*S*)-((1*S*,2*S*,4*S*,5*R*)-5-ethylquinuclidin-2-yl)(6-methoxyquinolin-4-yl)-methanamine, prepared from quinine following the literature procedure,² (488 mg, 1.5 mmol) in 10 mL dry dichloromethane and 2 mL triethylamine was cooled to 0°C. The corresponding carboxylic acid chloride (1.8 mmol) in 2 mL dichloromethane was added dropwise. After the reaction mixture was stirred overnight at room temperature, another 10 mL dichloromethane was added, the reaction was washed three times with aqueous Na₂CO₃ solution and dried over Na₂SO₄. The volatile solvent was removed and the product was purified by silica gel flash chromatography (ethyl acetate / methanol).



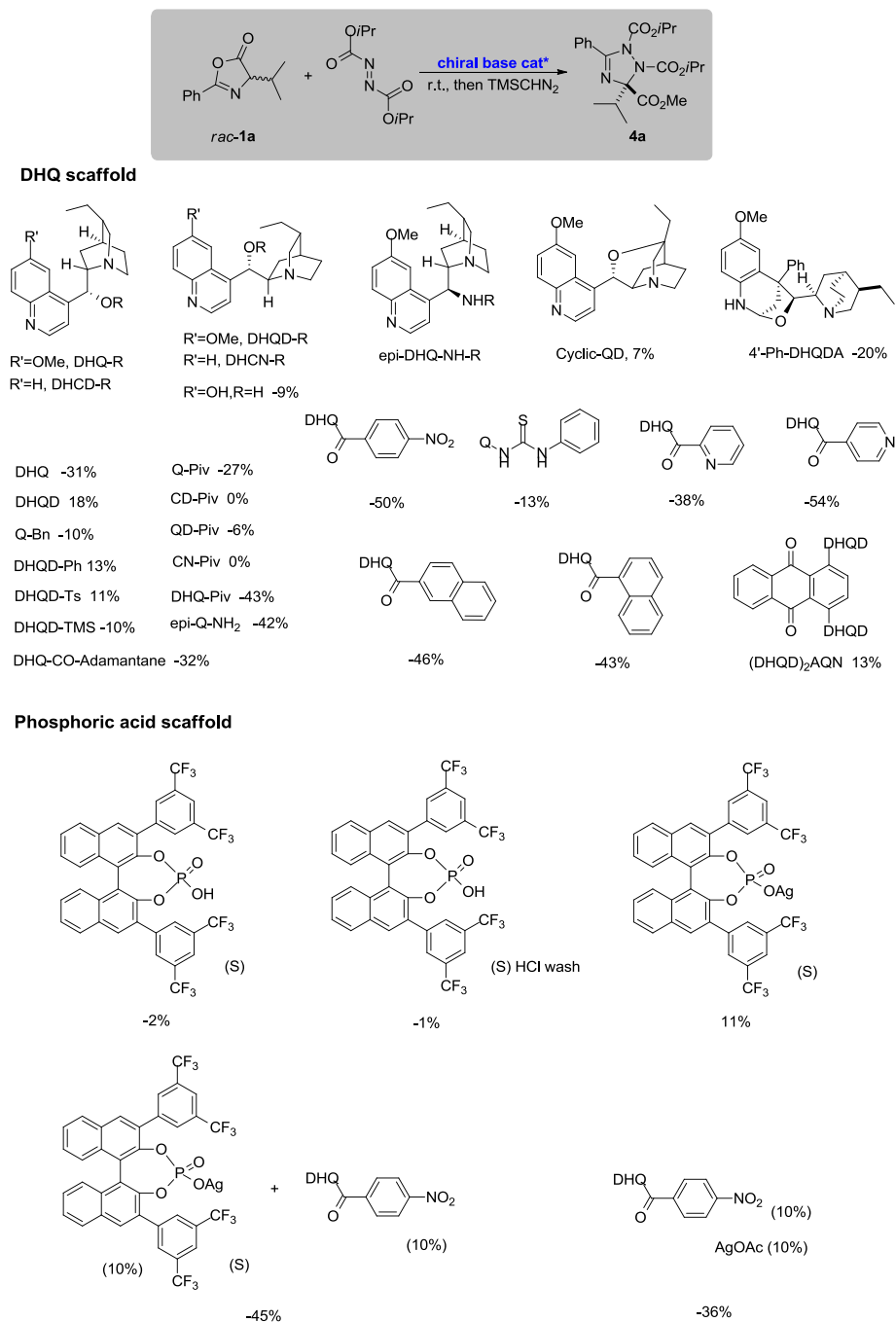
Catalyst **7d**:

85% yield, white powder. ^{27.8}[α]_D = -67 ° (c = 0.1, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 8.77 (d, *J* = 4.6 Hz, 1H), 8.26 (s, 2H), 8.08 (d, *J* = 9.2 Hz, 1H), 8.01 (s, 1H), 7.94 (s, 1H), 7.72 (d, *J* = 2.2 Hz, 1H), 7.49 – 7.40 (m, 2H), 5.45 (s, 1H), 4.03 (s, 3H), 3.31 (dd, *J* = 13.6, 10.0 Hz, 1H), 3.24 (s, 1H), 3.11 (s, 1H), 2.81 – 2.71 (m, 1H), 2.53 (dd, *J* = 13.7, 2.7 Hz, 1H), 1.78 (s, 3H), 1.71 (s, 2H), 1.63 – 1.55 (m, 1H), 1.53 – 1.42 (m, 2H), 1.33 – 1.25 (m, 2H), 1.05 (dd, *J* = 13.4, 6.7 Hz, 1H), 0.85 (t, *J* = 7.3 Hz, 3H); ¹³C NMR (CDCl₃, 100 MHz): δ 164.5, 158.1, 147.4, 144.7, 136.0, 132.5, 132.1, 131.8, 131.5, 128.3, 127.7, 127.0, 125.0, 124.3, 121.8, 121.6, 118.8, 101.8, 57.5, 55.6, 41.0, 37.0, 28.4, 27.3, 26.0, 25.0, 11.9; HRMS (ESI) Calcd. for C₂₉H₃₀F₆N₃O₂ ([M+H]⁺): 566.2242; Found: 566.2222.

Condition screening:

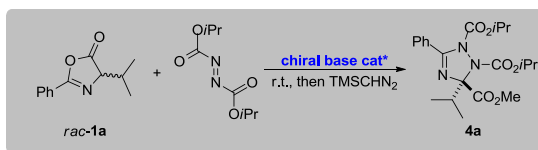
Screening for different catalysts, solvent, catalyst loading, additive, concentration and temperature.

Table S1. Catalyst screening in toluene at r.t.^a

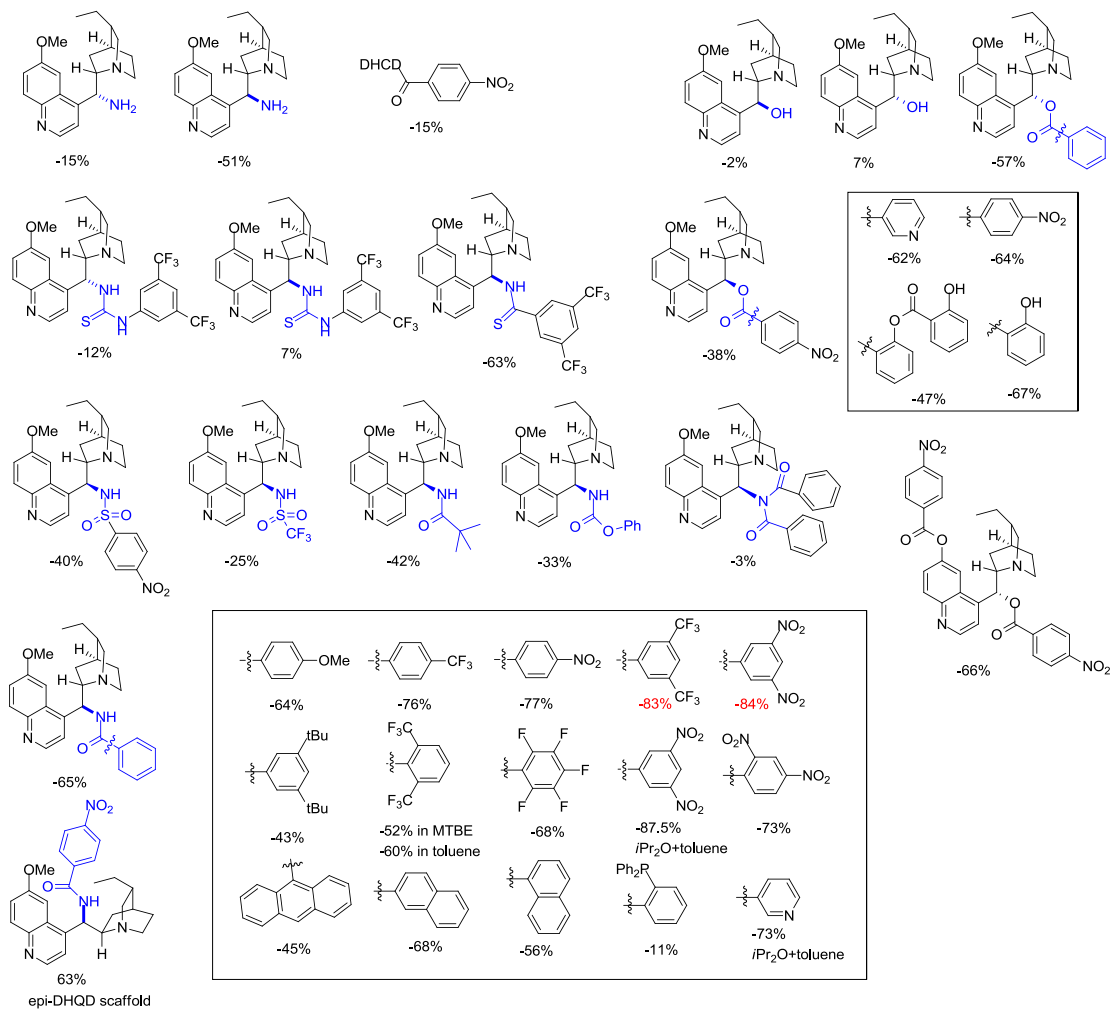


^a: reactions were carried out using **1** (0.1 mmol), DIAD (0.1 mmol), and catalyst (0.01 mmol, 10 mol%) in toluene (1 mL) at 25 °C for 12 hours, unless specified otherwise. ^b: the ee value was determined by chiral HPLC analysis.

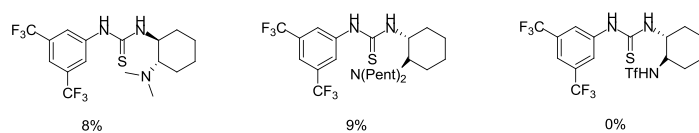
Table S2. Catalyst screening in TBME at r.t.^a



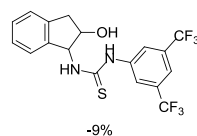
DHQ scaffold



Cyclohexane diamine scaffold



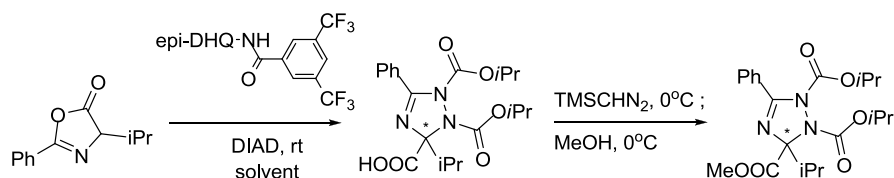
Other scaffold



^a: reactions were carried out using **1** (0.1 mmol), DIAD (0.1 mmol), and catalyst (0.01 mmol, 10

mol%) in MTBS (1 mL) at 25 °C for 12 hours, unless specified otherwise. ^b: the ee value was determined by chiral HPLC analysis.

Table S3. Solvent screening at r.t.



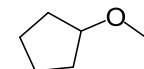
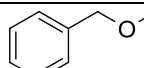
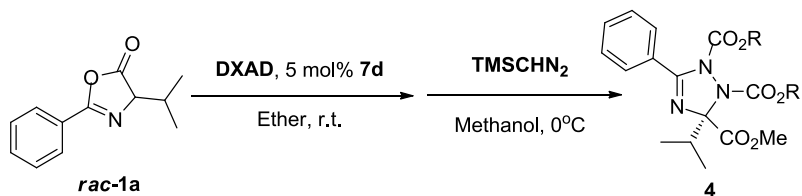
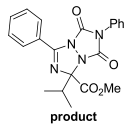
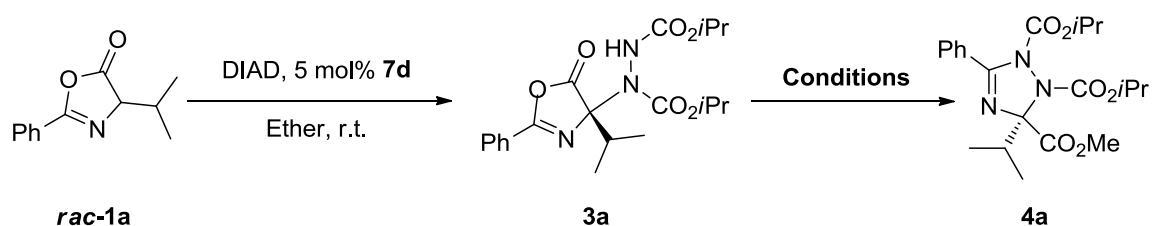
	Solvent	Ee%		Solvent	Ee%	
1	MTBE	-83		9	<i>i</i> Pr ₂ O	-91
2	DCM	-74		10	2-MeTHF	-72
3	MeCN	-29		11		-89
4	Et ₂ O	-91		12		-83
5	Toluene	-88		13	Dioxane	-70
6	Hexane	-80		14	MeOH	-13
7	THF	-70		15	Bn ₂ O	-82
8	EA	-76		16	Acetone	-45
				17	DME	-71

Table S4. Substrate Scope for Azodicarboxylates.



Entry	DXAD	R	Yield (%)	ee (%)
1	DEAD	Et	90	90
2	DIAD	<i>i</i> -Pr	81	93
3	DTBAD	<i>t</i> -Bu	72	90
4	DCAD	<i>p</i> -Cl-Bn	83	59
5	PTAD		52	0

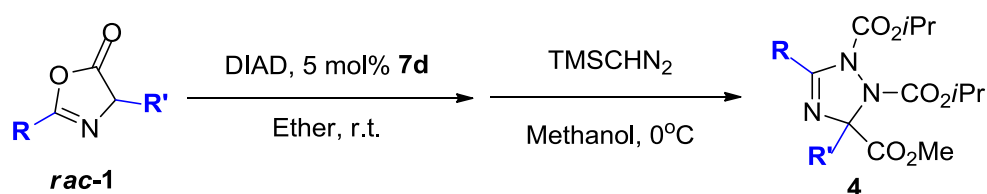
Mechanistic Studies (Table S5)



Conditions	Yield (%)
MeCN	NR
MeOH	NR
TMSCHN ₂	81
TFA	Hydrolysis of amination
HCl	Hydrolysis of azlactone

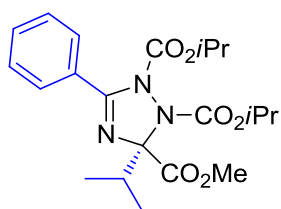
While Tepe proposed a step-wise addition-cyclization mechanism for his un-catalyzed system, we found that the initial addition products could not undergo subsequent cyclization to give triazolines under his standard protocol. The primary addition product **3a** was isolated and subjected under MeCN conditions. No reaction occurred (**Table S5**). The cyclization only occurred upon treatment with TMSCHN₂. This observation suggests that although our catalyzed reactions proceeded through the step-wise, TMSCHN₂ promoted cyclization mechanism, the Tepe reaction was most likely a [3+2] cycloaddition for small size azodicarboxylates (DEAD and DIAD). When DTBAD was employed under the Tepe conditions, only the addition product was observed. Interception of **3a** with electrophiles other than TMSCHN₂ was also attempted and the results are summarized in **Table S5**.

General Procedure for the Synthesis of 3-Quaternized 1,2,4-Triazolines:



One equivalent of the azodicarboxylate was added to a solution of azlactone *rac-1* (0.1 mmol) and 5 mol% **7d** in 1 mL of ether in a 2-dram scintillation vial at room temperature. The reaction mixture was stirred at room temperature for 6 hours, which led to the disappearance of color. At this point the reaction mixture was cooled to 0 °C and (trimethylsilyl)diazomethane (2.0M solution in diethyl ether, 0.15 mL, 0.3 mmol, *Caution: due to the potential explosive nature of this chemical, sharp objects should be avoided during handling and the reaction should be carried out behind a blast shield*) was added in a drop wise manner. The reaction mixture was stirred for 15 minutes and methanol (0.3 mL) was added in drop wise manner. The reaction temperature was allowed to warm to ambient temperature. The progress of the reaction was monitored by TLC. About 6-24 hours later, the reaction mixture was concentrated to a minimal residue and purified by silica-gel flash chromatography to afford product **4**.

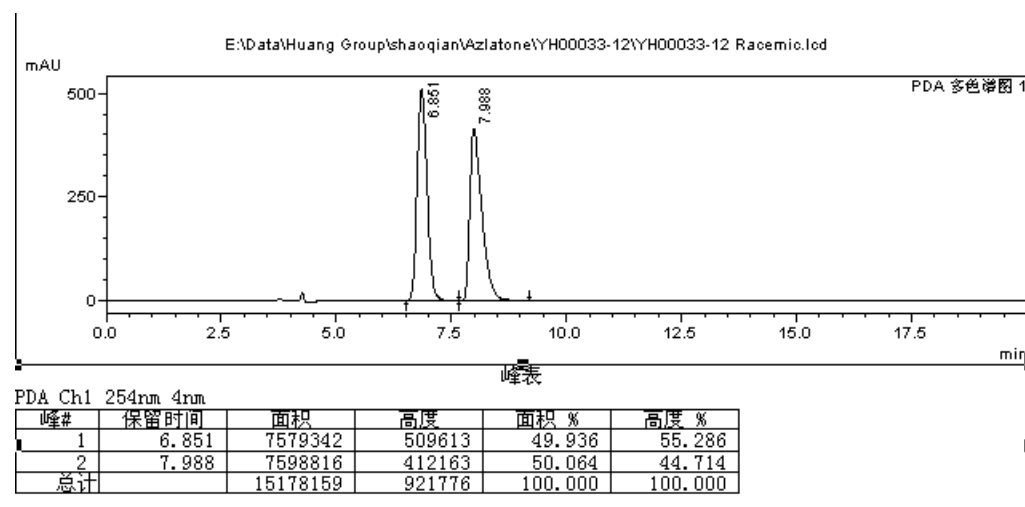
Analytical Data and HPLC Chromatograms for 1,2,4-Triazolines Products:

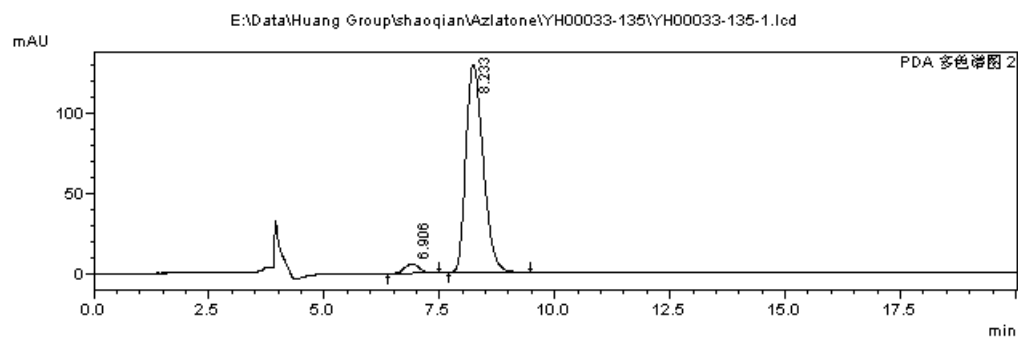


Methyl 1,2-bis(isopropoxycarbonyl)-3-isopropyl-5-phenyl-2,3-dihydro-1H-1,2,4-triazole-3-carboxylate (4a):

81% yield, colorless oil. ^1H NMR (500 MHz, CDCl_3) δ 7.84 – 7.79 (m, 1H), 7.49 (t, $J = 7.4$ Hz, 1H), 7.41 (t, $J = 7.6$ Hz, 1H), 4.99 (dt, $J = 12.5, 6.3$ Hz, 1H), 4.88 (dt, $J = 12.5, 6.2$ Hz, 1H), 3.68 (s, 2H), 2.66 (dt, $J = 13.5, 6.7$ Hz, 1H), 1.31 (d, $J = 6.2$ Hz, 2H), 1.28 (d, $J = 6.3$ Hz, 2H), 1.11 (dd, $J = 6.4, 4.8$ Hz, 3H), 1.08 (d, $J = 6.2$ Hz, 2H), 0.96 (d, $J = 6.8$ Hz, 2H). ^{13}C NMR (126 MHz, CDCl_3) δ 167.53, 158.45, 154.82, 152.01, 131.44, 129.55, 129.19, 127.70, 95.84, 77.24, 76.99, 76.74, 71.89, 70.76, 52.49, 33.49, 21.92, 21.71, 21.40, 21.36, 17.23, 16.28. HRMS (ESI) Calcd. for $\text{C}_{21}\text{H}_{30}\text{N}_3\text{O}_6$ ($[\text{M}+\text{H}]^+$): 420.2135; Found: 420.2131.

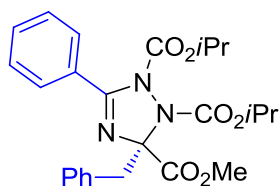
The ee was determined by HPLC using a Chiralcel OD-H column [*n*-hexane/EtOH (99:1)]; flow rate 1.0 mL/min; t_{R} major = 8.233 min, t_{R} minor = 6.906 min (93% ee). $^{24.6}[\alpha]_{\text{D}} = +84^\circ$ ($c = 0.1$, CHCl_3).





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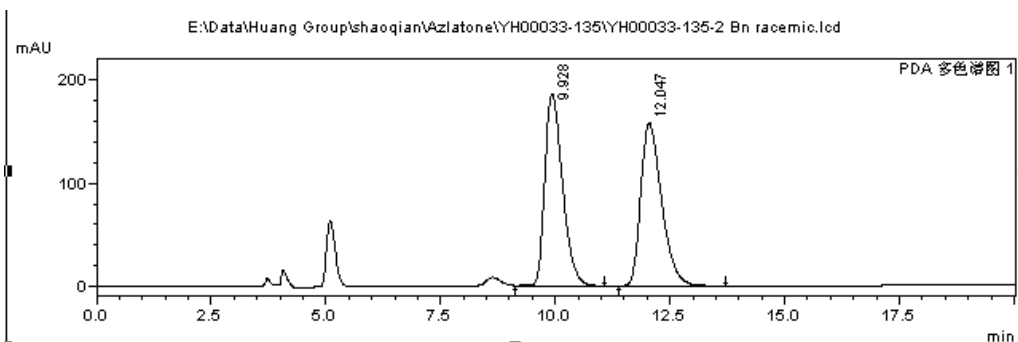
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1	6.906	126394	5645	3.589	4.183
2	8.233	3395520	129323	96.411	95.817
总计		3521914	134968	100.000	100.000



Methyl 1,2-bis(isopropoxycarbonyl)-3-benzyl-5-phenyl-2,3-dihydro-1H-1,2,4-triazole-3-carboxylate (4b):

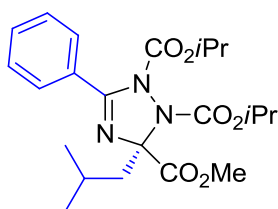
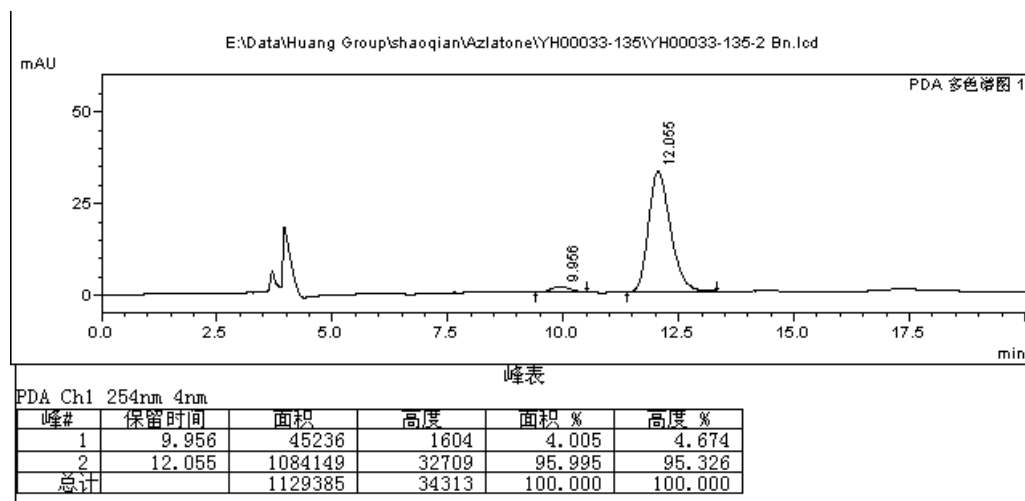
65% yield, colorless oil. ^1H NMR (500 MHz, CDCl_3) δ 7.64 – 7.59 (m, 2H), 7.43 (t, $J = 7.5$ Hz, 1H), 7.34 (t, $J = 7.7$ Hz, 2H), 7.29 (d, $J = 7.3$ Hz, 2H), 7.21 (t, $J = 7.5$ Hz, 2H), 7.13 (t, $J = 7.3$ Hz, 1H), 5.03 (dt, $J = 12.5, 6.3$ Hz, 1H), 4.43 (dt, $J = 12.5, 6.2$ Hz, 1H), 3.76 (s, 3H), 3.63 (d, $J = 14.1$ Hz, 1H), 3.43 (d, $J = 14.1$ Hz, 1H), 1.35 (d, $J = 6.2$ Hz, 3H), 1.29 (d, $J = 6.3$ Hz, 3H), 0.95 (d, $J = 6.3$ Hz, 3H), 0.73 (d, $J = 6.2$ Hz, 3H). ^{13}C NMR (126 MHz, CDCl_3) δ 168.37, 159.16, 154.09, 150.54, 133.86, 131.24, 131.13, 129.43, 129.17, 127.61, 127.54, 126.76, 92.87, 77.30, 77.05, 76.79, 71.70, 70.76, 52.93, 41.18, 22.00, 21.68, 21.17, 21.02. HRMS (ESI) Calcd. for $\text{C}_{25}\text{H}_{30}\text{N}_3\text{O}_6$ ($[\text{M}+\text{H}]^+$): 468.2135; Found: 468.2142,

The ee was determined by HPLC using a Chiralcel OD column [n-hexane/EtOH (99:1)]; flow rate 1.0 mL/min; t_{R} major = 12.055 min, t_{R} minor = 9.956 min (92% ee). $^{24.6}[\alpha]_{\text{D}} = +105^\circ$ ($c = 0.1$, CHCl_3).



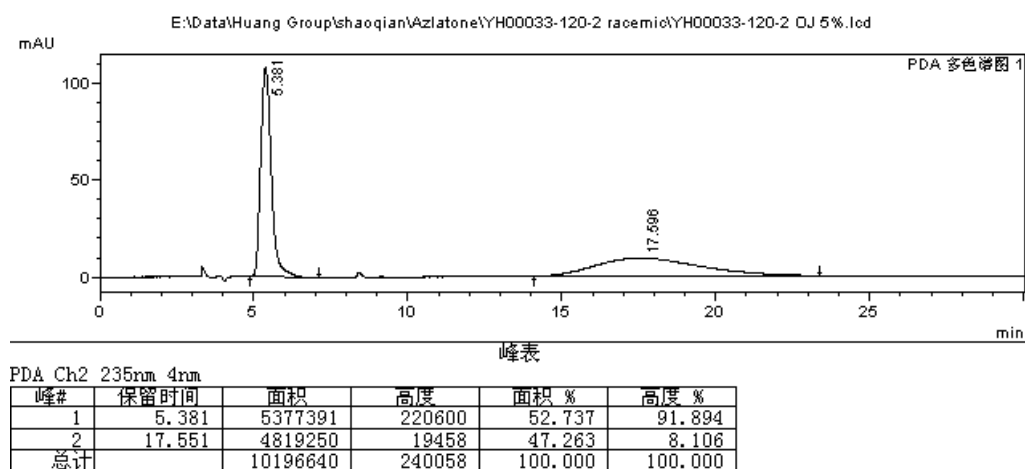
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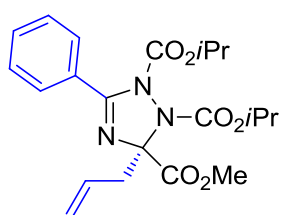
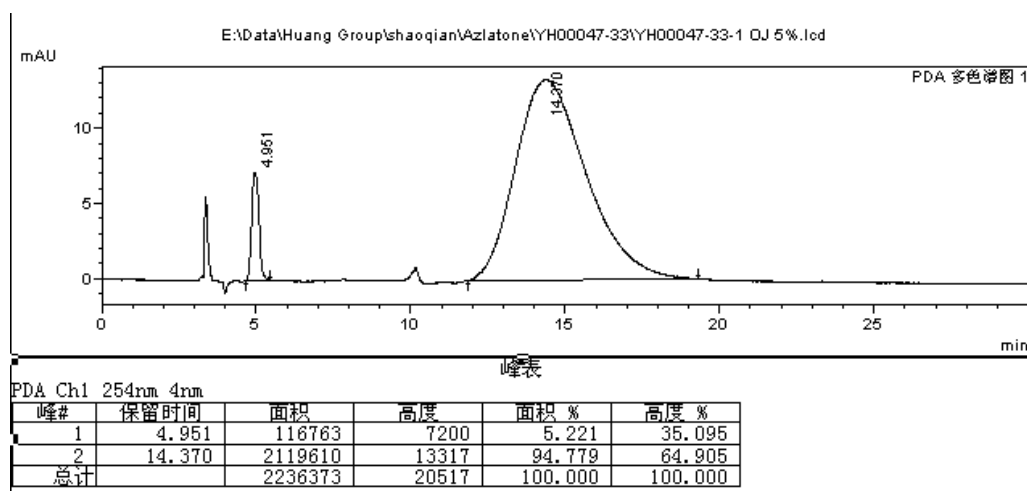
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1	9.928	5013568	186575	50.032	54.197
2	12.047	5007210	157680	49.968	45.803
总计		10020778	344255	100.000	100.000



Methyl 1,2-bis(isopropoxycarbonyl)-3-isobutyl-5-phenyl-2,3-dihydro-1H-1,2,4-triazole-3-carboxylate (4c):

63% yield, colorless oil. ^1H NMR (500 MHz, CDCl_3) δ 7.83 – 7.77 (m, 2H), 7.49 (t, J = 7.4 Hz, 1H), 7.40 (t, J = 7.6 Hz, 2H), 5.00 (dt, J = 12.5, 6.2 Hz, 1H), 4.88 (dt, J = 12.5, 6.2 Hz, 1H), 3.69 (s, 3H), 2.17 (d, J = 5.9 Hz, 2H), 1.82 – 1.76 (m, 1H), 1.30 (d, J = 6.2 Hz, 3H), 1.26 (d, J = 6.2 Hz, 3H), 1.11 (d, J = 6.2 Hz, 3H), 1.06 (d, J = 6.2 Hz, 3H), 1.00 (d, J = 6.7 Hz, 3H), 0.95 (d, J = 6.6 Hz, 3H). ^{13}C NMR (126 MHz, CDCl_3) δ 168.62, 158.64, 154.02, 152.13, 131.42, 129.62, 129.17, 127.68, 93.32, 77.26, 77.00, 76.75, 72.10, 70.60, 52.78, 43.31, 24.69, 23.78, 23.39, 21.93, 21.73, 21.34, 21.27. HRMS (ESI) Calcd. for $\text{C}_{22}\text{H}_{32}\text{N}_3\text{O}_6$ ($[\text{M}+\text{H}]^+$): 434.2291; Found: 434.2280. The ee was determined by HPLC using a Chiralcel OJ column [*n*-hexane/EtOH (95:5)]; flow rate 1.0 mL/min; t_{R} major = 14.370 min, t_{R} minor = 4.951 min (90% ee). $^{24,6}[\alpha]_{\text{D}} = +82^\circ$ (c = 0.1, CHCl_3).

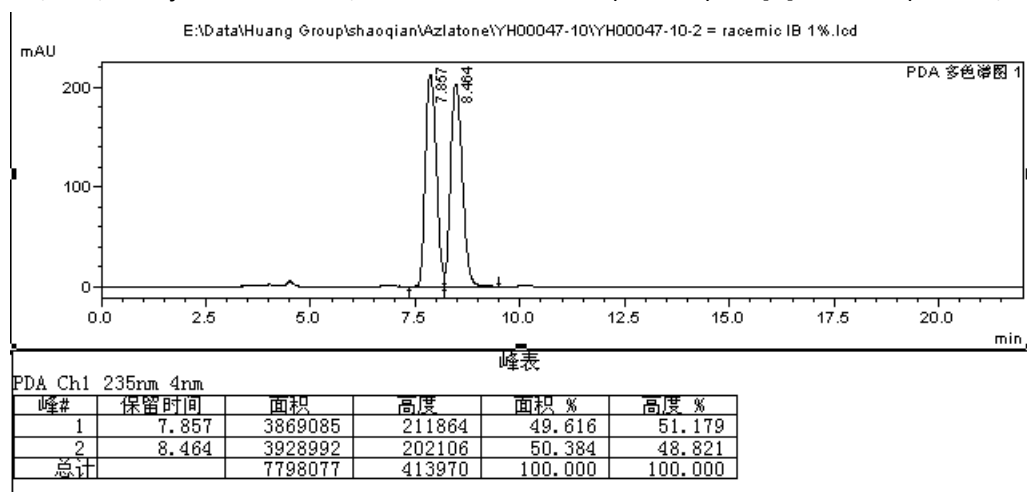


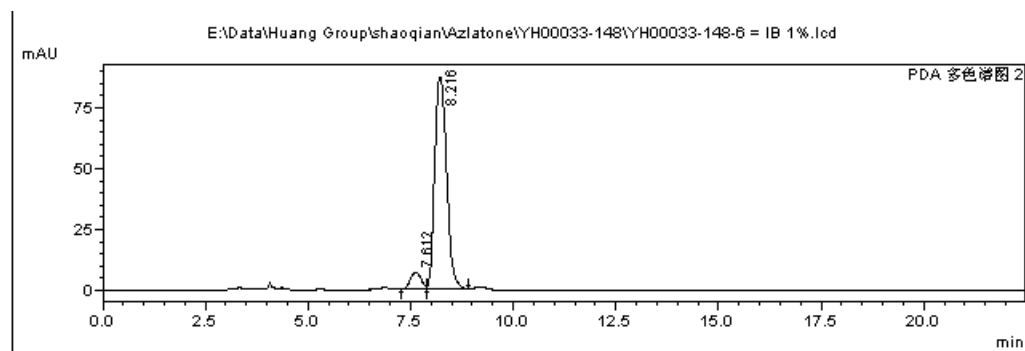


Methyl 1,2-bis(isopropoxycarbonyl)-3-allyl-5-phenyl-2,3-dihydro-1H-1,2,4-triazole-3-carboxylate (4d):

61% yield, colorless oil. ^1H NMR (500 MHz, CDCl_3) δ 7.78 (d, $J = 7.3$ Hz, 2H), 7.49 (t, $J = 7.4$ Hz, 1H), 7.40 (t, $J = 7.7$ Hz, 2H), 5.69 (ddt, $J = 17.3, 10.1, 7.3$ Hz, 1H), 5.22 (d, $J = 17.2$ Hz, 1H), 5.11 (dd, $J = 10.2, 1.5$ Hz, 1H), 5.00 (dt, $J = 12.5, 6.2$ Hz, 1H), 4.85 (dq, $J = 12.5, 6.2$ Hz, 1H), 3.73 (s, 3H), 3.00 – 2.91 (m, 2H), 1.32 (d, $J = 6.2$ Hz, 3H), 1.28 (d, $J = 6.3$ Hz, 3H), 1.10 (d, $J = 6.2$ Hz, 3H), 1.06 (d, $J = 6.2$ Hz, 3H). ^{13}C NMR (126 MHz, CDCl_3) δ 168.04, 159.45, 153.75, 151.86, 131.49, 130.60, 129.60, 129.11, 127.67, 120.66, 91.90, 77.25, 76.99, 76.74, 72.01, 70.74, 52.82, 39.24, 21.94, 21.72, 21.36. HRMS (ESI) Calcd. for $\text{C}_{21}\text{H}_{28}\text{N}_3\text{O}_6$ ($[\text{M}+\text{H}]^+$): 418.1978; Found: 418.1980,

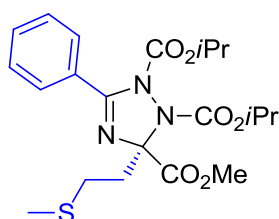
The ee was determined by HPLC using IB column [n-hexane/EtOH (99:1)]; flow rate 1.0 mL/min; t_{R} major = 8.216 min, t_{R} minor = 7.612 min (86% ee). $^{24.6}[\alpha]_{\text{D}} = +21^\circ$ ($c = 0.1$, CHCl_3).





峰表

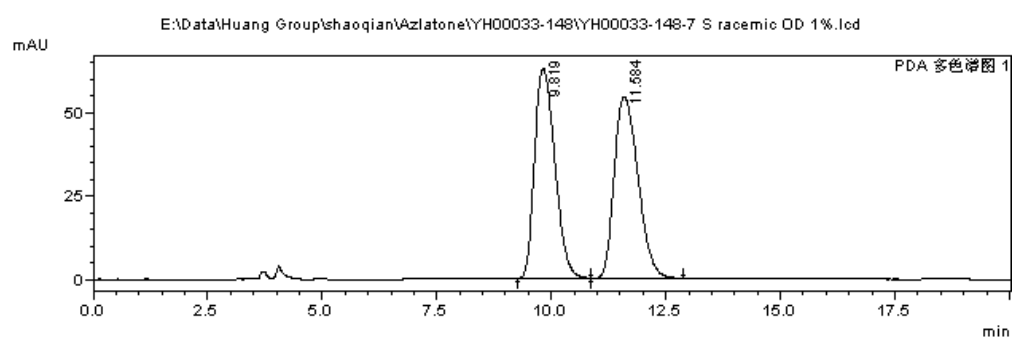
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2	8.216	1765846	87123	93.049	92.612
总计		1897757	94074	100.000	100.000



Methyl 1,2-bis(isopropoxycarbonyl)-3-(2-(methylthio)ethyl)-5-phenyl-2,3-dihydro-1H-1,2,4-triazole-3-carboxylate (4e):

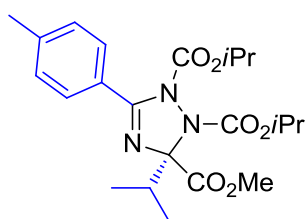
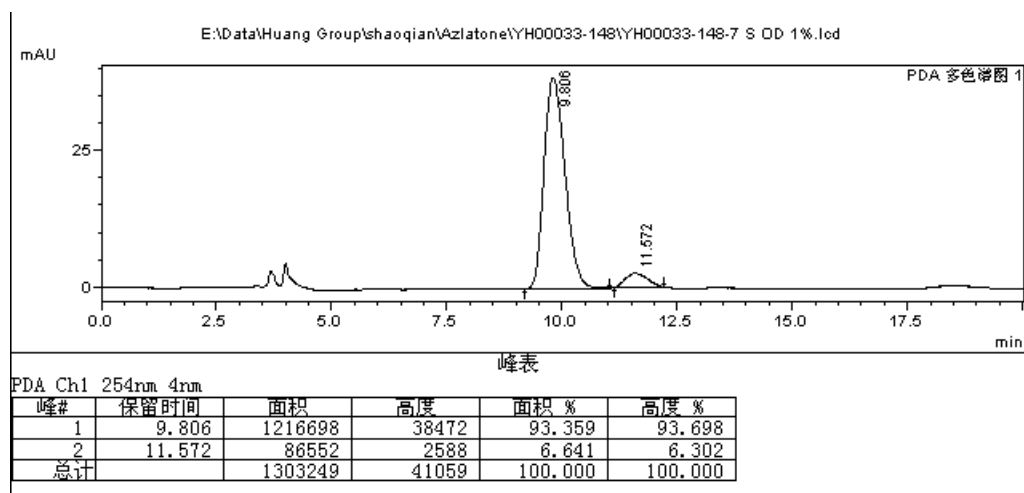
78% yield, colorless oil. ¹H NMR (400 MHz, CDCl₃) δ 7.80 (d, *J* = 7.6 Hz, 2H), 7.50 (t, *J* = 7.4 Hz, 1H), 7.41 (t, *J* = 7.6 Hz, 2H), 4.99 (dt, *J* = 12.5, 6.3 Hz, 1H), 4.87 (dt, *J* = 12.4, 6.2 Hz, 1H), 3.71 (s, 3H), 2.64 – 2.45 (m, 4H), 2.11 (s, 3H), 1.31 (d, *J* = 6.2 Hz, 3H), 1.26 (d, *J* = 6.2 Hz, 3H), 1.13 (d, *J* = 6.2 Hz, 3H), 1.02 (d, *J* = 6.2 Hz, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 168.04, 159.52, 153.81, 152.02, 131.69, 129.85, 128.91, 127.74, 92.22, 77.39, 77.07, 76.75, 72.43, 70.98, 52.99, 34.93, 27.79, 22.00, 21.96, 21.79, 21.53, 21.30, 15.50, 0.99. HRMS (ESI) Calcd. for C₂₁H₃₀N₃O₆S ([M+H]⁺): 452.1855; Found: 452.1845.

The ee was determined by HPLC using a Chiralcel OD column [n-hexane/EtOH (99:1)]; flow rate 1.0 mL/min; *t_R*major = 9.806 min, *t_R*minor = 11.572 min (87% ee). ^{24,6}[α]_D = +33 ° (c = 0.1, CHCl₃).



峰表

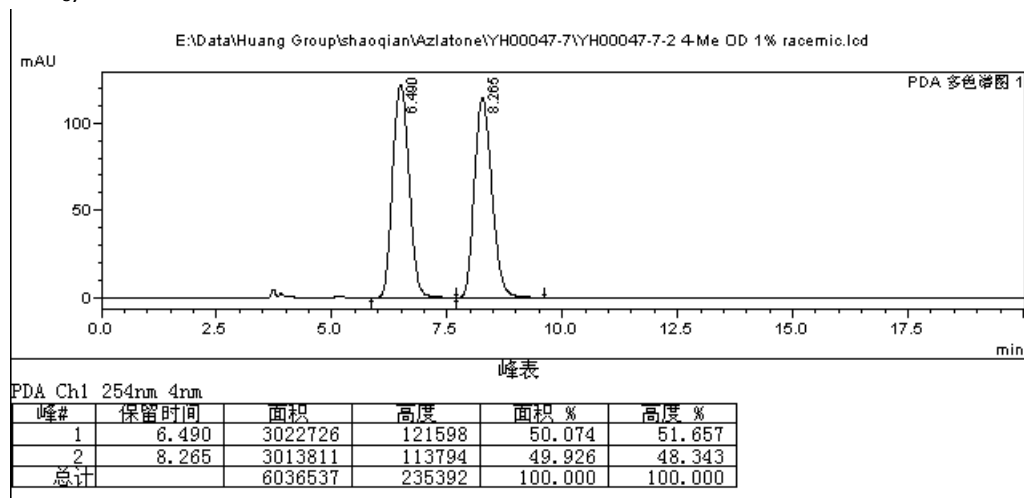
峰#	保留时间	面积	高度	面积 %	高度 %
1	9.819	1953132	63075	49.779	53.684
2	11.584	1970460	54417	50.221	46.316
总计		3923592	117492	100.000	100.000

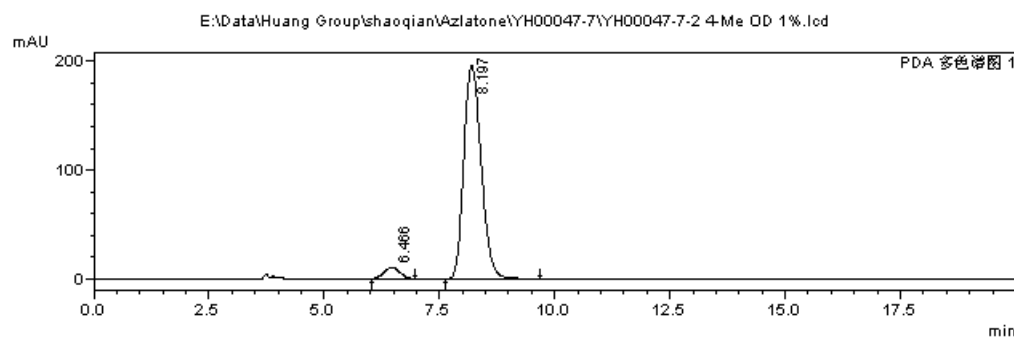


Methyl 1,2-bis(isopropoxycarbonyl)-3-isopropyl-5-*p*-tolyl-2,3-dihydro-1H-1,2,4-triazole-3-carboxylate (4f):

83% yield, colorless oil. ^1H NMR (500 MHz, CDCl_3) δ 7.72 (d, $J = 8.1$ Hz, 2H), 7.21 (d, $J = 8.0$ Hz, 2H), 4.97 (dd, $J = 12.5, 6.2$ Hz, 1H), 4.89 (dt, $J = 12.5, 6.2$ Hz, 1H), 3.68 (s, 3H), 2.64 (dt, $J = 13.4, 6.7$ Hz, 1H), 2.39 (s, 3H), 1.30 (d, $J = 6.2$ Hz, 3H), 1.27 (d, $J = 6.3$ Hz, 3H), 1.14 – 1.09 (m, 9H), 0.94 (d, $J = 6.8$ Hz, 3H). ^{13}C NMR (126 MHz, CDCl_3) δ 167.62, 158.44, 154.85, 152.15, 142.00, 129.62, 128.39, 126.20, 95.70, 77.25, 76.99, 76.74, 71.83, 70.69, 52.46, 33.50, 21.93, 21.71, 21.46, 21.41, 17.25, 16.27. HRMS (ESI): Calcd. for $\text{C}_{22}\text{H}_{32}\text{N}_3\text{O}_6$ ($[\text{M}+\text{H}]^+$): 434.2291; Found: 434.2277.

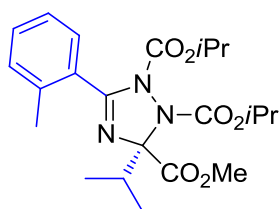
The ee was determined by HPLC using a Chiralcel OD column [n-hexane/EtOH (99:1)]; flow rate 1.0 mL/min; t_{R} major = 8.197 min, t_{R} minor = 6.466 min (91% ee). $^{24.6}[\alpha]_{\text{D}} = +44^\circ$ ($c = 0.1$, CHCl_3).





峰表

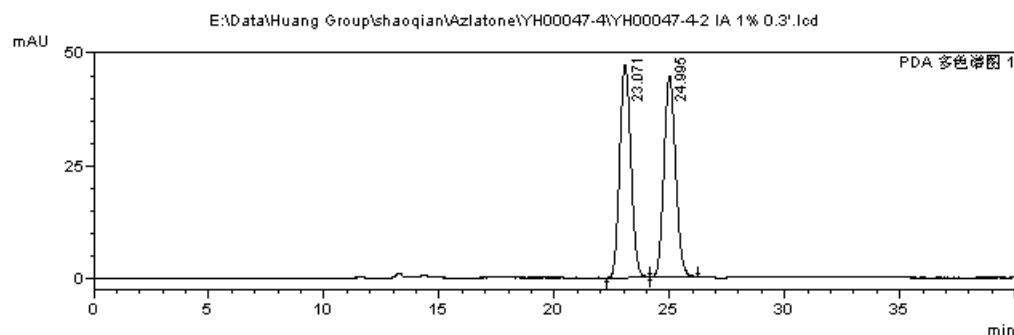
峰#	保留时间	面积	高度	面积 %	高度 %
1	6.466	245645	10160	4.559	4.926
2	8.197	5142422	196111	95.441	95.074
总计		5388068	206271	100.000	100.000



Methyl 1,2-bis(isopropoxycarbonyl)-3-isopropyl-5-*o*-tolyl-2,3-dihydro-1H-1,2,4-triazole-3-carboxylate (4g):

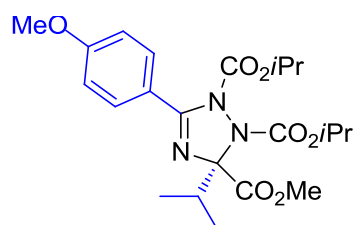
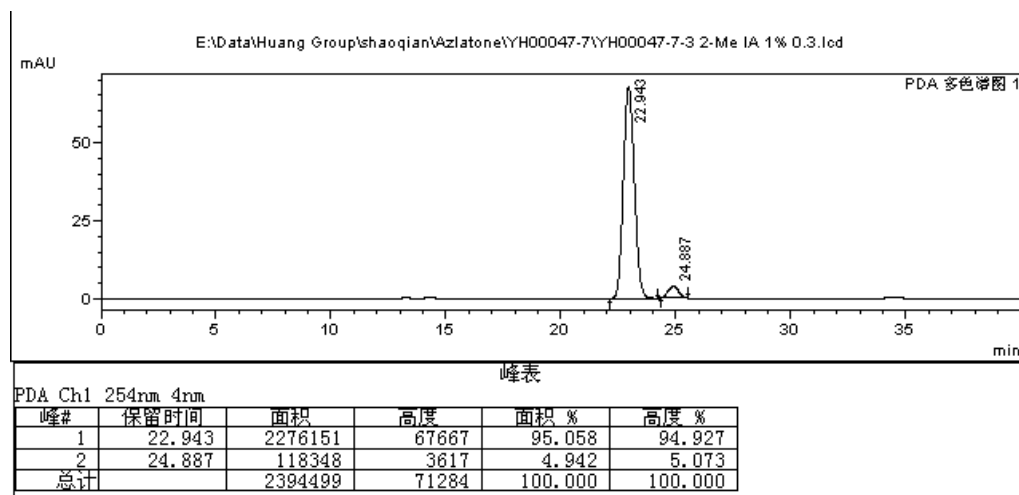
94% yield, colorless oil. ^1H NMR (500 MHz, CDCl_3) δ 7.52 – 7.42 (m, 1H), 7.35 (td, $J = 7.6, 0.9$ Hz, 1H), 7.25 – 7.16 (m, 2H), 4.99 (dt, $J = 12.5, 6.2$ Hz, 1H), 4.82 (dt, $J = 12.4, 6.2$ Hz, 1H), 3.72 (s, 3H), 2.69 (dt, $J = 13.5, 6.7$ Hz, 1H), 2.47 (d, $J = 6.6$ Hz, 3H), 1.28 (dd, $J = 13.2, 6.2$ Hz, 7H), 1.14 (d, $J = 6.8$ Hz, 3H), 1.05 – 1.01 (m, 6H), 0.94 (d, $J = 6.2$ Hz, 3H). ^{13}C NMR (126 MHz, CDCl_3) δ 167.57, 157.72, 155.10, 150.78, 137.53, 130.45, 130.14, 129.63, 129.08, 125.36, 96.13, 77.23, 76.97, 76.72, 71.43, 70.80, 52.51, 33.44, 21.91, 21.69, 21.24, 21.14, 19.55, 17.21, 16.45. HRMS (ESI) Calcd. for $\text{C}_{22}\text{H}_{32}\text{N}_3\text{O}_6$ ($[\text{M}+\text{H}]^+$): 434.2291; Found: 434.2274.

The ee was determined by HPLC using IA column [*n*-hexane/EtOH (99:1)]; flow rate 0.3 mL/min; t_{R} major = 22.943 min, t_{R} minor = 24.887 min (90% ee). $^{24.6}[\alpha]_{\text{D}} = +79^\circ$ ($c = 0.1$, CHCl_3).



峰表

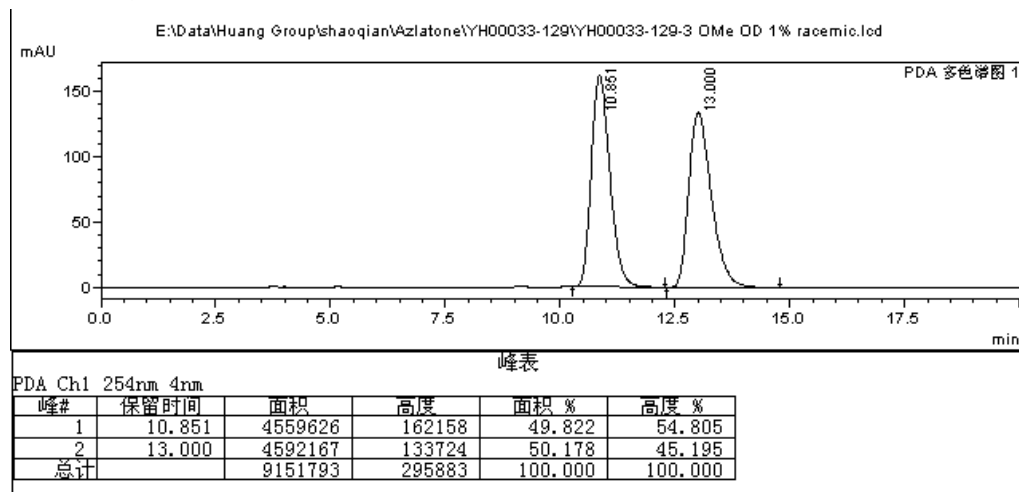
峰#	保留时间	面积	高度	面积 %	高度 %
1	23.071	1595157	47152	50.119	51.432
2	24.995	1587596	44527	49.881	48.568
总计		3182752	91679	100.000	100.000

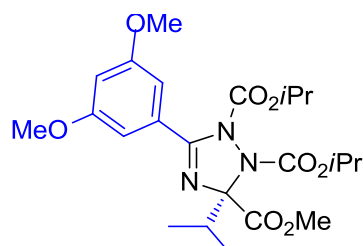
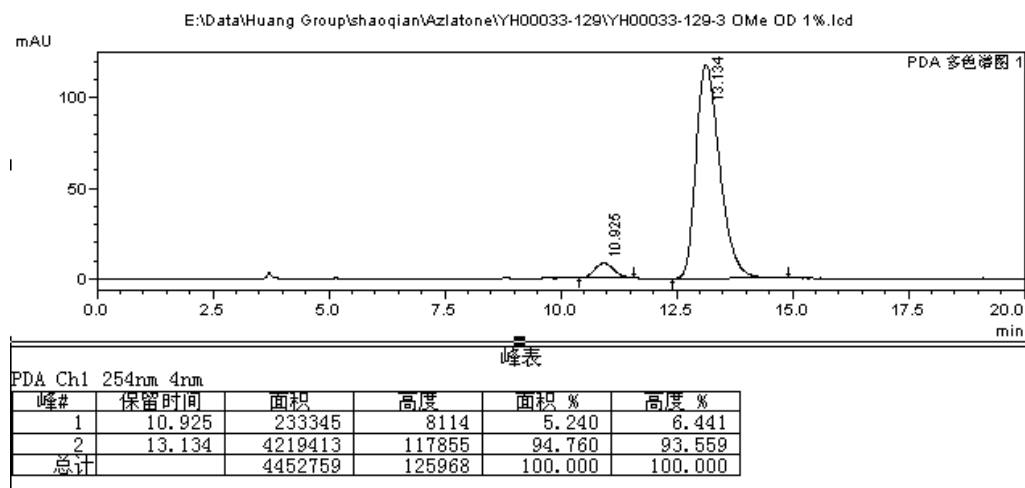


Methyl 1,2-bis(isopropoxycarbonyl)-3-isopropyl-5-(4-methoxyphenyl)-2,3-dihydro-1H-1,2,4-triazole-3-carboxylate (4h):

67% yield, colorless oil. ^1H NMR (500 MHz, CDCl_3) δ 7.78 (d, $J = 8.7$ Hz, 1H), 6.91 (d, $J = 8.7$ Hz, 1H), 4.97 (dt, $J = 12.4, 6.2$ Hz, 1H), 4.89 (dt, $J = 12.4, 6.2$ Hz, 1H), 3.83 (s, 2H), 3.67 (s, 2H), 2.62 (dt, $J = 13.0, 6.3$ Hz, 1H), 1.29 (d, $J = 6.2$ Hz, 2H), 1.26 (d, $J = 6.3$ Hz, 2H), 1.16 – 1.08 (m, 5H), 0.93 (d, $J = 6.8$ Hz, 1H). ^{13}C NMR (126 MHz, CDCl_3) δ 167.70, 162.38, 158.01, 154.85, 152.23, 131.56, 121.19, 113.13, 95.53, 77.26, 77.00, 76.75, 71.87, 70.73, 55.31, 52.46, 33.50, 21.90, 21.70, 21.48, 21.44, 17.24, 16.27. HRMS (ESI) Calcd. for $\text{C}_{22}\text{H}_{32}\text{N}_3\text{O}_7$ ($[\text{M}+\text{H}]^+$): 450.2240; Found: 450.2216.

The ee was determined by HPLC using a Chiralcel OD column [n-hexane/EtOH (99:1)]; flow rate 1.0 mL/min; $t_{\text{R major}} = 13.134$ min, $t_{\text{R minor}} = 10.925$ min (90% ee). $^{27.8}[\alpha]_{\text{D}} = +48^\circ$ ($c = 0.1$, CHCl_3).

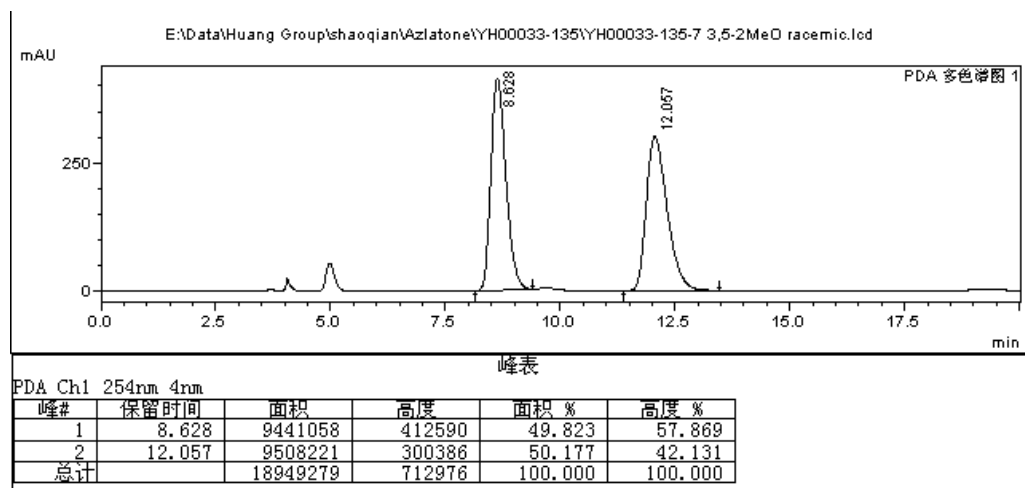


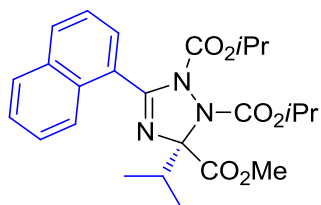
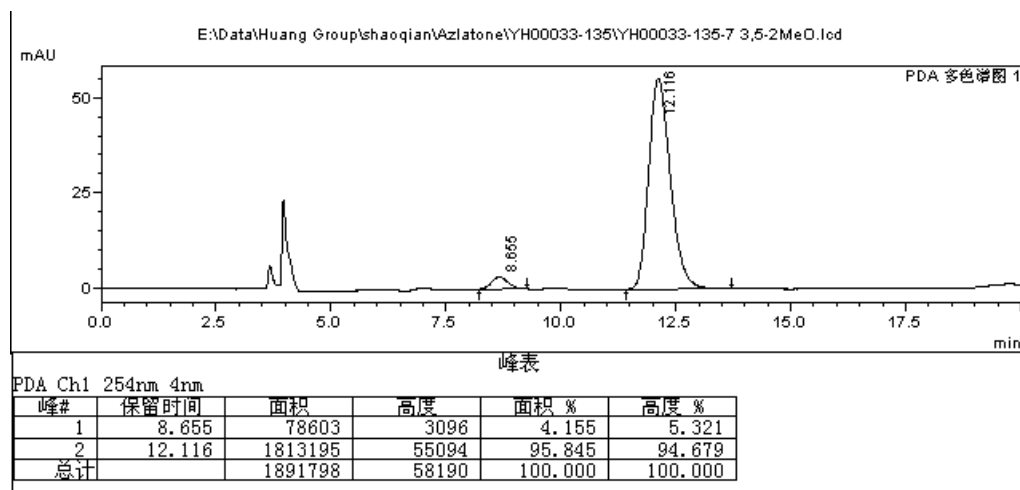


Methyl 1,2-bis(isopropoxycarbonyl)-3-isopropyl-5-(3,5-dimethoxyphenyl)-2,3-dihydro-1H-1,2,4-triazole-3-carboxylate (4i):

95% yield, colorless oil. ^1H NMR (500 MHz, CDCl_3) δ 6.89 (d, $J = 2.3$ Hz, 2H), 6.54 (t, $J = 2.3$ Hz, 1H), 4.93 (dt, $J = 12.5, 6.3$ Hz, 1H), 4.84 (dt, $J = 12.4, 6.2$ Hz, 1H), 3.76 (s, 6H), 3.63 (s, 3H), 2.59 (dt, $J = 13.4, 6.7$ Hz, 1H), 1.25 (d, $J = 6.2$ Hz, 3H), 1.22 (d, $J = 6.3$ Hz, 3H), 1.09 – 1.03 (m, 9H), 0.89 (d, $J = 6.8$ Hz, 3H). ^{13}C NMR (126 MHz, CDCl_3) δ 167.48, 160.19, 158.42, 154.81, 151.97, 130.84, 107.56, 103.89, 95.83, 77.44, 77.18, 76.93, 71.91, 70.80, 55.46, 52.52, 33.44, 21.90, 21.70, 21.43, 21.40, 17.26, 16.26. HRMS (ESI) Calcd. for $\text{C}_{23}\text{H}_{34}\text{N}_3\text{O}_8$ ($[\text{M}+\text{H}]^+$): 480.2346; Found: 480.2353.

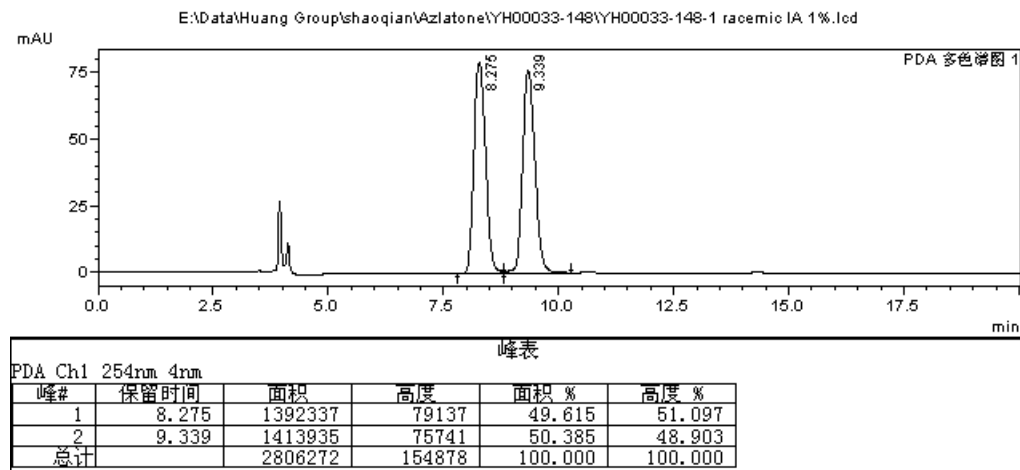
The ee was determined by HPLC using a Chiralcel OD column [n-hexane/EtOH (99:1)]; flow rate 1.0 mL/min; t_{R} major = 12.116 min, t_{R} minor = 8.655 min (92% ee). $^{27.8}[\alpha]_{\text{D}} = +36^\circ$ ($c = 0.1$, CHCl_3).

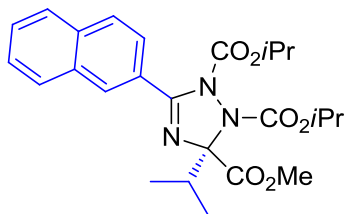
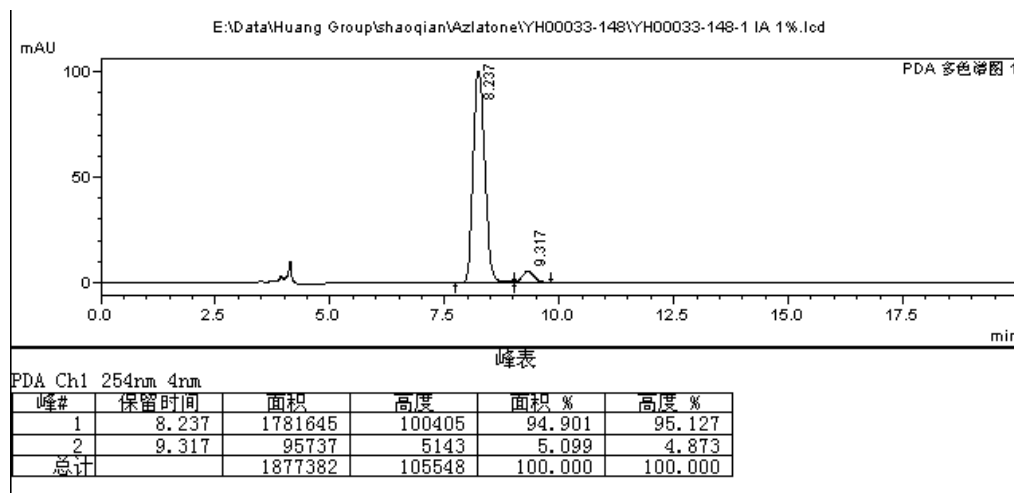




Methyl 1,2-bis(isopropoxycarbonyl)-3-isopropyl-5-(naphthalen-1-yl)-2,3-dihydro-1H-1,2,4-triazole-3-carboxylate (4j):

91% yield, colorless oil. ^1H NMR (500 MHz, CDCl_3) δ 8.40 (d, $J = 8.4$ Hz, 1H), 7.97 (d, $J = 8.3$ Hz, 1H), 7.87 (d, $J = 8.0$ Hz, 1H), 7.80 (dd, $J = 7.0, 0.7$ Hz, 1H), 7.58 – 7.47 (m, 3H), 5.07 (dt, $J = 12.5, 6.2$ Hz, 1H), 4.67 (dt, $J = 12.4, 6.2$ Hz, 1H), 3.74 (s, 3H), 2.78 (dt, $J = 13.4, 6.7$ Hz, 1H), 1.38 (d, $J = 6.2$ Hz, 3H), 1.32 (d, $J = 6.3$ Hz, 3H), 1.21 (d, $J = 6.8$ Hz, 3H), 1.11 (d, $J = 6.8$ Hz, 3H), 0.73 (d, $J = 6.2$ Hz, 3H), 0.68 (d, $J = 6.2$ Hz, 3H). ^{13}C NMR (126 MHz, CDCl_3) δ 167.57, 157.31, 155.26, 150.64, 133.16, 131.46, 131.31, 128.20, 128.01, 127.33, 127.06, 126.15, 124.94, 124.54, 96.31, 77.24, 76.99, 76.73, 71.37, 70.94, 52.62, 33.59, 22.01, 21.75, 20.97, 20.85, 17.31, 16.53. HRMS (ESI) Calcd. for $\text{C}_{25}\text{H}_{31}\text{N}_3\text{O}_6\text{Na}$ ($[\text{M}+\text{Na}]^+$): 492.2111; Found: 492.2082. The ee was determined by HPLC using IA column [n-hexane/EtOH (99:1)]; flow rate 1.0 mL/min; $t_{\text{Rmajor}} = 8.237$ min, $t_{\text{Rminor}} = 9.317$ min (90% ee). $^{27.8}[\alpha]_{\text{D}} = +78^\circ$ ($c = 0.1$, CHCl_3).

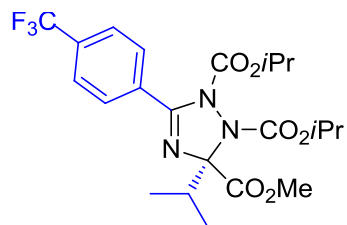
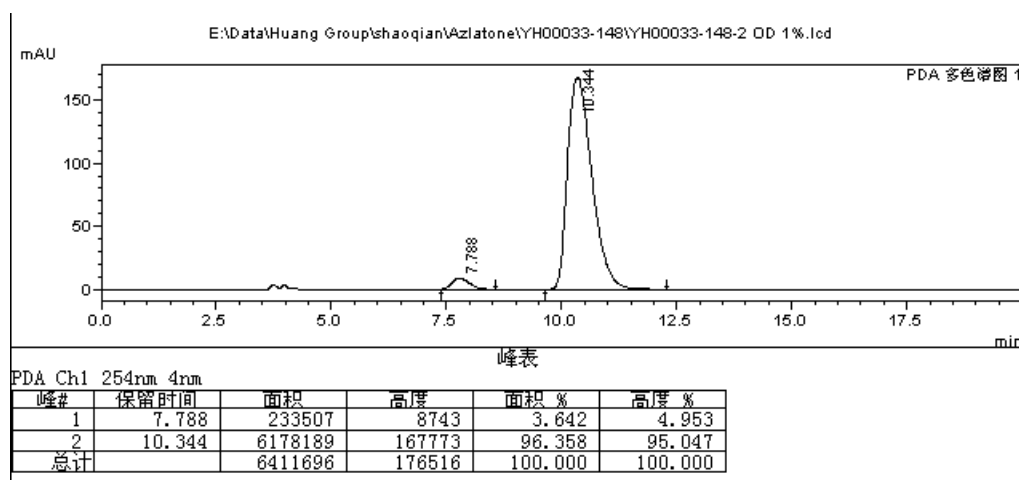
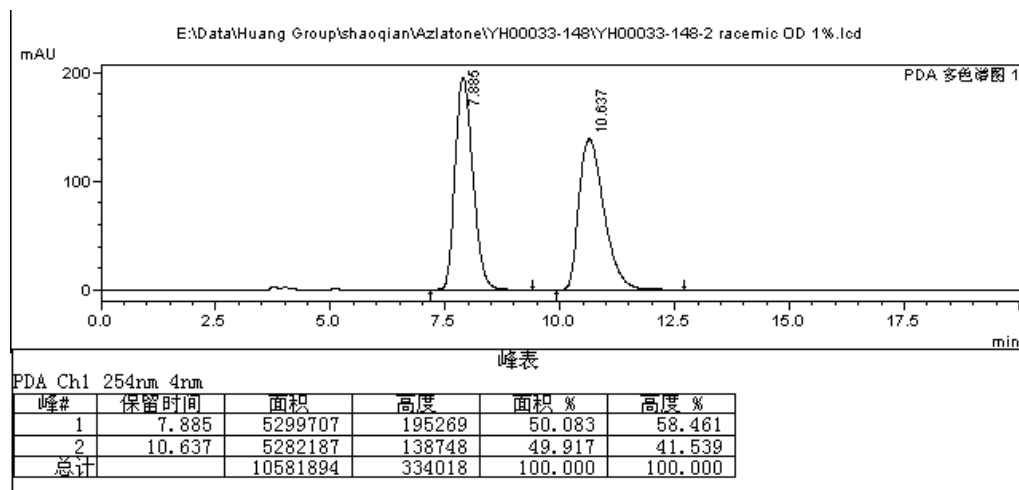




Methyl 1,2-bis(isopropoxycarbonyl)-3-isopropyl-5-(naphthalen-2-yl)-2,3-dihydro-1H-1,2,4-triazole-3-carboxylate (4k):

93% yield, colorless oil. ^1H NMR (500 MHz, CDCl_3) δ 8.38 (s, 1H), 7.89 (ddd, $J = 13.5, 12.9, 8.5$ Hz, 4H), 7.58 – 7.51 (m, 2H), 5.03 (dt, $J = 12.5, 6.3$ Hz, 1H), 4.90 (dt, $J = 12.5, 6.2$ Hz, 1H), 3.70 (s, 3H), 2.73 (dt, $J = 13.5, 6.7$ Hz, 1H), 1.35 (d, $J = 6.2$ Hz, 3H), 1.31 (d, $J = 6.3$ Hz, 3H), 1.17 (d, $J = 6.8$ Hz, 3H), 1.08 (d, $J = 6.2$ Hz, 3H), 1.06 (d, $J = 6.2$ Hz, 3H), 1.03 (d, $J = 6.8$ Hz, 3H). ^{13}C NMR (126 MHz, CDCl_3) δ 167.58, 158.59, 154.85, 152.12, 134.80, 132.26, 130.25, 128.79, 127.68, 127.63, 127.27, 126.52, 126.40, 126.05, 95.94, 77.23, 76.97, 76.72, 71.98, 70.83, 52.52, 33.58, 21.95, 21.74, 21.41, 21.38, 17.31, 16.37. HRMS (ESI) Calcd. for $\text{C}_{25}\text{H}_{32}\text{N}_3\text{O}_6$ ($[\text{M}+\text{H}]^+$): 470.2291; Found: 470.2280.

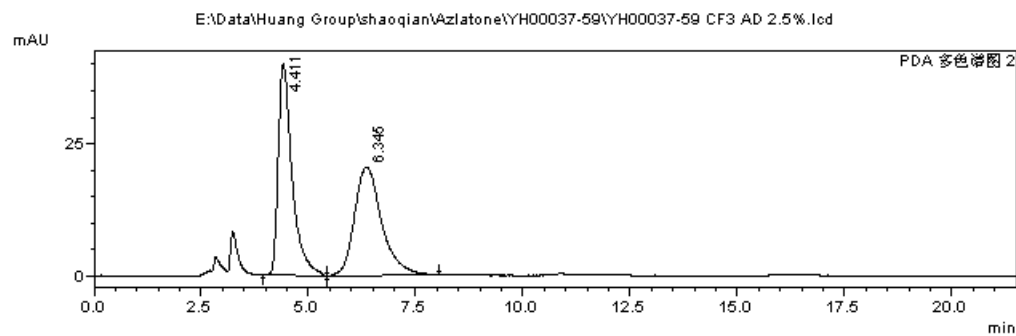
The ee was determined by HPLC using a Chiralcel OD column [*n*-hexane/EtOH (99:1)]; flow rate 1.0 mL/min; $t_{\text{Rmajor}} = 10.344$ min, $t_{\text{Rminor}} = 7.788$ min (93% ee). $^{27.8}[\alpha]_{\text{D}} = +62^\circ$ ($c = 0.1$, CHCl_3).



Methyl 1,2-bis(isopropoxycarbonyl)-3-isopropyl-5-(4-(trifluoromethyl)phenyl)-2,3-dihydro-1H-1,2,4-triazole-3-carboxylate (4I):

66% yield, colorless oil. ^1H NMR (500 MHz, CDCl_3) δ 7.98 (d, J = 8.0 Hz, 2H), 7.71 (d, J = 8.2 Hz, 2H), 5.02 (dd, J = 12.5, 6.2 Hz, 1H), 4.93 (dt, J = 12.4, 6.2 Hz, 1H), 3.73 (s, 3H), 2.76 – 2.64 (m, 1H), 1.34 (d, J = 6.2 Hz, 3H), 1.31 (d, J = 6.3 Hz, 3H), 1.15 (t, J = 6.2 Hz, 9H), 0.98 (d, J = 6.8 Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 167.28, 157.42, 154.82, 152.01, 133.39, 133.13, 132.68, 130.02, 124.79, 122.59, 72.37, 71.05, 52.66, 33.54, 21.96, 21.75, 21.46, 17.26, 16.34. HRMS (ESI) Calcd. for $\text{C}_{22}\text{H}_{28}\text{F}_3\text{N}_3\text{O}_6\text{Na}$ ($[\text{M}+\text{Na}]^+$): 510.1828; Found: 510.1817.

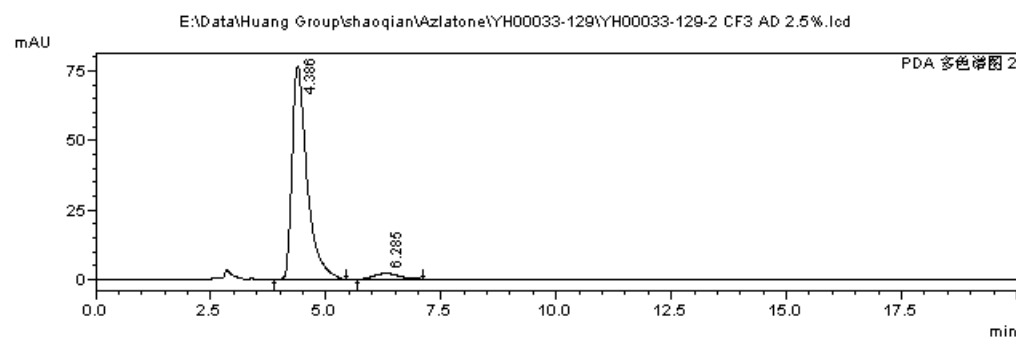
The ee was determined by HPLC using Chiralpak AD-H column [n-hexane/EtOH (97.5:2.5)]; flow rate 1.0 mL/min; $t_{\text{R major}}$ = 4.386 min, $t_{\text{R minor}}$ = 6.285 min (92% ee). $^{27.8}[\alpha]_{\text{D}}$ = +87° (c = 0.1, CHCl_3).



峰表

PDA Ch2 235nm 4nm

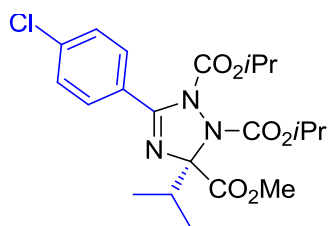
峰#	保留时间	面积	高度	面积 %	高度 %
1	4.411	907536	40133	49.969	66.095
2	6.345	908644	20588	50.031	33.905
总计		1816181	60721	100.000	100.000



峰表

PDA Ch2 235nm 4nm

峰#	保留时间	面积	高度	面积 %	高度 %
1	4.386	1743869	76882	95.902	97.476
2	6.285	74520	1990	4.098	2.524
总计		1818388	78873	100.000	100.000

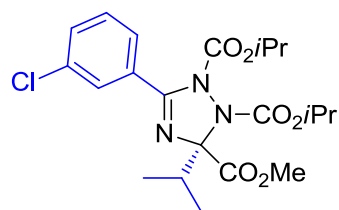
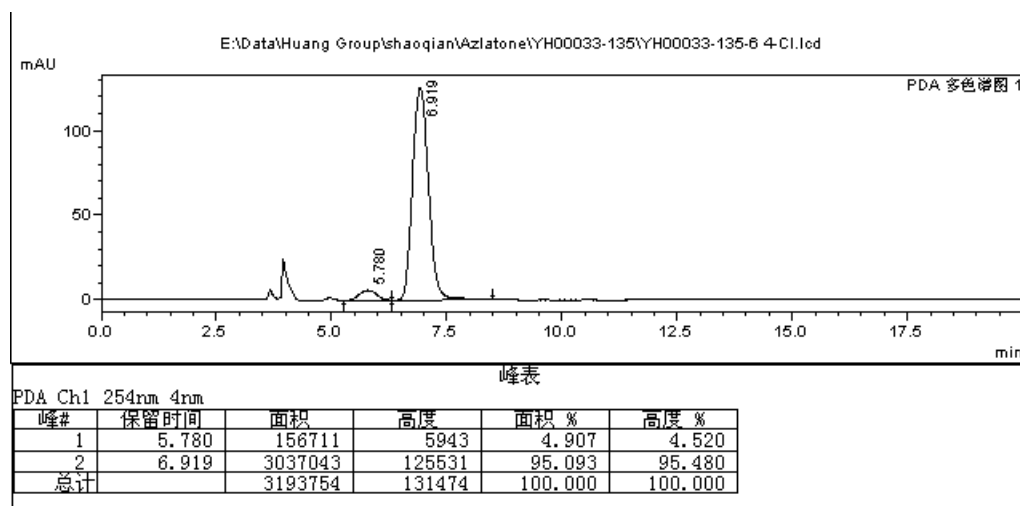
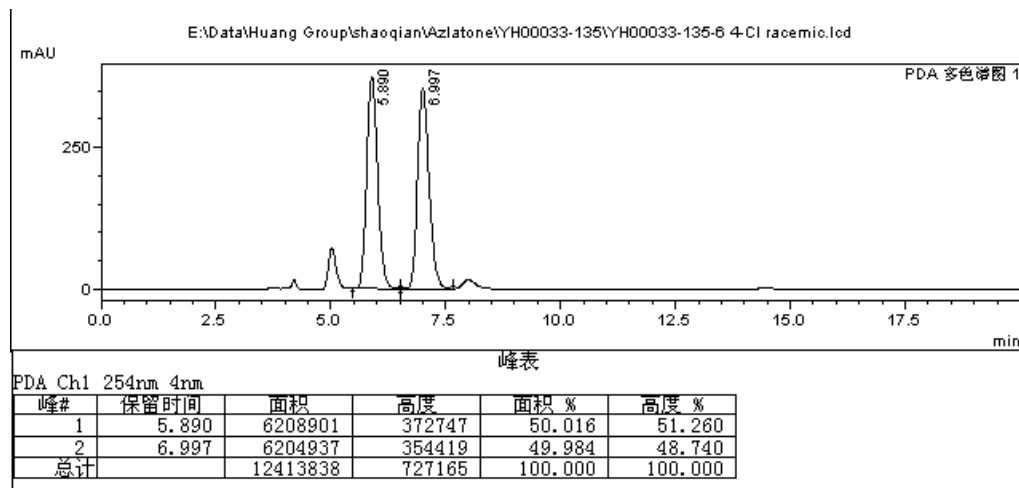


Methyl 1,2-bis(isopropoxycarbonyl)-3-isopropyl-5-(4-chlorophenyl)-2,3-dihydro-1H-1,2,4-triazole-3-carboxylate (4m):

75% yield, colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 7.77 (dd, $J = 4.6, 4.0$ Hz, 2H), 7.38 (dd, $J = 8.6, 1.2$ Hz, 2H), 4.98 (dd, $J = 12.3, 6.2$ Hz, 1H), 4.89 (dt, $J = 12.4, 6.2$ Hz, 1H), 3.68 (s, 1H), 2.64 (dt, $J = 13.1, 6.5$ Hz, 1H), 1.30 (d, $J = 6.2$ Hz, 3H), 1.27 (d, $J = 6.4$ Hz, 3H), 1.16 – 1.09 (m, 9H), 0.93 (d, $J = 6.8$ Hz, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 167.42, 157.59, 154.83, 152.07, 137.85, 131.04, 128.10, 127.52, 95.94, 77.39, 77.08, 76.76, 72.25, 70.95, 52.65, 33.50, 21.97, 21.76, 21.52, 21.48, 17.29, 16.30. HRMS (ESI) Calcd. for $\text{C}_{21}\text{H}_{29}\text{ClN}_3\text{O}_6$ ($[\text{M}+\text{H}]^+$): 454.1745; Found: 454.1728.

The ee was determined by HPLC using a Chiralcel OD column [n-hexane/EtOH (99:1)]; flow rate 1.0 mL/min; t_{R} major = 6.919 min, t_{R} minor = 5.780 min (90% ee). $^{27.8}[\alpha]_{\text{D}} = +80^\circ$ ($c = 0.1$,

CHCl₃).

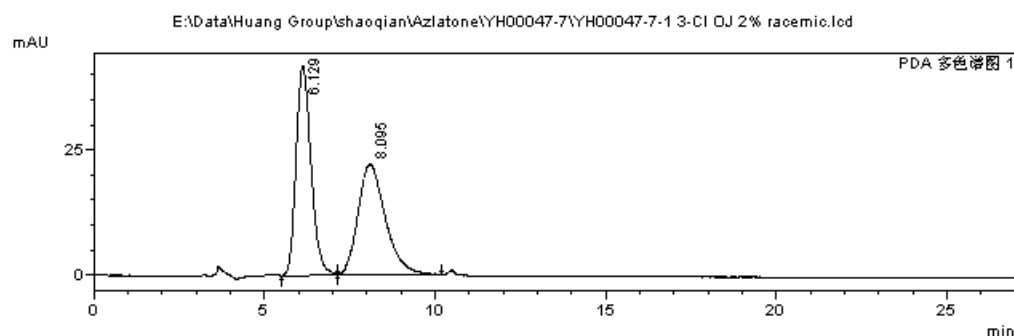


Methyl 1,2-bis(isopropoxycarbonyl)-3-isopropyl-5-(3-chlorophenyl)-2,3-dihydro-1H-1,2,4-triazole-3-carboxylate (4n):

77% yield, colorless oil. ¹H NMR (500 MHz, CDCl₃) δ 7.82 (t, *J* = 1.7 Hz, 1H), 7.72 (dd, *J* = 6.7, 1.1 Hz, 1H), 7.48 (ddd, *J* = 7.9, 1.9, 0.9 Hz, 1H), 7.36 (t, *J* = 7.9 Hz, 1H), 4.99 (dd, *J* = 12.5, 6.2 Hz, 1H), 4.90 (dd, *J* = 12.5, 6.2 Hz, 1H), 3.70 (s, 3H), 2.66 (dt, *J* = 13.5, 6.7 Hz, 1H), 1.31 (d, *J* = 6.2 Hz, 3H), 1.28 (d, *J* = 6.3 Hz, 3H), 1.14 (d, *J* = 6.2 Hz, 3H), 1.11 (dd, *J* = 6.5, 1.7 Hz, 6H), 0.95 (d, *J* = 6.8 Hz, 3H). ¹³C NMR (126 MHz, CDCl₃) δ 167.31, 157.27, 154.73, 151.84, 133.83, 131.47, 130.84, 129.58, 129.01, 127.78, 95.99, 77.20, 76.95, 76.69, 72.21, 70.94, 52.58, 33.47, 21.91, 21.70, 21.42, 17.20, 16.29. HRMS (ESI) Calcd. for C₂₁H₂₈ClN₃O₆Na ([M+Na]⁺): 476.1564; Found: 476.1557.

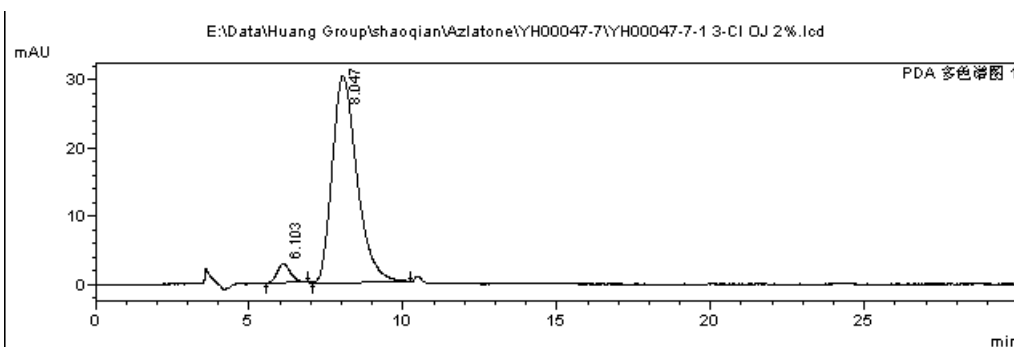
The ee was determined by HPLC using a Chiralcel OJ column [n-hexane/EtOH (98:2)]; flow

rate 1.0 mL/min; $t_{R\text{major}} = 8.047$ min, $t_{R\text{minor}} = 6.103$ min (92% ee). $^{27.8}[\alpha]_D = +94^\circ$ (c = 0.1, CHCl₃).



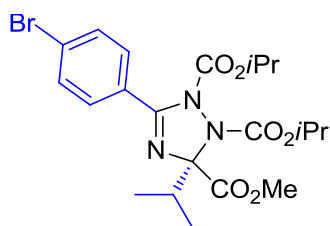
峰表

峰#	保留时间	面积	高度	面积 %	高度 %
1	6.129	1270203	41710	50.718	65.434
2	8.095	1234222	22034	49.282	34.566
总计		2504425	63743	100.000	100.000



峰表

峰#	保留时间	面积	高度	面积 %	高度 %
1	6.103	89360	2898	5.004	8.737
2	8.047	1696484	30273	94.996	91.263
总计		1785845	33171	100.000	100.000

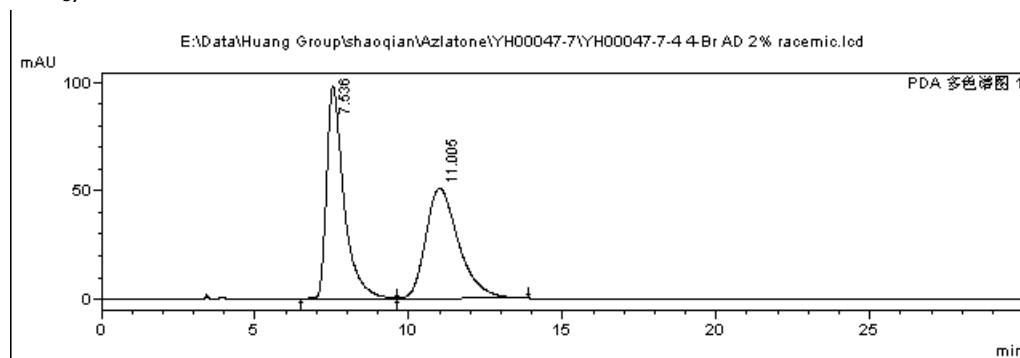


Methyl 1,2-bis(isopropoxycarbonyl)-3-isopropyl-5-(4-bromophenyl)-2,3-dihydro-1H-1,2,4-triazole-3-carboxylate (4o):

65% yield, colorless oil. ¹H NMR (500 MHz, CDCl₃) δ 7.70 (d, *J* = 8.2 Hz, 2H), 7.55 (d, *J* = 8.1 Hz, 2H), 4.98 (dd, *J* = 12.3, 6.2 Hz, 1H), 4.89 (dt, *J* = 12.4, 6.2 Hz, 1H), 3.69 (s, 3H), 2.64 (dt, *J* = 13.2, 6.5 Hz, 1H), 1.30 (d, *J* = 6.2 Hz, 3H), 1.27 (d, *J* = 6.4 Hz, 3H), 1.16 – 1.09 (m, 9H), 0.93 (d, *J* = 6.8 Hz, 3H). ¹³C NMR (126 MHz, CDCl₃) δ 167.34, 157.62, 154.75, 152.02, 131.13, 131.02, 128.00, 126.20, 95.96, 77.24, 76.98, 76.73, 72.18, 70.87, 52.55, 33.45, 21.90, 21.69, 21.46, 21.42, 17.21, 16.27. HRMS (ESI) Calcd. for C₂₁H₂₉BrN₃O₆ ([M+H]⁺): 498.1240; Found: 498.1243.

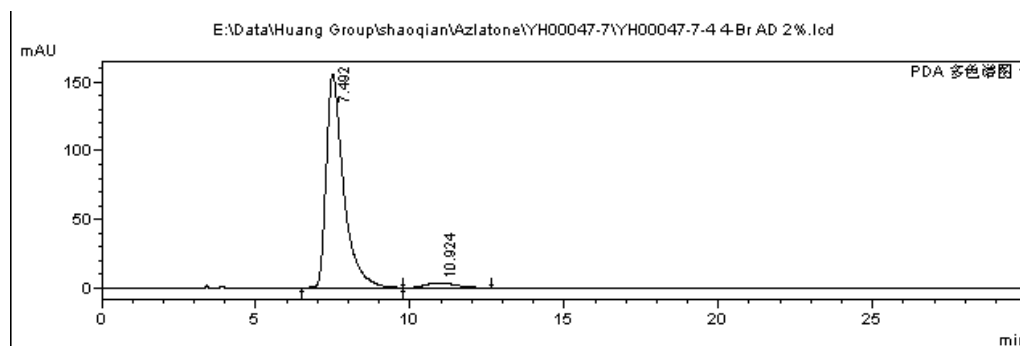
The ee was determined by HPLC using Chiralpak AD-H column [n-hexane/EtOH (98:2)]; flow rate 1.0 mL/min; $t_{R\text{major}} = 7.492$ min, $t_{R\text{minor}} = 10.924$ min (91% ee). $^{27.8}[\alpha]_D = +83^\circ$ (c = 0.1,

CHCl₃).



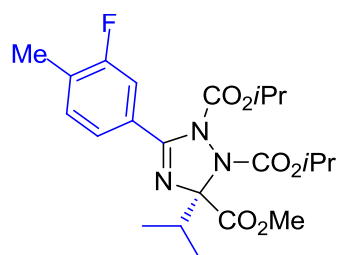
峰表

峰#	保留时间	面积	高度	面积 %	高度 %
1	7.536	3861871	98323	50.462	65.847
2	11.005	3791155	50997	49.538	34.153
总计		7653026	149320	100.000	100.000



峰表

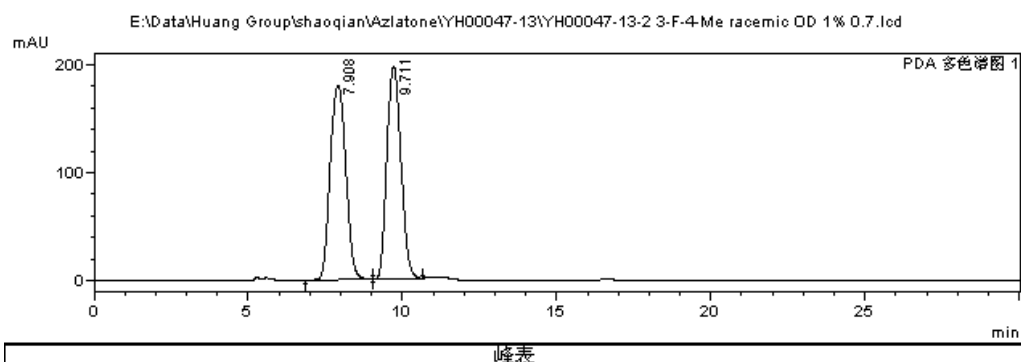
峰#	保留时间	面积	高度	面积 %	高度 %
1	7.492	6136609	155513	95.650	97.527
2	10.924	279092	3944	4.350	2.473
总计		6415700	159457	100.000	100.000



Methyl 1,2-bis(isopropoxycarbonyl)-3-isopropyl-5-(3-fluoro-4-methylphenyl)-2,3-dihydro-1H-1,2,4-triazole-3-carboxylate (4p):

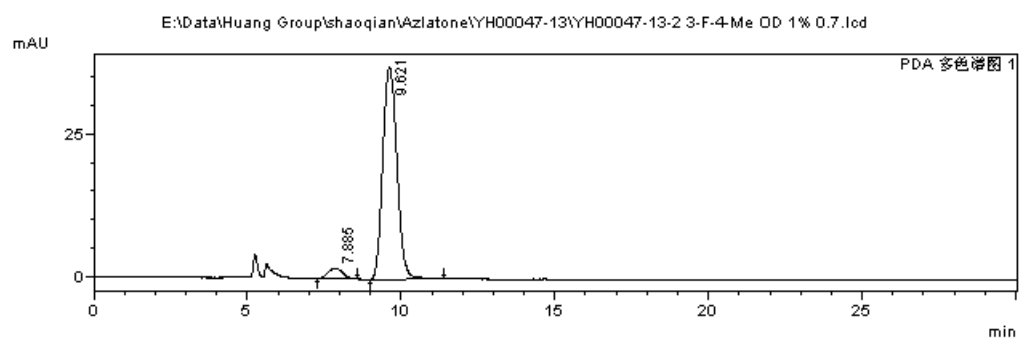
87% yield, colorless oil. ¹H NMR (400 MHz, CDCl₃) δ 7.55 – 7.46 (m, 2H), 7.23 (t, *J* = 7.7 Hz, 1H), 4.98 (dt, *J* = 12.6, 6.3 Hz, 1H), 4.91 (dt, *J* = 12.5, 6.3 Hz, 1H), 3.69 (s, 3H), 2.64 (dt, *J* = 13.4, 6.7 Hz, 1H), 2.32 (s, 3H), 1.29 (dd, *J* = 10.7, 6.3 Hz, 6H), 1.15 (dd, *J* = 6.2, 4.3 Hz, 6H), 1.11 (d, *J* = 6.8 Hz, 3H), 0.94 (d, *J* = 6.8 Hz, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 167.49, 161.67, 159.23, 157.52, 154.87, 152.14, 130.83, 130.78, 129.09, 128.91, 128.37, 128.29, 125.28, 125.24, 116.45, 116.20, 95.87, 77.35, 77.04, 76.72, 72.16, 70.91, 52.62, 33.52, 21.98, 21.77, 21.52, 21.50, 17.28, 16.32, 14.72, 14.69. ¹⁹F NMR (376 MHz, CDCl₃) δ -117.51. HRMS (ESI) Calcd. for C₂₂H₃₁FN₃O₆ ([M+H]⁺): 452.2197; Found: 452.2200.

The ee was determined by HPLC using a Chiralcel OD column [n-hexane/EtOH (99:1)]; flow rate 1.0 mL/min; t_{R} major = 9.621 min, t_{R} minor = 7.885 min (90% ee). $^{27.8}[\alpha]_D = +67^\circ$ (c = 0.1, CHCl₃).



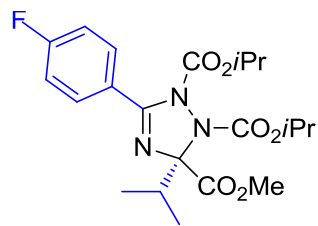
峰表

峰#	保留时间	面积	高度	面积 %	高度 %
1	7.908	6398191	180481	50.582	47.777
2	9.711	6251043	197279	49.418	52.223
总计		12649235	377760	100.000	100.000



峰表

峰#	保留时间	面积	高度	面积 %	高度 %
1	7.885	63866	1840	5.084	4.703
2	9.621	1192359	37287	94.916	95.297
总计		1256225	39127	100.000	100.000

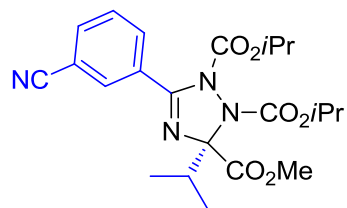
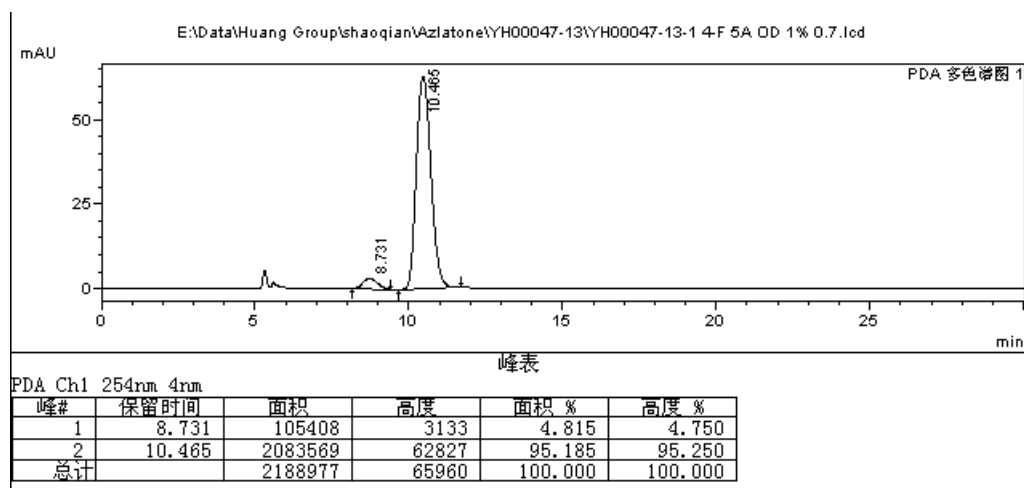
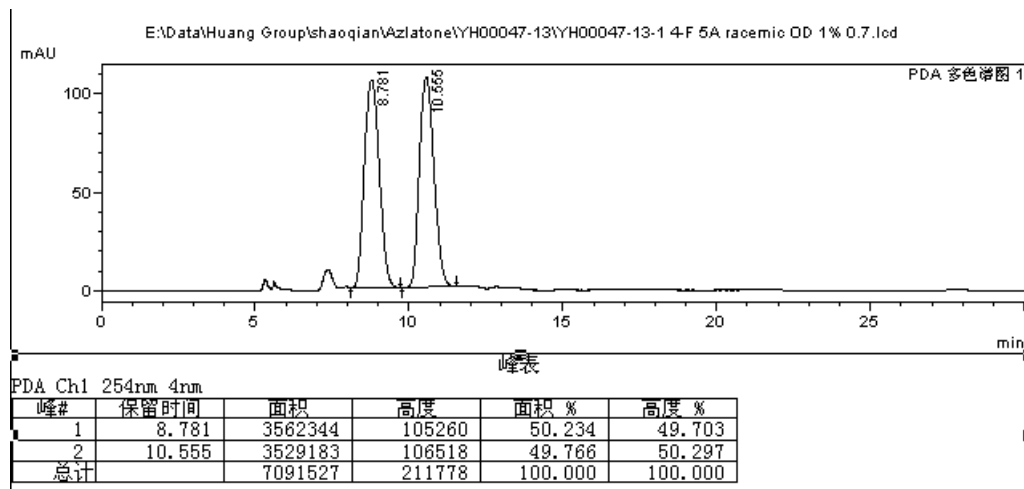


Methyl 1,2-bis(isopropoxycarbonyl)-3-isopropyl-5-(4-fluorophenyl)-2,3-dihydro-1H-1,2,4-triazole-3-carboxylate (4q):

65% yield, colorless oil. ¹H NMR (400 MHz, CDCl₃) δ 7.55 – 7.46 (m, 2H), 7.23 (t, *J* = 7.7 Hz, 1H), 4.98 (dt, *J* = 12.6, 6.3 Hz, 1H), 4.91 (dt, *J* = 12.5, 6.3 Hz, 1H), 3.69 (s, 3H), 2.64 (dt, *J* = 13.4, 6.7 Hz, 1H), 2.32 (s, 3H), 1.29 (dd, *J* = 10.7, 6.3 Hz, 6H), 1.15 (dd, *J* = 6.2, 4.3 Hz, 6H), 1.11 (d, *J* = 6.8 Hz, 3H), 0.94 (d, *J* = 6.8 Hz, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 167.49, 161.67, 159.23, 157.52, 154.87, 152.14, 130.83, 130.78, 129.09, 128.91, 128.37, 128.29, 125.28, 125.24, 116.45, 116.20, 95.87, 77.35, 77.04, 76.72, 72.16, 70.91, 52.62, 33.52, 21.98, 21.77, 21.52, 21.50, 17.28, 16.32, 14.72, 14.69. HRMS (ESI) Calcd. for C₂₁H₂₉FN₃O₆ ([M+H]⁺): 438.2040; Found: 438.2048.

The ee was determined by HPLC using a Chiralcel OD column [n-hexane/EtOH (99:1)]; flow

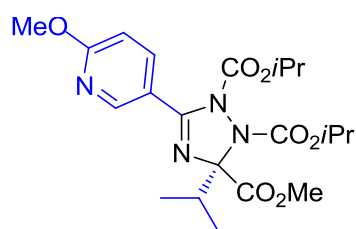
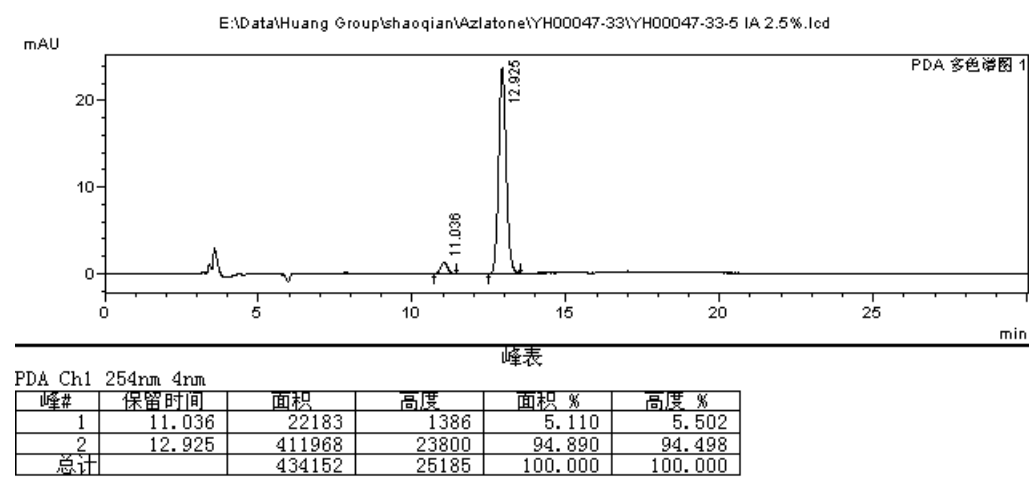
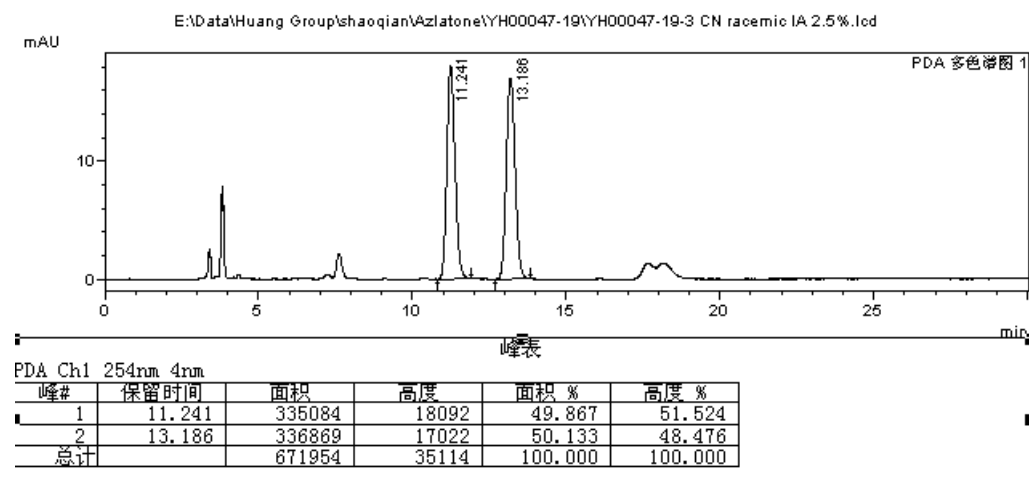
rate 1.0 mL/min; $t_{R\text{major}} = 10.465$ min, $t_{R\text{minor}} = 8.731$ min (90% ee). $^{27.8}[\alpha]_D = +77^\circ$ ($c = 0.1$, CHCl_3).



Methyl 1,2-bis(isopropoxycarbonyl)-3-isopropyl-5-(3-cyanophenyl)-2,3-dihydro-1H-1,2,4-triazole-3-carboxylate (4r):

51% yield, colorless oil. ^1H NMR (500 MHz, CDCl_3) δ 8.14 (s, 1H), 8.08 (d, $J = 7.9$ Hz, 1H), 7.79 (d, $J = 7.7$ Hz, 1H), 7.56 (t, $J = 7.8$ Hz, 1H), 5.03 – 4.99 (m, 1H), 4.91 (dd, $J = 12.4, 6.2$ Hz, 1H), 3.71 (s, 3H), 2.68 (dt, $J = 13.0, 6.4$ Hz, 1H), 1.33 (d, $J = 6.2$ Hz, 3H), 1.30 (d, $J = 6.3$ Hz, 3H), 1.16 (t, $J = 5.8$ Hz, 6H), 1.12 (d, $J = 6.7$ Hz, 3H), 0.96 (d, $J = 6.8$ Hz, 3H). ^{13}C NMR (126 MHz, CDCl_3) δ 167.12, 156.65, 154.73, 151.90, 134.51, 133.68, 133.25, 130.51, 128.66, 117.74, 112.45, 96.27, 77.17, 76.92, 76.66, 72.50, 71.11, 52.63, 33.48, 21.90, 21.68, 21.47, 21.43, 17.16, 16.31. HRMS (ESI) Calcd. for $\text{C}_{22}\text{H}_{28}\text{N}_4\text{O}_6\text{Na}$ ($[\text{M}+\text{Na}]^+$): 467.1907; Found: 467.1895. The ee was determined by HPLC using IA column [*n*-hexane/EtOH (97.5:2.5)]; flow rate 1.0 mL/min; $t_{R\text{major}} = 12.925$ min, $t_{R\text{minor}} = 11.036$ min (90% ee). $^{27.8}[\alpha]_D = +16^\circ$ ($c = 0.1$,

CHCl₃).

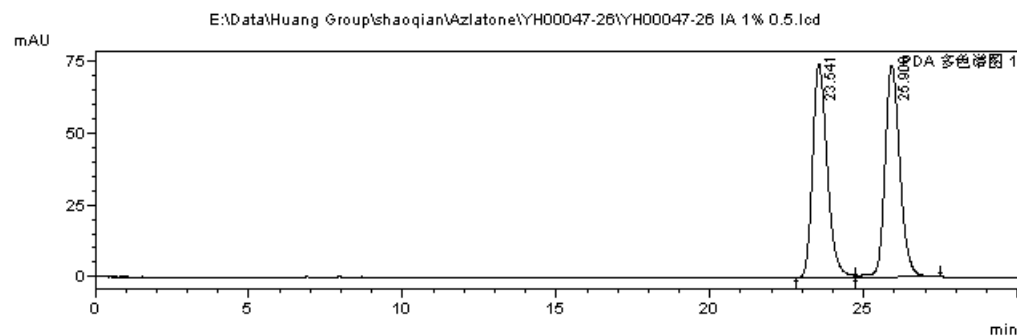


Methyl 1,2-bis(isopropoxycarbonyl)-3-isopropyl-5-(6-methoxypyridin-3-yl)-2,3-dihydro-1H-1,2,4-triazole-3-carboxylate (4s):

50% yield, colorless oil. ¹H NMR (500 MHz, CDCl₃) δ 8.63 (s, 1H), 8.02 – 7.95 (m, 1H), 6.77 – 6.71 (m, 1H), 4.99 – 4.94 (m, 1H), 4.92 – 4.86 (m, 1H), 3.96 (d, *J* = 1.7 Hz, 3H), 3.68 (d, *J* = 1.5 Hz, 3H), 2.61 (dd, *J* = 12.8, 6.3 Hz, 1H), 1.29 – 1.25 (m, 6H), 1.18 – 1.13 (m, 6H), 1.08 (d, *J* = 6.6 Hz, 3H), 0.91 (d, *J* = 6.7 Hz, 3H). ¹³C NMR (126 MHz, CDCl₃) δ 167.47, 165.99, 156.02, 154.74, 152.04, 149.09, 139.62, 118.37, 109.79, 95.68, 77.24, 76.98, 76.73, 72.14, 70.79, 53.76, 52.48, 33.49, 21.88, 21.67, 21.49, 21.44, 17.17, 16.26. HRMS (ESI) Calcd. for C₂₁H₃₁N₄O₇ ([M+H]⁺): 451.2193; Found: 451.2178.

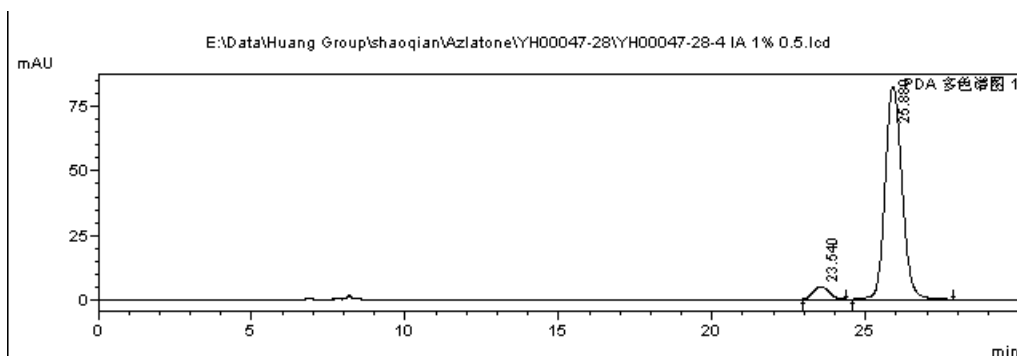
The ee was determined by HPLC using IA column [n-hexane/EtOH (99:1)]; flow rate 0.5

mL/min; $t_{R\text{major}} = 25.889$ min, $t_{R\text{minor}} = 23.540$ min (90% ee). $^{27.8}[\alpha]_D = +46^\circ$ ($c = 0.1$, CHCl_3).



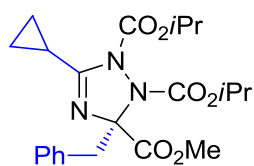
峰表

峰#	保留时间	面积	高度	面积 %	高度 %
1	23.541	2451943	74166	49.717	50.257
2	25.908	2479821	73406	50.283	49.743
总计		4931764	147573	100.000	100.000



峰表

峰#	保留时间	面积	高度	面积 %	高度 %
1	23.540	170622	4745	5.134	5.448
2	25.889	3152766	82360	94.866	94.552
总计		3323388	87105	100.000	100.000

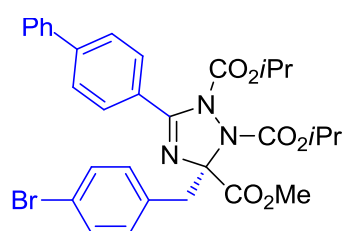
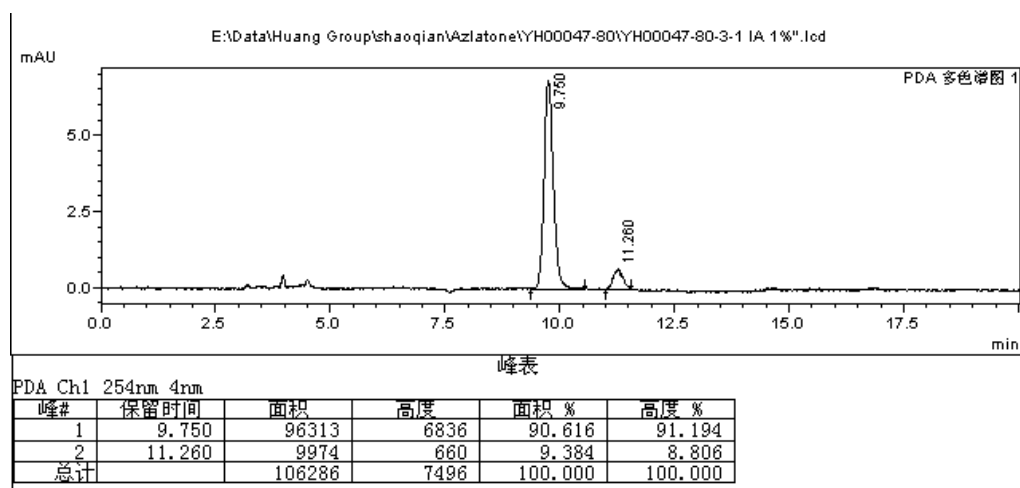
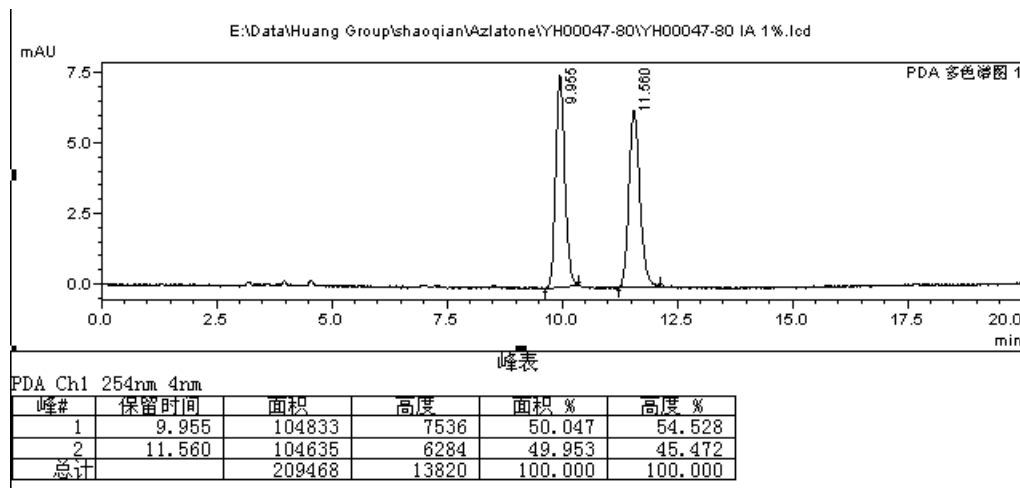


Methyl 1,2-bis(isopropoxycarbonyl)-3-benzyl-5-cyclopropyl-2,3-dihydro-1H-1,2,4-triazole-3-carboxylate (4t):

82% yield, colorless oil. ^1H NMR (500 MHz, CDCl_3) δ 7.24 – 7.15 (m, 3H), 7.13 (d, $J = 7.7$ Hz, 2H), 4.97 (dt, $J = 12.5, 6.2$ Hz, 1H), 4.77 (dt, $J = 12.5, 6.2$ Hz, 1H), 3.77 (s, 3H), 3.43 (d, $J = 14.0$ Hz, 1H), 3.30 (d, $J = 14.0$ Hz, 1H), 2.04 – 1.97 (m, 1H), 1.32 (d, $J = 6.2$ Hz, 3H), 1.25 (d, $J = 6.3$ Hz, 4H), 1.21 (d, $J = 6.3$ Hz, 3H), 1.15 (d, $J = 6.2$ Hz, 3H), 0.91 – 0.85 (m, 1H), 0.80 – 0.73 (m, 1H), 0.52 – 0.46 (m, 1H). ^{13}C NMR (126 MHz, CDCl_3) δ 168.82, 161.87, 154.09, 150.35, 134.09, 131.25, 127.44, 126.60, 92.08, 77.21, 76.96, 76.71, 71.53, 70.67, 52.79, 41.11, 21.98, 21.65, 21.61, 21.49, 10.09, 9.70, 8.29. HRMS (ESI) Calcd. for $\text{C}_{22}\text{H}_{30}\text{N}_3\text{O}_6$ ($[\text{M}+\text{H}]^+$): 432.2135; Found: 432.2131.

The ee was determined by HPLC using IA column [n-hexane/EtOH (99:1)]; flow rate 1.0

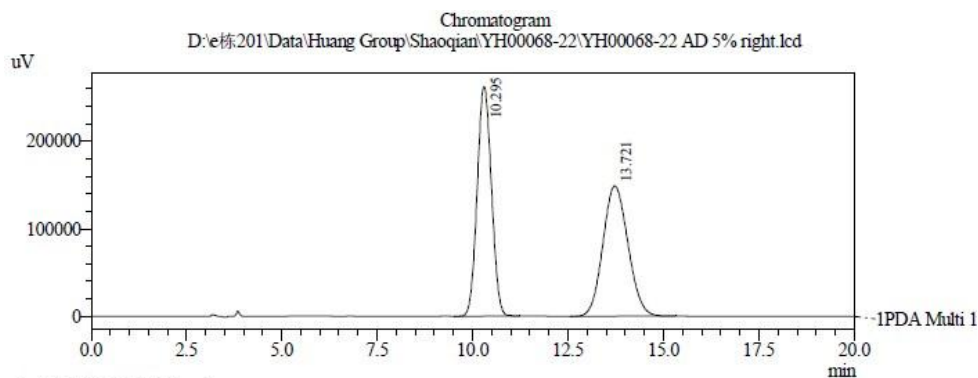
mL/min; $t_{R\text{major}} = 9.750$ min, $t_{R\text{minor}} = 11.260$ min (81% ee). $^{27.8}[\alpha]_D = +12^\circ$ ($c = 0.1$, CHCl_3).



Methyl 1,2-bis(isopropoxycarbonyl)-3-(4-bromophenyl)-5-([1,1'-biphenyl]-4-yl)-2,3-dihydro-1H-1,2,4-triazole-3-carboxylate (4u):

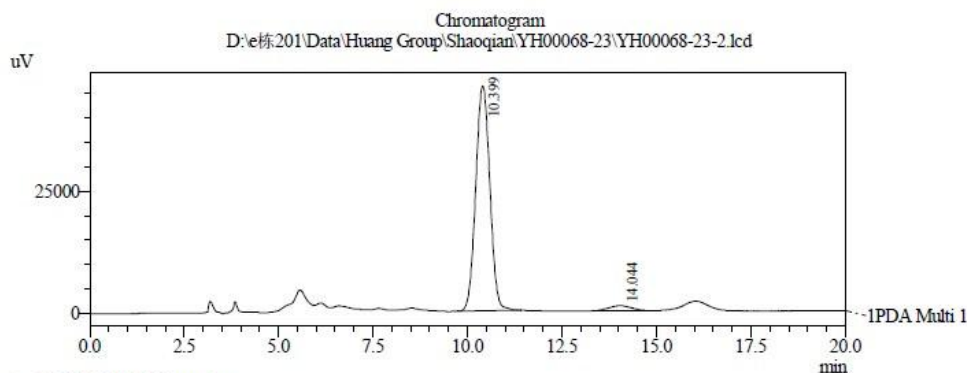
42% yield, colorless oil. ^1H NMR (500 MHz, CDCl_3) δ 7.74 (d, $J = 8.4$ Hz, 2H), 7.64 – 7.57 (m, 4H), 7.46 (t, $J = 7.6$ Hz, 2H), 7.38 (dd, $J = 15.6, 7.9$ Hz, 3H), 7.19 (d, $J = 8.4$ Hz, 2H), 5.05 (dt, $J = 12.5, 6.2$ Hz, 1H), 4.53 (dt, $J = 12.4, 6.2$ Hz, 1H), 3.78 (s, 3H), 3.60 (d, $J = 14.1$ Hz, 1H), 3.43 (d, $J = 14.1$ Hz, 1H), 1.36 (d, $J = 6.2$ Hz, 3H), 1.30 (d, $J = 6.3$ Hz, 3H), 0.99 (d, $J = 6.2$ Hz, 3H), 0.81 (d, $J = 6.2$ Hz, 3H). ^{13}C NMR (126 MHz, CDCl_3) δ 168.26, 159.36, 150.73, 144.38, 140.10, 133.07, 132.99, 130.86, 129.85, 128.94, 128.04, 127.20, 126.38, 121.13, 92.59, 72.35, 71.01, 53.18, 40.67, 22.13, 21.81, 21.34, 21.24. HRMS (ESI) Calcd. for $\text{C}_{31}\text{H}_{33}\text{BrN}_3\text{O}_6$ ($[\text{M}+\text{H}]^+$): 622.1553; Found: 622.1547.

The ee was determined by HPLC using AD column [n-hexane/EtOH (95:5)]; flow rate 1.0 mL/min; $t_{R\text{major}} = 10.399$ min, $t_{R\text{minor}} = 14.044$ min (93% ee). $^{27.8}[\alpha]_D = +74^\circ$ ($c = 0.1$, CHCl_3).



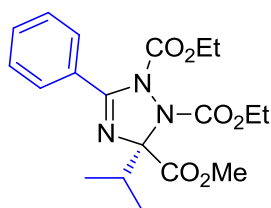
PeakTable

Peak#	Ret. Time	Area	Height	Area %	Height %
1	10.295	6821916	262266	50.040	63.819
2	13.721	6811105	148690	49.960	36.181
Total		13633021	410956	100.000	100.000



PeakTable

Peak#	Ret. Time	Area	Height	Area %	Height %
1	10.399	1200626	46078	96.663	97.830
2	14.044	41451	1022	3.337	2.170
Total		1242078	47100	100.000	100.000

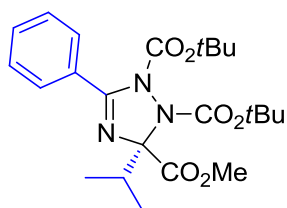
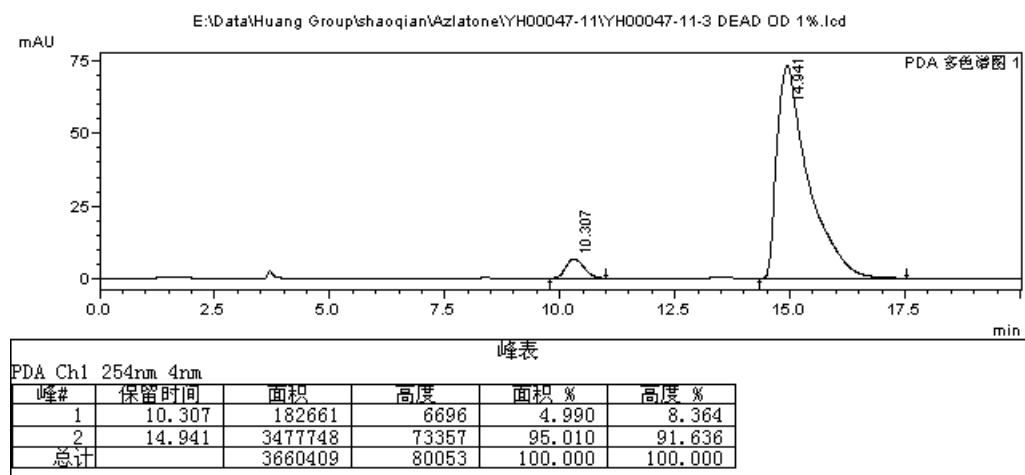
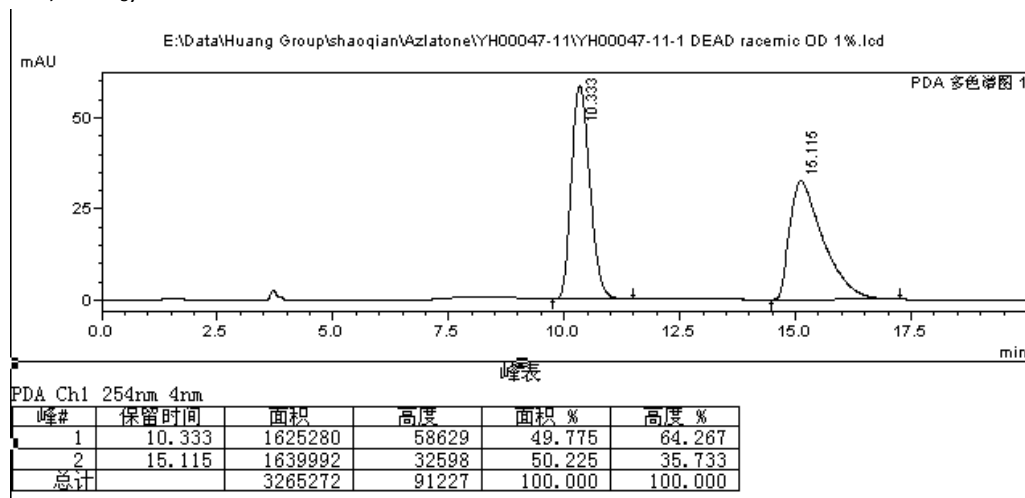


Methyl 1,2-bis(ethoxycarbonyl)-3-isopropyl-5-phenyl-2,3-dihydro-1H-1,2,4-triazole-3-carboxylate (DEAD-product):

90% yield, colorless oil. ^1H NMR (500 MHz, CDCl_3) δ 7.85 – 7.80 (m, 2H), 7.50 (t, $J = 7.4$ Hz, 1H), 7.42 (t, $J = 7.7$ Hz, 2H), 4.31 – 4.24 (m, 1H), 4.23 – 4.09 (m, 3H), 3.70 (s, 3H), 2.67 (dt, $J = 13.5$, 6.7 Hz, 1H), 1.30 (t, $J = 7.1$ Hz, 3H), 1.10 (dd, $J = 13.9$, 6.9 Hz, 6H), 0.97 (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 167.46, 158.30, 155.35, 152.52, 131.57, 129.55, 128.93, 127.76, 96.10, 77.24, 76.98, 76.73, 63.55, 62.68, 52.60, 33.53, 17.13, 16.31, 14.19, 13.80.

HRMS (ESI) Calcd. for $\text{C}_{19}\text{H}_{26}\text{N}_3\text{O}_6$ ($[\text{M}+\text{H}]^+$): 392.1822; Found: 392.1820.

The ee was determined by HPLC using a Chiralcel OD column [n-hexane/EtOH (99:1)]; flow rate 1.0 mL/min; $t_{R\text{major}} = 14.941$ min, $t_{R\text{minor}} = 10.307$ min (90% ee). $^{27.8}[\alpha]_D = +61^\circ$ ($c = 0.1$, CHCl_3).

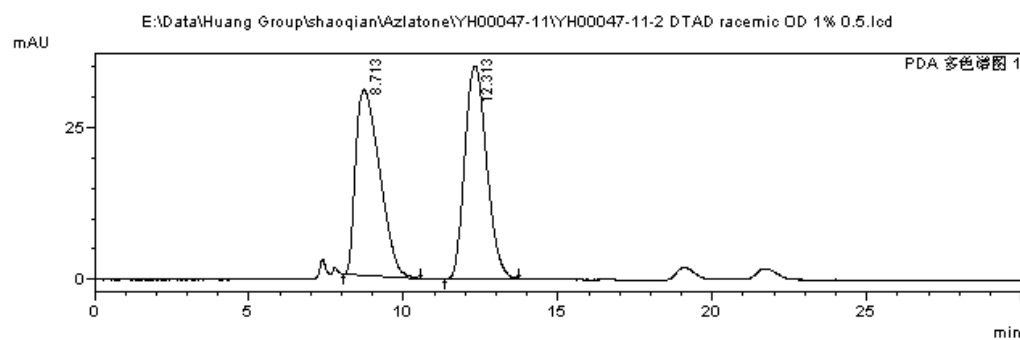


Methyl 1,2-bis(tertbutoxycarbonyl)-3-isopropyl-5-phenyl-2,3-dihydro-1H-1,2,4-triazole-3-carboxylate (DTBAD-product):

72% yield, colorless oil. ^1H NMR (500 MHz, CDCl_3) δ 7.80 (d, $J = 7.7$ Hz, 2H), 7.48 (t, $J = 7.4$ Hz, 1H), 7.40 (t, $J = 7.6$ Hz, 2H), 3.68 (s, 3H), 2.63 (dt, $J = 13.3, 6.6$ Hz, 1H), 1.50 (s, 9H), 1.28 (s, 9H), 1.13 (d, $J = 6.7$ Hz, 3H), 0.97 (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 167.78, 158.73, 153.80, 150.84, 131.21, 129.44, 128.37, 127.73, 95.21, 83.75, 82.30, 77.22, 76.97, 76.71, 52.37, 33.54, 28.01, 27.56, 17.23, 16.29. HRMS (ESI) Calcd. for $\text{C}_{23}\text{H}_{34}\text{N}_3\text{O}_6$ ($[\text{M}+\text{H}]^+$): 448.2448; Found: 448.2487.

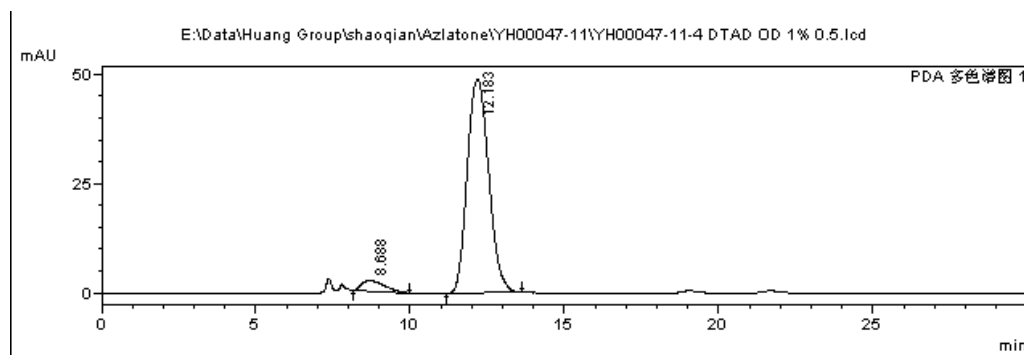
The ee was determined by HPLC using a Chiralcel OD column [n-hexane/EtOH (99:1)]; flow rate 0.5 mL/min; $t_{R\text{major}} = 12.183$ min, $t_{R\text{minor}} = 8.688$ min (90% ee). $^{27.8}[\alpha]_D = +66^\circ$ ($c =$

0.1, CHCl₃).



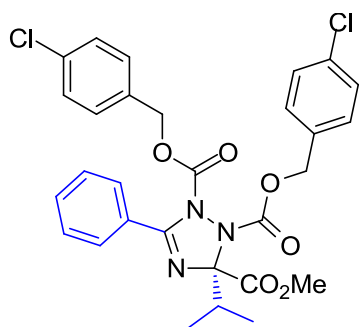
峰表

峰#	保留时间	面积	高度	面积 %	高度 %
1	8.713	1649222	30422	48.848	46.606
2	12.313	1727043	34853	51.152	53.394
总计		3376266	65276	100.000	100.000



峰表

峰#	保留时间	面积	高度	面积 %	高度 %
1	8.688	120048	2377	4.811	4.635
2	12.183	2375090	48915	95.189	95.365
总计		2495138	51292	100.000	100.000

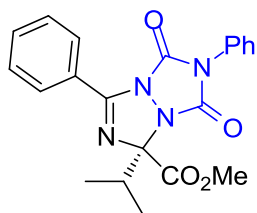
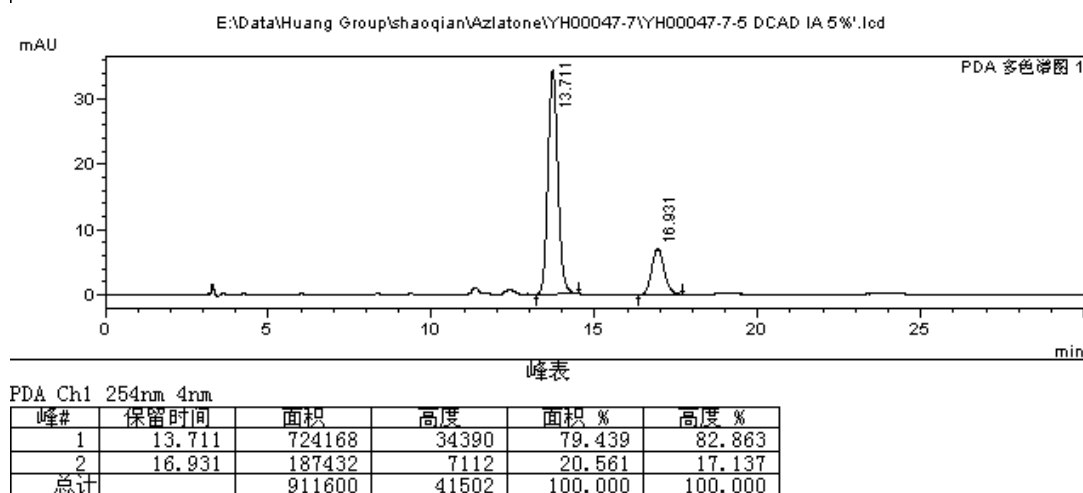
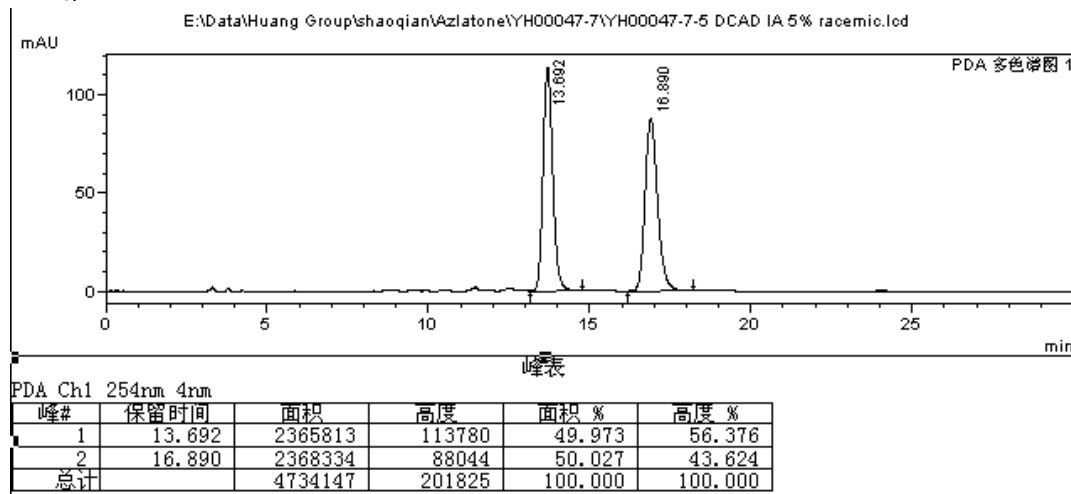


Methyl 1,2-bis(4-chlorobenzoyloxycarbonyl)-3-isopropyl-5-phenyl-2,3-dihydro-1H-1,2,4-triazole-3-carboxylate (DCAD-product):

83% yield, colorless oil. ¹H NMR (500 MHz, CDCl₃) δ 7.83 – 7.77 (m, 2H), 7.51 (t, *J* = 7.4 Hz, 1H), 7.40 (t, *J* = 7.7 Hz, 2H), 7.32 (q, *J* = 8.5 Hz, 4H), 7.22 (d, *J* = 8.3 Hz, 2H), 6.95 (d, *J* = 8.3 Hz, 2H), 5.21 (d, *J* = 12.4 Hz, 1H), 5.12 (d, *J* = 12.4 Hz, 1H), 5.05 (q, *J* = 12.4 Hz, 2H), 3.51 (s, 3H), 2.65 (dt, *J* = 13.2, 6.5 Hz, 1H), 1.06 (d, *J* = 6.8 Hz, 3H), 0.90 (d, *J* = 6.8 Hz, 3H); ¹³C NMR (126 MHz, CDCl₃) δ 167.16, 157.88, 155.15, 152.34, 134.40, 134.34, 133.83, 132.82, 131.76, 129.60, 129.50, 129.27, 128.70, 128.60, 127.98, 96.38, 77.27, 77.02, 76.76, 68.30, 67.51,

52.63, 33.46, 17.15, 16.27. HRMS (ESI) Calcd. for $C_{29}H_{28}Cl_2N_3O_6$ ($[M+H]^+$): 584.1355; Found: 584.1344.

The ee was determined by HPLC using IA column [n-hexane/EtOH (95:5)]; flow rate 1.0 mL/min; t_{R} major = 13.711 min, t_{R} minor = 16.931 min (59% ee). $^{27.8}[\alpha]_D = +46^\circ$ (c = 0.1, $CHCl_3$).

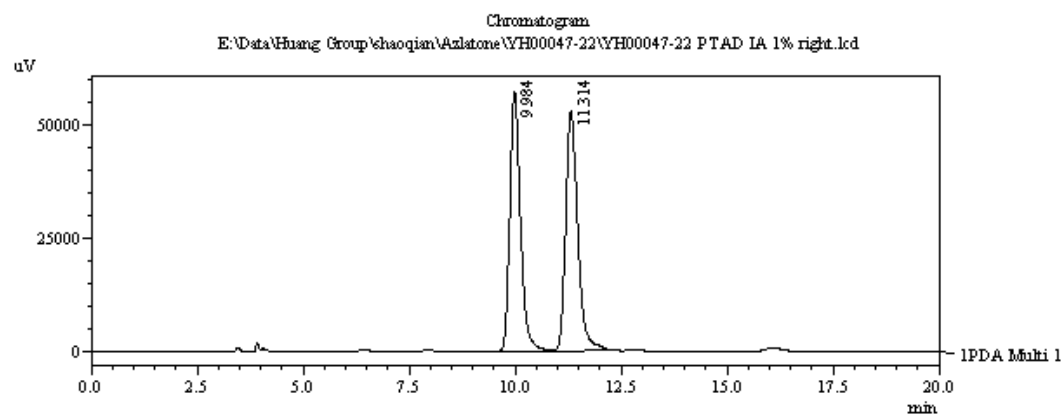


Methyl 1-isopropyl-5,7-dioxo-3,6-diphenyl-1,5,6,7-tetrahydro-[1,2,4]triazolo[1,2-a][1,2,4]triazole-1-carboxylate (PTAD-product):

52% yield, colorless oil. 1H NMR (500 MHz, $CDCl_3$) δ 8.13 – 8.07 (m, 2H), 7.60 (t, $J = 7.5$ Hz, 1H), 7.49 (q, $J = 8.2$ Hz, 6H), 7.43 – 7.39 (m, 1H), 3.85 (s, 3H), 2.92 (dt, $J = 13.5, 6.8$ Hz, 1H), 1.25 (d, $J = 6.8$ Hz, 3H), 1.06 (d, $J = 6.7$ Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.52, 153.75, 153.61, 148.69, 133.13, 131.01, 130.39, 129.16, 128.80, 128.27, 126.08, 125.04, 98.09, 77.25, 77.00, 76.75, 53.46, 33.08, 17.56, 16.11. HRMS (ESI) Calcd. for $C_{21}H_{20}N_4O_4$ ($[M+H]^+$): 393.1563; Found: 393.1555.

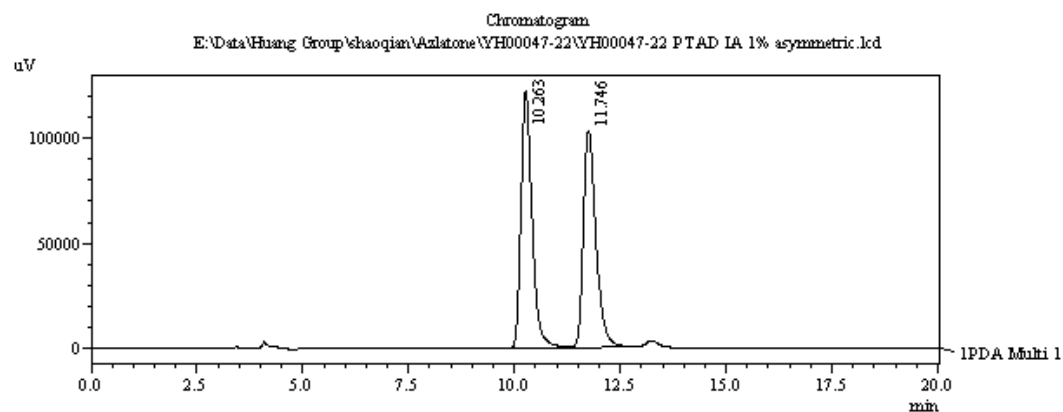
The ee was determined by HPLC using a Chiralcel IA column [n-hexane/EtOH (99:1)]; flow

rate 1.0 mL/min; $t_{R\text{major}} = 10.263$ min, $t_{R\text{minor}} = 11.746$ min (2% ee). $^{27.8}[\alpha]_D = +18^\circ$ (c = 0.1, CHCl_3).



Peak Table

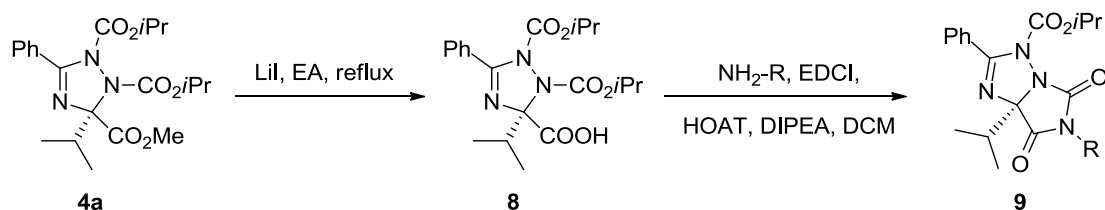
Peak#	Ret. Time	Area	Height	Area %	Height %
1	9.984	1010027	57410	48.995	52.064
2	11.314	1051461	52859	51.005	47.936
Total		2061488	110269	100.000	100.000



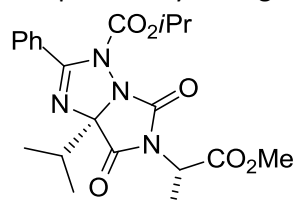
Peak Table

Peak#	Ret. Time	Area	Height	Area %	Height %
1	10.263	2222465	122350	51.063	54.329
2	11.746	2129931	102851	48.937	45.671
Total		4352396	225201	100.000	100.000

Derivatization and Characterization of Triazoline Products



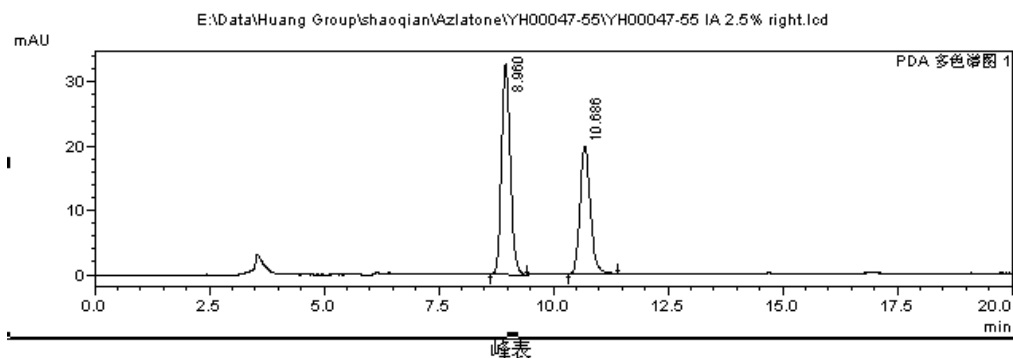
Three equivalents of LiI was added to a solution of **4a** in EA and refluxed overnight. The progress of the reaction was monitored by TLC. The reaction was washed three times with aqueous NH_4Cl solution and dried over Na_2SO_4 . The volatile solvent was removed and the product **8** was used directly without further purification. A solution of **8**, EDCI (2 equiv.) and HOAT (2 equiv.) in dry dichloromethane was cooled to 0°C , and followed this, DIPEA (8 equiv.) was added. After the reaction mixture was stirred for 5min, the amine (1.5 equiv.) was added dropwise. The progress of the reaction was monitored by TLC. Up on complete consumption of the starting material **8**, the reaction was washed three times with aqueous NaHCO_3 solution and dried over Na_2SO_4 . The volatile solvent was removed and the product was purified by silica gel flash chromatography (ethyl acetate / hexane).



Isopropyl 7a-isopropyl-6-((S)-1-methoxy-1-oxopropan-2-yl)-5,7-dioxo-2-phenyl-5,6,7,7a-tetrahydro-3H-imidazo[1,5-b][1,2,4]triazole-3-carboxylate (**9a**):

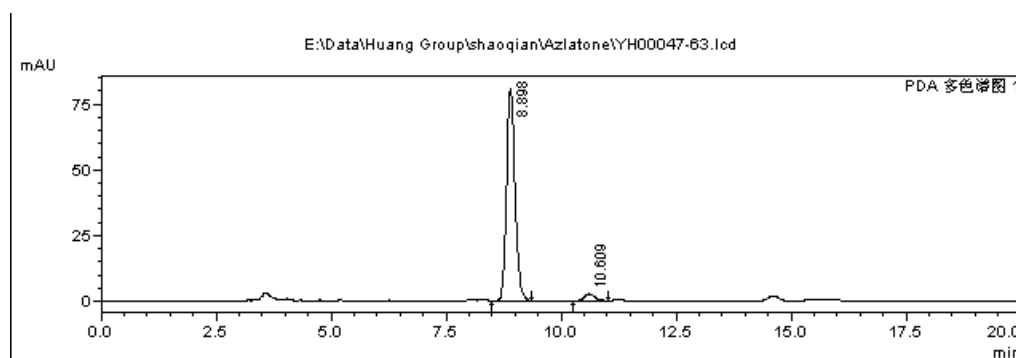
85% yield, colorless oil. ^1H NMR (500 MHz, CDCl_3) δ 7.89 – 7.81 (m, 2H), 7.53 (dd, $J = 10.6$, 4.3 Hz, 1H), 7.43 (t, $J = 7.7$ Hz, 2H), 4.99 (dt, $J = 12.5$, 6.2 Hz, 1H), 4.79 (q, $J = 7.3$ Hz, 1H), 3.71 (s, 3H), 2.52 (dd, $J = 13.8$, 6.9 Hz, 1H), 1.66 – 1.62 (m, 3H), 1.21 (d, $J = 6.2$ Hz, 3H), 1.16 (d, $J = 6.2$ Hz, 3H), 1.11 (d, $J = 6.8$ Hz, 3H), 0.92 (d, $J = 7.0$ Hz, 3H). ^{13}C NMR (126 MHz, CDCl_3) δ 169.75, 168.77, 161.29, 160.18, 152.40, 132.15, 129.81, 128.35, 127.97, 96.25, 77.17, 76.92, 76.67, 72.49, 52.68, 49.05, 32.04, 29.30, 21.52, 21.41, 16.07, 14.92, 14.38. HRMS (ESI) Calcd. for $\text{C}_{21}\text{H}_{27}\text{N}_4\text{O}_6$ ($[\text{M}+\text{H}]^+$): 431.1931; Found: 431.1932.

The ee was determined by HPLC using IA column [n-hexane/EtOH (97.5:2.5)]; flow rate 1.0 mL/min; t_{R} major = 8.898 min, t_{R} minor = 10.609 min (92% ee). $^{27.8}[\alpha]_{\text{D}} = +136^\circ$ ($c = 0.1$, CHCl_3).



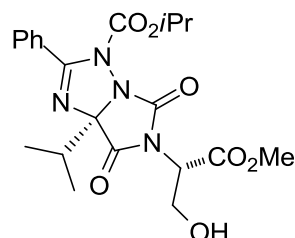
PDA Ch1 254nm 4nm

峰#	保留时间	面积	高度	面积 %	高度 %
1	8.960	434877	32779	58.281	62.405
2	10.686	311298	19747	41.719	37.595
总计		746176	52527	100.000	100.000



PDA Ch1 254nm 4nm

峰#	保留时间	面积	高度	面积 %	高度 %
1	8.898	1038204	80831	96.117	96.797
2	10.609	41938	2675	3.883	3.203
总计		1080142	83506	100.000	100.000

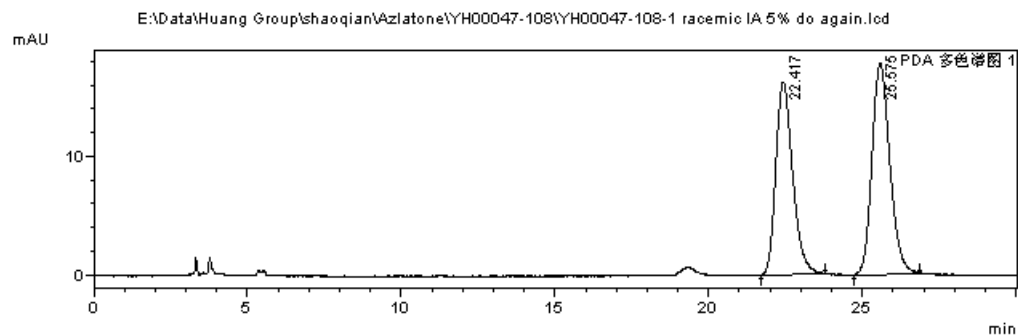


Isopropyl 6-((S)-3-hydroxy-1-methoxy-1-oxopropan-2-yl)-7a-isopropyl-5,7-dioxo-2-phenyl-5,6,7,7a-tetrahydro-3H-imidazo[1,5-b][1,2,4]triazole-3-carboxylate (9b):

83% yield, colourless oil. ^1H NMR (500 MHz, CDCl_3) δ 7.89 – 7.82 (m, 2H), 7.55 (t, $J = 7.4$ Hz, 1H), 7.45 (t, $J = 7.6$ Hz, 2H), 5.00 (dt, $J = 12.3, 6.2$ Hz, 1H), 4.89 (dt, $J = 9.3, 4.8$ Hz, 1H), 4.15 (ddd, $J = 14.9, 12.4, 9.2$ Hz, 2H), 3.79 (d, $J = 4.0$ Hz, 3H), 2.54 (dd, $J = 14.7, 7.7$ Hz, 1H), 1.22 (dd, $J = 6.1, 2.1$ Hz, 3H), 1.18 (dd, $J = 6.1, 3.6$ Hz, 3H), 1.14 (dd, $J = 16.9, 6.8$ Hz, 3H), 0.95 (d, $J = 6.9$ Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 170.96, 170.61, 167.13, 167.09, 162.18, 161.64, 160.41, 160.37, 152.34, 132.31, 129.95, 129.88, 128.26, 128.05, 128.03, 96.40, 96.37, 72.69, 60.33, 60.28, 60.10, 56.20, 53.03, 52.88, 32.33, 32.17, 21.56, 21.46, 16.18, 16.15, 14.95.

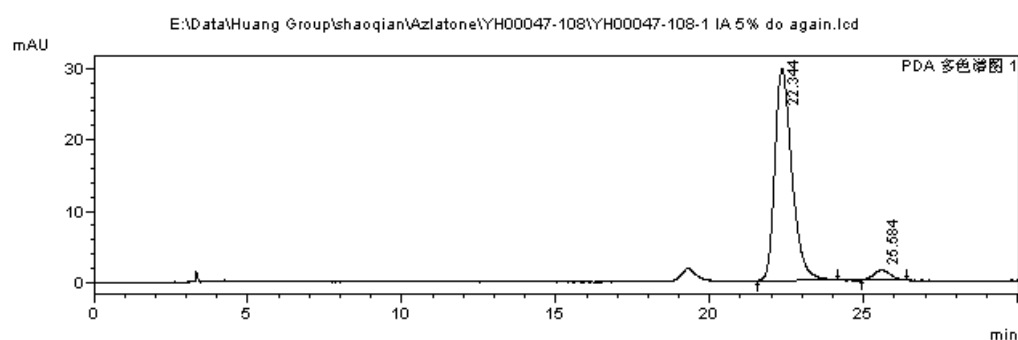
HRMS (ESI) Calcd. for $\text{C}_{21}\text{H}_{27}\text{N}_4\text{O}_7$ ($[\text{M}+\text{H}]^+$): 447.1880; Found: 447.1875.

The ee was determined by HPLC using IA column [n-hexane/EtOH (95:5)]; flow rate 1.0 mL/min; $t_{\text{R major}} = 22.344$ min, $t_{\text{R minor}} = 25.584$ min (91% ee). $^{27.8}[\alpha]_{\text{D}} = +168^\circ$ ($c = 0.1$, CHCl_3).



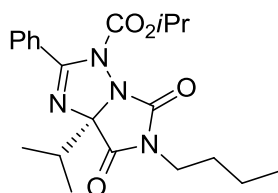
峰表

峰#	保留时间	面积	高度	面积 %	高度 %
1	22.417	621358	16247	46.422	47.745
2	25.575	717155	17782	53.578	52.255
总计		1338514	34029	100.000	100.000



峰表

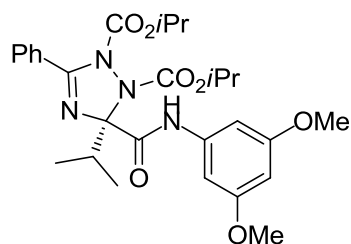
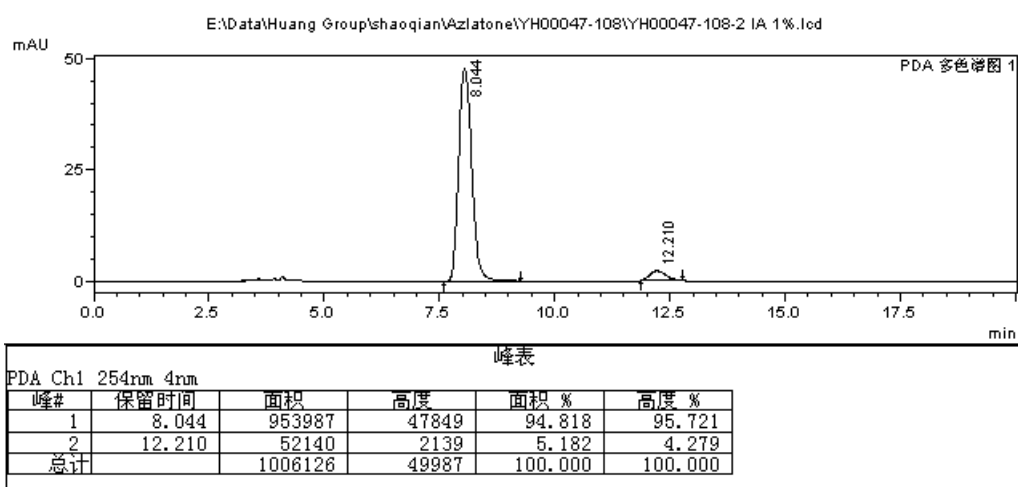
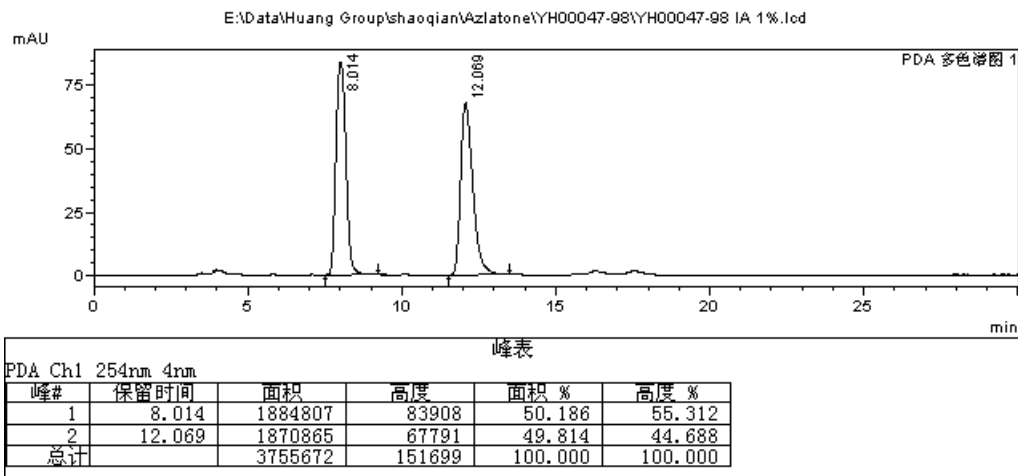
峰#	保留时间	面积	高度	面积 %	高度 %
1	22.344	1147445	29717	95.494	95.427
2	25.584	54145	1424	4.506	4.573
总计		1201590	31141	100.000	100.000



Isopropyl 6-butyl-7a-isopropyl-5,7-dioxo-2-phenyl-5,6,7,7a-tetrahydro-3H-imidazo[1,5-b][1,2,4]triazole-3-carboxylate (9c):

81% yield, colourless oil. ^1H NMR (400 MHz, CDCl_3) δ 7.89 – 7.78 (m, 2H), 7.52 (t, $J = 7.4$ Hz, 1H), 7.42 (t, $J = 7.6$ Hz, 2H), 4.98 (dt, $J = 12.5, 6.2$ Hz, 1H), 3.56 (td, $J = 7.1, 4.6$ Hz, 2H), 2.51 (dt, $J = 13.7, 6.9$ Hz, 1H), 1.61 (dd, $J = 8.3, 5.2$ Hz, 2H), 1.36 – 1.29 (m, 2H), 1.19 (d, $J = 6.2$ Hz, 3H), 1.15 (d, $J = 6.2$ Hz, 3H), 1.06 (d, $J = 6.8$ Hz, 3H), 0.92 (dd, $J = 13.5, 7.1$ Hz, 6H). ^{13}C NMR (101 MHz, CDCl_3) δ 170.73, 162.43, 160.20, 152.56, 132.17, 129.86, 128.45, 127.99, 96.21, 72.49, 39.32, 31.89, 29.56, 21.60, 21.47, 19.83, 16.29, 14.88, 13.49. HRMS (ESI) Calcd. for $\text{C}_{21}\text{H}_{29}\text{N}_4\text{O}_4$ ($[\text{M}+\text{H}]^+$): 401.2189; Found: 401.2187.

The ee was determined by HPLC using IA column [n-hexane/EtOH (99:1)]; flow rate 1.0 mL/min; $t_{\text{R major}} = 8.044$ min, $t_{\text{R minor}} = 12.210$ min (90% ee). $^{27.8}[\alpha]_{\text{D}} = +81^\circ$ ($c = 0.1$, CHCl_3).

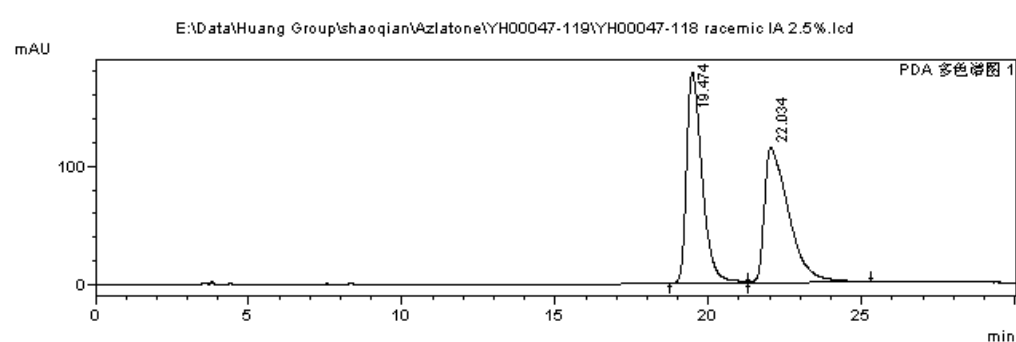


Diisopropyl 3-((3,5-dimethoxyphenyl)carbamoyl)-3-isopropyl-5-phenyl-1H-1,2,4-triazole-1,2(3H)-dicarboxylate (9d):

85% yield, colourless oil. ^1H NMR (500 MHz, CDCl_3) δ 8.49 (s, 1H), 8.28 (d, $J = 9.5$ Hz, 1H), 7.94 (d, $J = 7.3$ Hz, 2H), 7.55 (d, $J = 7.4$ Hz, 1H), 7.47 (t, $J = 7.6$ Hz, 2H), 6.47 (d, $J = 7.0$ Hz, 2H), 5.05 (dt, $J = 12.2, 6.1$ Hz, 1H), 4.83 (dt, $J = 12.3, 6.1$ Hz, 1H), 3.80 (d, $J = 6.9$ Hz, 6H), 3.19 (s, 1H), 1.34 (d, $J = 6.2$ Hz, 3H), 1.28 (d, $J = 5.4$ Hz, 3H), 1.17 (d, $J = 6.7$ Hz, 3H), 1.10 – 1.01 (m, 6H), 0.96 (d, $J = 4.8$ Hz, 3H). ^{13}C NMR (126 MHz, CDCl_3) δ 165.57, 158.85, 156.55, 154.14, 151.87, 149.52, 131.63, 129.86, 129.19, 127.78, 121.10, 120.48, 103.91, 98.76, 96.45, 72.12, 70.82, 55.84, 55.50, 21.84, 21.82, 21.36, 21.29, 17.79, 16.19. HRMS (ESI) Calcd. for $\text{C}_{28}\text{H}_{37}\text{N}_4\text{O}_7$ ($[\text{M}+\text{H}]^+$): 541.2662; Found: 541.2656.

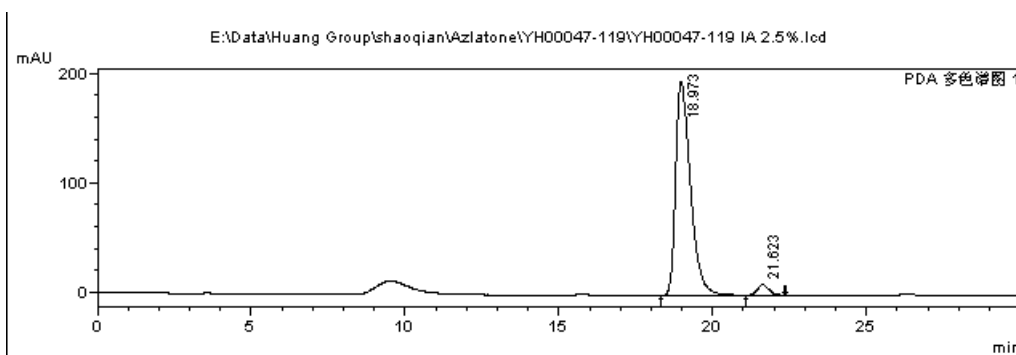
The ee was determined by HPLC using IA column [n-hexane/EtOH (97.5:2.5)]; flow rate 1.0 mL/min; $t_{\text{Rmajor}} = 18.973$ min, $t_{\text{Rminor}} = 21.623$ min (93% ee). $^{27.8}[\alpha]_{\text{D}} = +102^\circ$ ($c = 0.1$,

CHCl₃).



峰表

峰#	保留时间	面积	高度	面积 %	高度 %
1	19.474	6269697	177896	50.110	60.998
2	22.034	6242204	113746	49.890	39.002
总计		12511901	291643	100.000	100.000



峰表

峰#	保留时间	面积	高度	面积 %	高度 %
1	18.973	6524652	194792	96.398	95.314
2	21.623	243773	9576	3.602	4.686
总计		6768425	204369	100.000	100.000

References

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NMR Spectra Images

