Supporting Information

CHIRAL 1,2-DIAMINOCYCLOHEXANES–α-AMINO ACIDS-DERIVED AMIDPHOS/Ag(I)-CATALYZED DIVERGENT ENANTIOSELECTIVE 1,3-DIPOLAR CYCLOADDITION OF AZOMETHINE YLIDES

Haifei Wang[1], Chuliang Gong[1], Zhipeng Zhou[1], Jie Luo[1], Qingxia Zhou[1], Youshi Liu[1,*], Guangjun Hua[2,*]

([1]College of Life Science and Chemistry, Hunan University of Technology, Zhuzhou 412007, P. R. of China; [2]College of Packaging and Materials Engineering, Hunan University of Technology, Zhuzhou 412007, P. R. of China; E-mail:471606483@qq.com; hgj757@126.com)

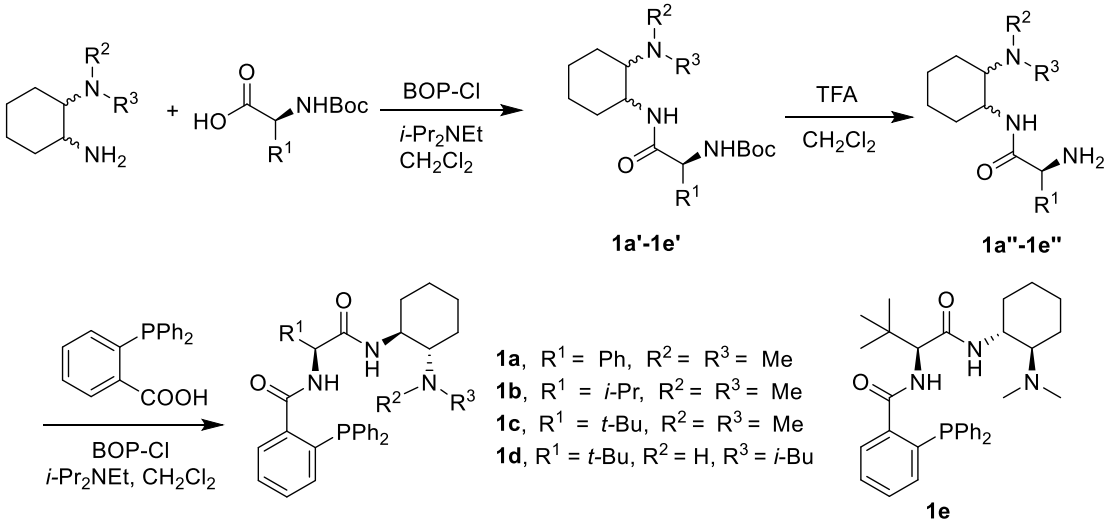
Table of Contents

1. General Information

Most chemical reagents were purchased from Adamas-beta® Co., Ltd. (Shanghai, China), aladdin® Co., Ltd. (Shanghai, China) and Sigma-Aldrich Co. (St. Louis, Missouri, USA) and were used as received without further purification. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AV-400 spectrometer in $CDCl_3$. $CDCl_3$ served as the internal standard (δ = 7.26) for ^{1}H NMR and (δ = 77.0) for ^{13}C NMR. Chiral HPLC was performed on a Agilent 1260 apparatus equipped with a spectrophotometric detector (monitoring at 205–230 nm) with Daicel chiral AS-H and AD-H columns. High-resolution mass spectrometry was recorded on Shimadzu LCMS-IT-TOF mass spectrometer. Optical rotations were measured on an Insmark IP-digi300/2 polarimeter. All reactions were monitored by thin-layer chromatography (TLC) plates (Qingdao Marine Chemistry Company, Qingdao, China). Flash column chromatography was completed by using silica gel 200–300 (particle size 0.0040–0.0750 mm) (Qingdao Marine Chemistry Company, Qingdao, China).

2. Preparation of the Catalysts

N-((*S*)-2-(((1*S*,2*S*)-2-(dimethylamino)cyclohexyl)amino)-2-oxo-1-phenylethyl)-2-(diphenylphosphino)benzamide (1a)



Typical procedure: the tert-butyl (S)-((1*S*,2*S*)-2-(dimethylamino)cyclohexylcarbamoyl)(phenyl) methylcarbamate **1a'** (375 mg, 1.0 mmol) prepared from *N*-Boc-*L*-phenylglycine and (1*S*,2*S*)-N',N'-dimethylcyclohexane-1,2-diamine according to the reported procedure[1] was dissolved in CH_2Cl_2 (10 mL) and trifluoroacetic acid (1 mL) was dropped at 0 °C. The reaction mixture was then stirred for 4 h at room temperature. All volatile compounds were removed in vacuo and the residue was dissolved in water and treated with saturated Na_2CO_3 solution. The resulting mixture

was extracted with CH_2Cl_2 and the combined organic layers were dried over Na_2SO_4. After filtration and then evaporation of the solvent to afford the free amine **1a"** as colourless oil which was used directly in the next step without further purification. To a stirred solution of crude **1a"** in CH_2Cl_2 (8 mL) at room temperature was added (benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate (BOP-Cl, 531 mg, 1.2 mmol), followed by the addition of diisopropylethylamine (0.2 mL, 1.2 mmol) and 2-(diphenylphosphino)benzoic acid (306 mg, 1 mmol). The reaction mixture was then stirred for 12 h at room temperature. The mixture was combined with CH_2Cl_2 and water and the organic layer was separated, washed with saturated $NaHCO_3$, and dried over Na_2SO_4. The solvent was removed in vacuo to afford the crude protected as colourless oil, the crude product was purified by flash chromatography (35% EtOAc in hexanes) yielding **1a** (394 mg, 70%) as a white solid.

Mp. 109–110 °C; $[\alpha]_D^{30}$ = 97.5 (*c* 0.80, CH_2Cl_2); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.85 (s, 1H), 7.76 (s, 1H), 7.46 (d, *J* = 6.8 Hz, 1H), 7.34–7.26 (m, 13H), 7.14 (d, *J* = 7.6 Hz, 3H), 6.9–6.90 (m, 2H), 5.05 (s, 1H), 3.96 (d, *J* = 8.0 Hz, 1H), 3.35 (s, 1H), 2.78 (s, 1H), 2.67 (d, *J* = 3.6 Hz, 3H), 2.45 (d, *J* = 3.2 Hz, 3H), 1.99 (s, 2H), 1.84–1.72 (m, 5H), 1.33–1.23 (m, 4H). ^{13}C-NMR (101 MHz, $CDCl_3$) δ 172.9, 170.0, 139.2, 138.9, 134.6, 134.1, 133.8, 133.6, 133.4, 131.4, 129.7, 129.4, 129.3, 129.1, 129.0, 128.9, 128.8, 128.6, 128.5, 127.2, 68.4, 62.0, 48.8, 42.6, 38.5, 37.1, 30.6, 24.3, 23.6, 22.7; ^{31}P-NMR (162 MHz, $CDCl_3$) δ -9.9; HRMS (ESI): *m*/*z* $[M+H]^+$ calcd. for $C_{35}H_{38}N_3O_2P$: 564.2774, found: 564.2782,

N-((*S*)-1-(((1*S*,2*S*)-2-(dimethylamino)cyclohexyl)amino)-3-methyl-1-oxobutan-2-yl)-2-(diphenylphosphino)benzamide (1b)

Catalyst **1b** was prepared according to the procedure used to synthesize catalyst **1a**, starting from **1b'** (341 mg, 1.0 mmol) to yield the desired product as a white solid (397 mg, 75%). Mp. 72–73 °C; $[\alpha]_D^{30}$ = 25.3(*c* 0.95, CH_2Cl_2); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.62 (dd, *J* = 7.2, 2.8 Hz, 1H), 7.39–7.37 (m, 1H), 7.35–7.26 (m, 12H), 6.97 (dd, *J* = 6.8, 4.0 Hz, 1H), 6.67 (d, *J* = 8.4 Hz, 1H), 6.42 (s, 1H), 4.34–4.30 (m, 1H), 3.49–3.42 (m, 1H), 2.48–2.45 (m, 1H), 2.28–2.24 (m, 1H), 2.18 (s, 6H), 2.01–2.03 (m, 1H), 1.84–1.79 (m, 2H), 1.68–1.65 (m, 1H), 1.27–1.10 (m, 4H), 0.87 (s, 3H), 0.86 (s, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 170.6, 168.6, 141.3, 141.1, 137.5, 137.4, 136.6, 136.4, 134.4, 133.9, 133.7, 130.3, 128.7, 128.7, 128.6, 128.5, 128.5, 128.5, 127.7, 127.6, 66.4, 58.9, 51.4, 39.9, 32.5, 31.5, 25.3, 24.7, 21.3, 18.8, 18.2; ^{31}P-NMR (162 MHz, $CDCl_3$) δ -10.0; HRMS (ESI): *m*/*z* $[M+H]^+$ calcd. for $C_{32}H_{40}N_3O_2P$: 530.2931, found: 530.2934.

N-((*S*)-1-(((1*S*,2*S*)-2-(dimethylamino)cyclohexyl)amino)-3,3-dimethyl-1-oxobutan-2-yl)-2-(diphenylphosphino)benzamide (1c)

Catalyst **1c** was prepared according to the procedure used to synthesize catalyst **1a**, starting from **1c'** (355 mg, 1.0 mmol) to yield the desired product as a white solid (391 mg, 72%). Mp. 82–83 °C; $[\alpha]_D^{30}$ = 80.6 (*c* 0.80, CH_2Cl_2); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.62–7.59 (m, 1H), 7.39–7.37 (m, 1H), 7.35–7.23 (m, 11H), 6.98–6.95 (m, 1H), 6.81 (d, *J* = 9.2 Hz, 1H), 6.37 (s, 1H), 4.31 (d, *J* = 9.2 Hz, 1H), 3.4–3.41 (m, 1H), 2.52–2.49 (m, 1H), 2.18 (s, 6H), 1.85–1.82 (m, 2H), 1.68–1.65 (m, 1H), 1.26–1.07 (m, 5H), 0.95 (s, 9H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 170.2, 168.5, 141.3, 141.0, 137.7, 137.6, 137.5, 136.7, 136.5, 134.4, 133.9, 133.7, 133.6, 133.5, 130.2, 128.6, 128.5, 128.4, 128.4, 128.3, 127.4, 66.3, 61.1, 51.3, 39.8, 35.1, 32.2, 26.5, 25.2, 24.5, 21.1, 15.2. ^{31}P-NMR (162 MHz, $CDCl_3$) δ-9.9; HRMS (ESI): *m*/*z* $[M+H]^+$ calcd. for $C_{33}H_{42}N_3O_2P$: 544.3087, found:544.3089.

2-(diphenylphosphino)-N-((*S*)-1-(((1*S*,2*S*)-2-(isobutylamino)cyclohexyl)amino)-3,3-dimethyl-

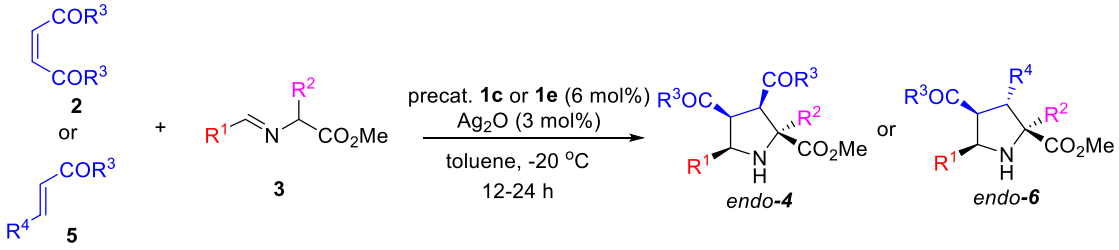
1-oxobutan-2-yl)benzamide (1d)

Catalyst **1d** was prepared according to the procedure used to synthesize catalyst **1a**, starting from **1d'** (383 mg, 1.0 mmol) to yield the desired product as a white solid (429 mg, 75%). Mp. 67–68 ^{o}C; $[\alpha]_D^{30}$ = 23.3 (*c* 1.80, CH_2Cl_2); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.62–7.0 (m, 1H), 7.38 (td, *J* = 7.6, 1.2 Hz, 1H), 7.32–7.30 (m, 7H), 7.26–7.21 (m, 4H), 6.98–6.95 (m, 1H), 6.70 (d, *J* = 8.8 Hz, 1H), 6.20 (d, *J* = 7.2 Hz, 1H), 4.28 (d, *J* = 8.8 Hz, 1H), 3.51 (qd, *J* = 10.8, 4.0 Hz, 1H), 2.50 (dd, *J* = 11.2, 6.8 Hz, 1H), 2.28 (td, *J* = 10.2, 3.6 Hz, 1H), 2.21 (dd, *J* = 11.2, 6.8 Hz, 1H), 2.14–2.04 (m, 2H), 1.72–1.58 (m, 4H), 1.31–1.06 (m, 4H), 0.93 (s, 9H), 0.85 (d, *J* = 6.4 Hz, 6H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 170.3, 168.9, 141.4, 141.1, 137.1, 136.0, 135.8, 134.5, 133.8, 133.6, 130.4, 128.8, 128.7, 128.6, 127.7, 61.8, 60.8, 54.3, 53.5, 34.5, 32.2, 31.4, 28.9, 26.7, 24.6, 20.7; ^{31}P-NMR (162 MHz, $CDCl_3$) δ-10.6; HRMS (ESI): *m/z* $[M+H]^+$ calcd. for $C_{35}H_{46}N_3O_2P$ $[M+H]^+$ 572.3400, found: 572.3406.

N-((*S*)-1-(((1*R*,2*R*)-2-(dimethylamino)cyclohexyl)amino)-3,3-dimethyl-1-oxobutan-2-yl)-2-(diphenylphosphino)benzamide (1e)

Catalyst **1e** was prepared according to the procedure used to synthesize catalyst **1a**, starting from **1e'** (355 mg, 1.0 mmol) to yield the desired product as a white solid(407 mg, 75%) Mp. 101–102 ^{o}C; $[\alpha]_D^{30}$ = -10.4 (*c* 0.80, CH_2Cl_2); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.59 (dd, *J* = 6.8, 3.6 Hz, 1H), 7.39 (t, *J* = 7.6 Hz, 1H), 7.35–7.22 (m, 11H), 6.98 (dd, *J* = 7.2, 3.6 Hz, 1H), 6.86 (d, *J* = 6.4 Hz, 1H), 6.78 (d, *J* = 7.2 Hz, 1H), 4.23 (d, *J* = 7.6 Hz, 1H), 3.71–3.62 (m, 2H), 2.51–2.47 (m, 1H), 2.25 (s, 6H), 1.80–1.83 (m, 2H), 1.69 (d, *J* = 7.6 Hz, 1H), 1.29–1.25 (m, 2H), 1.20–1.14 (m, 2H), 0.94 (s, 9H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 170.2, 169.4, 152.2, 141.0, 140.7, 137.1, 137.0, 136.5, 136.3, 134.5, 133.9, 133.7, 133.7, 133.5, 130.5, 128.9, 128.7, 128.6, 128.5, 128.5, 127.7, 127.7, 66.9, 62.1, 50.00, 39.7, 34.1, 32.1, 26.6, 24.6, 24.5, 21.6. ^{31}P-NMR (162 MHz, $CDCl_3$) δ-10.4; HRMS (ESI): *m/z* $[M+H]^+$ calcd. for $C_{33}H_{42}N_3O_2P$: 544.3087, found: 544.3092.

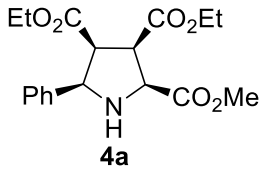
3. Representative procedure of 1,3-dipole cycloaddition



Precatalyst **1c** or **1e** (0.012 mmol) and Ag_2O (0.006 mmol) were dissolved in toluene (1.4 mL). The reaction mixture was stirred for 1 h at rt, followed by the addition of maleates **2** or **5** (0.20 mmol) and iminester substrates **3** (0.30 mmol). Once starting material had been consumed (monitored by TLC), the mixture was purified by column chromatography to give the corresponding cycloaddition product **4** or **6**, which was then directly analyzed by chiral HPLC.

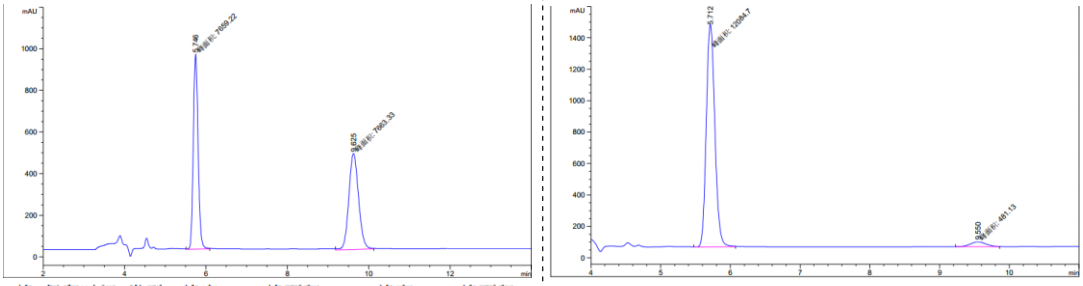
4. Analytical data of the [3 + 2] cyclization products

(2*S*,3*R*,4*S*,5*R*)-3,4-diethyl 2-methyl 5-phenylpyrrolidine-2,3,4-tricarboxylate (4a)[1]



4a

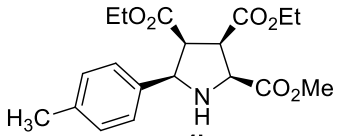
White solid, Mp. 118–119 °C; yield 94%; $[\alpha]_D^{30}$ = +52.1 (*c* 1.00, CH_2Cl_2); The ee value was 92%, t_R (major) = 5.71 min, t_R (minor) = 9.55 min (Chiralcel AS-H, λ = 205 nm, *i*PrOH/hexanes = 50:50, flow rate = 0.8 mL/min).



峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 [mAU*s]	峰高 [mAU]	峰面积 %
1	5.746	MM	0.1365	7659.22217	935.23352	49.9866
2	9.625	MM	0.2773	7663.33252	460.53204	50.0134

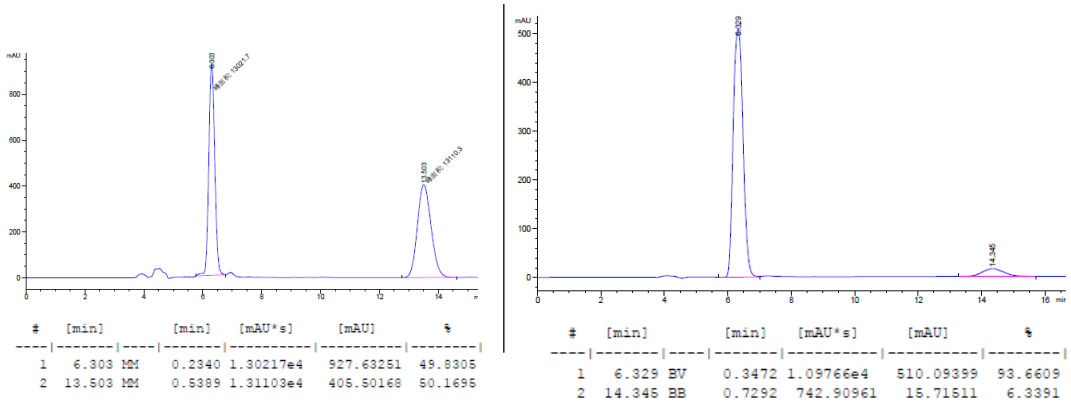
峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 [mAU*s]	峰高 [mAU]	峰面积 %
1	5.712	MM	0.1424	1.20847e4	1414.77319	96.1711
2	9.550	MF	0.2661	481.12970	30.13309	3.8289

(2*S*,3*R*,4*S*,5*R*)-3,4-diethyl 2-methyl 5-(p-tolyl)pyrrolidine-2,3,4-tricarboxylate (4b)[1]



4b

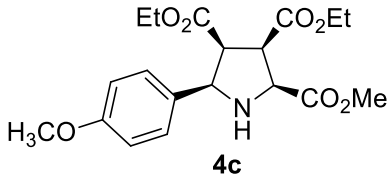
White solid, Mp. 115–116 °C; yield 92%; $[\alpha]_D^{30}$ = +46.8 (*c* 1.04, CH_2Cl_2); The ee value was 87%, t_R (major) = 6.33 min, t_R (minor) = 14.35 min, (Chiralcel AS-H, λ = 210 nm, *i*PrOH/hexanes 50:50, flow rate =0.8 mL/min).



#	[min]		[min]	[mAU*s]	[mAU]	%
1	6.303	MM	0.2340	1.30217e4	927.63251	49.8305
2	13.503	MM	0.5389	1.31103e4	405.50168	50.1695

#	[min]		[min]	[mAU*s]	[mAU]	%
1	6.329	BV	0.3472	1.09766e4	510.09399	93.6609
2	14.345	BB	0.7292	742.90961	15.71511	6.3391

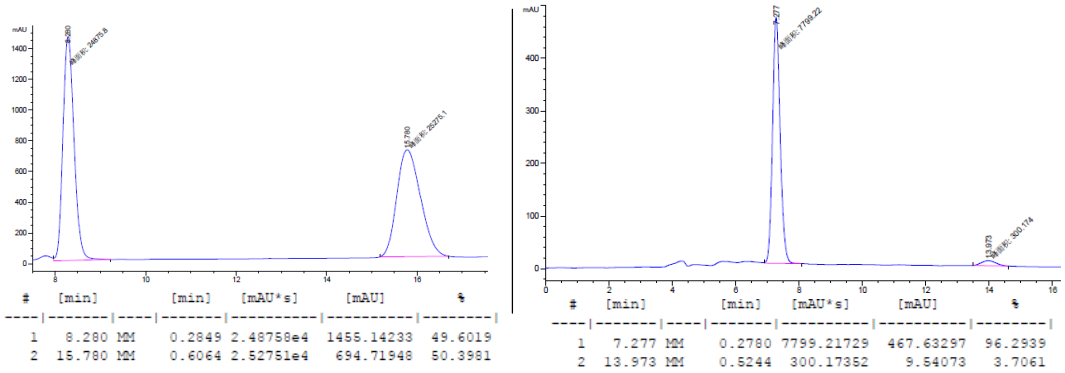
(2*S*,3*R*,4*S*,5*R*)-3,4-diethyl 2-methyl 5-(4-methoxyphenyl)pyrrolidine-2,3,4-tricarboxylate (4c)[1]



4c

White solid, Mp. 84–86 °C; yield 91%; $[\alpha]_D^{30}$ = +47.5 (c 1.02, CH_2Cl_2); The ee value was 93%, t_R

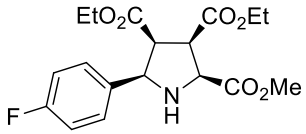
(major) = 7.28 min, t_R (minor) = 13.97 min, (Chiralcel AS-H, λ = 210 nm, *i*PrOH/hexanes 50:50, flow rate =0.8 mL/min).



#	[min]	[min]	[mAU*s]	[mAU]	%
1	8.280 MM	0.2849	2.48758e4	1455.14233	49.6019
2	15.780 MM	0.6064	2.52751e4	694.71948	50.3981

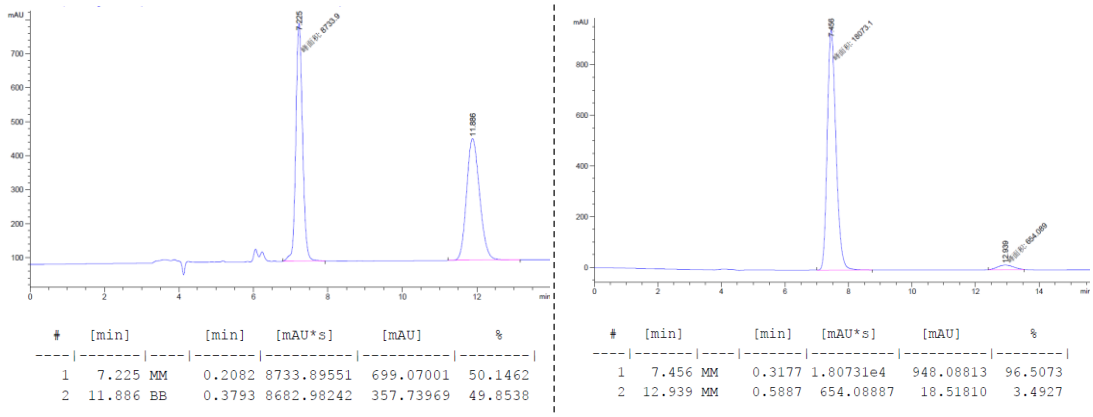
#	[min]	[min]	[mAU*s]	[mAU]	%
1	7.277 MM	0.2780	7799.21729	467.63297	96.2939
2	13.973 MM	0.5244	300.17352	9.54073	3.7061

(2*S*,3*R*,4*S*,5*R*)-3,4-diethyl 2-methyl 5-(4-fluorophenyl)pyrrolidine-2,3,4-tricarboxylate (4d)[1]



4d

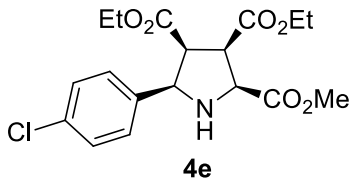
White solid, Mp. 101-103 °C; yield 97%; $[\alpha]_D^{30}$ = +51.4 (c 1.05, CH_2Cl_2); The ee value was 93%, t_R (major) = 7.46min, t_R (minor) = 12.94 min, (Chiralcel AS-H, λ = 210 nm, *i*PrOH/hexanes 50:50, flow rate =0.8 mL/min).



#	[min]	[min]	[mAU*s]	[mAU]	%
1	7.225 MM	0.2082	8733.89551	699.07001	50.1462
2	11.886 BB	0.3793	8682.98242	357.73969	49.8538

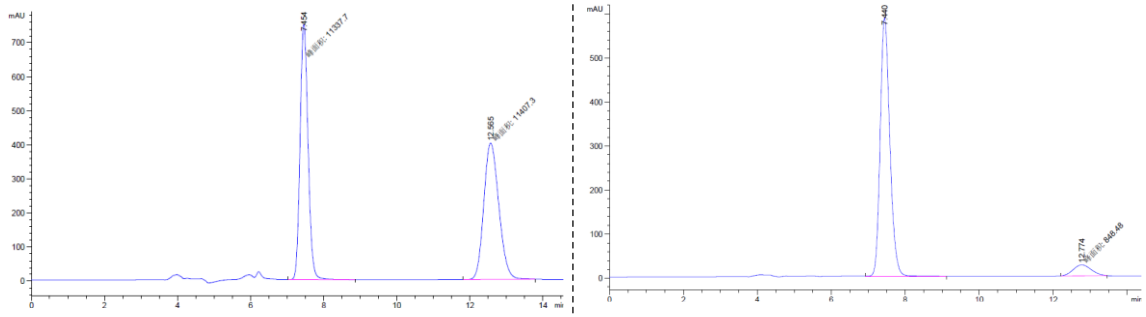
#	[min]	[min]	[mAU*s]	[mAU]	%
1	7.456 MM	0.3177	1.80731e4	948.08813	96.5073
2	12.939 MM	0.5887	654.08887	18.51810	3.4927

(2*S*,3*R*,4*S*,5*R*)-3,4-diethyl 2-methyl 5-(4-chlorophenyl)pyrrolidine-2,3,4-tricarboxylate (4e)[1]



4e

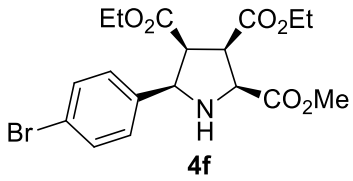
White solid, Mp. 117-118 °C; yield 97%; $[\alpha]_D^{30}$ = +47.0 (c 1.03, CH_2Cl_2); The ee value was 85%, t_R (major) = 7.44 min, t_R (minor) = 12.77 min, (Chiralcel AS-H, λ = 210 nm, *i*PrOH/hexanes 50:50, flow rate =0.8 mL/min).



#	[min]		[min]	[mAU*s]	[mAU]	%
1	7.454	MM	0.2522	1.13377e4	749.20978	49.8469
2	12.565	MM	0.4753	1.14073e4	400.03049	50.1531

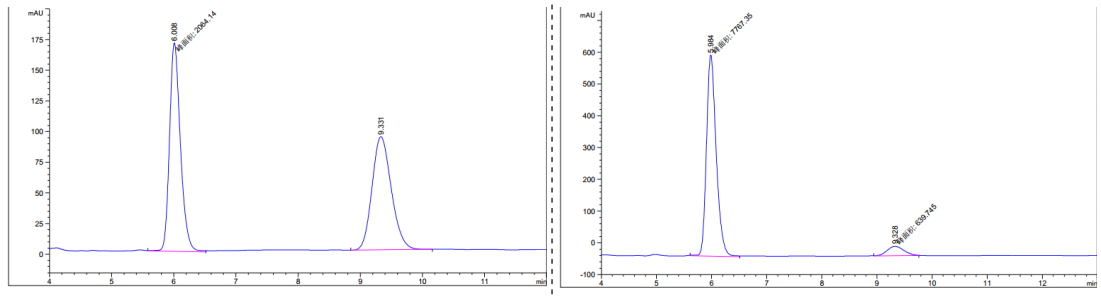
#	[min]		[min]	[mAU*s]	[mAU]	%
1	7.440	VB	0.2784	1.06372e4	586.97894	92.6127
2	12.774	MM	0.5681	848.48004	24.89030	7.3873

(2*S*,3*R*,4*S*,5*R*)-3,4-diethyl 2-methyl 5-(4-bromophenyl)pyrrolidine-2,3,4-tricarboxylate (4f)[1]



4f

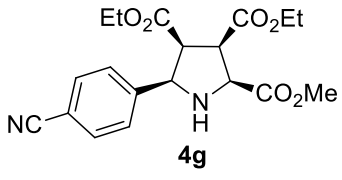
A white solid, Mp. 104–105 °C; yield 92%; $[\alpha]_D^{30}$ = +46.8 (*c* 1.10, CH_2Cl_2); The ee value was 85%, t_R (major) = 5.98 min, t_R (minor) = 9.33 min (Chiralcel AS-H, λ = 210 nm, *i*PrOH/hexanes = 50:50, flow rate = 1.0 mL/min).



峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 [mAU*s]	峰高 [mAU]	峰面积 %
1	6.008	MM	0.2026	2064.14185	169.80562	51.0148
2	9.331	BB	0.3324	1982.02478	92.17268	48.9852

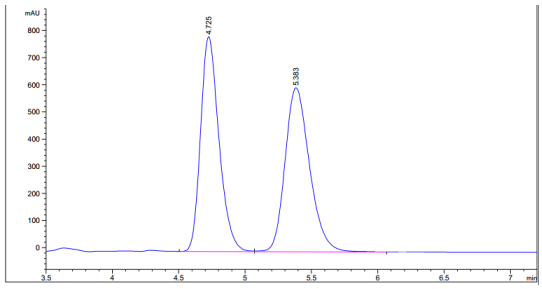
峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 [mAU*s]	峰高 [mAU]	峰面积 %
1	5.984	MM	0.2044	7767.35010	633.43005	92.3904
2	9.328	MM	0.3561	639.74548	29.94428	7.6096

(2*S*,3*R*,4*S*,5*R*)-3,4-diethyl 2-methyl 5-(4-cyanophenyl)pyrrolidine-2,3,4-tricarboxylate (4g)[1]

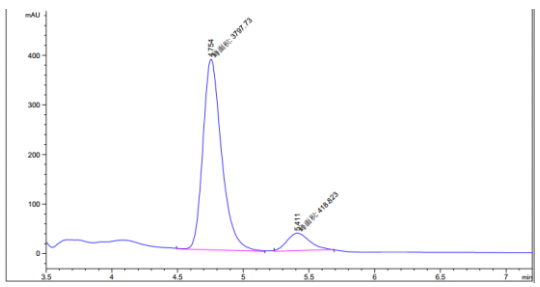


4g

White solid, Mp. 123–124 °C; yield 88%; $[\alpha]_D^{30}$ = +26.2 (*c* 0.70, CH_2Cl_2); The ee value was 80%, t_R (major) = 4.75 min, t_R (minor) = 5.41min (Chiralcel AS-H, λ = 210 nm, *i*PrOH/hexanes = 50:50, flow rate = 1.0 mL/min).

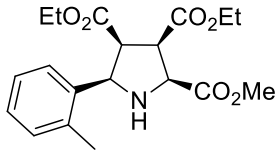


峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 [mAU*s]	峰高 [mAU]	峰面积 %
1	4.725	BV	0.1474	7627.75293	791.62213	49.5522
2	5.383	VV	0.1979	7765.61426	604.61731	50.4478



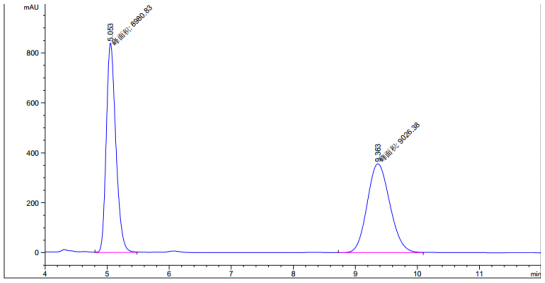
峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 [mAU*s]	峰高 [mAU]	峰面积 %
1	4.754	MM	0.1646	3797.73120	384.44531	90.0672
2	5.411	MM	0.1990	418.82324	35.08270	9.9328

(2*S*,3*R*,4*S*,5*R*)-3,4-diethyl 2-methyl 5-(o-tolyl)pyrrolidine-2,3,4-tricarboxylate (4h)

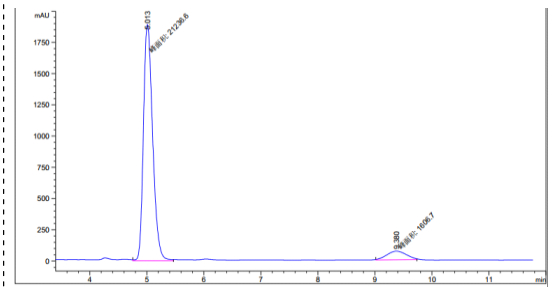


4h

White solid, Mp. 76–77 °C; yield 92%; $[\alpha]_D^{30}$ = +71.88 (*c* 1.30, CH_2Cl_2); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.37–7.35 (m, 1H), 7.16–7.11 (m, 3H), 4.56 (d, *J* = 6.4 Hz, 1H), 4.13–4.06 (m, 3H), 3.82 (s, 3H), 3.70 (dt, *J* = 15.2, 8.4 Hz, 2H), 3.63–3.51 (m, 2H), 3.07 (brs, 1H), 2.35 (s, 3H), 1.20 (t, *J* = 7.2 Hz, 3H), 0.73 (t, *J* = 7.2 Hz, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 171.1, 170.2, 135.6, 134.8, 130.0, 127.5, 125.9, 125.3, 62.0, 61.5, 61.0, 60.3, 52.2, 51.0, 50.8, 19.6, 13.9, 13.4; HRMS (ESI): *m*/*z* $[M+H]^+$ calcd. for $C_{19}H_{25}NO_6$: 364.1755, found 364.1758; The ee value was 86%, t_R (major) = 5.01 min, t_R (minor) = 9.38 min (Chiralcel AS-H, λ = 210 nm, *i*PrOH/hexanes = 50:50, flow rate = 1.0 mL/min).

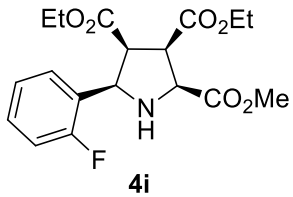


峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 [mAU*s]	峰高 [mAU]	峰面积 %
1	5.053	MM	0.1785	8980.83398	838.57635	49.8735
2	9.363	MF	0.4227	9026.37598	355.88013	50.1265



峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 [mAU*s]	峰高 [mAU]	峰面积 %
1	5.013	MM	0.1872	2.12366e4	1890.42590	92.9664
2	9.380	MF	0.3939	1606.70117	67.97493	7.0336

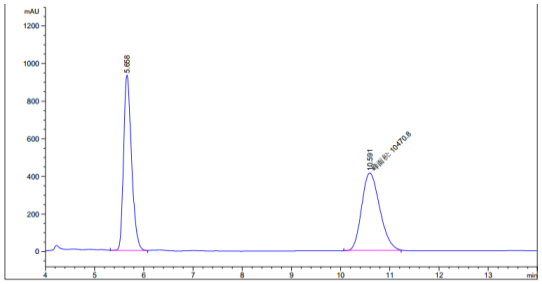
(2*S*,3*R*,4*S*,5*R*)-3,4-diethyl 2-methyl 5-(2-fluorophenyl)pyrrolidine-2,3,4-tricarboxylate (4i)



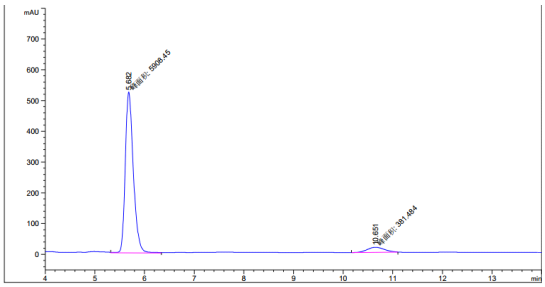
4i

White solid, Mp. 85–86 °C; yield 93%; $[\alpha]_D^{30}$ = +104.22 (*c* 1.15, CH_2Cl_2); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.40 (t, *J* = 7.2 Hz, 1H), 7.22 (td, *J* = 7.6, 1.6 Hz, 1H), 7.09 (t, *J* = 7.6 Hz, 1H), 7.01–

6.96 (m, 1H), 4.58 (d, *J* = 6.0 Hz, 1H), 4.09–4.04 (m, 3H), 3.78 (s, 3H), 3.93–3.62 (m, 4H), 3.18 (brs, 1H), 1.17 (t, *J* = 7.2 Hz, 3H), 0.76 (t, *J* = 7.2 Hz, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 170.9, 170.4, 169.9, 161.3, 158.9, 129.1, 127.2, 124.2, 124.1, 123.9, 114.8, 114.6, 61.2, 61.0, 60.3, 58.9, 58.8, 52.2, 51.4, 51.2, 13.9, 13.5; HRMS (ESI): *m/z* $[M+H]^+$ calcd. for $C_{18}H_{22}FNO_6$ $[M+H]^+$ 368.1504, found: 368.1506; The ee value was 88%, t_R (major) = 5.68 min, t_R (minor) = 10.65min (Chiralcel AS-H, λ = 210 nm, *i*PrOH/hexanes = 50:50, flow rate = 1.0 mL/min).

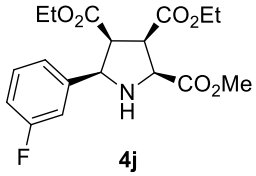


峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 [mAU*s]	峰高 [mAU]	峰面积 %
1	5.658	BV	0.1736	1.05045e4	932.83539	50.0803
2	10.591	MM	0.4241	1.04708e4	411.50583	49.9197



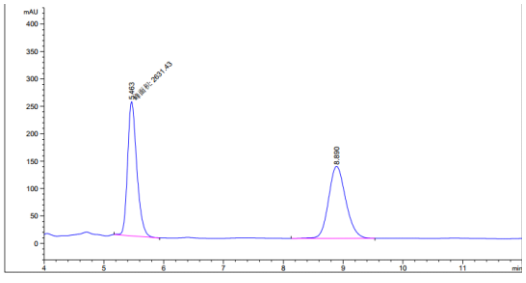
峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 [mAU*s]	峰高 [mAU]	峰面积 %
1	5.682	MM	0.1885	5908.45459	522.54541	93.9350
2	10.651	MF	0.3933	381.48376	16.16399	6.0650

(2*S*,3*R*,4*S*,5*R*)-3,4-diethyl 2-methyl 5-(3-fluorophenyl)pyrrolidine-2,3,4-tricarboxylate (4j)

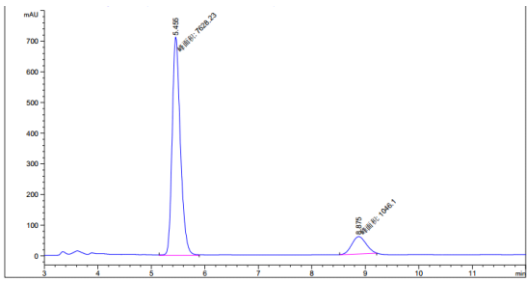


4j

White solid, Mp.99–100°C; yield 88%; $[\alpha]_D^{30}$ = +51.0 (*c* 1.25, CH_2Cl_2); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.30–7.25 (m, 1H), 7.15–7.08 (m, 2H), 6.9–6.92 (m, 1H), 4.44 (d, *J* = 6.8 Hz, 1H), 4.12 (q, *J* = 7.2 Hz, 3H), 3.79 (s, 3H), 3.78–3.68 (m, 3H), 3.58 (dd, *J* = 8.0, 7.2 Hz, 1H), 1.23 (t, *J* = 7.2 Hz, 3H), 0.85 (t, *J* = 7.2 Hz, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 170.9, 170.20, 170.17, 163.8, 161.4, 139.9, 129.8, 122.4, 114.2, 64.7, 62.0, 61.2, 60.5, 52.5, 52.3, 51.2, 14.0, 13.6; HRMS (ESI): *m/z* $[M+H]^+$ calcd. for $C_{18}H_{22}FNO_6$ $[M+H]^+$ 368.1504, found:368.1506; The ee value was 76%, t_R (major) = 5.46 min, t_R (minor) = 8.88 min (Chiralcel AS-H, λ = 210 nm, *i*PrOH/hexanes = 50:50, flow rate = 1.0 mL/min).

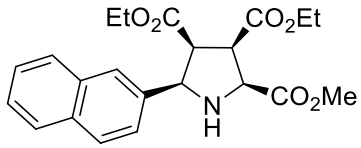


峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 [mAU*s]	峰高 [mAU]	峰面积 %
1	5.463	MM	0.1792	2631.42749	244.74727	50.0569
2	8.890	BB	0.3102	2625.44458	131.43527	49.9431



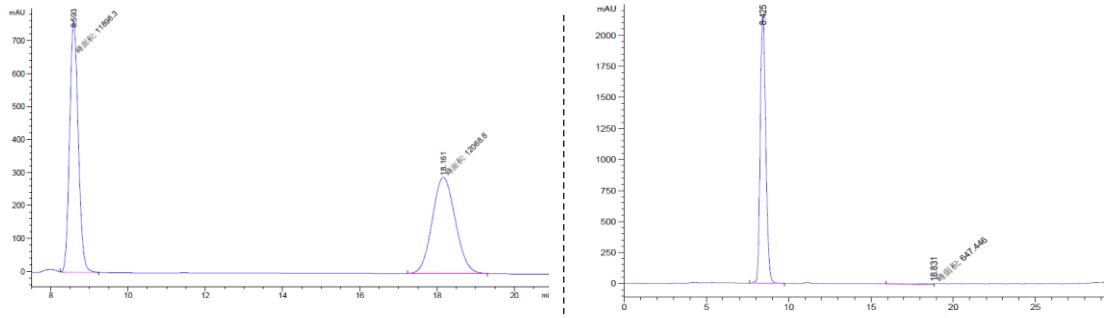
峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 [mAU*s]	峰高 [mAU]	峰面积 %
1	5.455	MM	0.1788	7628.23242	711.17511	87.9403
2	8.875	MF	0.3088	1046.10046	56.46661	12.0597

(2*S*,3*R*,4*S*,5*R*)-3,4-diethyl 2-methyl 5-(naphthalen-2-yl)pyrrolidine-2,3,4-tricarboxylate (4k)[1]



4k

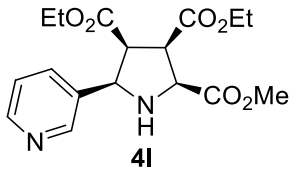
White solid, Mp. 122-124 ºC; yield 89%; $[\alpha]_D^{30}$ = +28.9 (*c* 1.06, CH_2Cl_2); The ee value was 97%, t_R (major) = 8.43 min, t_R (minor) = 18.83 min, (Chiralcel AS-H, λ = 210 nm, *i*PrOH/hexanes 50:50, flow rate =0.8 mL/min).



#	[min]		[min]	[mAU*s]	[mAU]	%
1	8.593	MM	0.2600	1.18963e4	762.55408	49.6401
2	18.161	MM	0.6902	1.20688e4	291.42694	50.3599

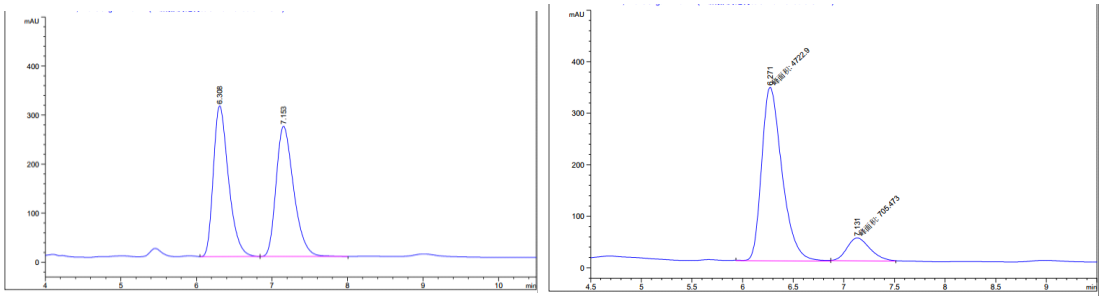
#	[min]		[min]	[mAU*s]	[mAU]	%
1	8.425	BB	0.3691	5.03516e4	2140.63550	98.7305
2	18.831	MM	2.2849	647.44647	4.72271	1.2695

(2*S*,3*R*,4*S*,5*R*)-3,4-diethyl 2-methyl 5-(pyridin-3-yl)pyrrolidine-2,3,4-tricarboxylate (4l)[2]



4l

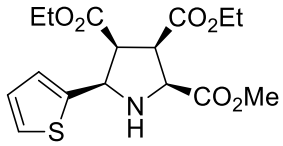
White solid, Mp. 100–101 ºC; yield: 89%; $[\alpha]_D^{30}$ = +44.2 (*c* 0.65, CH_2Cl_2); The ee value was 74%, t_R (major) = 6.27 min, t_R (minor) = 7.13 min (Chiralcel AS-H, λ = 210 nm, *i*PrOH/hexanes = 50:50, flow rate = 1.0 mL/min).



峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 [mAU*s]	峰高 [mAU]	峰面积 %
1	6.308	VB	0.2139	4293.85303	307.48459	49.9895
2	7.153	BB	0.2470	4295.65820	265.44943	50.0105

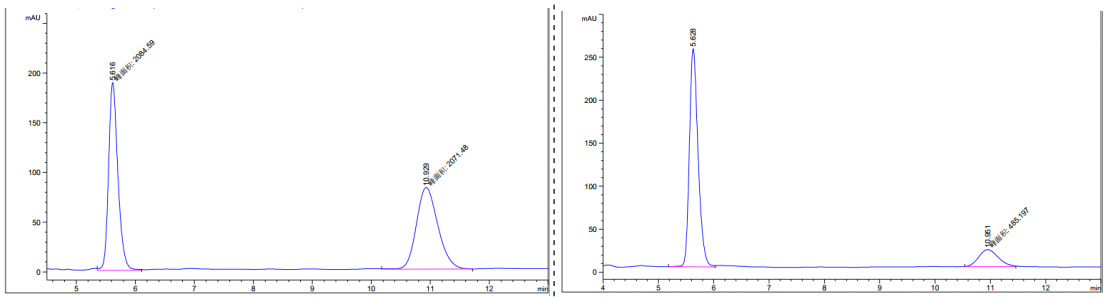
峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 [mAU*s]	峰高 [mAU]	峰面积 %
1	6.271	MM	0.2336	4722.89941	336.93103	87.0040
2	7.131	MM	0.2648	705.47321	44.39523	12.9960

(2*S*,3*R*,4*S*,5*R*)-3,4-diethyl 2-methyl 5-(thiophen-2-yl)pyrrolidine-2,3,4-tricarboxylate (4m)[1]



4m

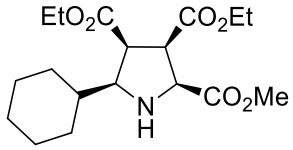
White solid, Mp. 85–86 °C; yield 80%; $[\alpha]_D^{30}$ = +32.6 (*c* 1.10, CH_2Cl_2); The ee value was 70%, t_R (major) = 5.63 min, t_R (minor) = 10.95 min (Chiralcel AS-H, λ = 210 nm, *i*PrOH/hexanes = 50:50, flow rate = 1.0 mL/min).



峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 [mAU*s]	峰高 [mAU]	峰面积 %
1	5.616	MM	0.1841	2084.59448	188.70624	50.1577
2	10.929	FM	0.4208	2071.48242	82.03603	49.8423

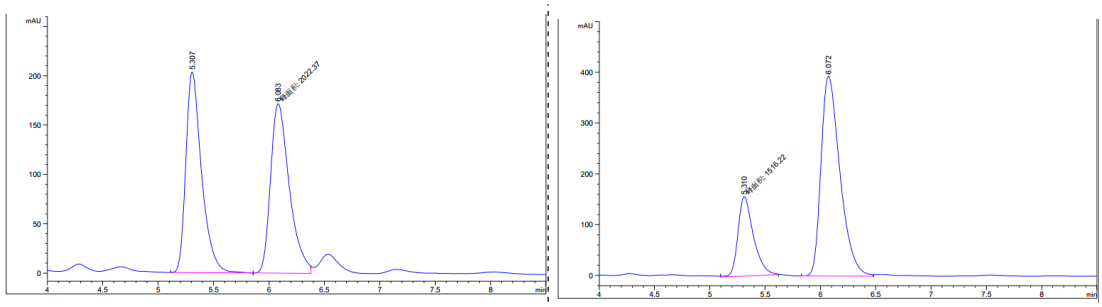
峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 [mAU*s]	峰高 [mAU]	峰面积 %
1	5.628	BV	0.1649	2763.06982	253.75302	85.0629
2	10.951	FM	0.4083	485.19745	19.80689	14.9371

(2*S*,3*R*,4*S*,5*S*)-3,4-diethyl 2-methyl 5-cyclohexylpyrrolidine-2,3,4-tricarboxylate (4n)[1]



4n

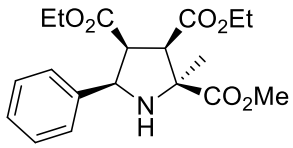
White solid, Mp. 80–81 °C; yield: 80%; $[\alpha]_D^{30}$ = +14.7 (c 0.90, CH_2Cl_2); The ee value was 51%, t_R (minor) = 5.31 min, t_R (major) = 6.07 min (Chiralcel AD-H, λ = 210 nm, *i*PrOH/hexanes 20:80, flow rate = 1 mL/min).



峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 [mAU*s]	峰高 [mAU]	峰面积 %
1	5.307	BB	0.1488	2009.10315	203.31778	49.8355
2	6.083	MF	0.1962	2022.37024	171.75139	50.1645

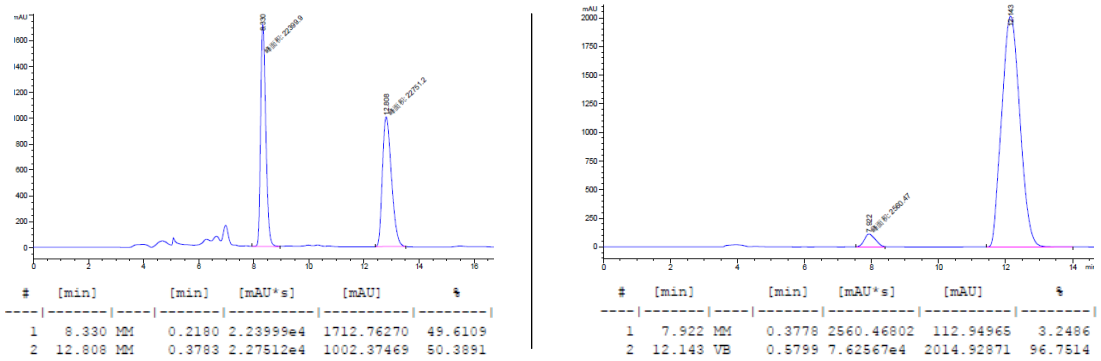
峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 [mAU*s]	峰高 [mAU]	峰面积 %
1	5.310	MF	0.1615	1516.22046	156.48764	24.4632
2	6.072	BV	0.1825	4681.74365	393.48880	75.5368

(2*S*,3*R*,4*S*,5*R*)-3,4-diethyl 2-methyl 2-methyl-5-phenylpyrrolidine-2,3,4-tricarboxylate (4o)[1]



4o

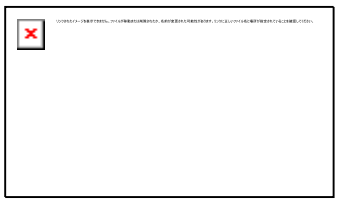
Colorless oil, yield 90%; $[\alpha]_D^{30}$ = +40.8 (*c* 1.20, CH_2Cl_2); The ee value was 93%, t_R (minor) = 7.92 min, t_R (major) = 12.14 min, (Chiralcel AD-H, λ = 205 nm, *i*PrOH/hexanes 15:85, flow rate =0.8 mL/min).



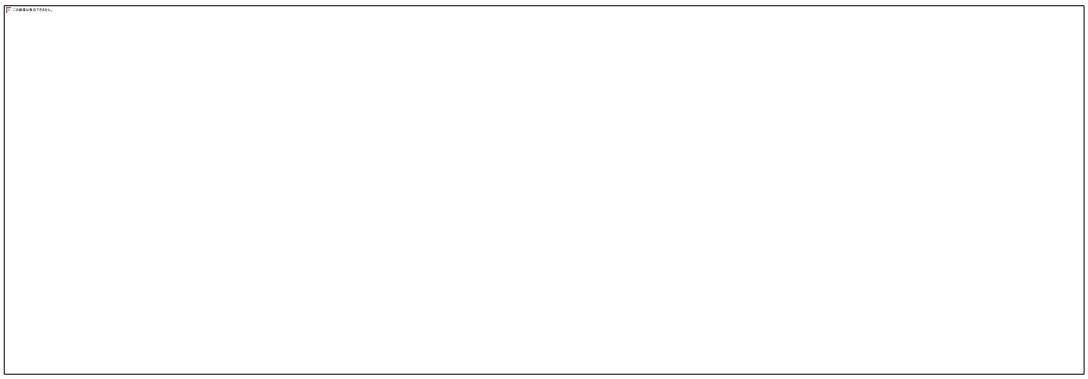
#	[min]		[min]	[mAU*s]	[mAU]	%
1	8.330	MM	0.2180	2.23999e4	1712.76270	49.6109
2	12.808	MM	0.3783	2.27512e4	1002.37469	50.3891

#	[min]		[min]	[mAU*s]	[mAU]	%
1	7.922	MM	0.3778	2560.46802	112.94965	3.2486
2	12.143	VB	0.5799	7.62567e4	2014.92871	96.7514

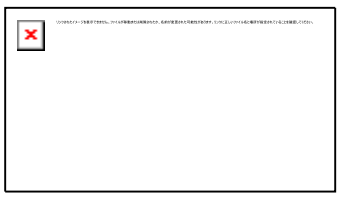
(2*S*,3*R*,4*S*,5*R*)-3,4-diethyl 2-methyl 2-methyl-5-(p-tolyl)pyrrolidine-2,3,4-tricarboxylate (4p)[1]



Colorless oil, yield 83%; $[\alpha]_D^{30}$ = +25.8 (*c* 1.00, CH_2Cl_2); The ee value was 94%, t_R (minor) = 7.45 min, t_R (major) = 10.28 min, (Chiralcel AD-H, λ = 210 nm, *i*PrOH/hexanes 15:85, flow rate =0.8 mL/min).

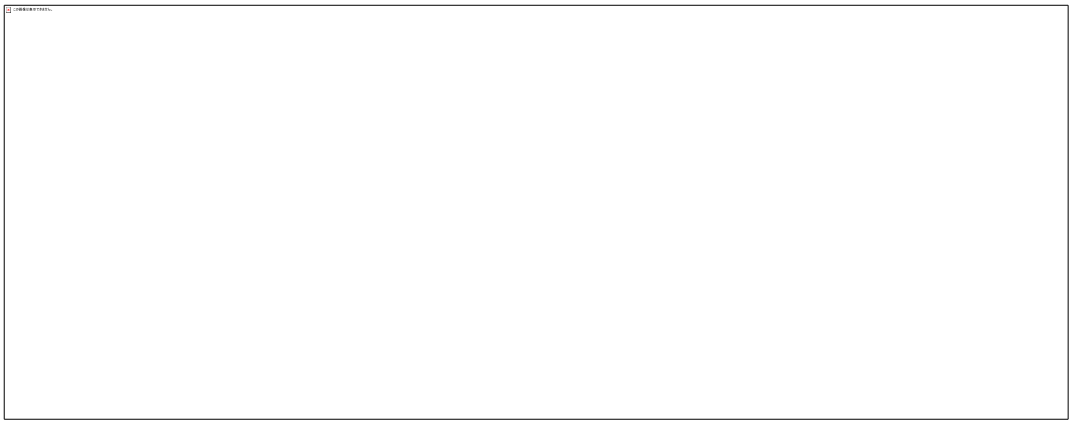


(2*S*,3*R*,4*S*,5*R*)-3,4-diethyl 2-methyl 5-(4-fluorophenyl)-2-methylpyrrolidine-2,3,4-tri-carboxylate (4q)[1]

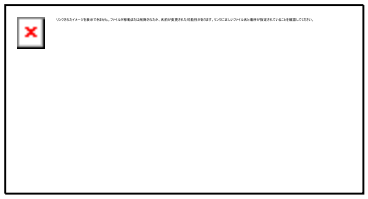


White solid, Mp. 87–88 °C; yield 82%; $[\alpha]_D^{30}$ = +41.2 (*c* 1.00, CH_2Cl_2); The ee value was 96%, t_R

(minor) = 8.14min, t_R (major) = 12.11 min, (Chiralcel AD-H, λ = 210 nm, *i*PrOH/hexanes 15:85, flow rate =0.8 mL/min).

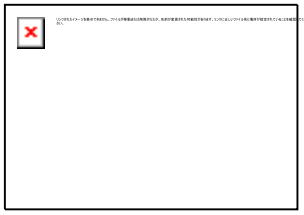


(2S,3R,4S,5R)-3,4-diethyl 2-methyl 2-methyl-5-(naphthalen-2-yl)pyrrolidine-2,3,4-tricarboxylate (4r)[1]



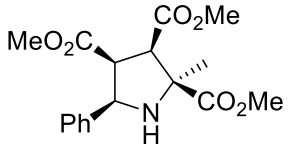
Colorless oil, yield 81%; $[\alpha]_D^{30}$ = +21.8 (*c* 0.95, CH_2Cl_2); The ee value was 88%, t_R (minor) = 18.2 min, t_R (major) = 19.9 min, (Chiralcel OD-H, λ = 210 nm, *i*PrOH/hexanes 15:85, flow rate =0.8 mL/min).

(2*S*,3*R*,4*S*,5*R*)-trimethyl 5-phenylpyrrolidine-2,3,4-tricarboxylate (4s)[1]



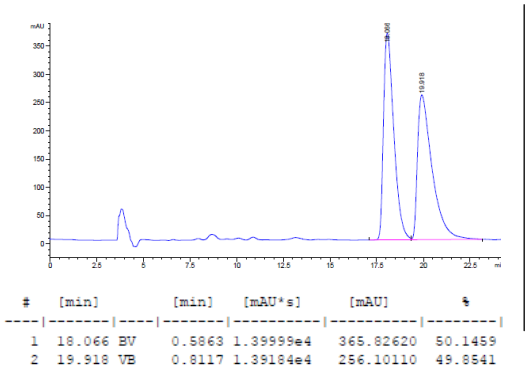
White solid, yield 91%; Mp. 94–95 °C; $[\alpha]_D^{30}$ = +72.8 (c 1.10, CH_2Cl_2); The ee value was 90%, t_R (major) = 7.47 min, t_R (minor) = 15.2 min, (Chiralcel AS-H, λ = 210 nm, *i*PrOH/hexanes 50:50, flow rate =0.8 mL/min).

(2*S*,3*R*,4*S*,5*R*)-trimethyl 2-methyl-5-phenylpyrrolidine-2,3,4-tricarboxylate (4t)[1]

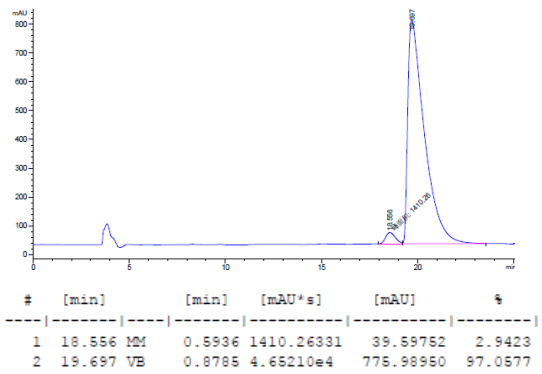


4t

Colorless oil, yield 82%; $[\alpha]_D^{30}$ = +80.6 (c 1.10, CH2Cl2) The ee value was 94%, t_R (minor) = 18.56 min, t_R (major) = 19.70 min, (Chiralcel OD-H, λ = 205 nm, *i*PrOH/hexanes 15:85, flow rate =0.8 mL/min).

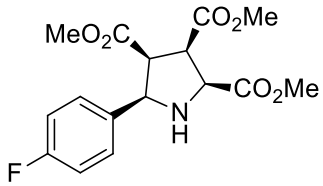


#	[min]		[min]	[mAU*s]	[mAU]	%
1	18.066	BV	0.5863	1.39999e4	365.82620	50.1459
2	19.918	VB	0.8117	1.39184e4	256.10110	49.8541



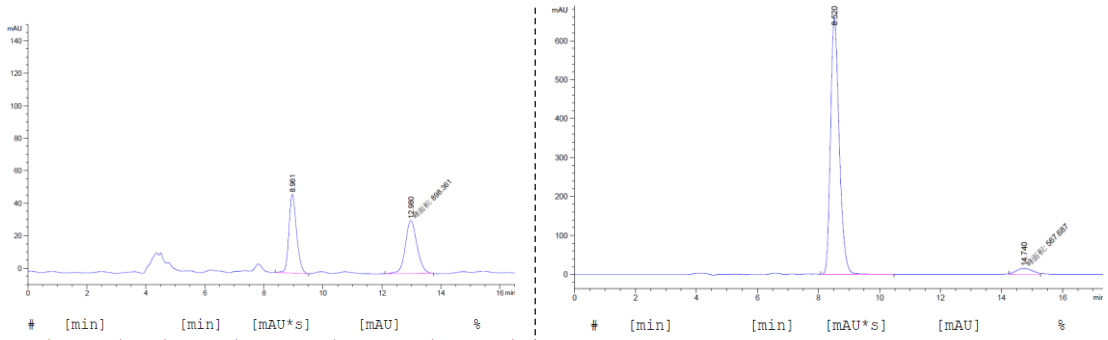
#	[min]		[min]	[mAU*s]	[mAU]	%
1	18.556	MM	0.5936	1410.26331	39.59752	2.9423
2	19.697	VB	0.8785	4.65210e4	775.98950	97.0577

(2*S*,3*R*,4*S*,5*R*)-trimethyl 5-(4-fluorophenyl)pyrrolidine-2,3,4-tricarboxylate (4u)



4u

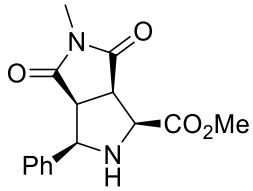
White solid, Mp. 94–95 °C; yield 87%; $[\alpha]_D^{30}$ = +69.7 (c 0.95, CH_2Cl_2); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.33–7.29 (m, 2H), 6.99 (t, *J* = 8.8 Hz, 2H), 4.45 (d, *J* = 6.8 Hz, 1H), 4.12 (d, *J* = 8.8 Hz, 1H), 3.78 (s, 3H), 3.71–3.9 (m, 1H), 3.67(s, 3H), 3.56–3.52 (m, 1H), 3.24 (s, 3H), 2.83 (s, 1H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 171., 170.8, 170.7, 163.3, 132.9, 128.5, 115.22, 64.6, 62.1, 52.4, 52.4, 52.1, 51.4, 50.7; HRMS (ESI): *m/z* $[M+H]^+$ calcd. for $C_{16}H_{18}FNO_6$: 340.1191, found: 340.1198; The ee value was 92%, t_R (major) = 8.52 min, t_R (minor) = 14.74 min, (Chiralcel AS-H, λ = 210 nm, *i*PrOH/hexanes 50:50, flow rate = 0.8 mL/min).



#	[min]		[min]	[mAU*s]	[mAU]	%
1	8.961	BB	0.2732	876.09882	48.54026	49.3727
2	12.980	MM	0.4588	898.36121	32.63707	50.6273

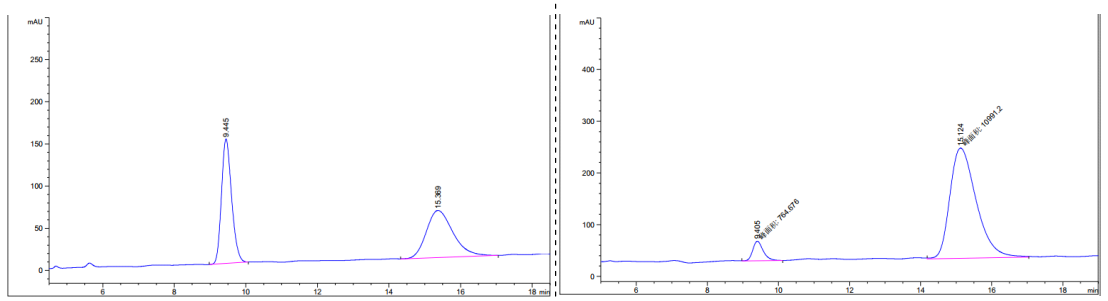
#	[min]		[min]	[mAU*s]	[mAU]	%
1	8.520	BB	0.3037	1.29782e4	655.65277	95.8092
2	14.740	MM	0.6086	567.68652	15.54742	4.1908

(1*S*,3*R*,3a*S*,6a*R*)-methyl 5-methyl-4,6-dioxo-3-phenyloctahydropyrrolo[3,4-c]pyrrole-1-carboxylate (4v)[1]



4v

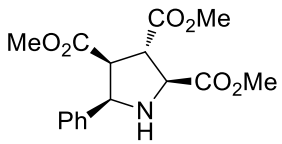
White solid, yield 91%; Mp. 164–165 °C; $[\alpha]_D^{30}$ = +70.6 (*c* 1.20, CH_2Cl_2); The ee value was 87%, t_R (minor) = 9.41 min, t_R (major) = 15.12 min, (Chiralcel AS-H, λ = 205 nm, *i*PrOH/hexanes 50:50, flow rate =1.0 mL/min).



峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 [mAU*s]	峰高 [mAU]	峰面积 %
1	9.445	BB	0.3013	2909.09937	147.56882	50.1973
2	15.369	BB	0.7998	2886.23364	55.81626	49.8027

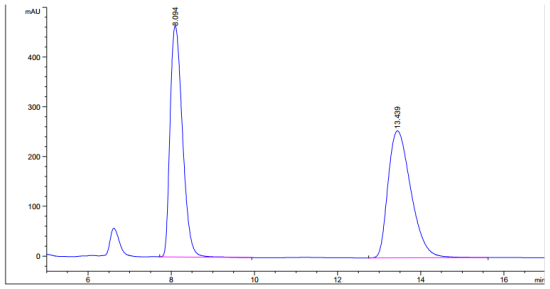
峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 [mAU*s]	峰高 [mAU]	峰面积 %
1	9.405	MM	0.3373	764.67596	37.78337	6.5047
2	15.124	MM	0.8590	1.09912e4	213.25989	93.4953

(2*S*,3*S*,4*S*,5*R*)-trimethyl 5-phenylpyrrolidine-2,3,4-tricarboxylate (6a)[1]

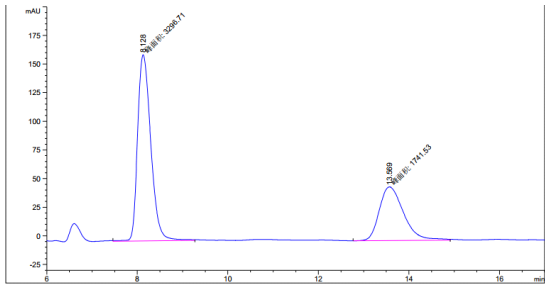


6a

Catalyzed by **1c**: colorless oil, yield 78%; $[\alpha]_D^{30}$ = +6.6 (*c* 1.10, CH_2Cl_2); The ee value was 31%, t_R (major) = 8.13 min, t_R (minor) = 13.57 min (Chiralcel OD-H, λ= 220 nm, iPrOH/hexanes = 40:60, flow rate = 1.0 mL/min).

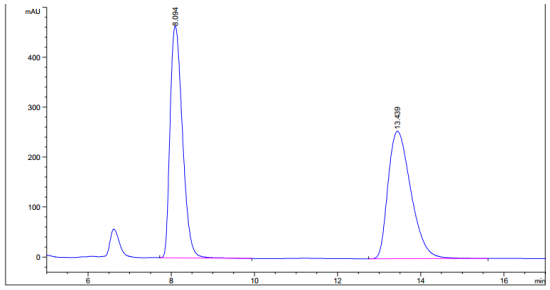


峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 [mAU*s]	峰高 [mAU]	峰面积 %
1	8.094	VB	0.3254	9584.34766	464.15735	49.5722
2	13.439	BB	0.5944	9749.76367	255.12340	50.4278

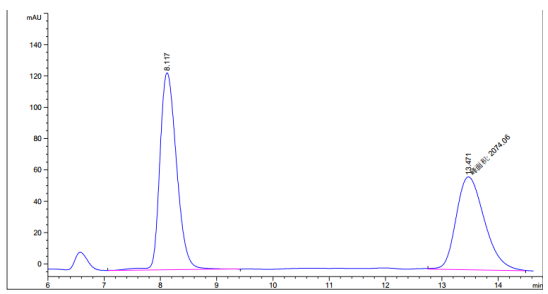


峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 [mAU*s]	峰高 [mAU]	峰面积 %
1	8.128	MF	0.3378	3296.70825	162.64555	65.4338
2	13.569	MF	0.6197	1741.52881	46.84081	34.5662

Catalyzed by **1e**: **c**olorless oil, yield 65%; $[\alpha]_D^{30}$ = +3.9 (*c* 1.10, CH_2Cl_2); The ee value was 11%, t_R (major) = 8.12 min, t_R (minor) = 13.47 min (Chiralcel OD-H, λ= 220 nm, iPrOH/hexanes = 40:60, flow rate = 1.0 mL/min).

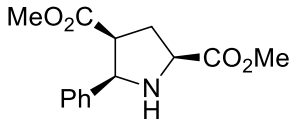


峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 [mAU*s]	峰高 [mAU]	峰面积 %
1	8.094	VB	0.3254	9584.34766	464.15735	49.5722
2	13.439	BB	0.5944	9749.76367	255.12340	50.4278



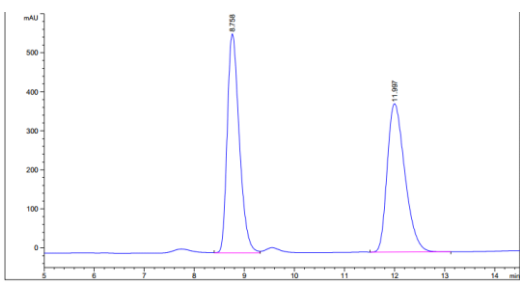
峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 [mAU*s]	峰高 [mAU]	峰面积 %
1	8.117	BB	0.3248	2588.86060	125.63798	55.5202
2	13.471	MF	0.5832	2074.05811	59.26960	44.4798

(2*S*,4*S*,5*R*)-dimethyl 5-phenylpyrrolidine-2,4-dicarboxylate (6b)[3]

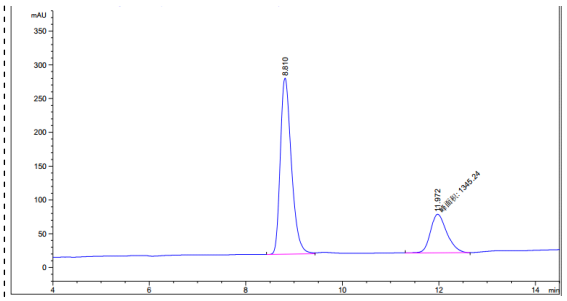


6b

Catalyzed by **1c**: white solid, Mp.70–71°C; yield 88%; $[\alpha]_D^{30}$ = +23.8 (*c* 1.10, CH_2Cl_2); The ee value was 51%, t_R (major) = 8.81 min, t_R (minor) = 11.97 min, (Chiralcel AS-H, λ = 205 nm, *i*PrOH/hexanes 20:80, flow rate =1.0 mL/min).

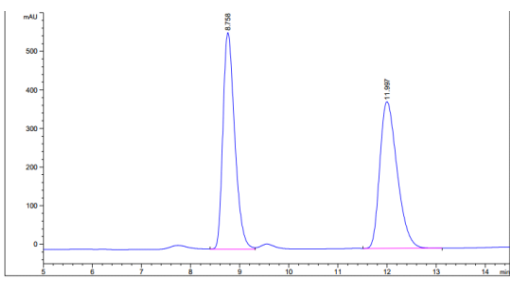


峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 [mAU*s]	峰高 [mAU]	峰面积 %
1	8.758	VV	0.2574	9373.21875	561.31519	50.0872
2	11.997	VB	0.3796	9340.59766	380.48575	49.9128

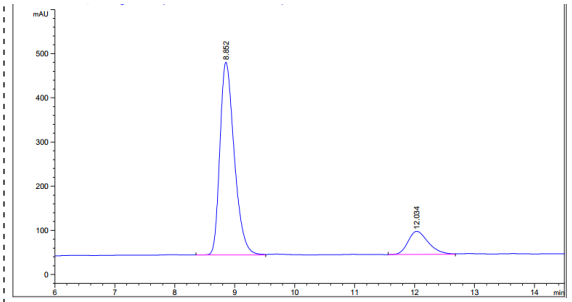


峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 [mAU*s]	峰高 [mAU]	峰面积 %
1	8.810	BV	0.2422	4140.49316	260.50595	75.4775
2	11.972	FM	0.3928	1345.23853	57.07861	24.5225

Catalyzed by **1e**: white solid, Mp.72–73ºC; yield 90%; $[\alpha]_D^{30}$ = +31.5 (*c* 1.00, CH_2Cl_2); The ee value was 71%, t_R (major) = 8.85 min, t_R (minor) = 12.03 min, (Chiralcel AS-H, λ = 205 nm, *i*PrOH/hexanes 20:80, flow rate =1.0 mL/min).

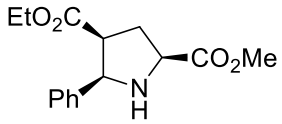


峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 [mAU*s]	峰高 [mAU]	峰面积 %
1	8.758	VV	0.2574	9373.21875	561.31519	50.0872
2	11.997	VB	0.3796	9340.59766	380.48575	49.9128



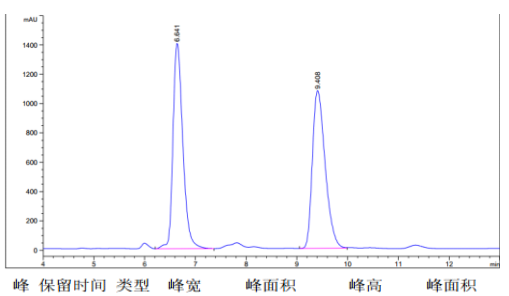
峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 [mAU*s]	峰高 [mAU]	峰面积 %
1	8.852	BV	0.2551	7254.98682	436.37183	85.5462
2	12.034	BV	0.3561	1225.79419	52.37110	14.4538

(2S,4S,5R)-4-ethyl 2-methyl 5-phenylpyrrolidine-2,4-dicarboxylate (6c)[3]

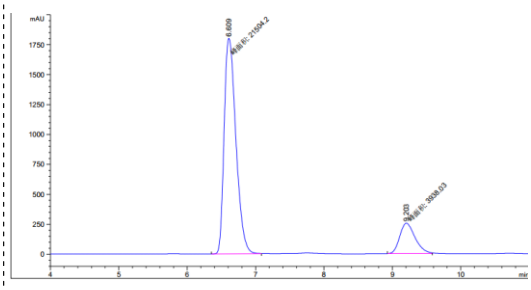


6c

White solid, Mp.69–70 ºC; yield 87%; $[\alpha]_D^{30}$ = +15.1 (*c* 1.10, CH_2Cl_2); The ee value was 69%, t_R (major) = 6.61 min, t_R (minor) = 9.20 min, (Chiralcel AS-H, λ = 205 nm, *i*PrOH/hexanes 20:80, flow rate =1.0 mL/min).

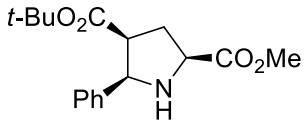


峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 [mAU*s]	峰高 [mAU]	峰面积 %
1	6.641	BB	0.2070	1.88894e4	1398.84766	50.1242
2	9.408	BV	0.2696	1.87958e4	1074.66174	49.8758



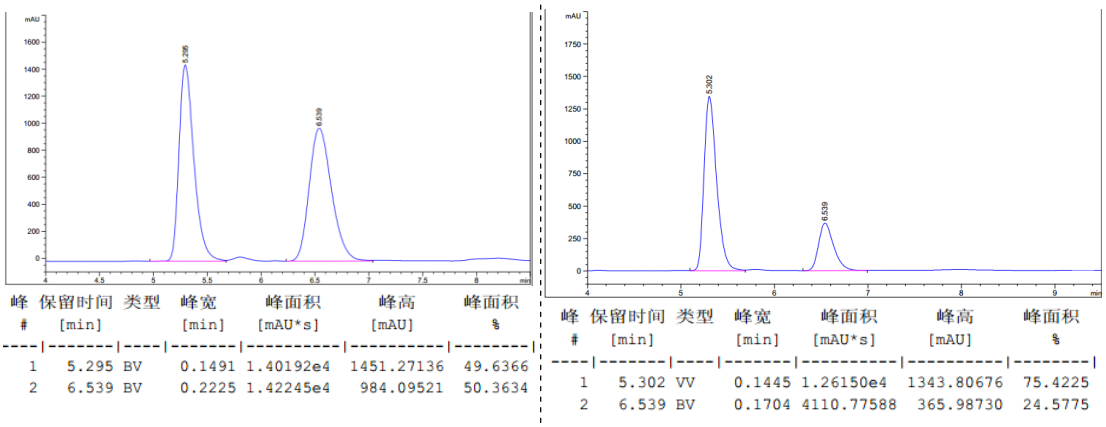
峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 [mAU*s]	峰高 [mAU]	峰面积 %
1	6.609	MF	0.1992	2.15042e4	1799.35327	84.5217
2	9.203	FM	0.2587	3938.03052	253.71158	15.4783

(2*S*,4*S*,5*R*)-4-tert-butyl 2-methyl 5-phenylpyrrolidine-2,4-dicarboxylate (6d)[3]



6d

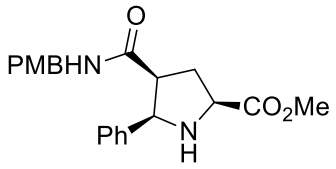
White solid, Mp.68–69 °C; yield 87%; $[\alpha]_D^{30}$ = +12.3 (*c* 0.10, CH_2Cl_2); The ee value was 51%, t_R (major) = 5.30 min, t_R (minor) = 6.54 min, (Chiralcel AS-H, λ = 205 nm, *i*PrOH/hexanes 20:80, flow rate =1.0 mL/min).



峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 [mAU*s]	峰高 [mAU]	峰面积 %
1	5.295	BV	0.1491	1.40192e4	1451.27136	49.6366
2	6.539	BV	0.2225	1.42245e4	984.09521	50.3634

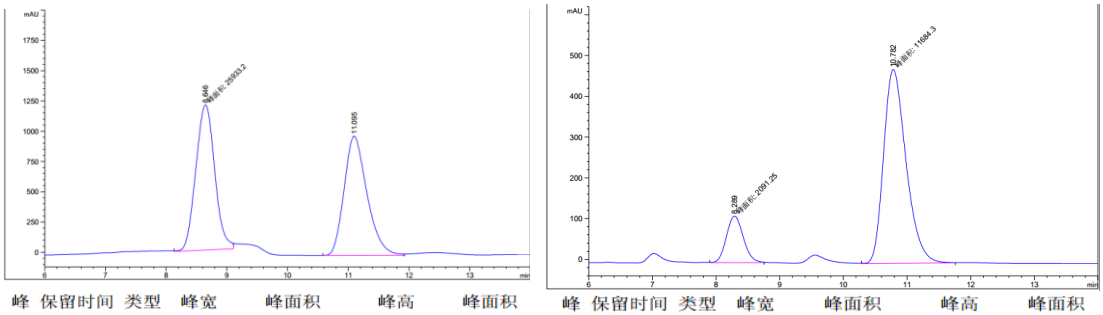
峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 [mAU*s]	峰高 [mAU]	峰面积 %
1	5.302	VV	0.1445	1.26150e4	1343.80676	75.4225
2	6.539	BV	0.1704	4110.77588	365.98730	24.5775

(2*S*,4*S*,5*R*)-methyl 4-((4-methoxybenzyl)carbamoyl)-5-phenylpyrrolidine-2-carboxylate (6e)[4]



6e

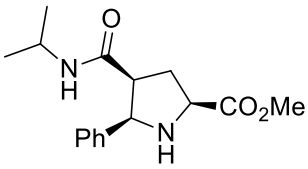
White solid, Mp. 82–83 °C; yield 87%; $[\alpha]_D^{30}$ = +25.6 (c 1.10, CH_2Cl_2); The ee value was 70%, t_R (minor) = 8.29 min, t_R (major) = 10.78 min. (Chiralcel AD-H, λ = 205 nm
^{i}PrOH/hexane = 20:80, flow rate = 1 mL/min).



峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 [mAU*s]	峰高 [mAU]	峰面积 %
1	8.646	MM	0.3607	2.59332e4	1198.29163	50.1834
2	11.095	BV	0.3957	2.57437e4	983.43164	49.8166

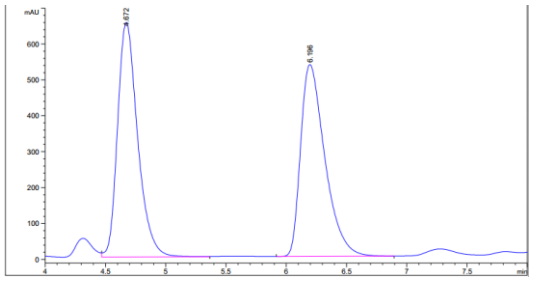
峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 [mAU*s]	峰高 [mAU]	峰面积 %
1	8.289	MM	0.3066	2091.25122	113.69623	15.1808
2	10.782	MM	0.4095	1.16843e4	475.56796	84.8192

(2*S*,4*S*,5*R*)-methyl 4-(isopropylcarbamoyl)-5-phenylpyrrolidine-2-carboxylate (6f)[4]

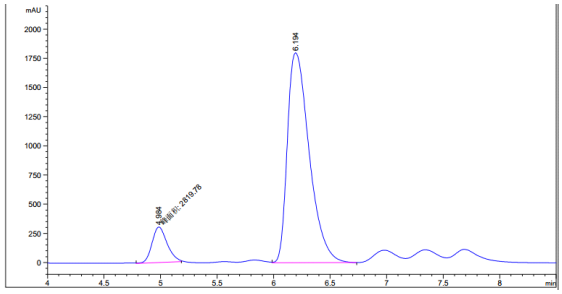


6f

White solid, Mp. 107–108 °C; yield 89%; $[\alpha]_D^{30}$ = +45.6 (*c* 1.10, CH_2Cl_2); The ee value was 79%, t_R(minor) = 4.98 min, t_R(major) = 6.19 min (Chiralcel AD-H, λ = 205 nm, ^{i}PrOH/hexane = 20:80, flow rate = 1 mL/min).

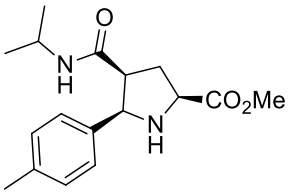


峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 [mAU*s]	峰高 [mAU]	峰面积 %
1	4.672	VV	0.1771	7556.47217	653.41949	50.2913
2	6.196	BB	0.2140	7468.92383	534.52008	49.7087



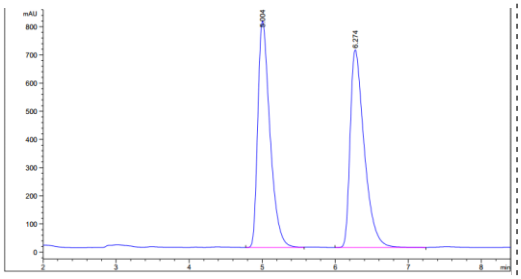
峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 [mAU*s]	峰高 [mAU]	峰面积 %
1	4.984	MM	0.1542	2819.78345	304.83487	10.4432
2	6.194	VB	0.2079	2.41814e4	1798.06921	89.5568

(2*S*,4*S*,5*R*)-methyl 4-(isopropylcarbamoyl)-5-(p-tolyl)pyrrolidine-2-carboxylate (6g)[4]

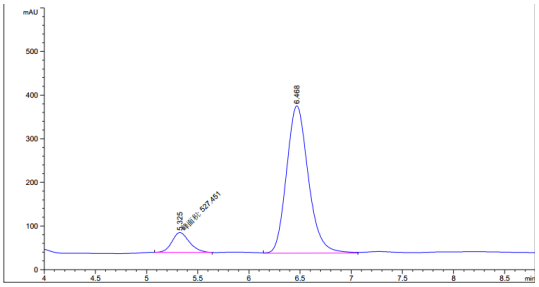


6g

White solid, Mp. 100–101 °C; yield 90%; $[\alpha]_D^{30}$ = +45.1 (*c* 0.75, CH_2Cl_2); The ee value was 81%, t_R (minor) = 5.33 min, t_R (major) = 6.47 min (Chiralcel AD-H, λ = 205 nm, ^{i}PrOH/hexane = 20:80, flow rate = 1 mL/min).

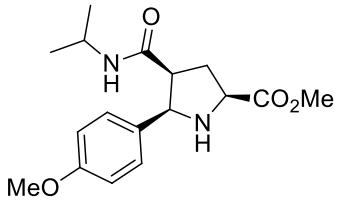


峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 [mAU*s]	峰高 [mAU]	峰面积 %
1	5.004	BV	0.1755	9281.57422	803.76678	49.7746
2	6.274	BV	0.2024	9365.63574	701.40503	50.2254



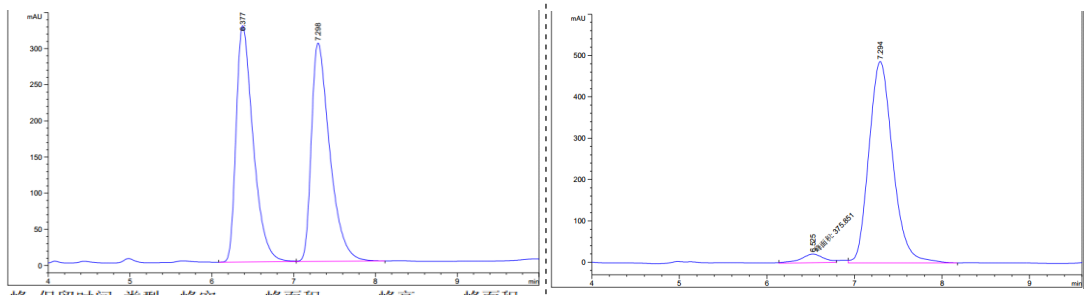
峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 [mAU*s]	峰高 [mAU]	峰面积 %
1	5.325	FM	0.1947	527.45105	45.14505	9.5318
2	6.468	VV	0.2282	5006.12012	337.90625	90.4682

(2*S*,4*S*,5*R*)-methyl 4-(isopropylcarbamoyl)-5-(4-methoxyphenyl)pyrrolidine-2-carboxylate (6h)[4]



6h

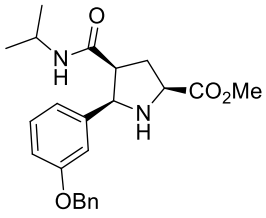
White solid, Mp. 99–100 °C; yield 92%; $[\alpha]_D^{30}$ = +11.2 (*c* 0.80, CH_2Cl_2); The ee value was 92%, t_R(minor) = 6.53 min, t_R(major) = 7.29 min (Chiralcel AD-H, λ = 205 nm, ^{i}PrOH/hexane = 20:80, flow rate = 1 mL/min).



峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 [mAU*s]	峰高 [mAU]	峰面积 %
1	6.377	BV	0.2201	4738.08105	326.89258	50.1516
2	7.298	VB	0.2343	4709.43359	302.10718	49.8484

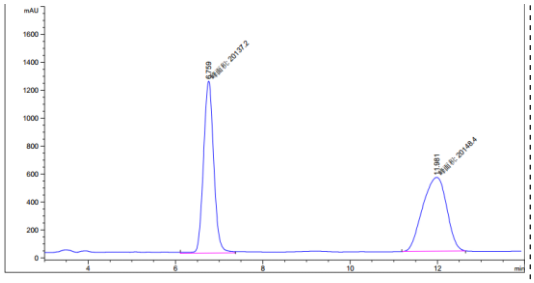
峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 [mAU*s]	峰高 [mAU]	峰面积 %
1	6.525	MM	0.3052	375.85089	20.52398	3.9181
2	7.294	VB	0.2937	9216.73633	486.85422	96.0819

(2*S*,4*S*,5*R*)-methyl 5-(3-(benzyloxy)phenyl)-4-(isopropylcarbamoyl)pyrrolidine-2-carboxylate (6i)

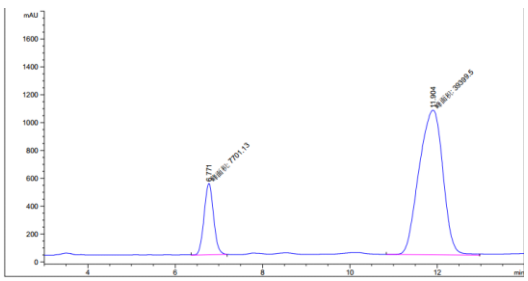


6i

Colorless oil, yield 85%; $[\alpha]_D^{30}$ = +17.9 (*c* 1.80, CH_2Cl_2); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.43–7.30 (m, 5H), 7.22 (t, *J* = 8.0 Hz, 1H), 6.99 (s, 1H), 6.94 (d, *J* = 7.6 Hz, 1H), 6.84 (dd, *J* = 8.0, 2.0 Hz, 1H), 5.99 (d, *J* = 8.0 Hz, 1H), 5.04 (s, 2H), 4.40 (d, *J* = 6.4 Hz, 1H), 4.00 (dd, *J* = 10.0, 6.0 Hz, 1H), 3.80 (s, 3H), 3.72–3.67 (m, 1H), 3.01–2.97 (m, 1H), 2.57–2.53 (m, 1H), 2.35–2.34 (m, 1H), 2.14 (brs, 1H), 0.81–0.78 (m, 6H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 174.0, 171.6, 158.7, 140.0, 136.9, 129.4, 128.5, 127.9, 127.5, 119.1, 113.4, 69.9, 65.0, 58.1, 52.3, 50.0, 40.6, 33.7, 22.2; HRMS (ESI): *m/z* $[M+H]^+$ calcd. for $C_{23}H_{28}N_2O_4$: 397.2122, found: 397.2127; The ee value was 67%, t_R(minor) = 6.77 min, t_R(major) = 11.90 min (Chiralcel AD-H, λ = 205 nm, ^{i}PrOH/hexane = 20:80, flow rate = 1 mL/min).

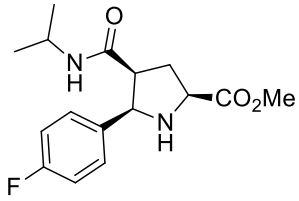


峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 [mAU*s]	峰高 [mAU]	峰面积 %
1	6.759	MM	0.2727	2.01372e4	1230.84985	49.9861
2	11.981	FM	0.6357	2.01484e4	528.22302	50.0139



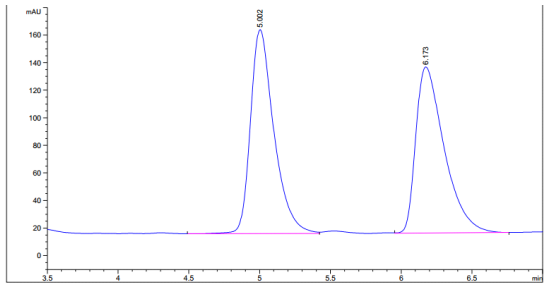
峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 [mAU*s]	峰高 [mAU]	峰面积 %
1	6.771	MM	0.2510	7701.12695	511.42978	16.3504
2	11.904	MM	0.6332	3.93995e4	1037.10974	83.6496

(2*S*,4*S*,5*R*)-methyl 5-(4-fluorophenyl)-4-(isopropylcarbamoyl)pyrrolidine-2-carboxylate (6j)[4]

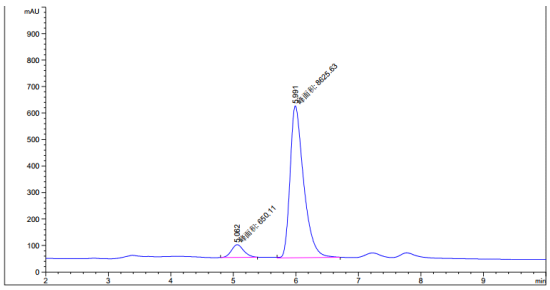


6j

White solid, Mp. 126–127 °C; yield 95%; $[\alpha]_D^{30}$ = +48.7 (*c* 0.95, CH_2Cl_2); The ee value was 86%, t_R(minor) = 5.06 min, t_R(major) = 5.99 min (Chiralcel AD-H, λ = 205 nm, ^{i}PrOH/hexane = 20:80, flow rate = 1 mL/min).

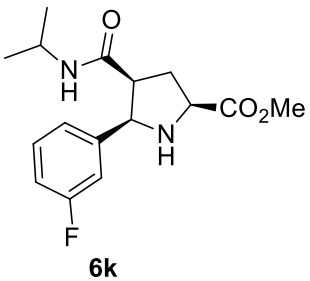


峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 [mAU*s]	峰高 [mAU]	峰面积 %
1	5.002	BV	0.1726	1707.40210	147.87270	50.4192
2	6.173	VB	0.2107	1679.00977	120.42619	49.5808



峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 [mAU*s]	峰高 [mAU]	峰面积 %
1	5.062	MM	0.2259	650.10992	47.96942	7.0087
2	5.991	MM	0.2508	8625.62891	573.28583	92.9913

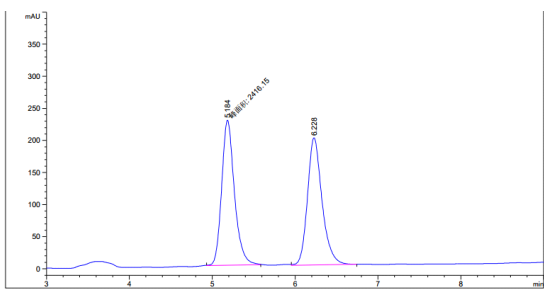
(2*S*,4*S*,5*R*)-methyl 5-(3-fluorophenyl)-4-(isopropylcarbamoyl)pyrrolidine-2-carboxylate (6k)

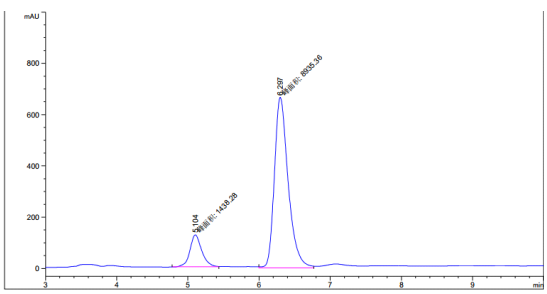


6k

White solid, Mp. 126–127 °C; yield 88%; $[\alpha]_D^{30}$ = 41.75 (*c* 1.00, CH_2Cl_2); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.29–7.24 (m, 1H), 7.10 (t, *J* = 1.0 Hz, 2H), 6.92 (td, *J* = 8.4, 2.1 Hz, 1H), 6.14 (d, *J* = 7.5 Hz, 1H), 4.42 (d, *J* = 6.8 Hz, 1H), 4.01 (dd, *J* = 10.0, 6.0 Hz, 1H), 3.80 (s, 3H), 3.74–3.67 (m, 1H), 3.0–2.99 (m, 1H), 2.61–2.53 (m, 1H), 2.35–2.29 (m, 2H), 2.22 (brs, 1H), 0.82 (dd, *J* = 2.0,

4.8 Hz, 6H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 173.9, 171.3, 163.9, 161.5, 141.0, 129.8, 122.3, 114.3, 113.7, 64.6, 58.0, 52.3, 50.0, 40.7, 33.6, 22.3; HRMS (ESI): *m/z* $[M+H]^+$ calcd. for $C_{16}H_{21}FN_2O_3$: 309.1609, found:
309.1615; The ee value was 72%, t_R(minor) = 5.10 min, t_R(major) = 6.30 min (Chiralcel AD-H, λ = 205 nm, ^{i}PrOH/hexane = 20:80, flow rate = 1 mL/min).

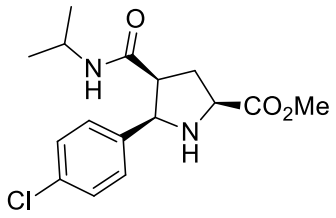




峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 [mAU*s]	峰高 [mAU]	峰面积 %
1	5.184	MM	0.1783	2416.14868	225.87682	49.9790
2	6.228	VB	0.1846	2418.17627	198.13126	50.0210

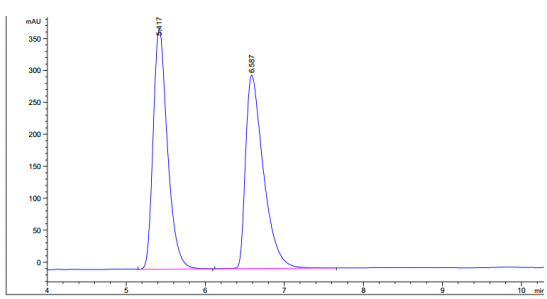
峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 [mAU*s]	峰高 [mAU]	峰面积 %
1	5.104	MM	0.1923	1438.27783	124.68163	13.8647
2	6.297	MM	0.2240	8935.36328	664.77710	86.1353

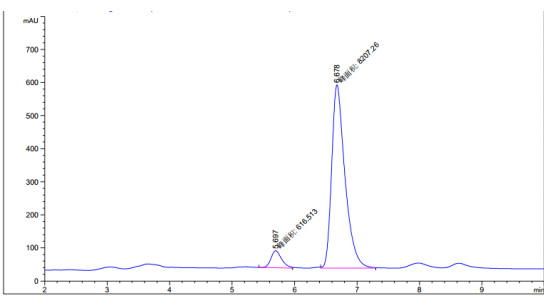
(2*S*,4*S*,5*R*)-methyl 5-(4-chlorophenyl)-4-(isopropylcarbamoyl)pyrrolidine-2-carboxylate (6l)[4]



6l

White solid, Mp. 128–129 °C; yield 89%; $[\alpha]_D^{30}$ = +51.3 (*c* 0.90, CH_2Cl_2); The ee value was 86%, t_R(minor) = 5.70 min, t_R(major) = 6.68 min (Chiralcel AD-H, λ = 205 nm, ^{i}PrOH/hexane = 20:80, flow rate = 1 mL/min).





峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 [mAU*s]	峰高 [mAU]	峰面积 %
1	5.417	VB	0.1907	4735.09521	375.62595	50.0135
2	6.587	BB	0.2349	4732.53711	302.54657	49.9865

峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 [mAU*s]	峰高 [mAU]	峰面积 %
1	5.697	MM	0.1983	616.51263	51.80881	6.9870
2	6.678	MF	0.2468	8207.25781	554.31323	93.0130

5. Reference

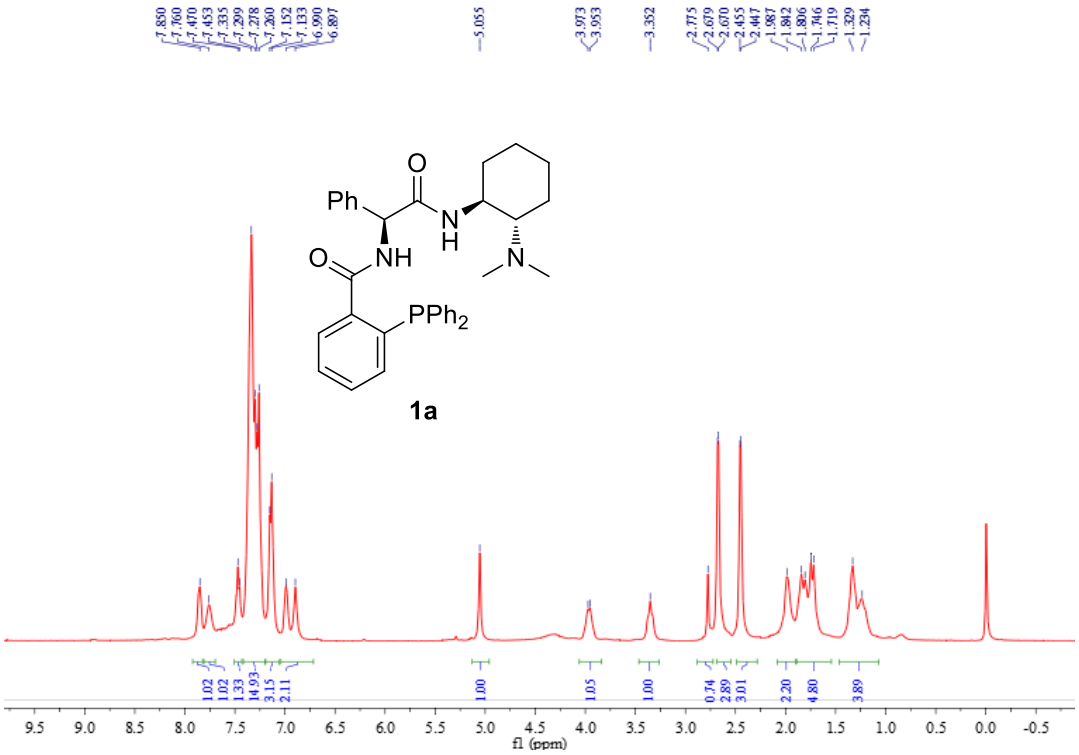
1. H. Wang, Q. Deng, Z. Zhou, S. Hu, Z. Liu, and L.-Y. Zhou, *Org. Lett.*, 2016, **18**, 404.

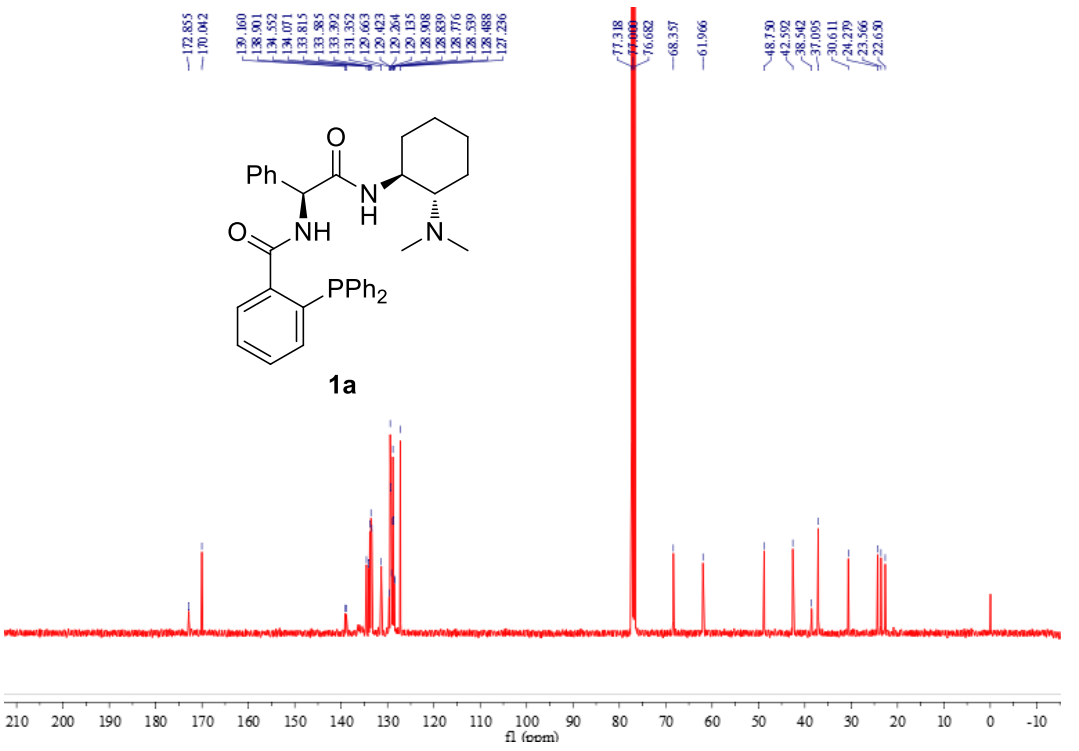
2. Z. Zhou, X. Zheng, J. Liu, J. Li, P. Wen, and H. Wang, *Synlett*, 2017, **28**, 999.

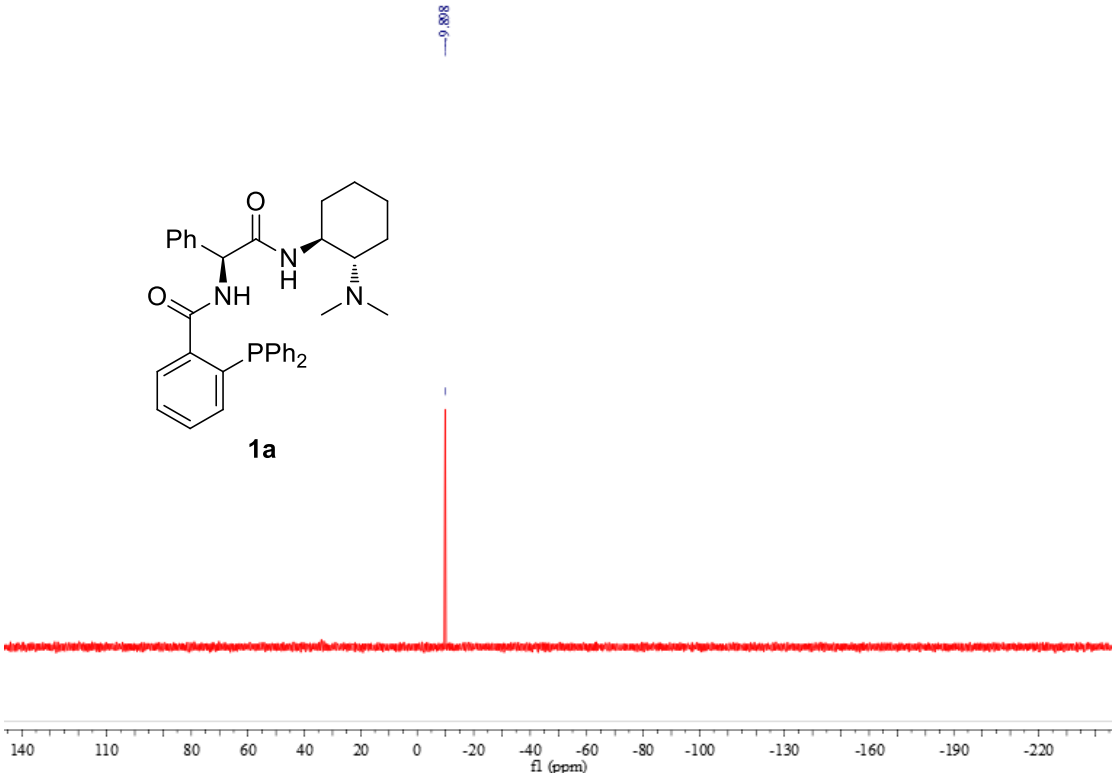
3. H. Wang, C. Gong, C. Zhang, X. Zheng, Q. Hou, Q. Zhou, G. Zhou, and Y. Chen, *Synlett*, 2021, **32**, 1437.

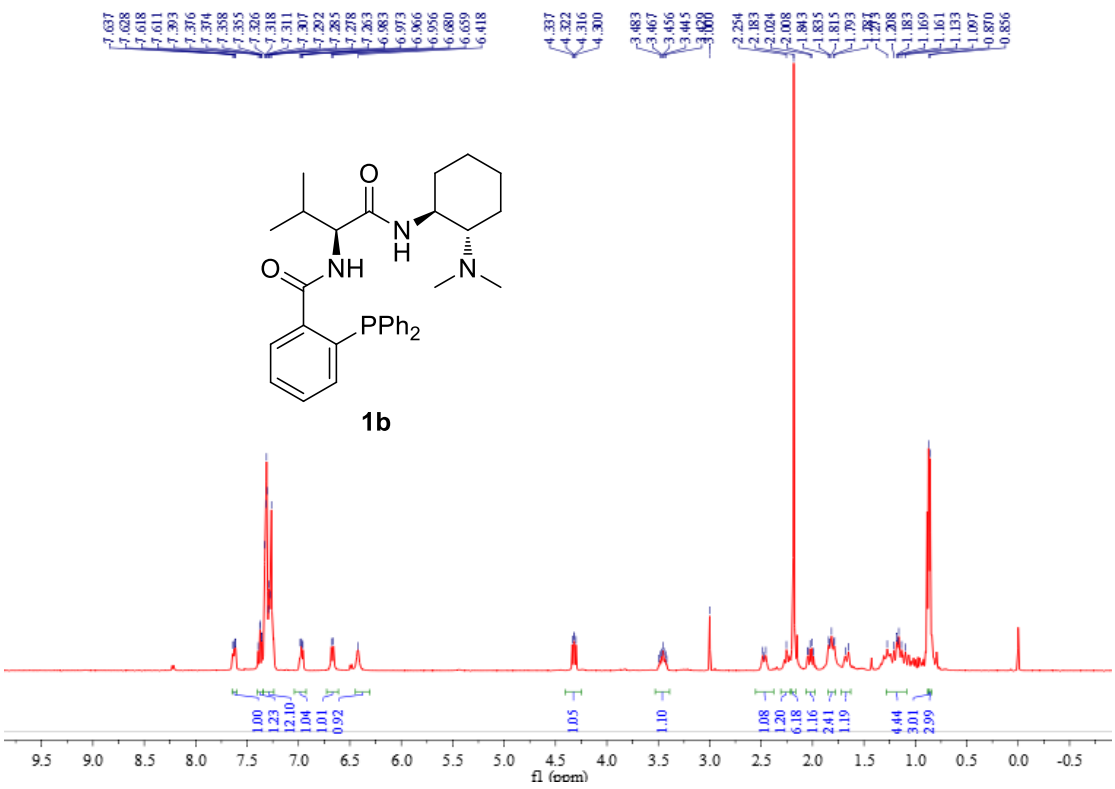
4. K.-Q. Zhang, Q.-F. Deng, J. Luo, C.-L. Gong, Z.-G. Chen, W. Zhong, S.-Q. Hu, and H.-F. Wang, *ACS Catal.*, 2021, **11**, 5100.

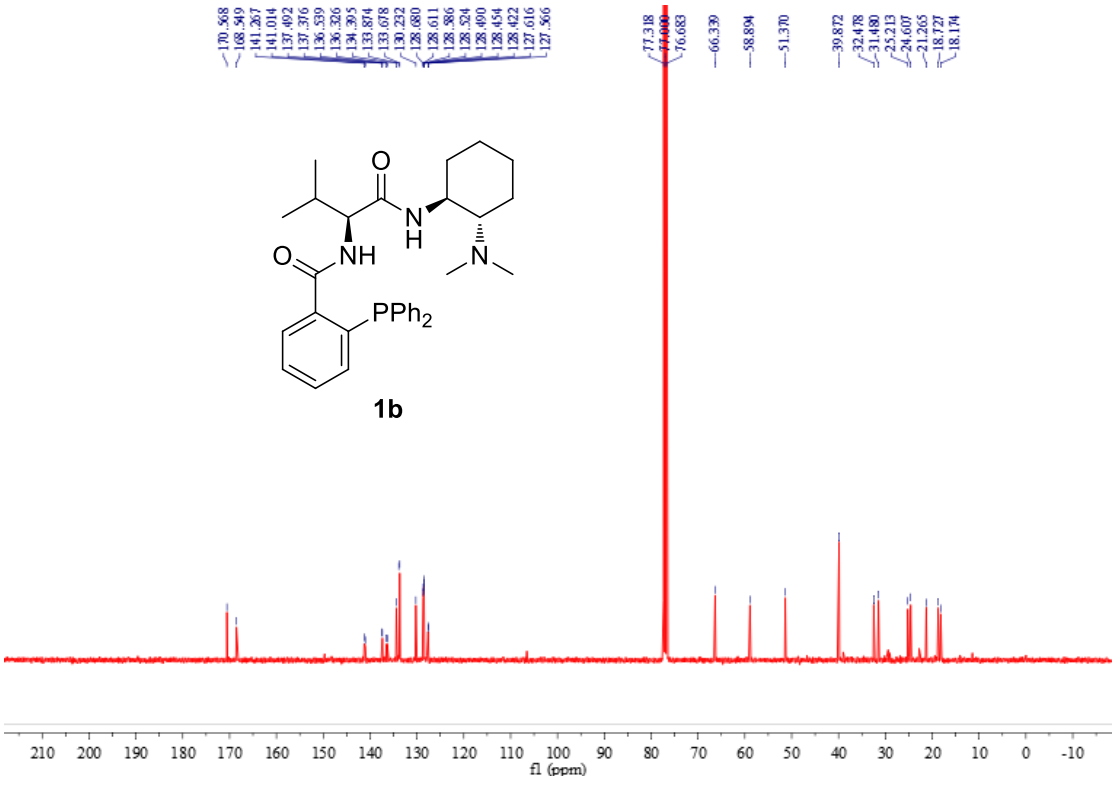
6. Copies of NMR Spectra

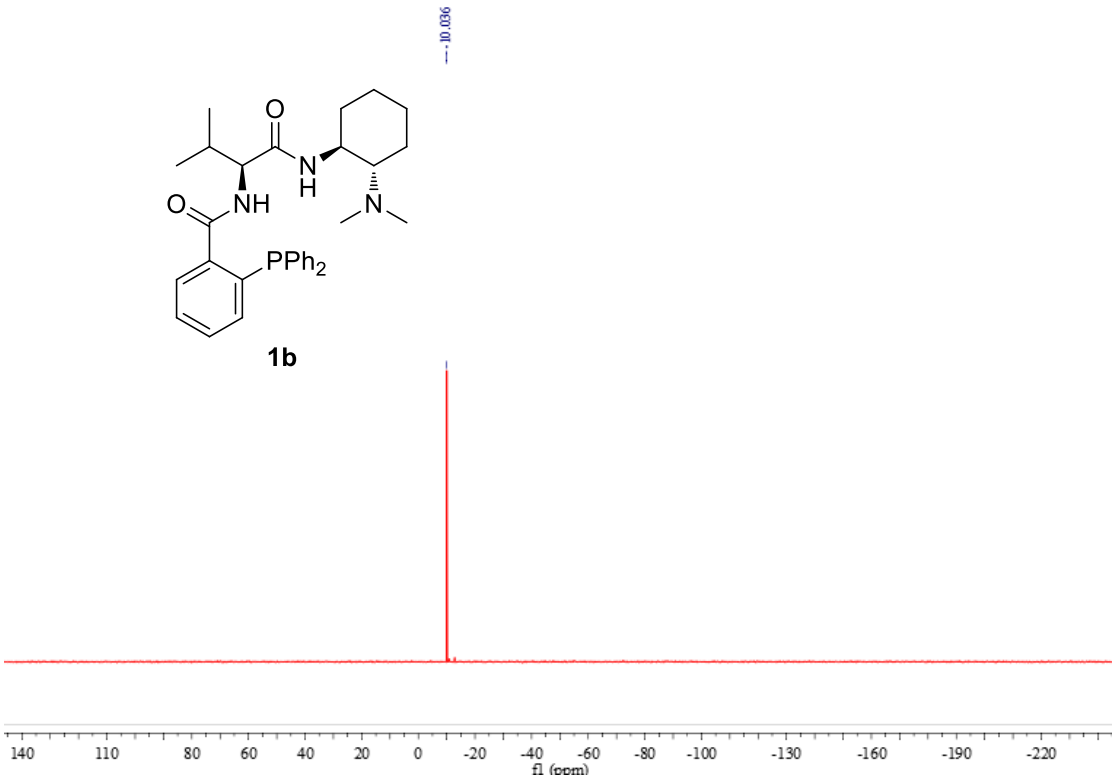


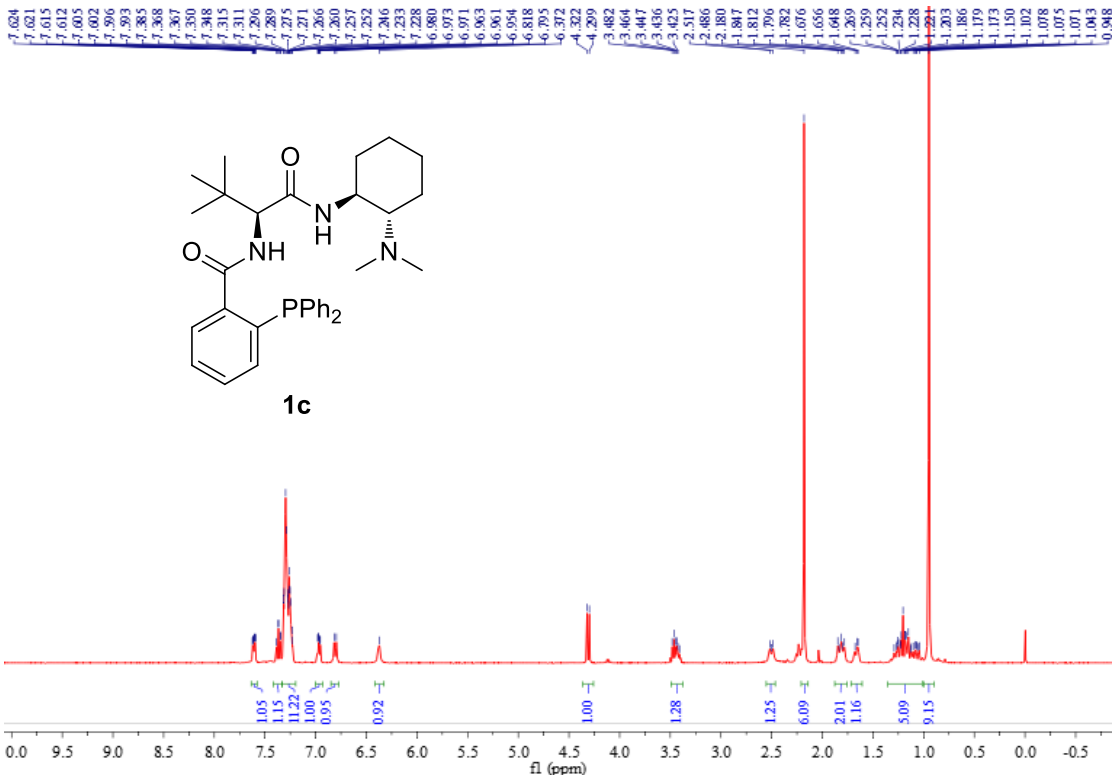



9.898
Ph
O
N
H
NH
O
N
PPh2
1a
140
110
80
60
40
20
0
-20
-40
-60
-80
-100
-130
-160
-190
-220
f1 (ppm)

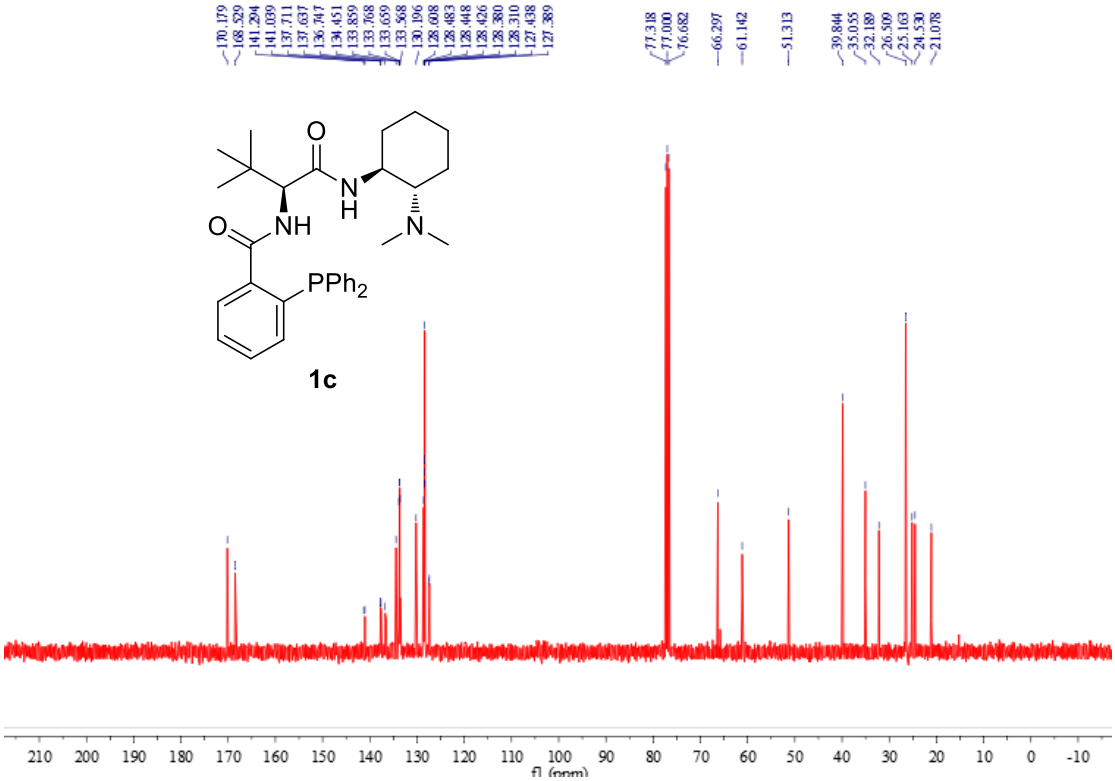

7.637
7.628
7.618
7.611
7.393
7.376
7.374
7.358
7.355
7.326
7.318
7.311
7.307
7.292
7.285
7.278
7.263
6.983
6.973
6.966
6.956
6.680
6.659
6.418
4.337
4.322
4.316
4.300
3.483
3.467
3.456
3.445
2.254
2.183
2.024
2.008
1.843
1.835
1.815
1.793
1.208
1.183
1.169
1.161
1.133
1.097
0.870
0.856
O
N
H
NH
O
N
PPh2
1b
1.00
1.23
12.10
1.04
1.01
0.92
1.05
1.10
1.08
1.20
6.18
1.16
2.41
1.19
4.44
3.01
2.99
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)


170.568
168.949
141.267
141.014
137.492
137.376
136.539
136.326
134.395
133.874
133.678
130.232
128.680
128.611
128.386
128.324
128.490
128.454
128.422
127.616
127.566
77.318
77.000
76.683
66.339
58.894
51.370
39.872
32.478
31.480
25.213
24.607
21.265
18.727
18.174
O
N
H
NH
O
N
PPh2
1b
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

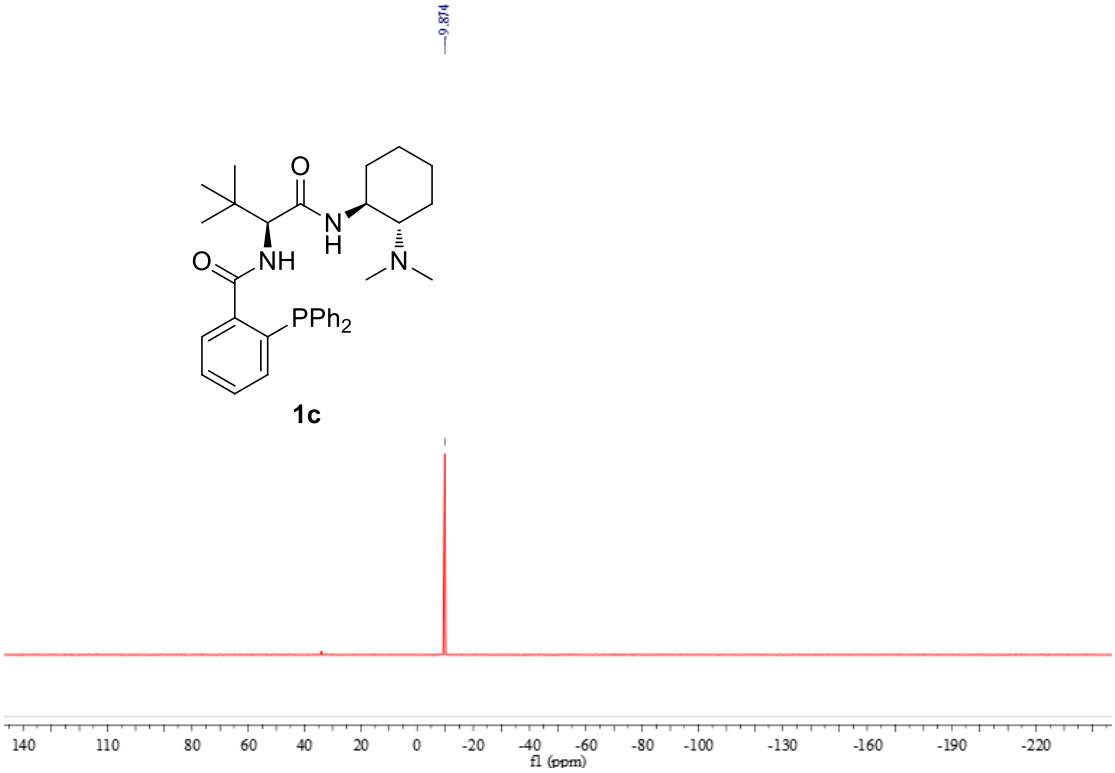

10.036
O
N
H
NH
O
N
PPh2
1b
140 110 80 60 40 20 0 -20 -40 -60 -80 -100 -130 -160 -190 -220
f1 (ppm)

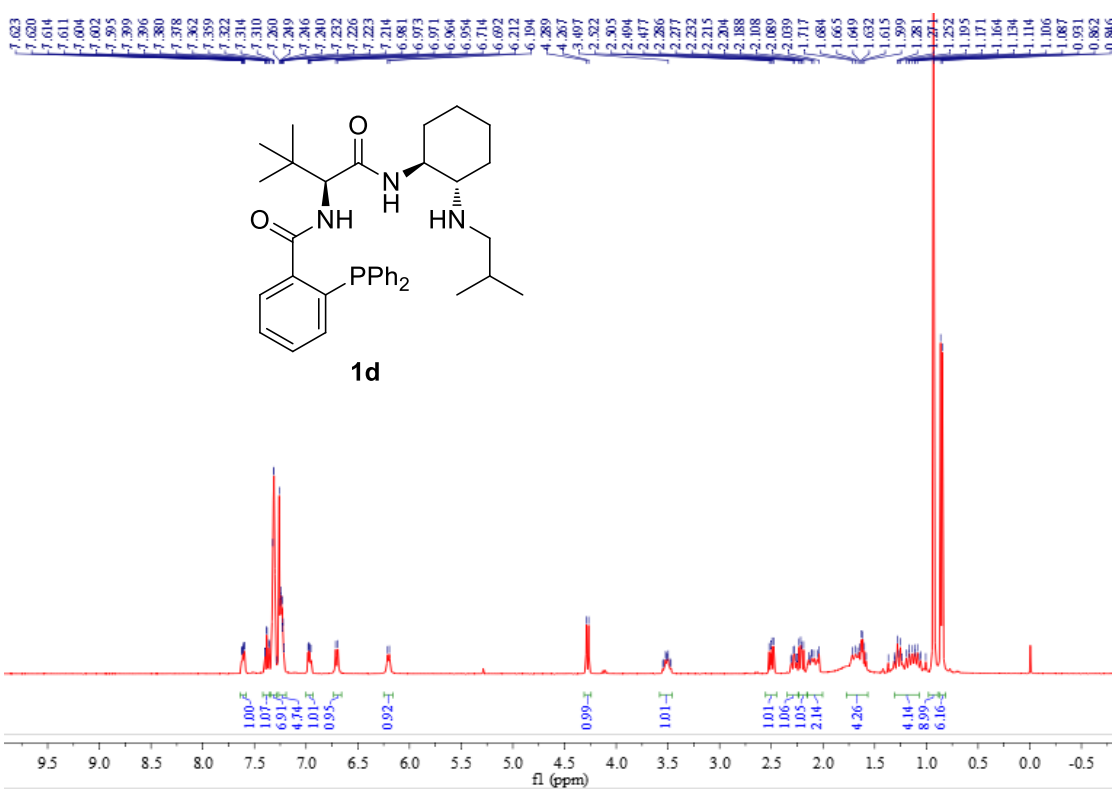


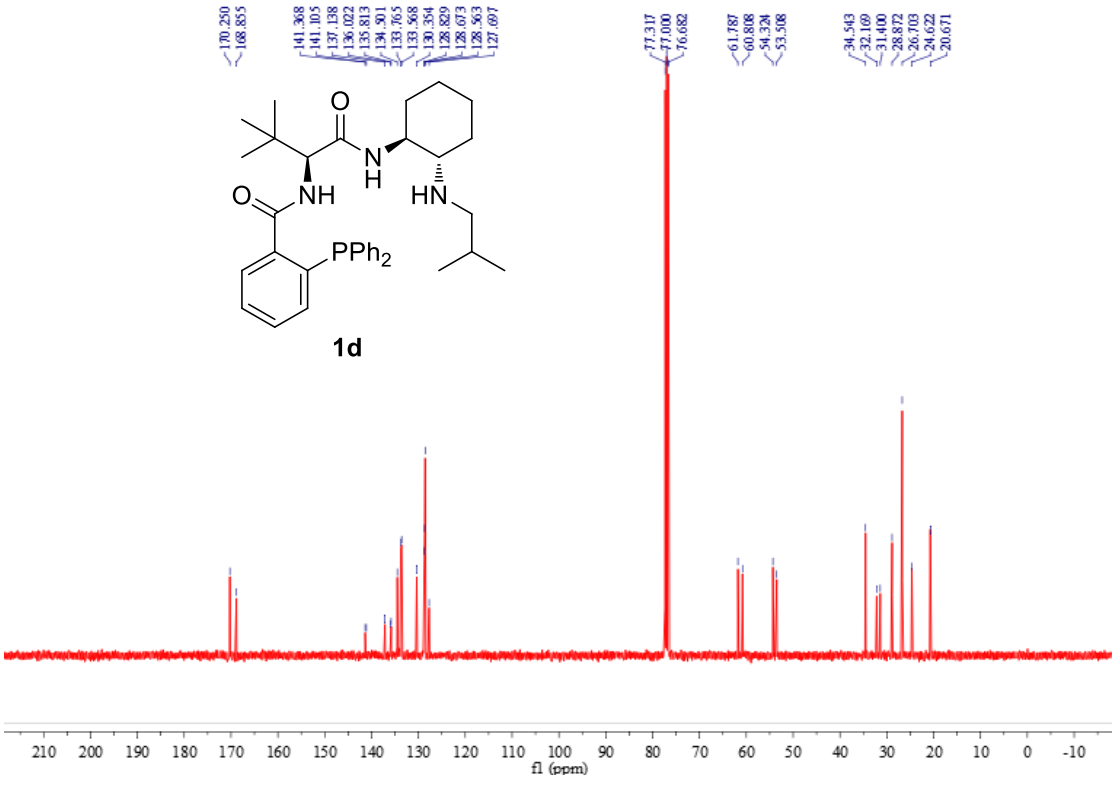
1c

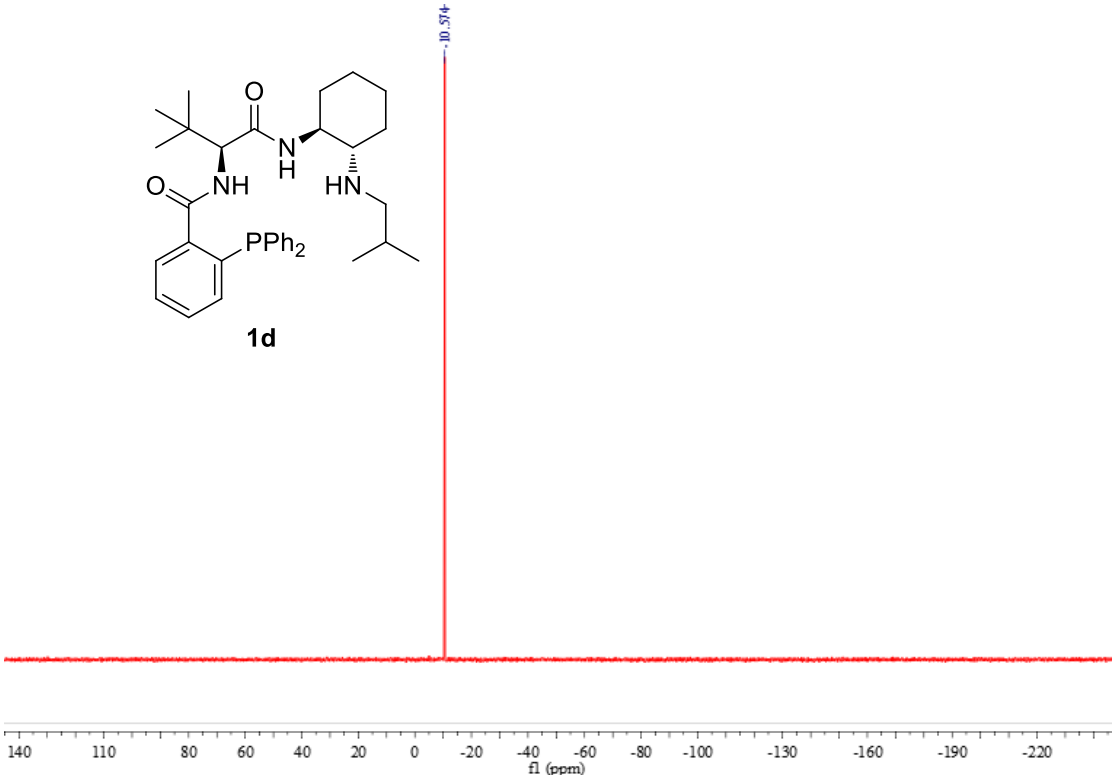


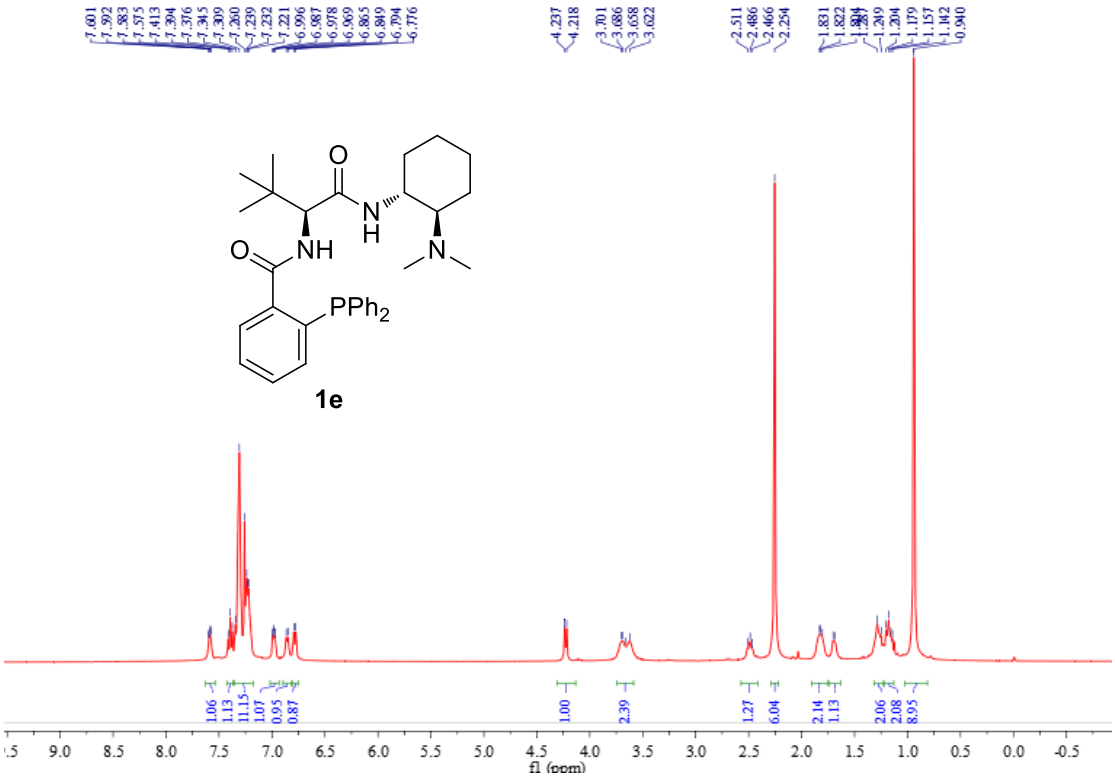
1c

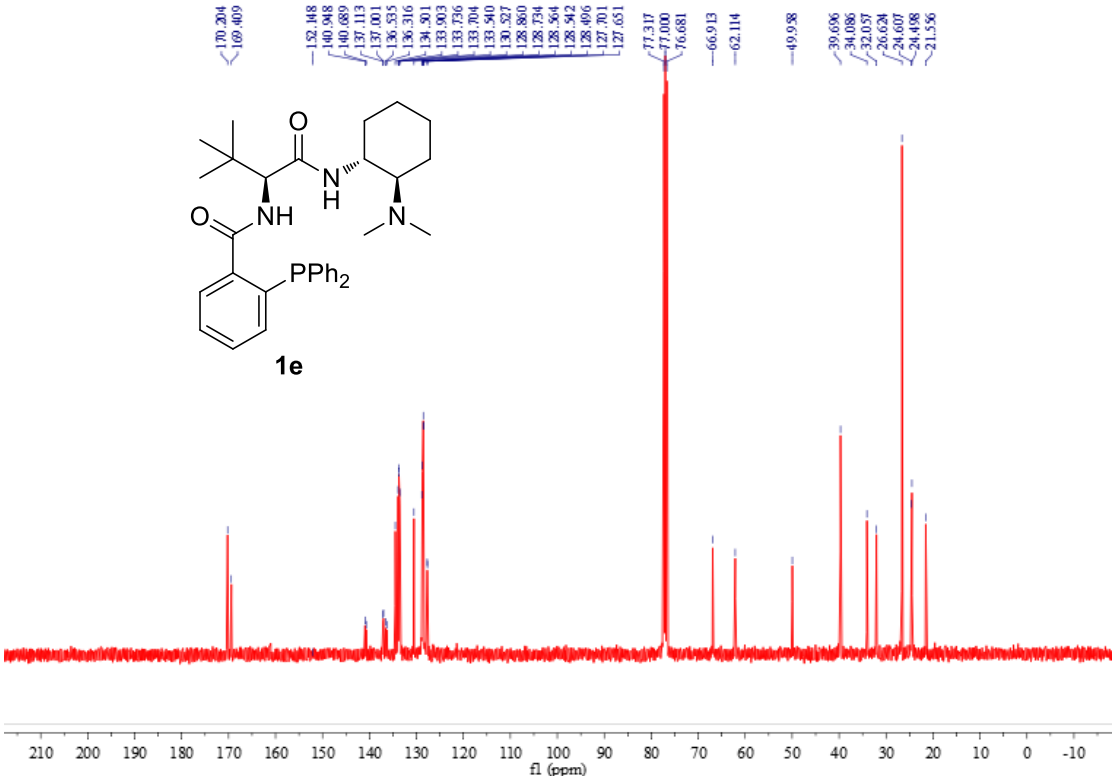

9.874
O
N
H
O
NH
N
PPh2
1c
140
110
80
60
40
20
0
-20
-40
-60
-80
-100
-130
-160
-190
-220
f1 (ppm)

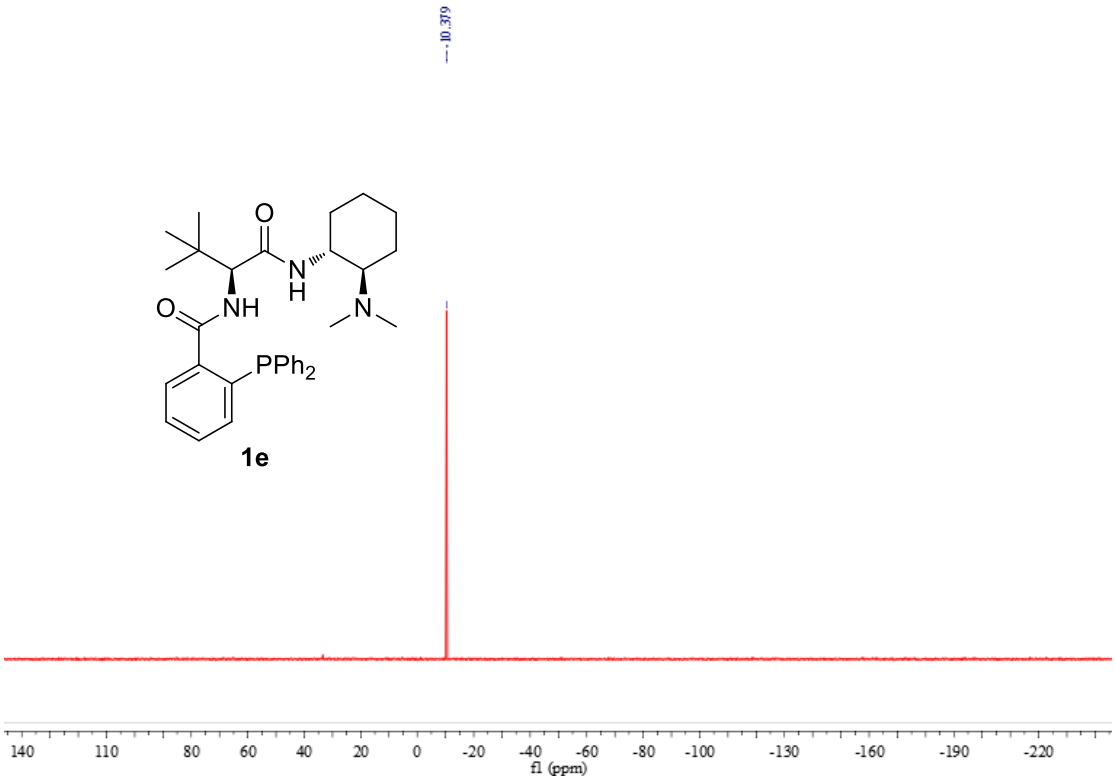

O
N
H
O
NH
HN
PPh2
1d
1.00
1.07
6.91
4.74
1.01
0.95
0.92
0.99
1.01
1.01
1.06
1.05
2.14
4.26
4.14
8.99
6.16
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

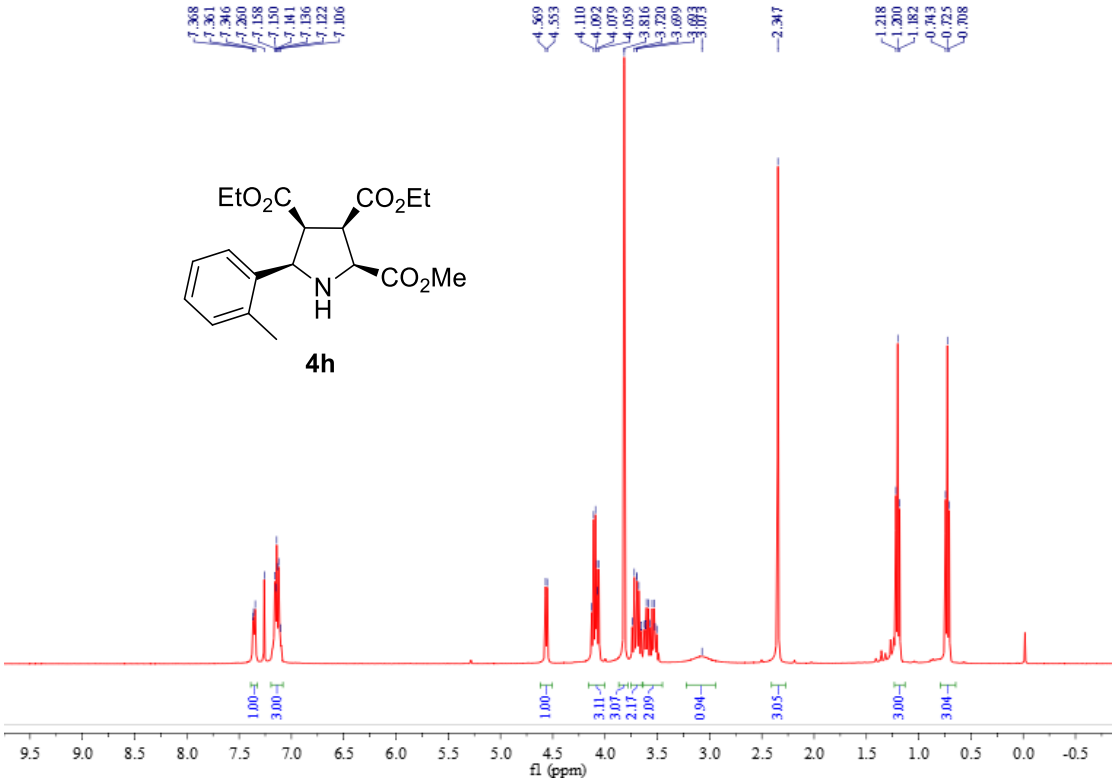

170.250
168.855
141.368
141.105
137.138
136.022
135.813
134.301
133.765
133.568
130.354
128.829
128.673
128.563
127.697
77.317
77.000
76.682
61.787
60.808
54.324
53.508
34.543
32.169
31.400
28.872
26.703
24.622
20.671
O
N
H
NH
HN
O
PPh2
1d
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

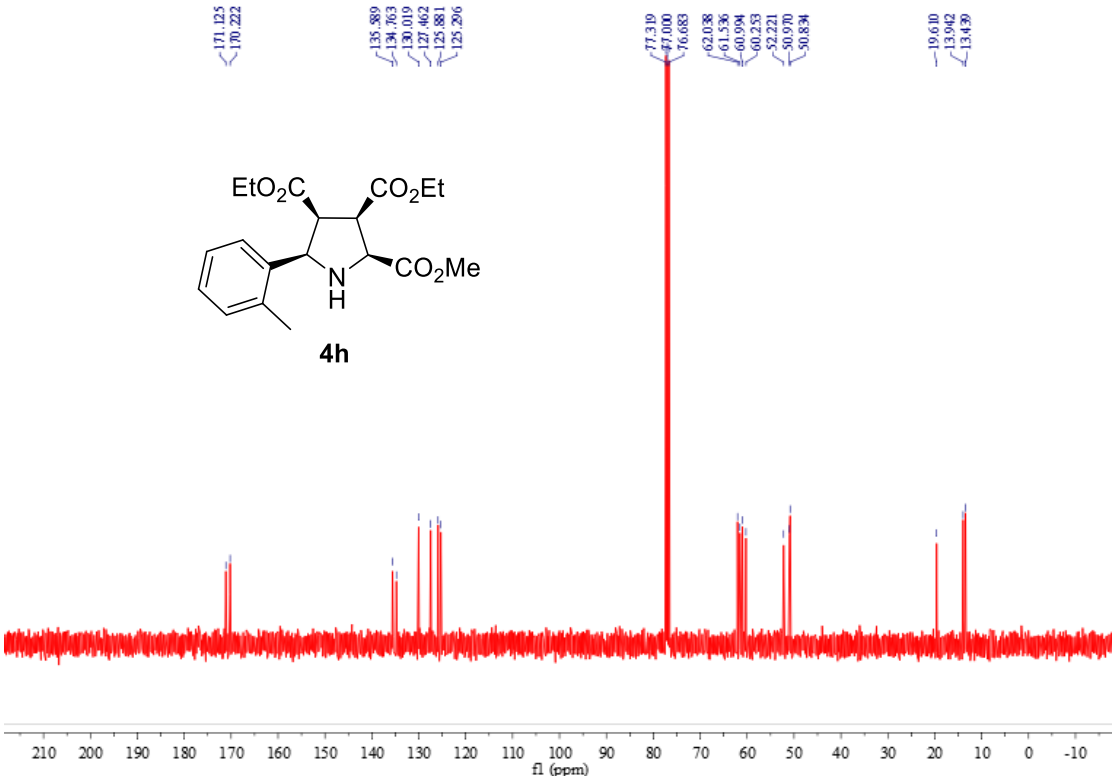

10.574
O
N
H
NH
HN
O
PPh2
1d
140 110 80 60 40 20 0 -20 -40 -60 -80 -100 -130 -160 -190 -220
f1 (ppm)

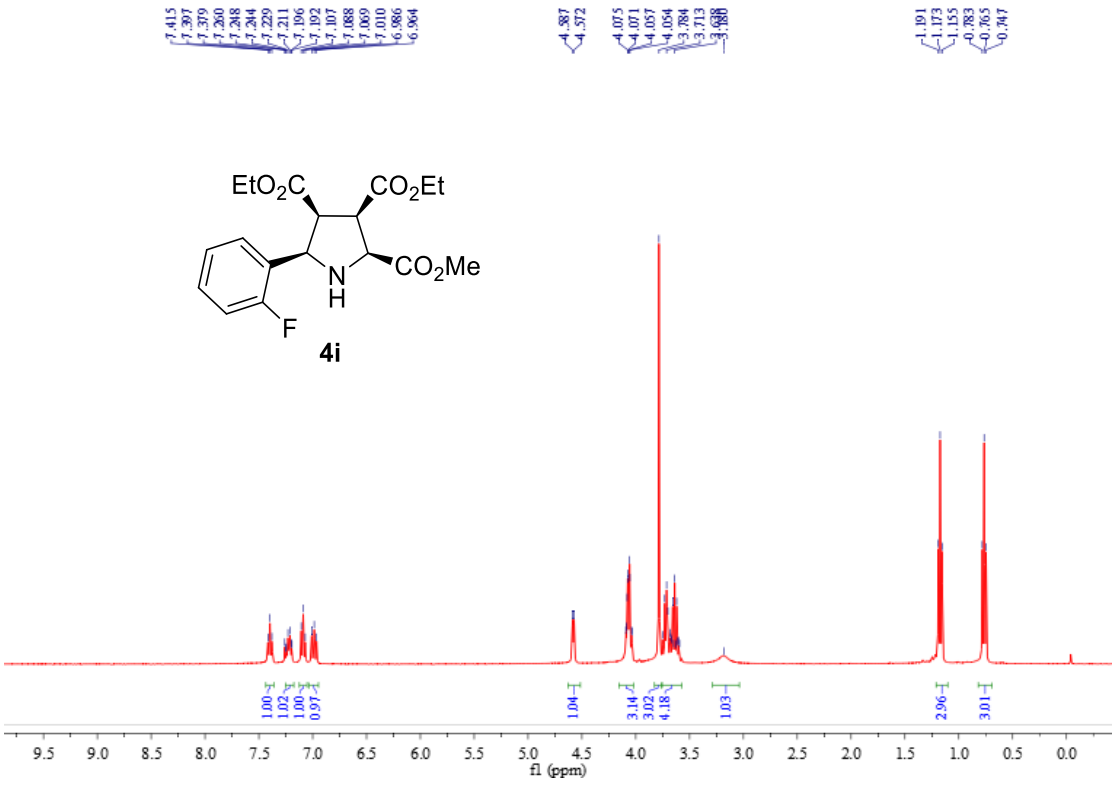

O
N
H
NH
O
N
PPh2
1e
fl (ppm)

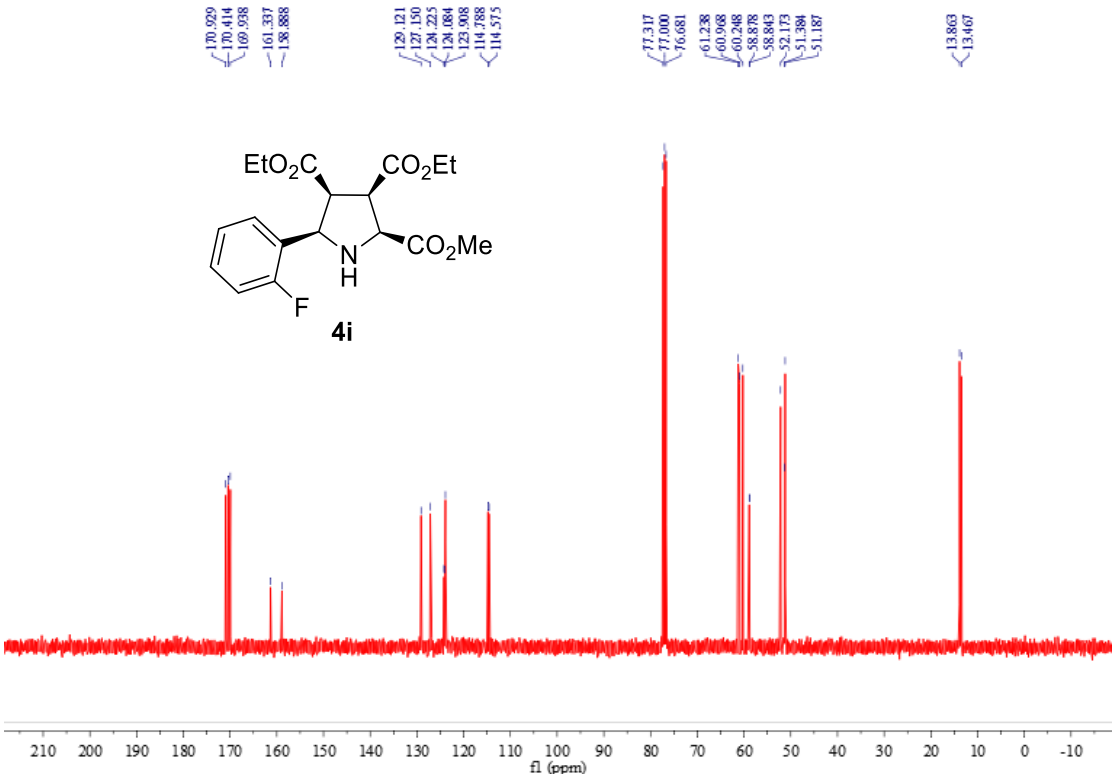

O
N
H
NH
O
N
PPh2
1e
fl (ppm)

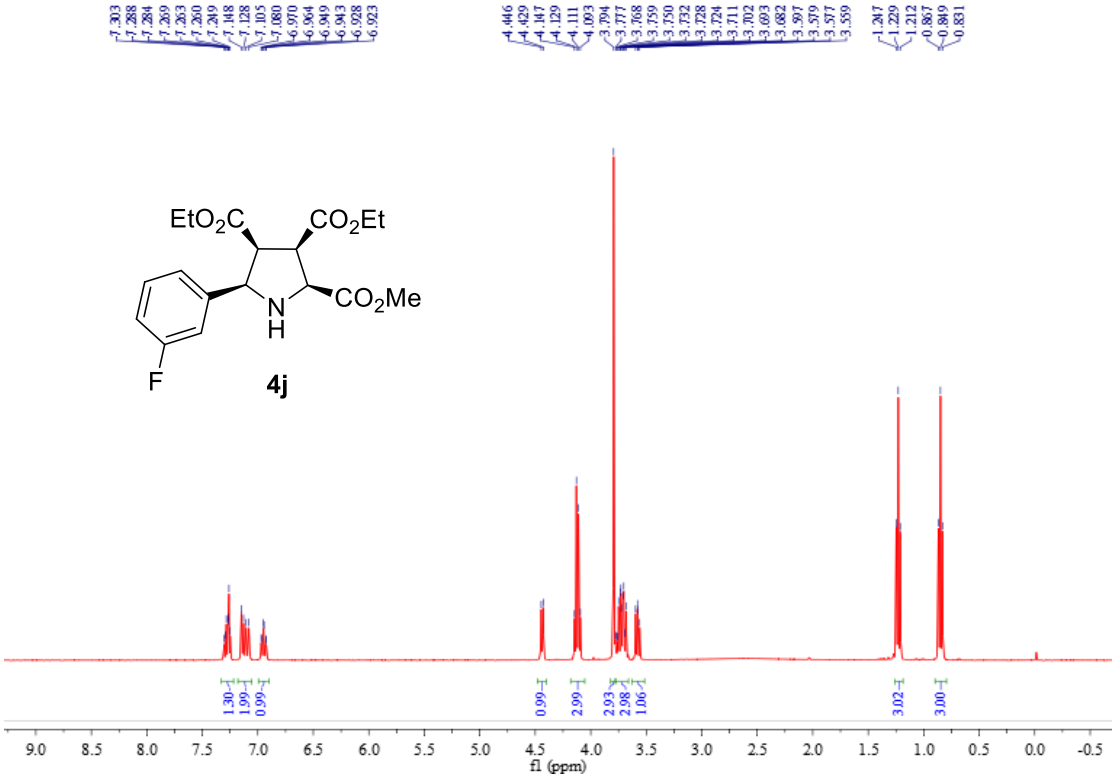

10.379
O
N
H
NH
O
N
PPh2
1e
140
110
80
60
40
20
0
-20
-40
-60
-80
-100
-130
-160
-190
-220
f1 (ppm)

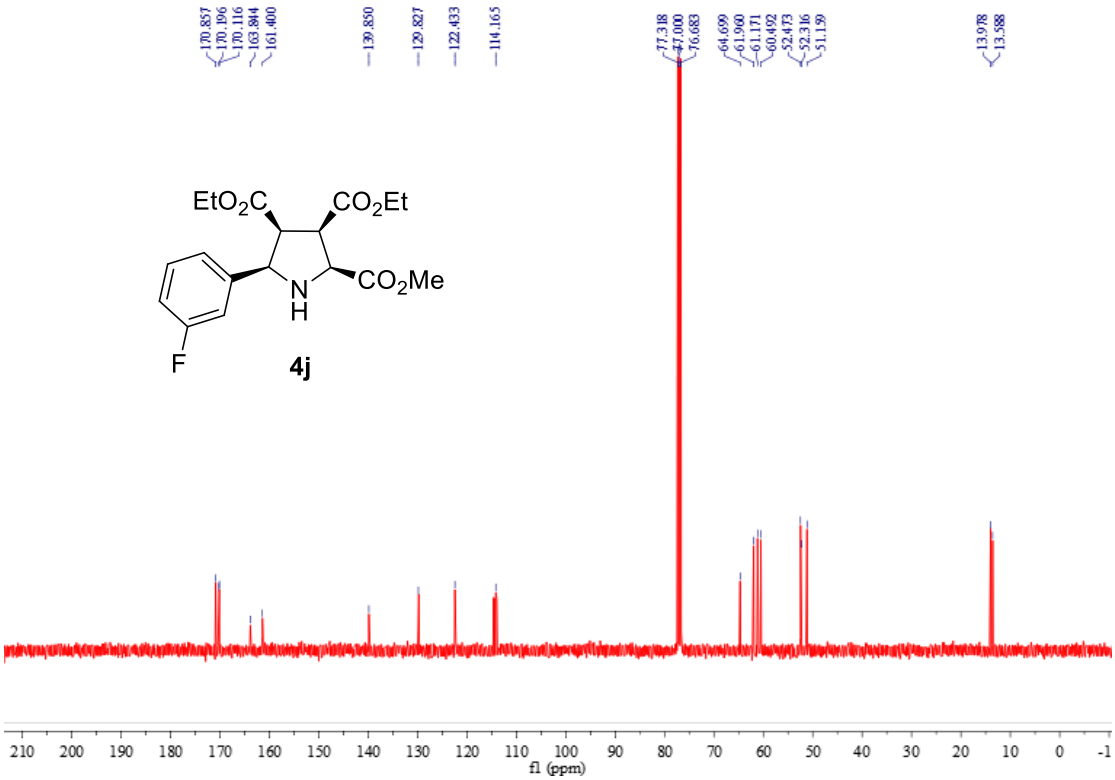

7.308
7.301
7.346
7.260
7.158
7.150
7.141
7.136
7.122
7.106
4.569
4.553
4.110
4.092
4.079
4.059
3.816
3.720
3.699
2.347
1.218
1.200
1.182
0.743
0.725
0.708
EtO2C
CO2Et
CO2Me
N
H
4h
1.00
3.00
1.00
3.11
3.07
2.17
2.09
0.94
3.05
3.00
3.04
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

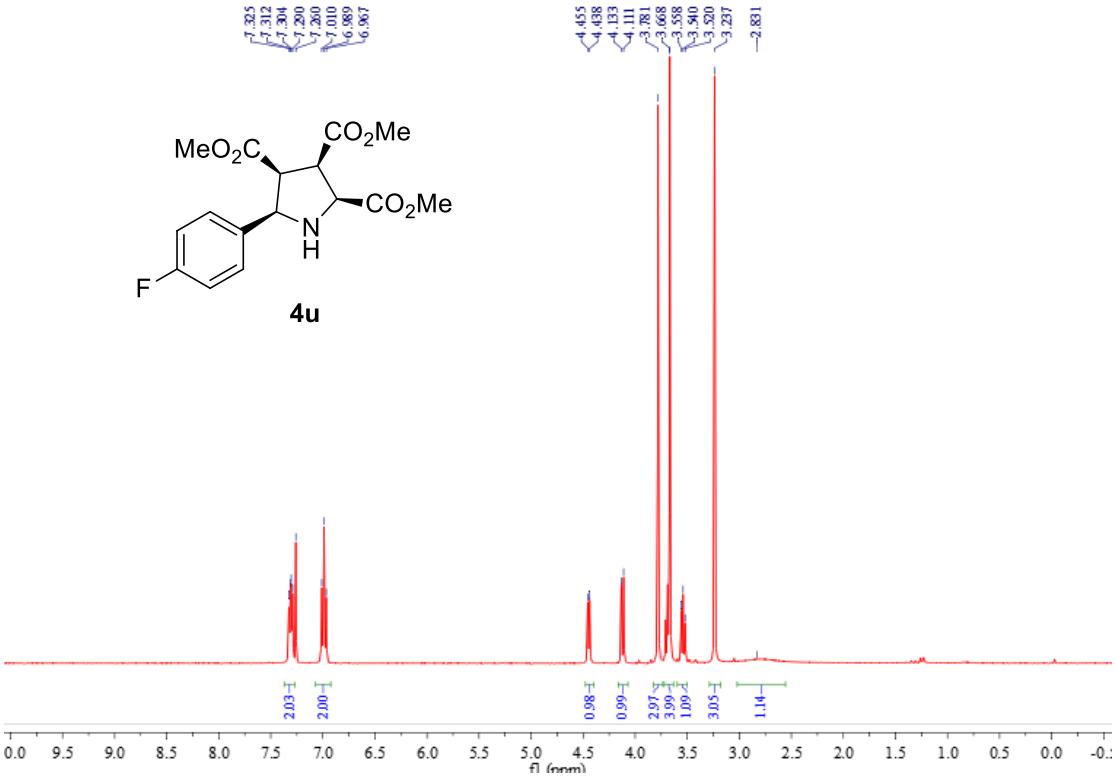

171.125
170.222
135.389
134.763
130.019
127.462
125.881
125.296
77.319
77.000
76.683
62.038
61.536
60.994
60.253
52.221
50.970
50.834
19.610
13.942
13.439
EtO2C
CO2Et
CO2Me
N
H
4h
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

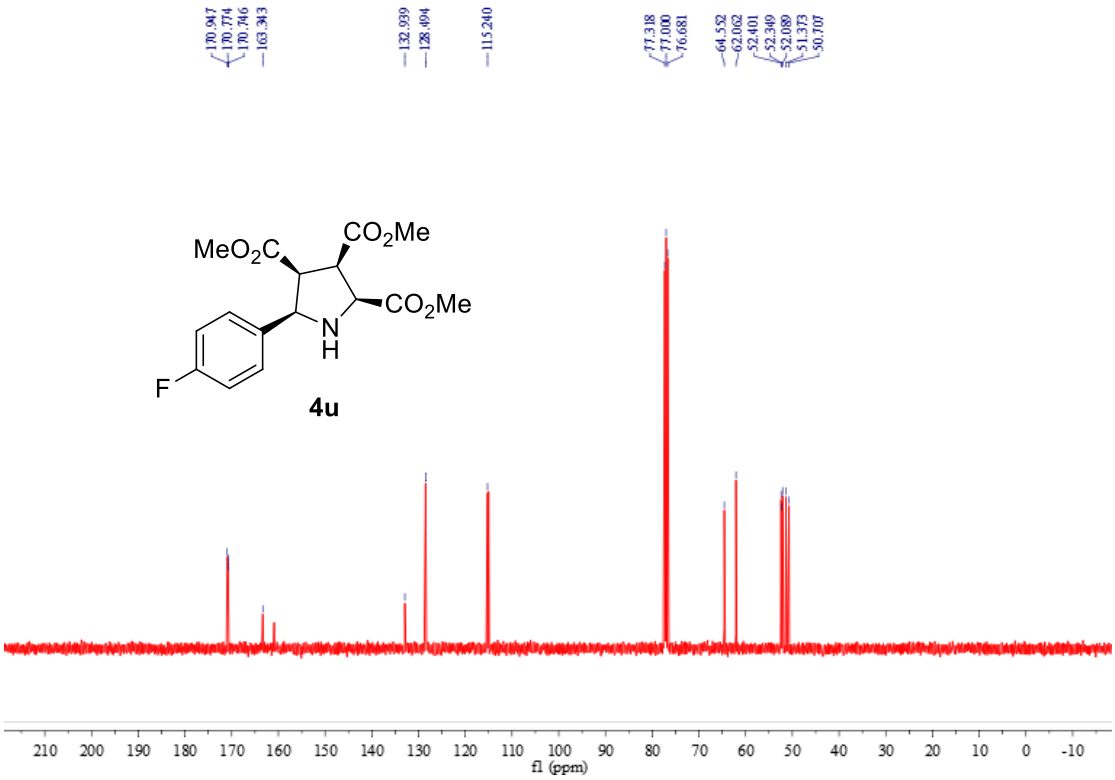

7.415
7.397
7.379
7.260
7.248
7.244
7.229
7.211
7.196
7.192
7.107
7.088
7.069
7.010
6.986
6.964
4.587
4.572
4.075
4.071
4.057
4.054
3.784
3.713
1.191
1.173
1.155
0.783
0.765
0.747
EtO2C
CO2Et
CO2Me
N
H
F
4i
1.00
1.02
1.00
0.97
1.04
3.14
3.02
4.18
1.03
2.96
3.01
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

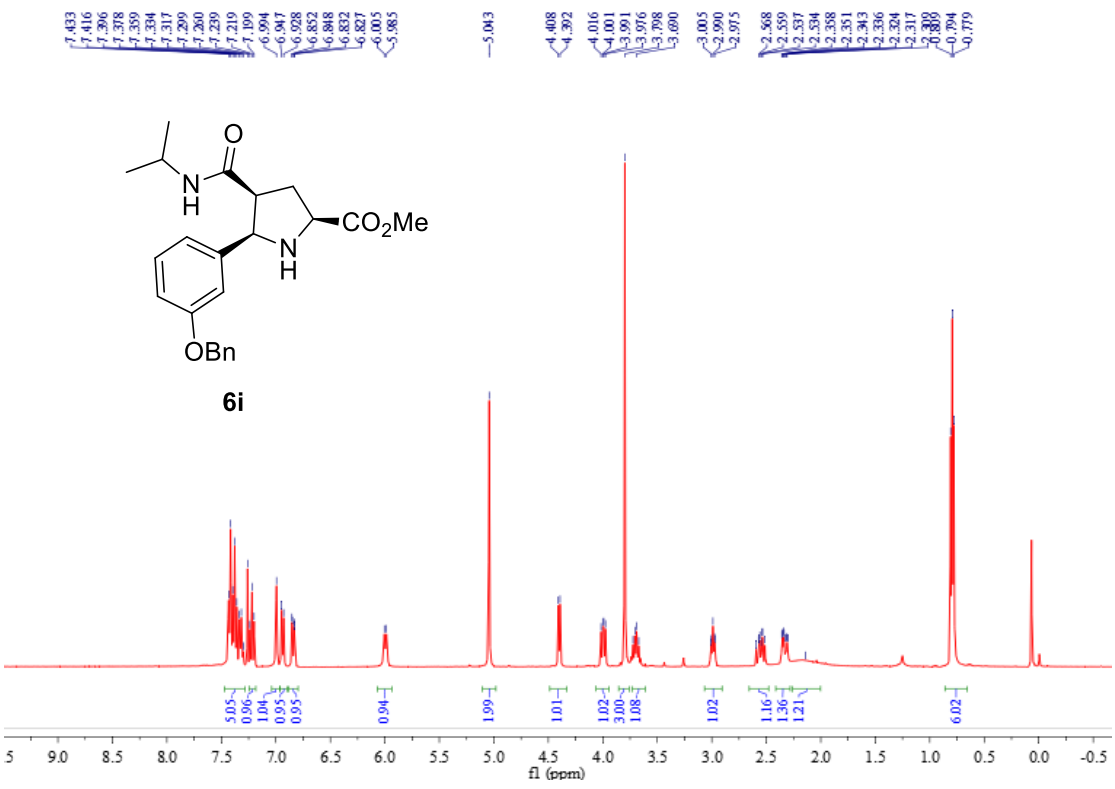

170.929
170.414
169.938
161.337
158.888
129.121
127.150
124.225
124.084
123.908
114.788
114.575
77.317
77.000
76.681
61.238
60.968
60.248
58.878
58.843
52.173
51.384
51.187
13.863
13.467
EtO2C
CO2Et
CO2Me
N
H
F
4i
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

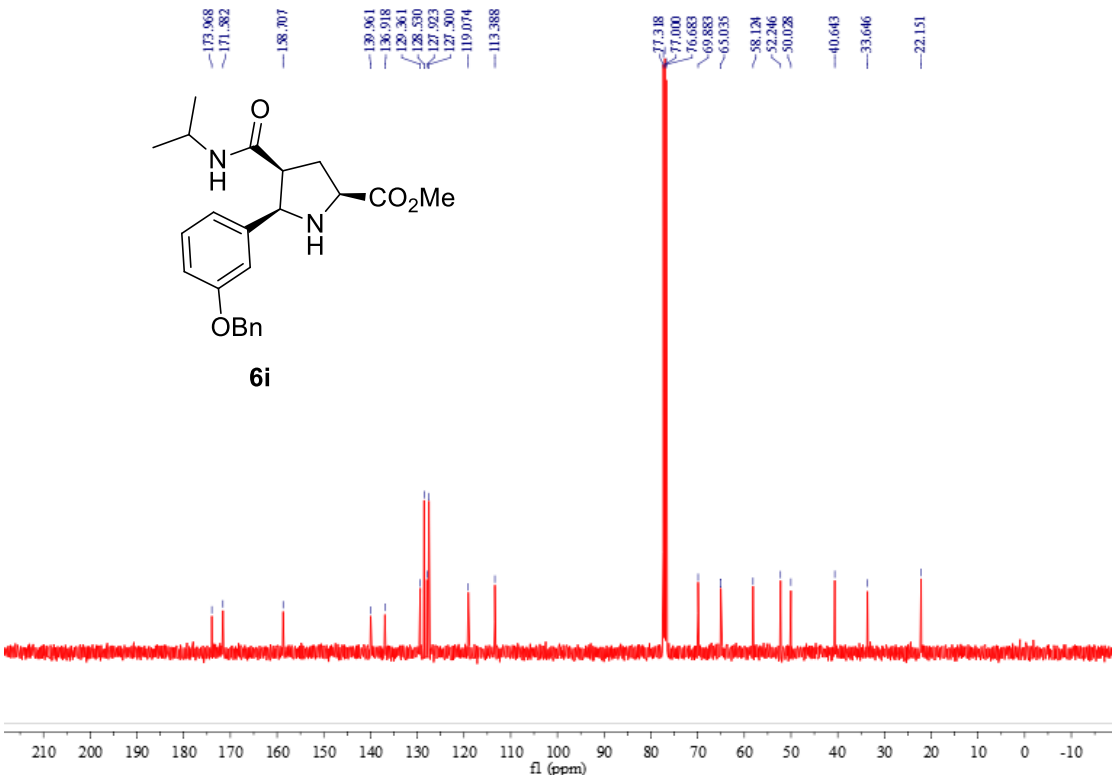

7.303
7.288
7.284
7.269
7.263
7.260
7.249
7.148
7.128
7.105
7.080
6.970
6.964
6.949
6.943
6.928
6.923
4.446
4.429
4.147
4.129
4.111
4.093
3.794
3.777
3.768
3.759
3.750
3.732
3.728
3.724
3.711
3.702
3.693
3.682
3.597
3.579
3.577
3.559
1.247
1.229
1.212
0.867
0.849
0.831
EtO2C
CO2Et
CO2Me
N
H
F
4j
1.30
1.99
0.99
0.99
2.99
2.93
2.98
1.06
3.02
3.00
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

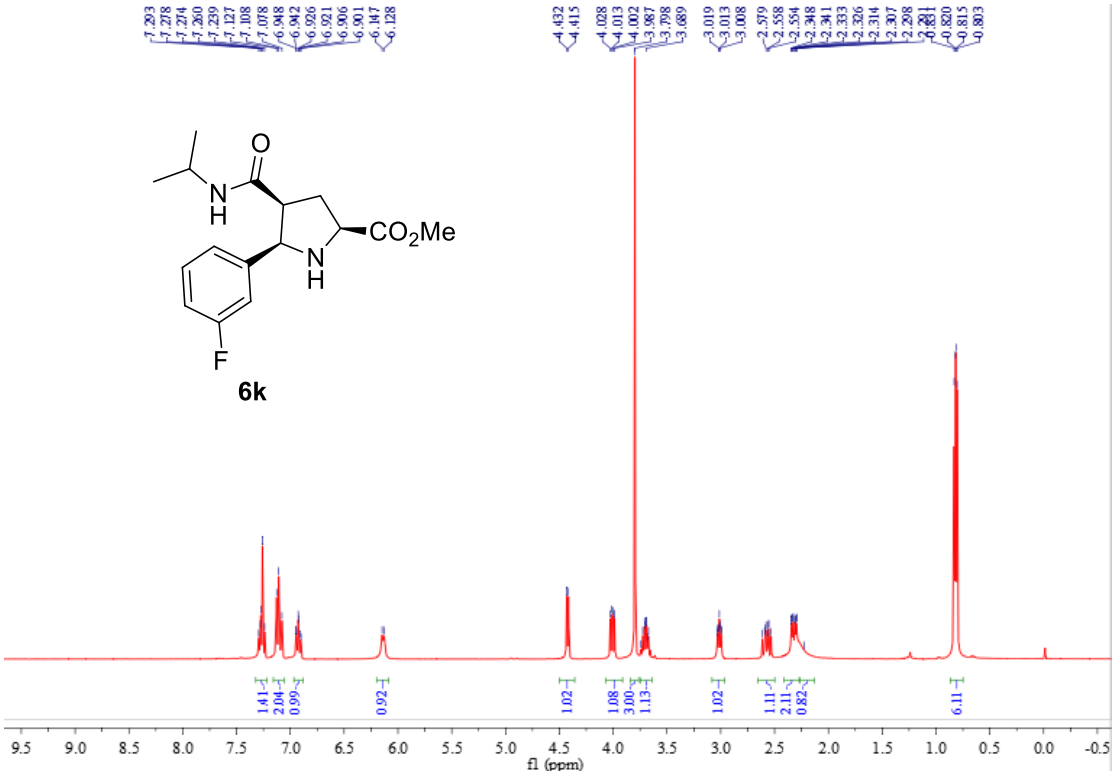

170.857
170.196
170.116
163.844
161.400
139.850
129.827
122.433
114.165
77.318
77.000
76.683
64.699
61.960
61.171
60.492
52.473
52.316
51.139
13.978
13.588
EtO2C
CO2Et
CO2Me
N
H
F
4j
fl (ppm)

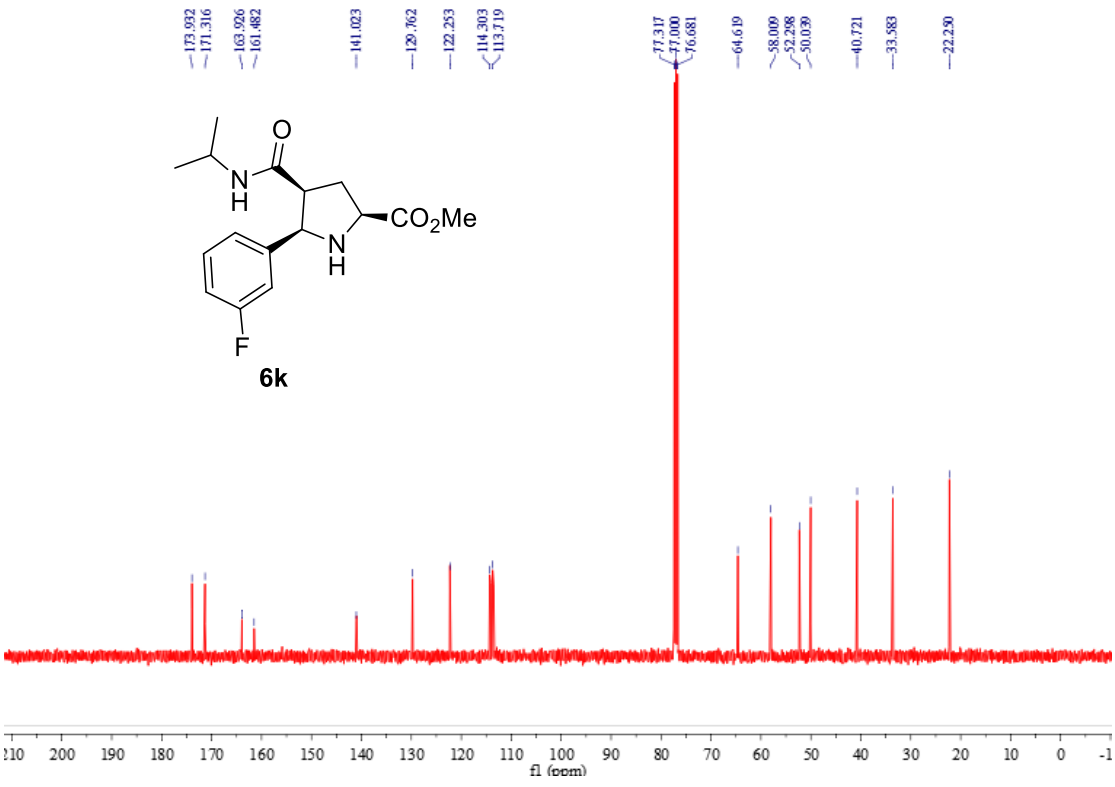

7.325
7.312
7.304
7.290
7.260
7.010
6.989
6.967
4.455
4.438
4.133
4.111
3.781
3.668
3.558
3.540
3.520
3.237
2.831
MeO2C
CO2Me
CO2Me
N
H
F
4u
2.03
2.00
0.98
0.99
2.97
3.99
1.09
3.05
1.14
fl (ppm)


170.947
170.774
170.746
163.343
132.939
128.494
115.240
77.318
77.000
76.681
64.552
62.062
52.401
52.349
52.089
51.373
50.707
MeO2C
CO2Me
CO2Me
N
H
F
4u
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


7.433
7.416
7.396
7.378
7.359
7.334
7.317
7.299
7.260
7.239
7.219
7.199
6.994
6.947
6.928
6.852
6.848
6.832
6.827
6.005
5.985
5.043
4.408
4.392
4.016
4.001
3.991
3.976
3.798
3.690
3.005
2.990
2.975
2.568
2.559
2.537
2.534
2.358
2.351
2.343
2.336
2.324
2.317
0.794
0.779
O
N
H
CO2Me
N
H
OBn
6i
5.05
0.96
1.04
0.95
0.95
0.94
1.99
1.01
1.02
3.00
1.08
1.02
1.16
1.36
1.21
6.02
5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)


173.968
171.382
138.707
130.961
130.918
129.361
128.530
127.923
127.300
119.074
113.388
77.318
77.000
76.683
69.883
65.035
58.124
52.246
50.028
40.643
33.646
22.151
O
N
H
CO2Me
N
H
OBn
6i
f1 (ppm)


7.293
7.278
7.274
7.260
7.239
7.127
7.108
7.078
6.948
6.942
6.926
6.921
6.906
6.901
6.147
6.128
4.432
4.415
4.028
4.013
4.002
3.987
3.798
3.689
3.019
3.013
3.008
2.579
2.558
2.554
2.348
2.341
2.333
2.326
2.314
2.307
2.298
0.820
0.815
0.803
O
N
H
CO2Me
N
H
F
6k
1.41
2.04
0.99
0.92
1.02
1.08
3.00
1.13
1.02
1.11
2.11
0.82
6.11
f1 (ppm)


173.932
171.316
163.926
161.482
141.023
129.762
122.253
114.303
113.719
77.317
77.000
76.681
64.619
58.009
52.298
50.039
40.721
33.583
22.250
O
N
H
CO2Me
N
H
F
6k
f1 (ppm)