

Supporting Information
for

Rapid and efficient syntheses of tryptophans using continuous-flow quaternization-substitution reaction of gramines with a chiral nucleophilic glycine equivalent

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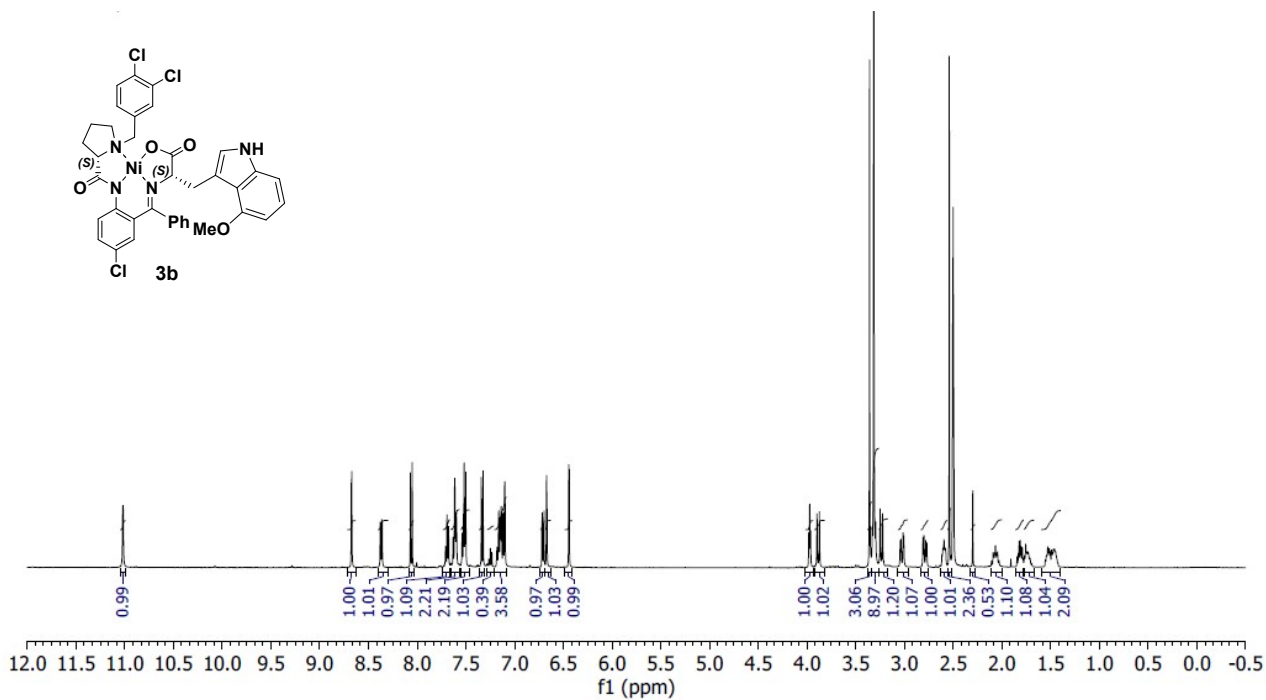
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^b*Hamari Chemicals USA, Inc. 11558 Sorrento Valley Rd Suite 3, San Diego, California, 92121, USA*

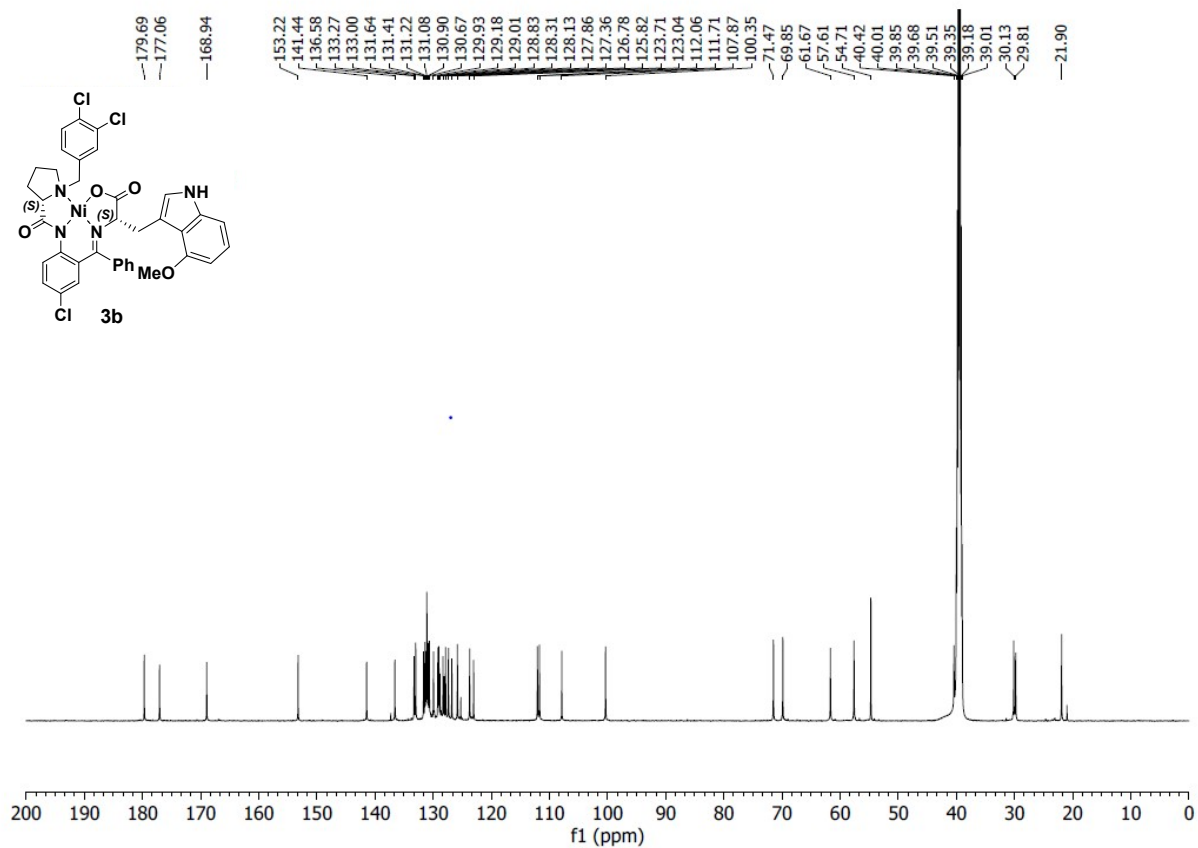
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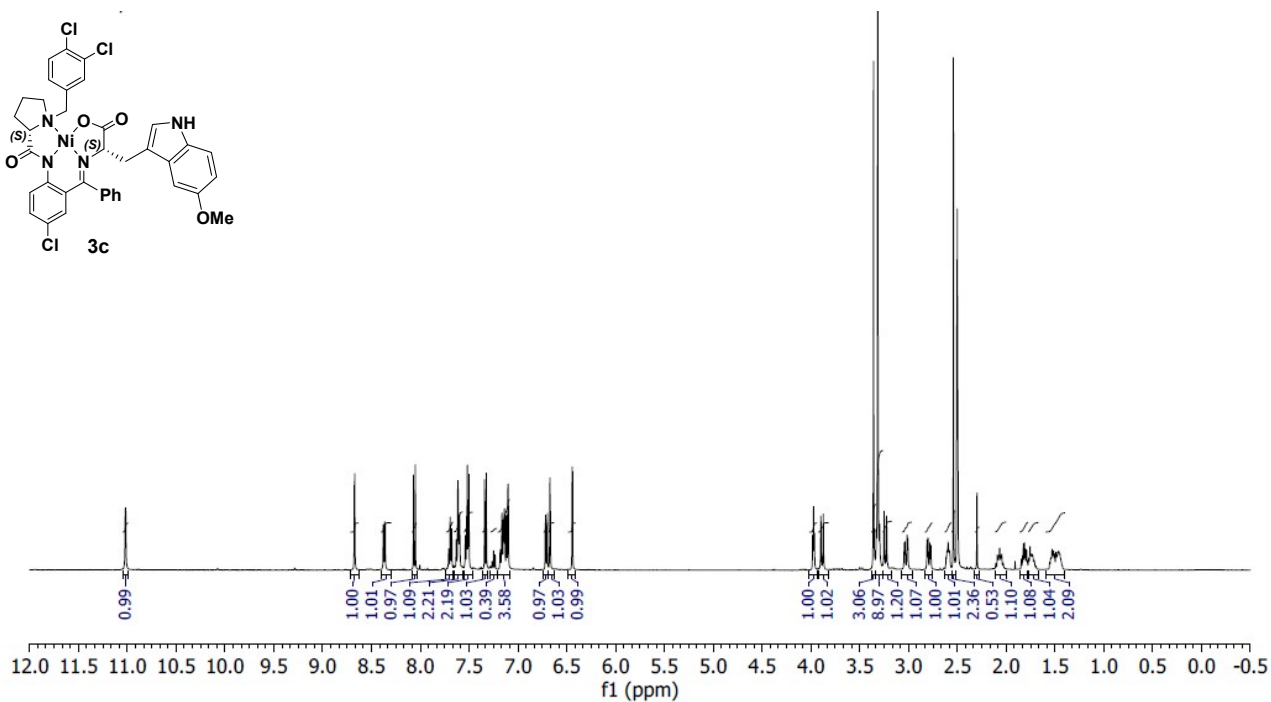
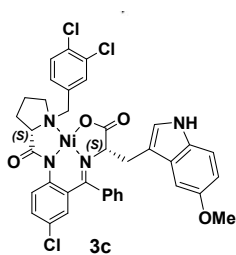
¹H NMR spectrum of 3b (500 MHz, DMSO-d₆)



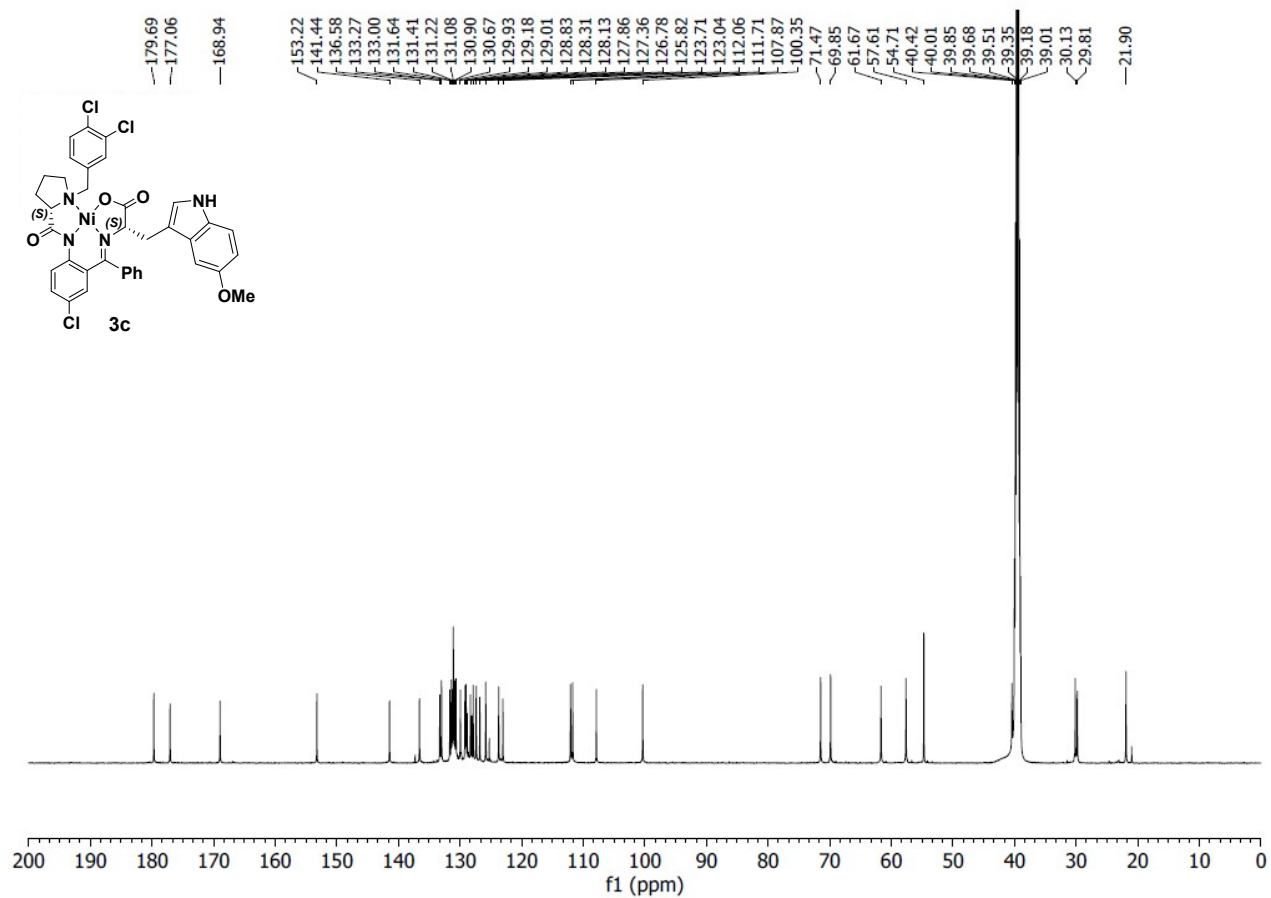
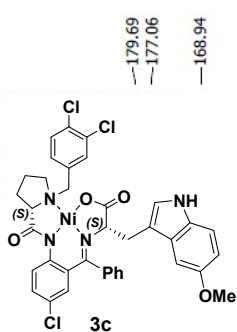
¹³C NMR spectrum of 3b (125 MHz, DMSO-d₆)



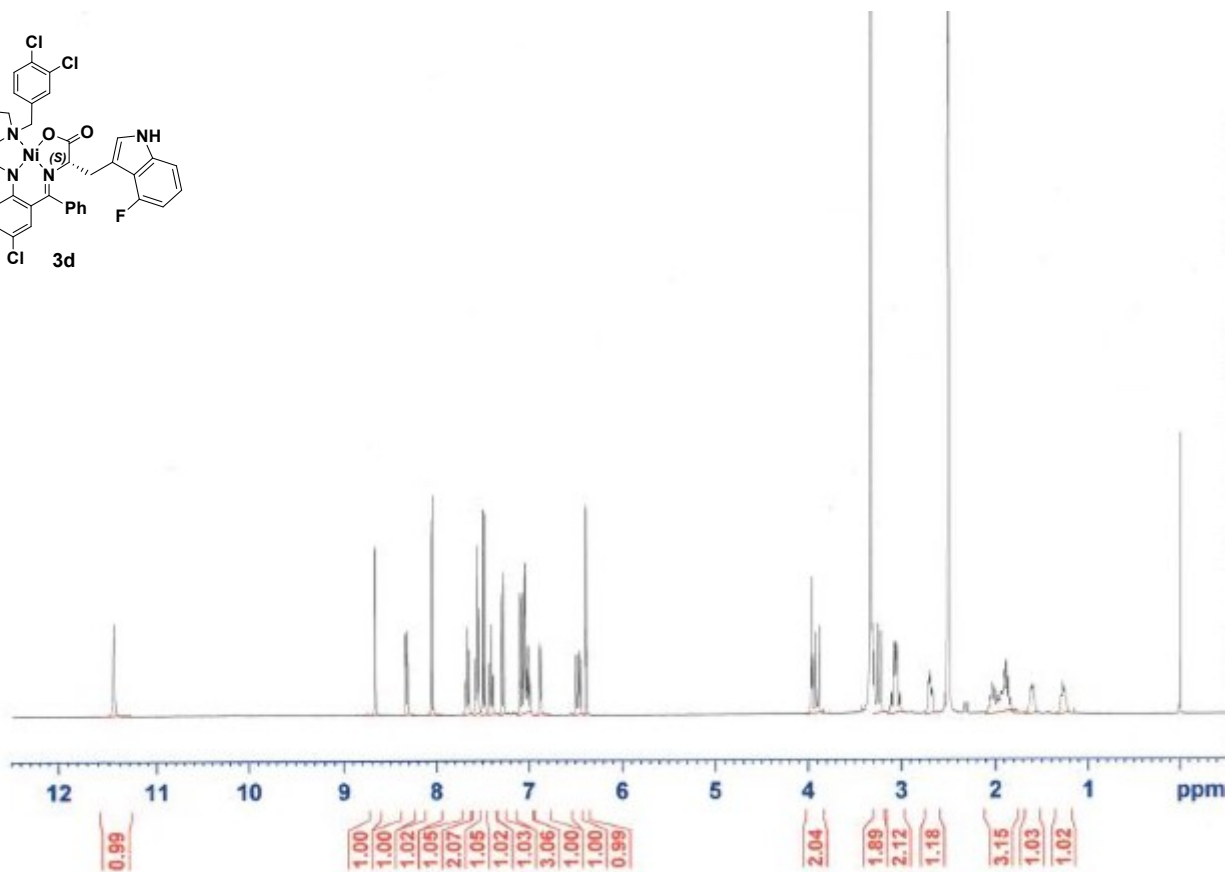
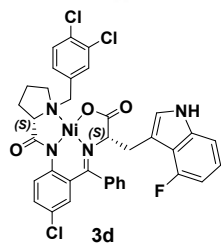
¹H NMR spectrum of 3c (500 MHz, DMSO-*d*₆)



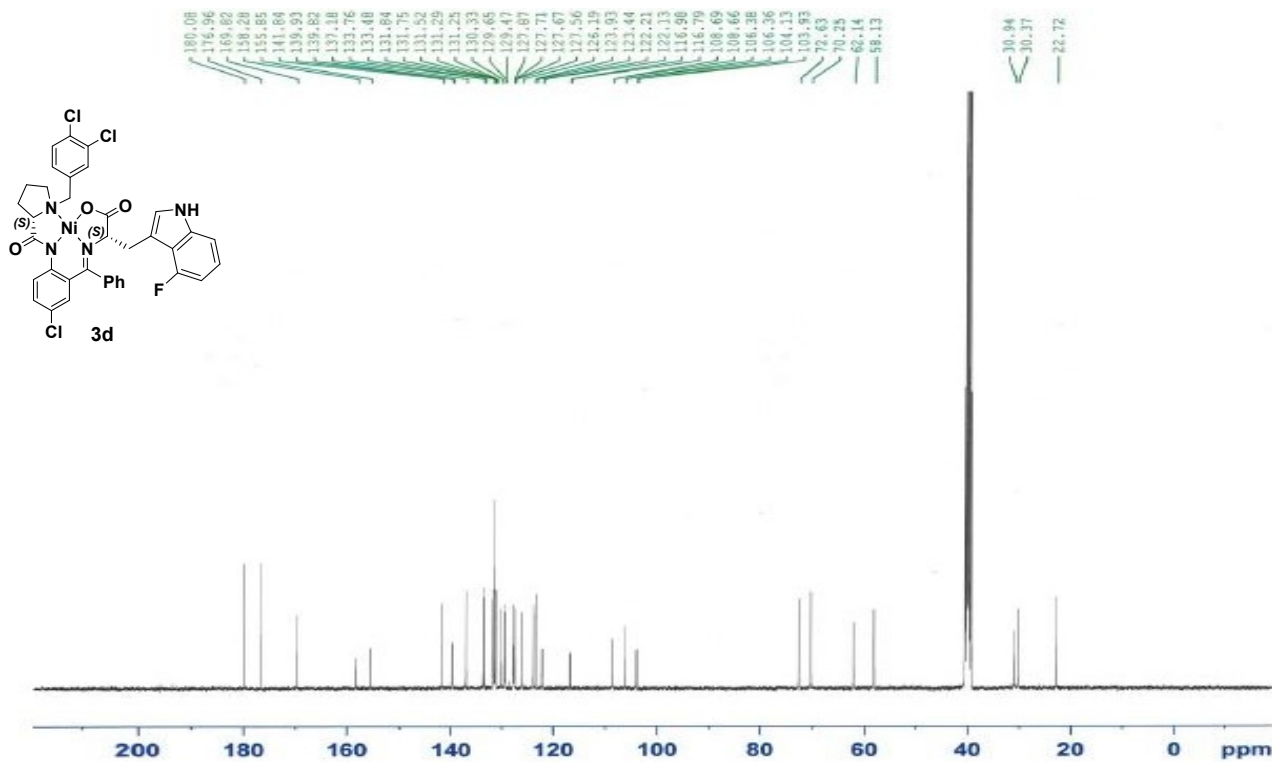
¹³C NMR spectrum of 3c (126 MHz, DMSO-*d*₆)



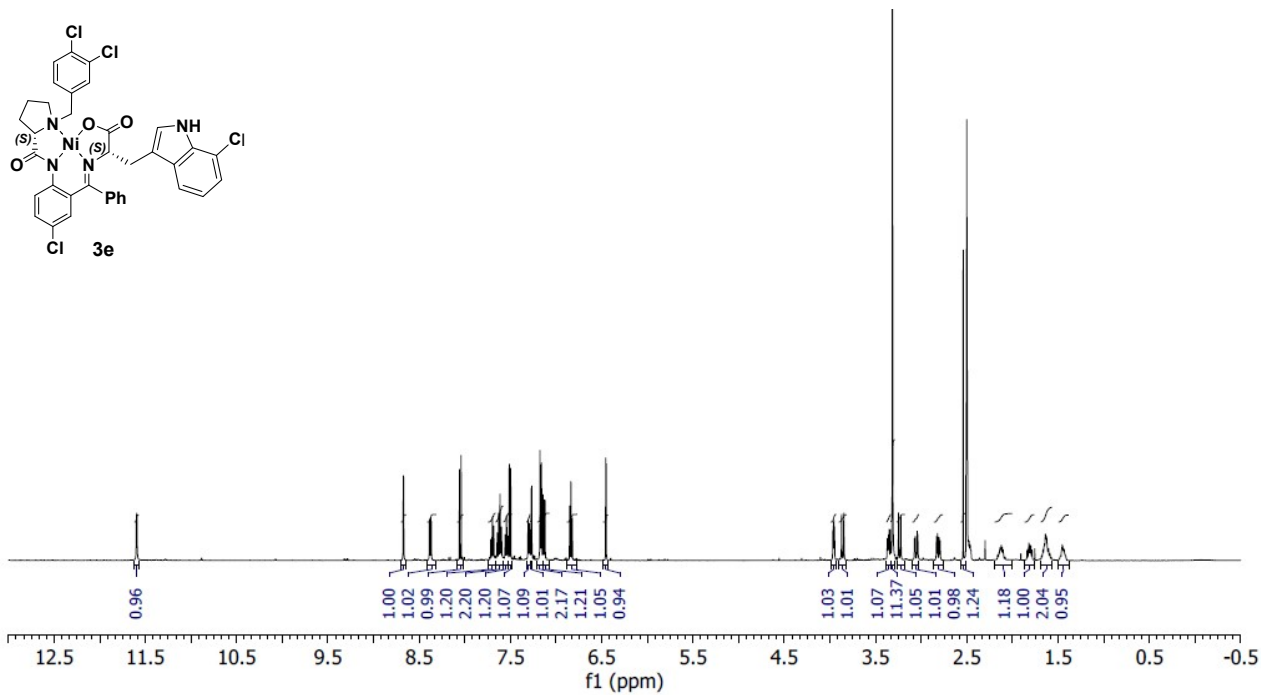
¹H NMR spectrum of 3d (400 MHz, DMSO-*d*₆)



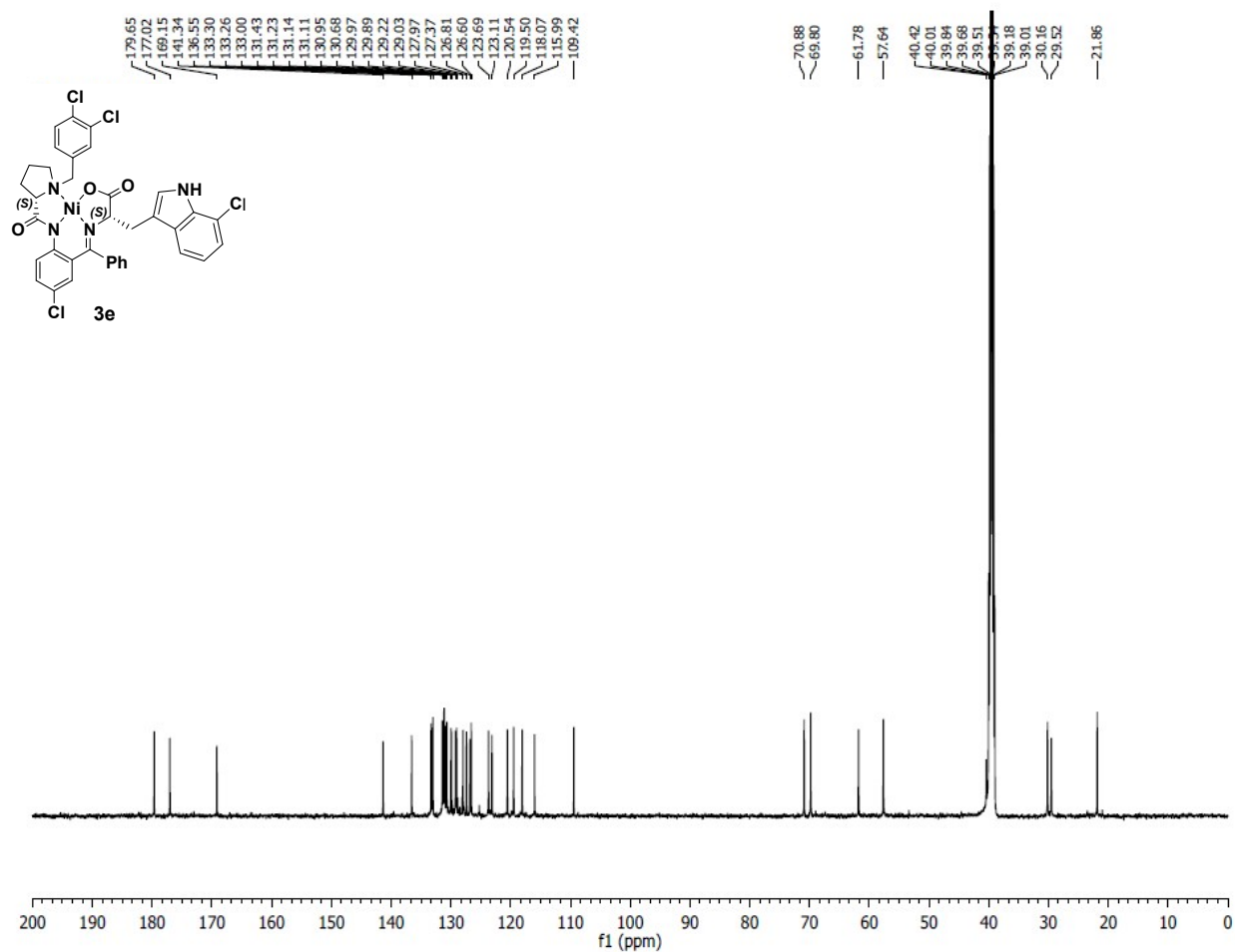
¹³C NMR spectrum of 3d (126 MHz, DMSO-*d*₆)



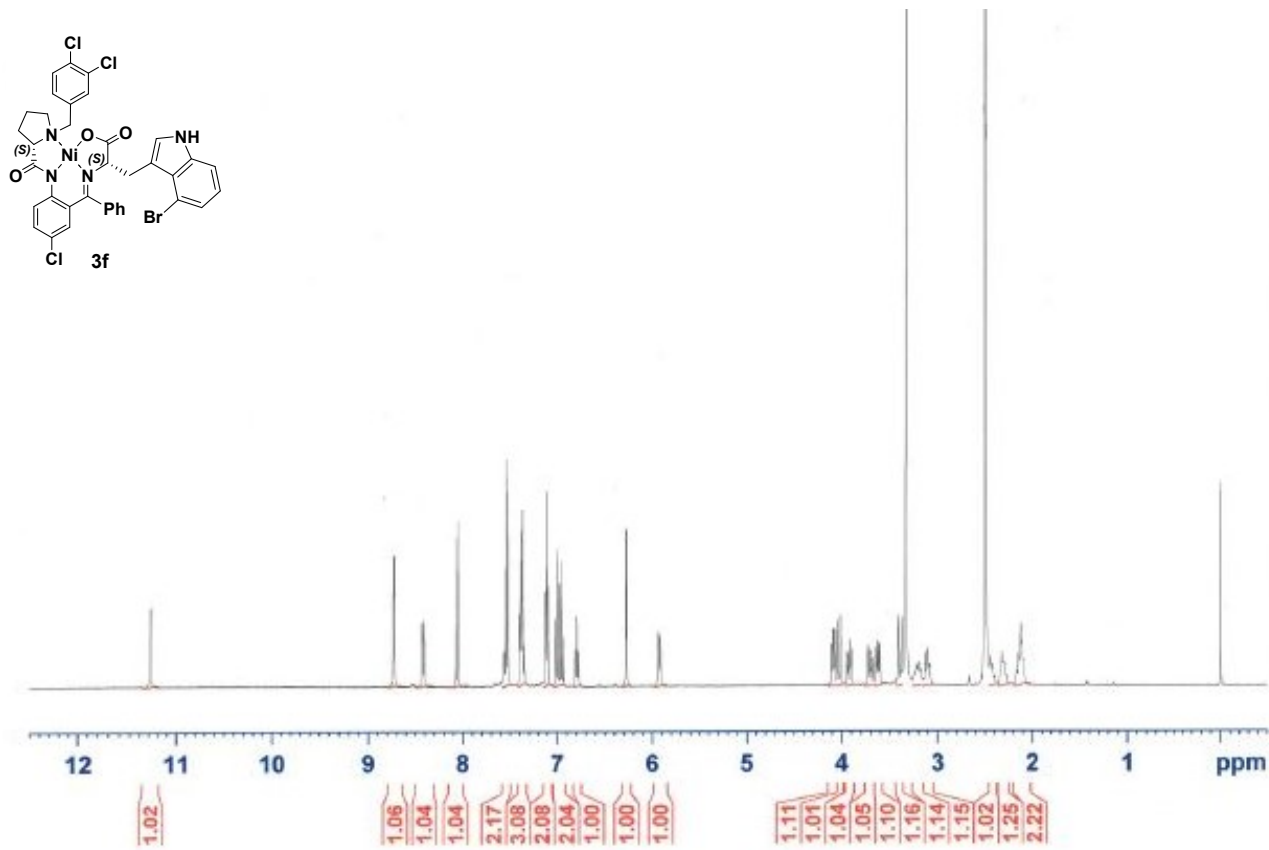
¹H NMR spectrum of 3e (500 MHz, DMSO-d₆)



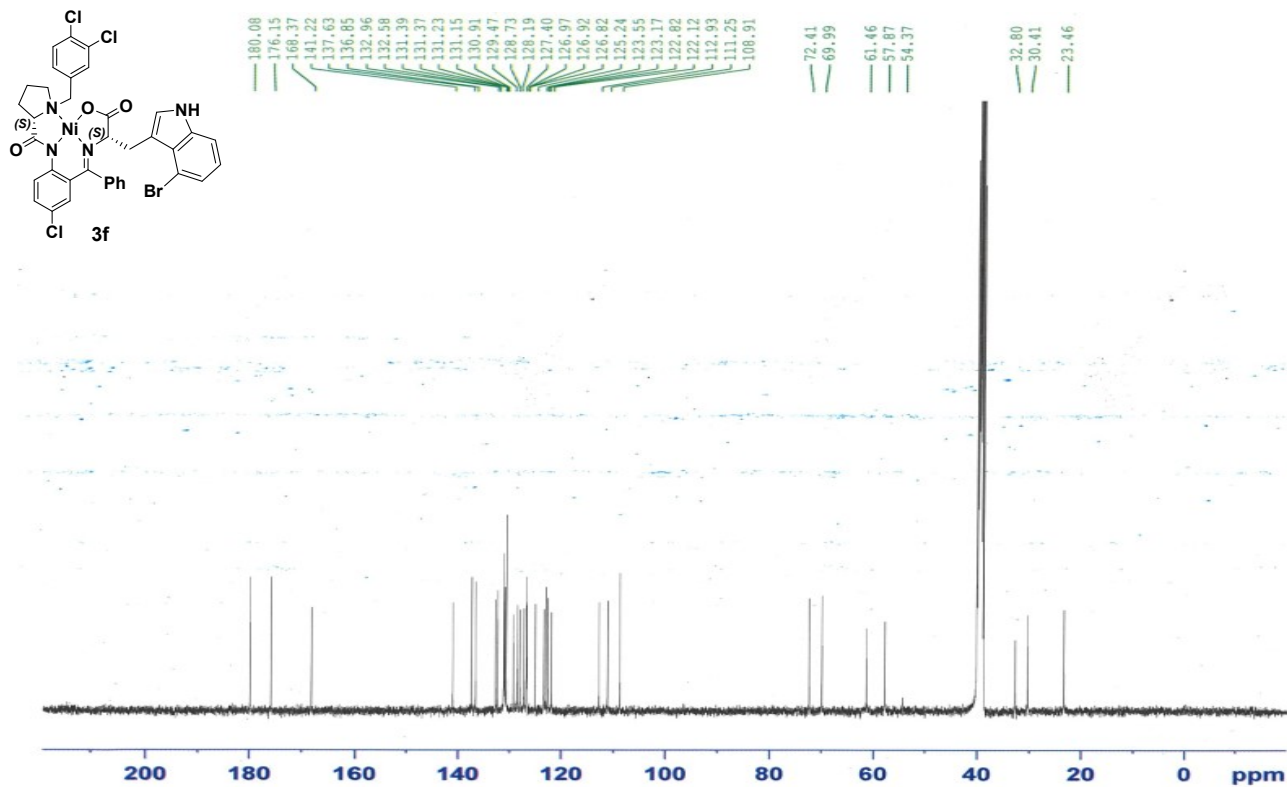
¹³C NMR spectrum of 3e (126 MHz, DMSO-d₆)



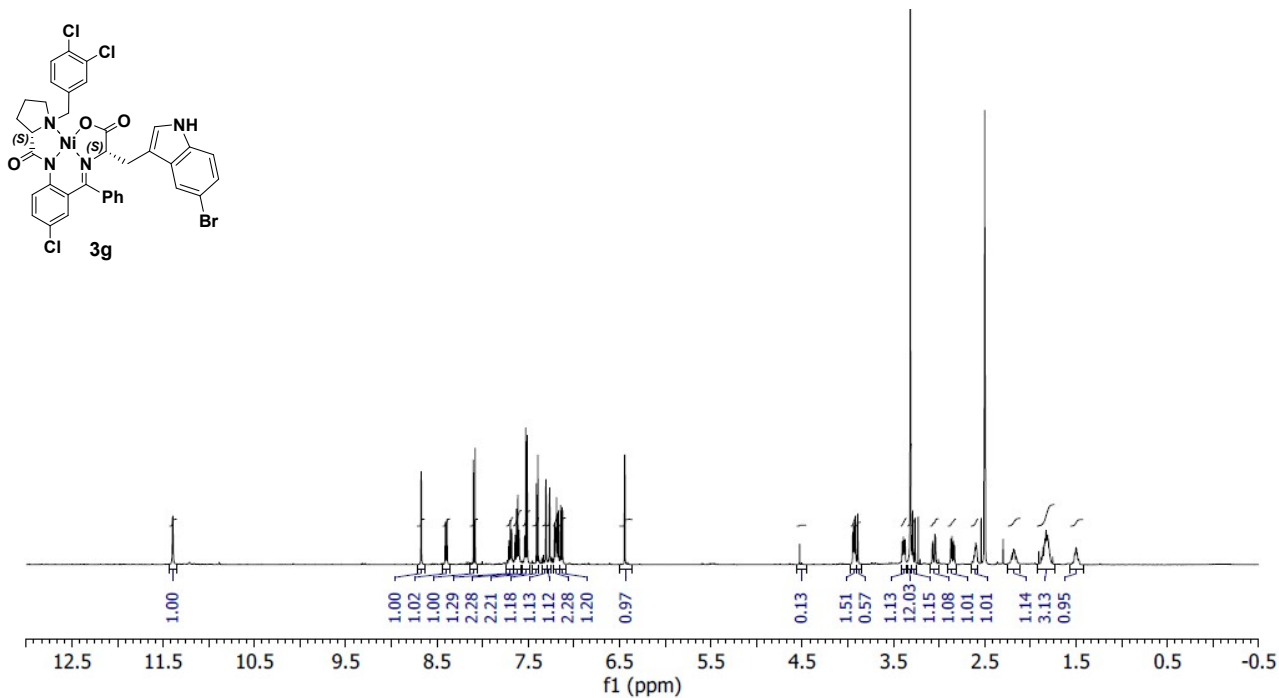
¹H NMR spectrum of 3f (400 MHz, DMSO-*d*₆)



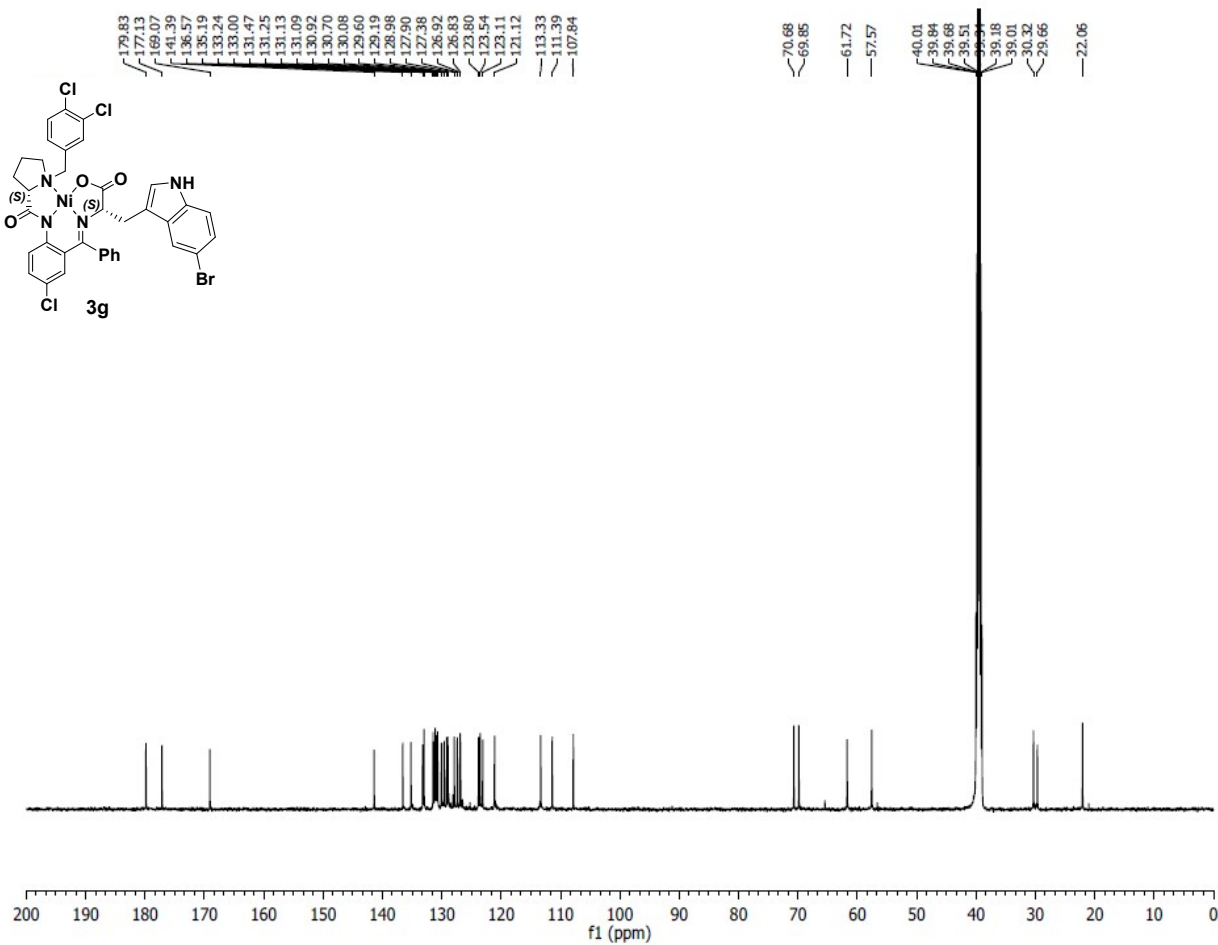
¹³C NMR spectrum of 3f (100 MHz, DMSO-*d*₆)



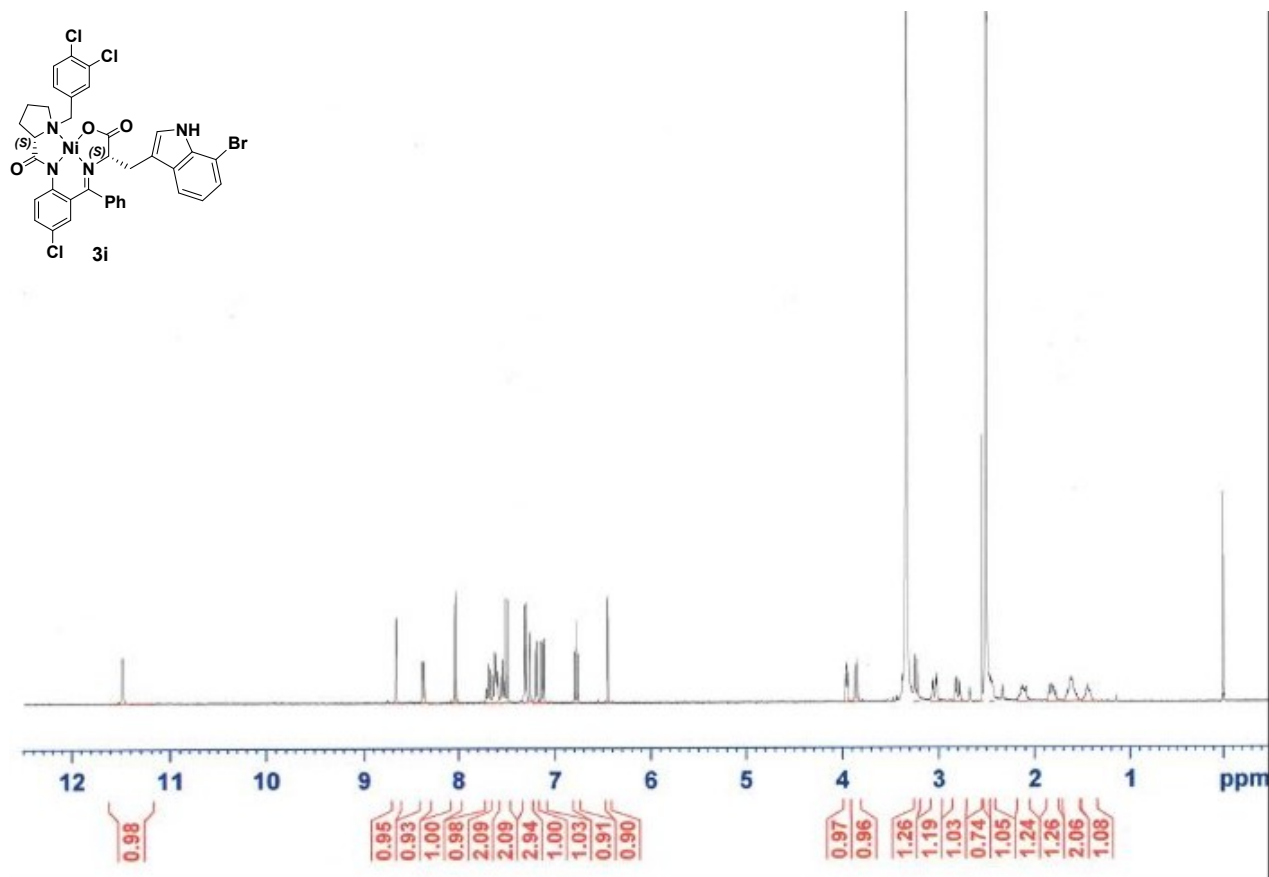
¹H NMR spectrum of 3g (500 MHz, DMSO-d₆)



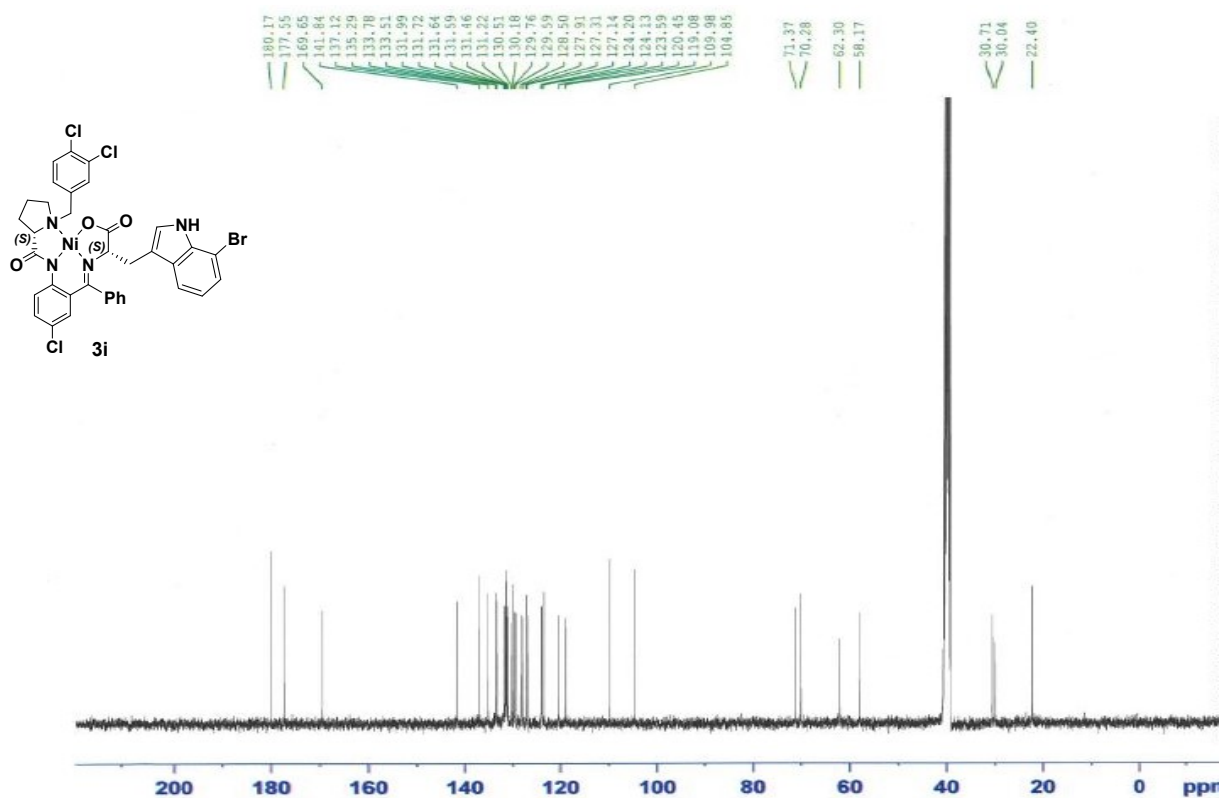
¹³C NMR spectrum of 3g (125 MHz, DMSO-d₆)



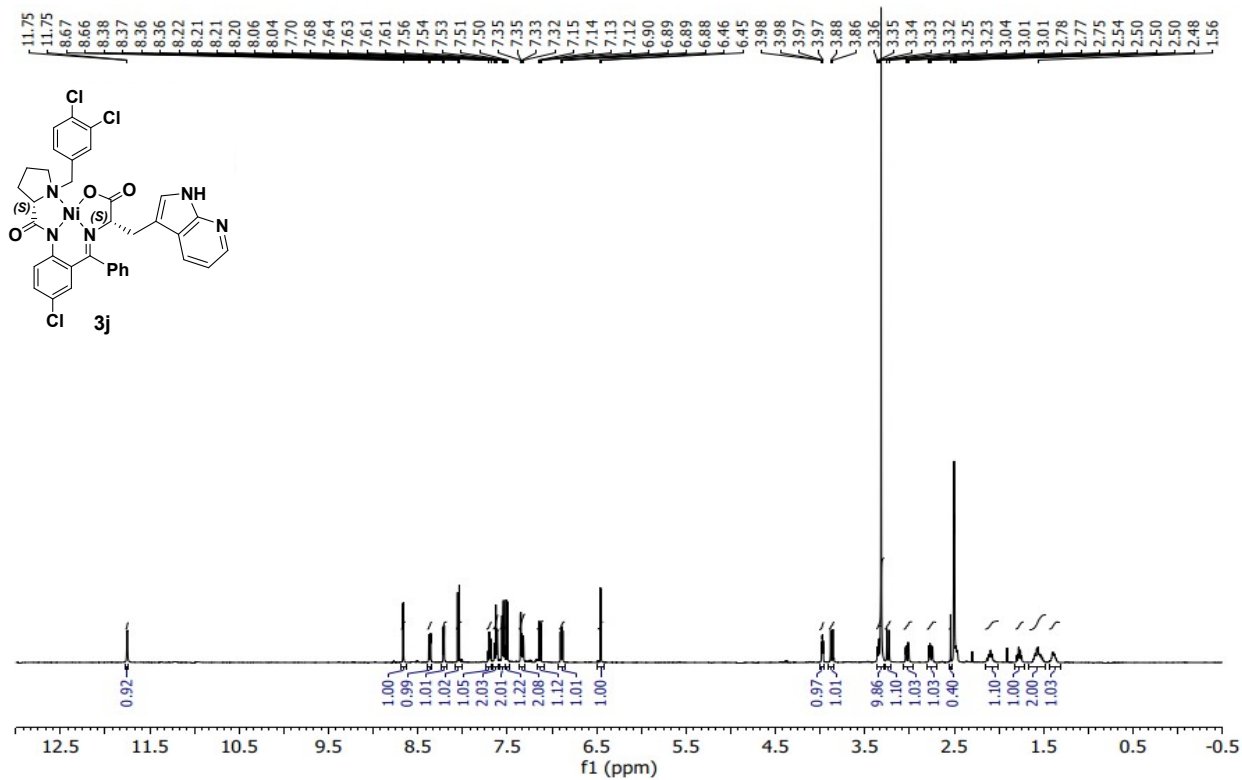
¹H NMR spectrum of 3i (400 MHz, DMSO-d₆)



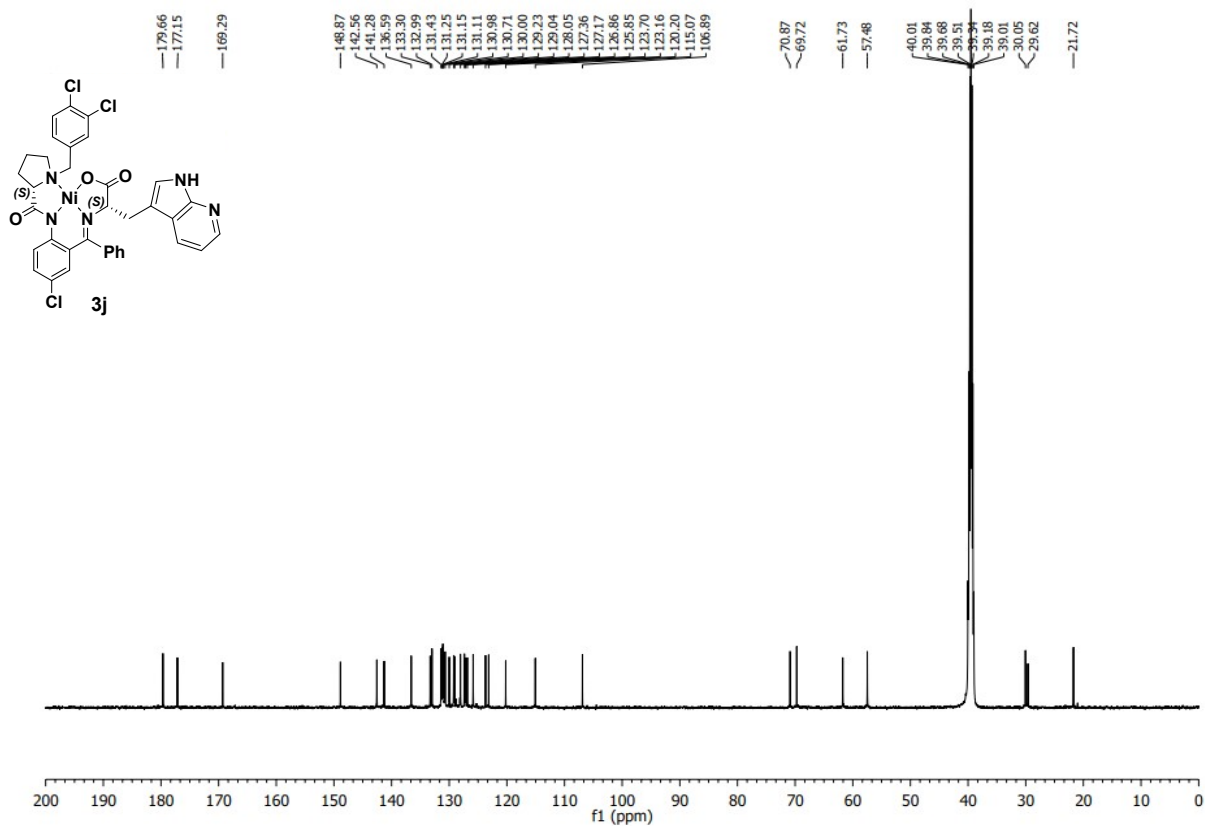
¹³C NMR spectrum of 3i (100 MHz, DMSO-d₆)



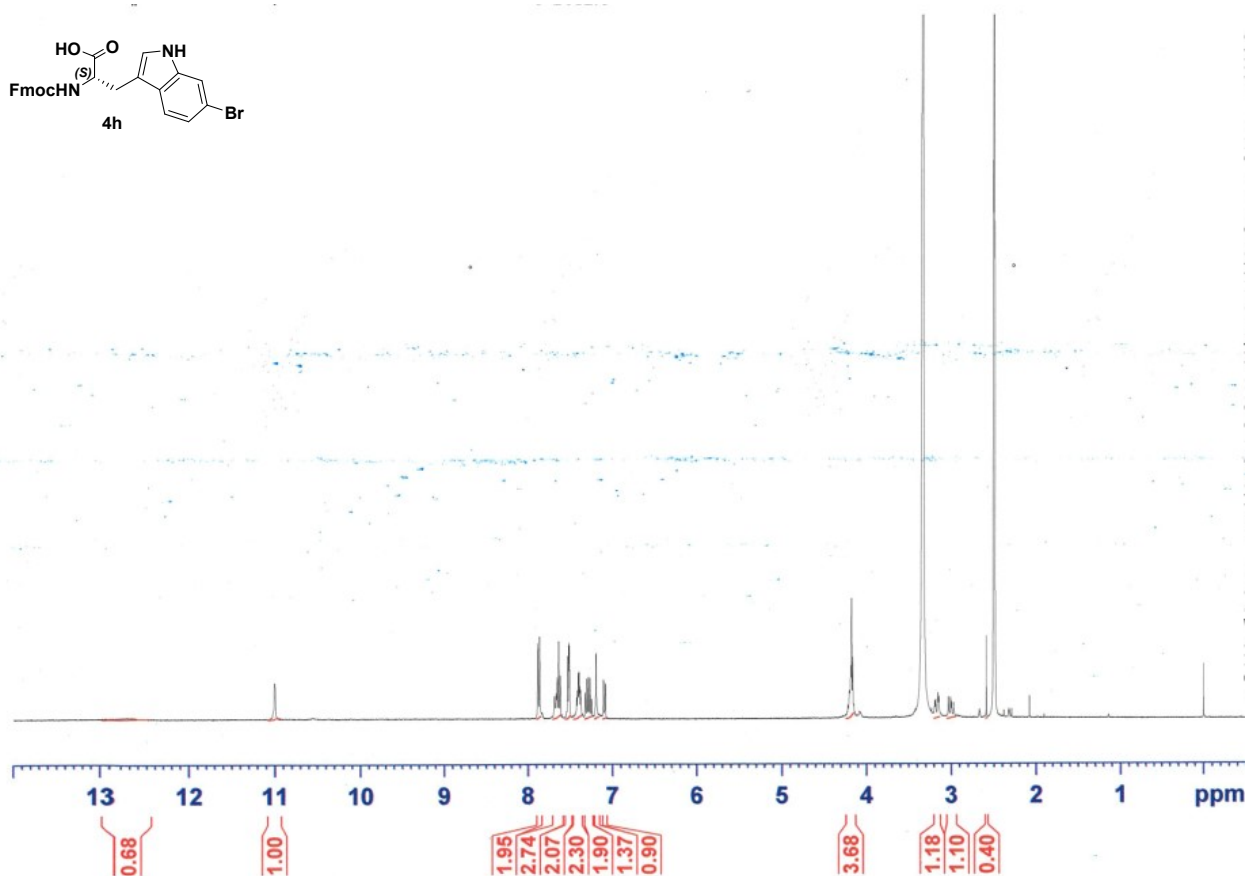
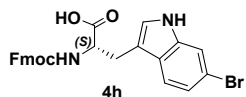
¹H NMR spectrum of 3j (500 MHz, DMSO-d₆)



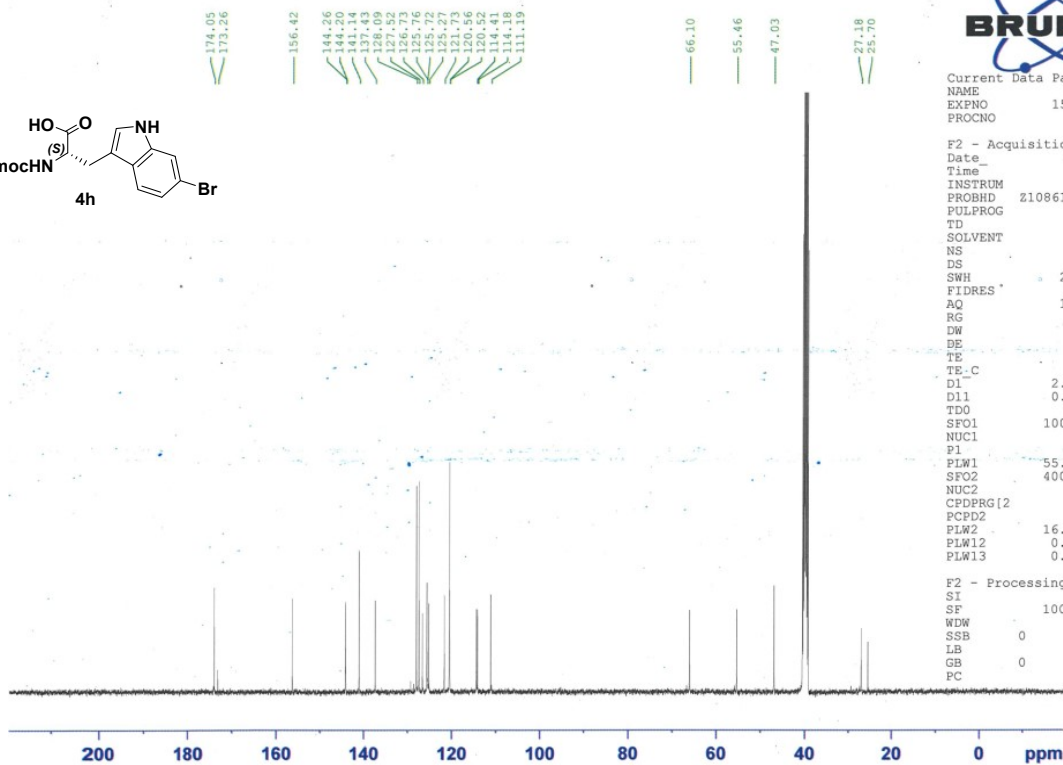
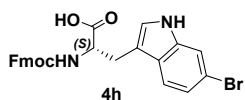
¹³C NMR spectrum of 3j (126 MHz, DMSO-d₆)



¹H NMR spectrum of 4h (400 MHz, DMSO-d₆)



¹³C NMR spectrum of 4h (100 MHz, DMSO-d₆)



Current Data Parameters
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 PROCNO 1

F2 - Acquisition Parameters
 Date 20220830
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 PROBHD Z108618_0909 ()
 PULPROG zgpg30
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 SOLVENT DMSO
 NS 4096
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 FIDRES 0.733596 Hz
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 DE 6.50 usec
 TE 297.4 K
 TE-C 24.3 deg.
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 D11 0.03000000 sec
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 SFO2 400.1316005 MHz
 NUC2 1H
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 PLW2 16.50000000 W
 PLW12 0.39926001 W
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F2 - Processing parameters
 SI 32768
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 WDW EM
 SSB 0
 LB 1.00 Hz
 GB 0
 PC 1.40

HPLC spectra for ee determination of compounds 4a – 4j

Methods for HPLC analyses (A-G)

Method A

Column: Chiral pak IC 5 μ m, 156 x 4.6 mm, S/N IC00CD-PK013

Eluent: A= 0.1% phosphoric acid in H₂O, B= 0.1% phosphoric acid in MeCN

Flow rate: 0.4 mL/ min

Temp: 30 °C

Gradient program:

Time (min)	0.00	15.00	20.00	23.00	23.10	30.00
Mobile phase A (%)	60	50	0	0	60	60
Mobile phase B (%)	40	50	100	100	40	40

Method B

Column: Chiral pak IC 5 μ m, 156 x 4.6 mm, S/N IC00CD-PK013

Eluent: A= 0.1% phosphoric acid in H₂O, B= 0.1% phosphoric acid in MeCN

Flow rate: 0.8 mL/ min

Temp: 30 °C

Gradient program:

Time (min)	0.00	30.00	30.00
Mobile phase A (%)	82	82	STOP
Mobile phase B (%)	18	18	

Method C

Column: Chiral pak IC 5 μ m, 156 x 4.6 mm, S/N IC00CD-PK013

Eluent: A= 0.1% phosphoric acid in H₂O, B= 0.1% phosphoric acid in MeCN

Flow rate: 0.5 mL/ min

Temp: 30 °C

Gradient program:

Time (min)	0.00	30.00	30.00
Mobile phase A (%)	65	65	STOP
Mobile phase B (%)	35	35	

Method D

Column: Chiral pak IC 5 μ m, 156 x 4.6 mm, S/N IC00CD-PK013

Eluent: A= 0.1% phosphoric acid in H₂O, B= 0.1% phosphoric acid in MeCN

Flow rate: 0.5 mL/ min

Temp: 30 °C

Gradient program:

Time (min)	0.00	60.00	60.00
Mobile phase A (%)	65	65	STOP
Mobile phase B (%)	35	35	

Method E

Column: Chiral pak IB 5 μ m, 156 x 4.6 mm, S/N IC00CD-PK013

Eluent: A= 0.1% phosphoric acid in H₂O, B= 0.1% phosphoric acid in MeCN

Flow rate: 0.5 mL/ min

Temp: 30 °C

Gradient program:

Time (min)	0.00	30.00	30.00
Mobile phase A (%)	53	53	STOP
Mobile phase B (%)	47	47	

Method F

Column: Chiral pak IC 5 μm , 156 x 4.6 mm, S/N IC00CD-PK013

Eluent: A= 0.1% phosphoric acid in H_2O , B= 0.1% phosphoric acid in MeCN

Flow rate: 0.8 mL/ min

Temp: 30 $^\circ\text{C}$

Gradient program:

Time (min)	0.00	30.00	30.00
Mobile phase A (%)	80	80	STOP
Mobile phase B (%)	20	20	

Method G

Column: Chiral pak IC 5 μm , 156 x 4.6 mm, S/N IC00CD-PK013

Eluent: A= 0.1% phosphoric acid in H_2O , B= 0.1% phosphoric acid in MeCN

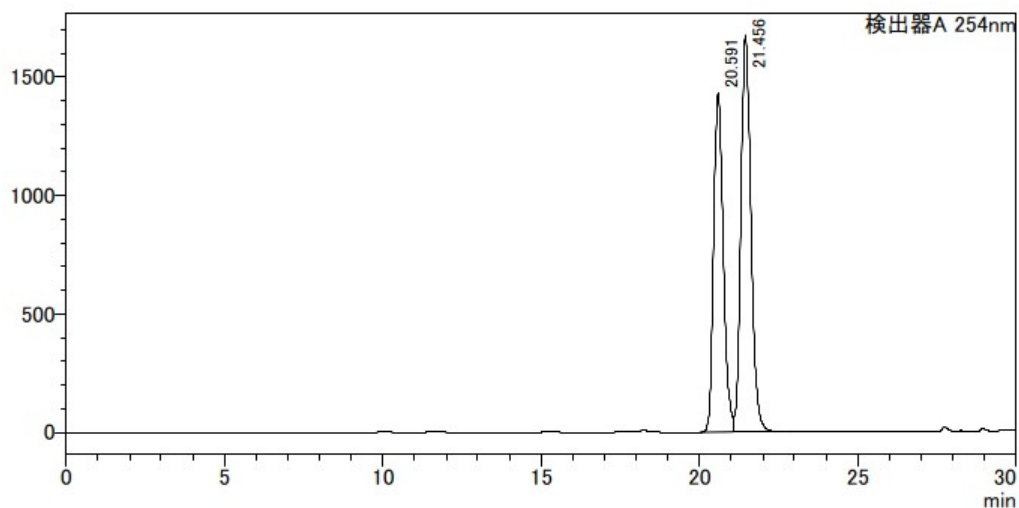
Flow rate: 0.5 mL/ min

Temp: 30 $^\circ\text{C}$

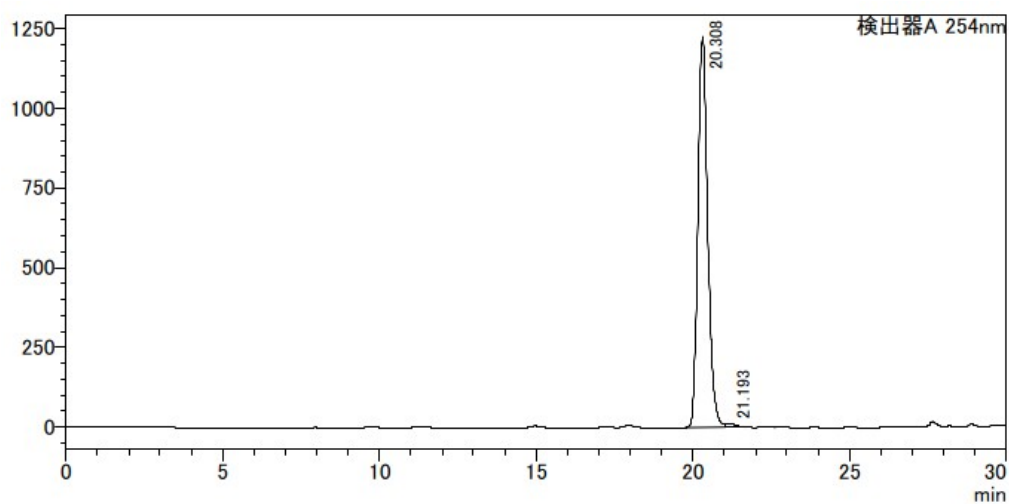
Gradient program:

Time (min)	0.00	30.00	30.00
Mobile phase A (%)	80	80	STOP
Mobile phase B (%)	20	20	

Mixture of (S) and (R)-4a³⁰



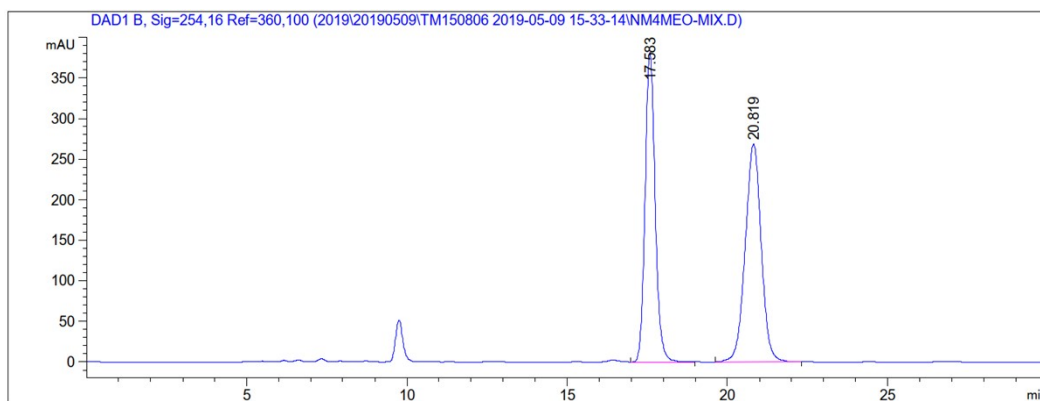
(S)-4a³⁰



Peak#	RetTime	Area	Area%
1	20.308	26730355	99.150
2	21.193	229289	0.850

The ee was determined by an HPLC according to the Method A.

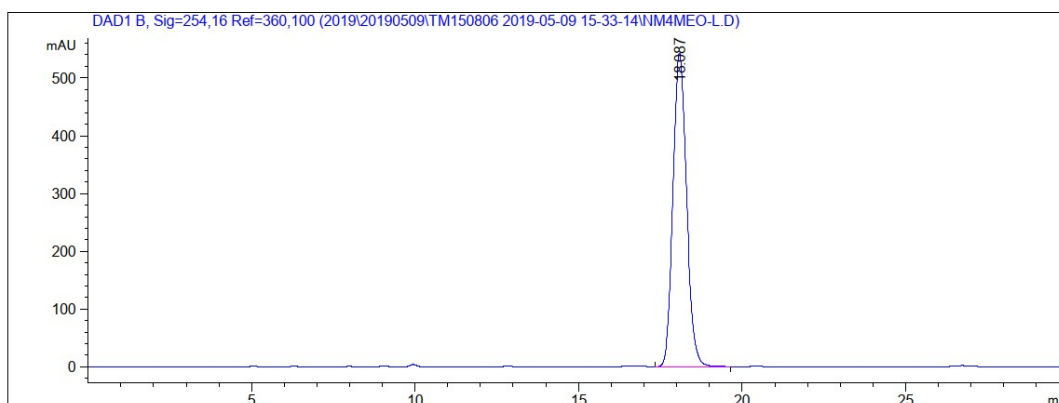
Mixture of (S) and (R)-4b



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	17.583	VB	0.3384	8330.66016	381.99365	47.1586
2	20.819	BB	0.5416	9334.52148	268.52713	52.8414

Totals : 1.76652e4 650.52078

(S)-4b

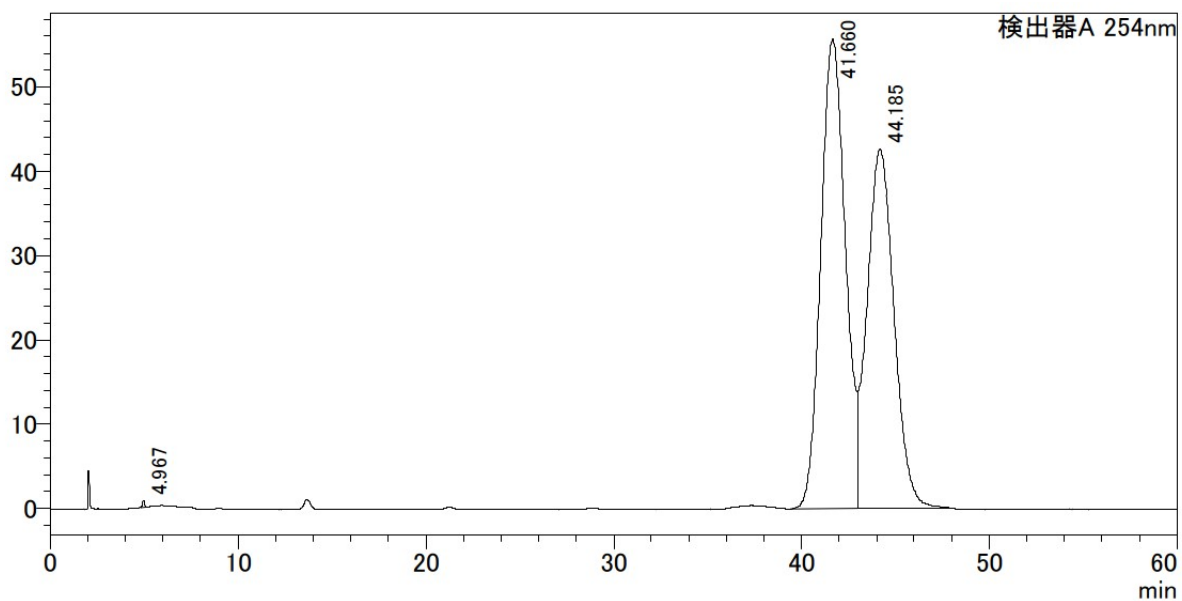


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	18.087	VB	0.4540	1.57237e4	542.77966	100.0000

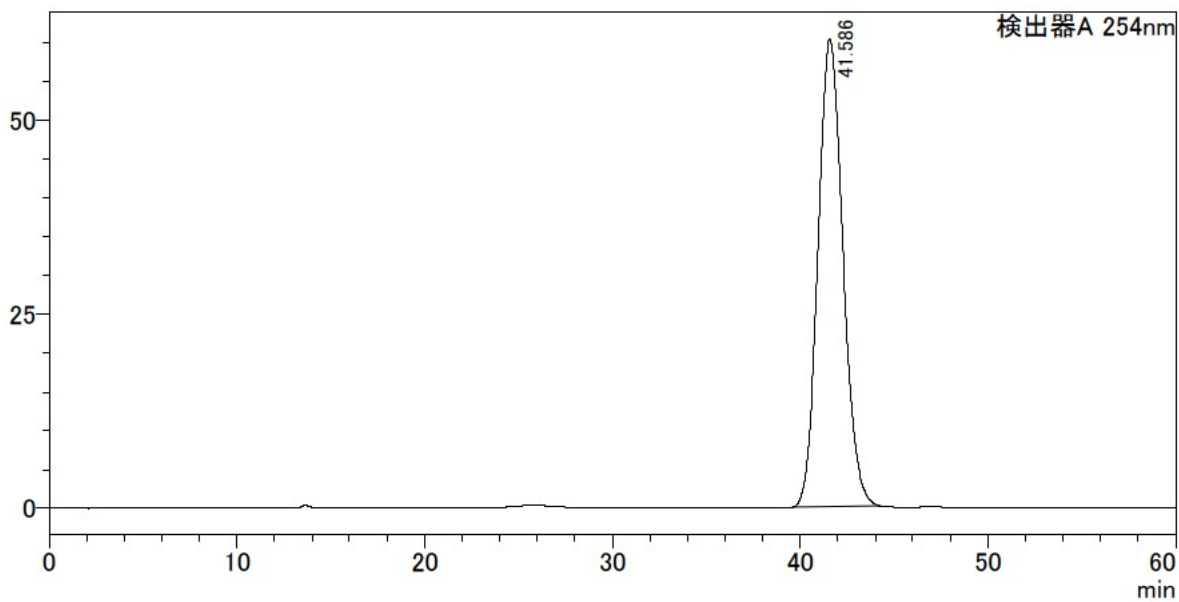
Totals : 1.57237e4 542.77966

The ee was determined by an HPLC according to the Method B.

Mixture of (S) and (R)-4c



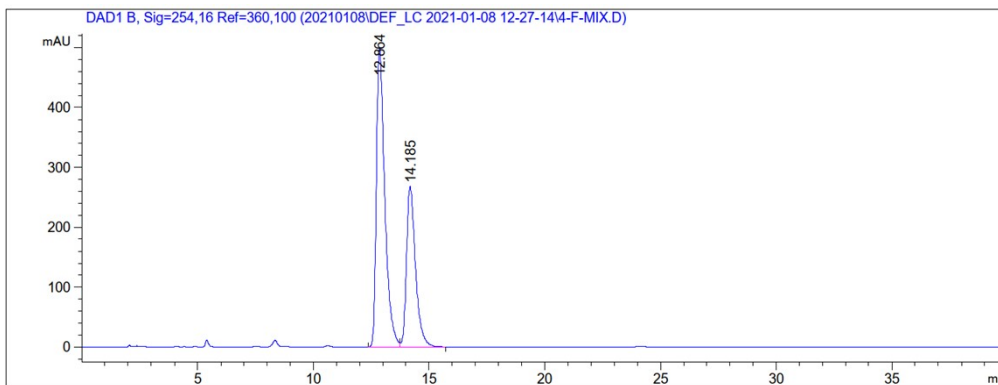
(S)-4c



Peak#	RetTime	Area	Area%
1	41.586	5557198	100.000

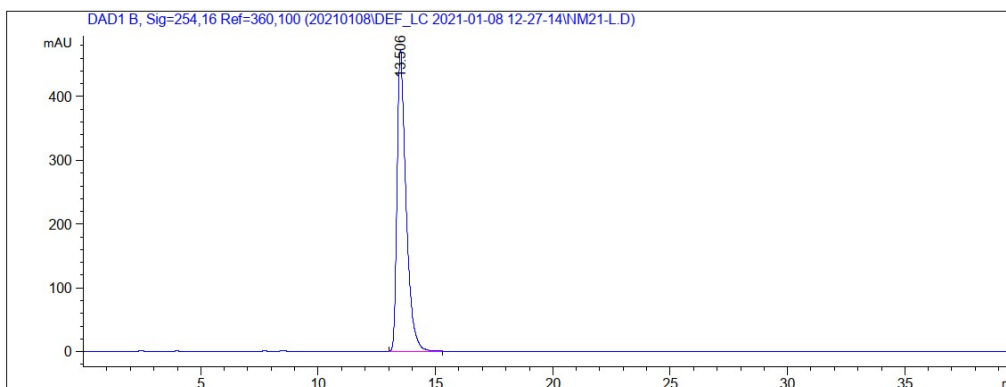
The ee was determined by an HPLC according to the Method D

Mixture of (S) and (R)-4d



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.864	BV	0.3793	1.26181e4	498.46561	63.4863
2	14.185	VB	0.4120	7257.19385	267.91455	36.5137
Totals :				1.98752e4	766.38016	

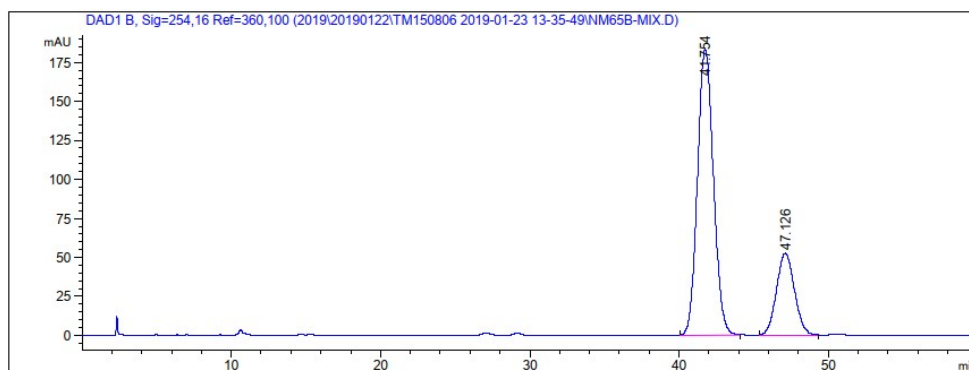
(S)-4d



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	13.506	BB	0.4052	1.26794e4	472.24341	100.0000
Totals :				1.26794e4	472.24341	

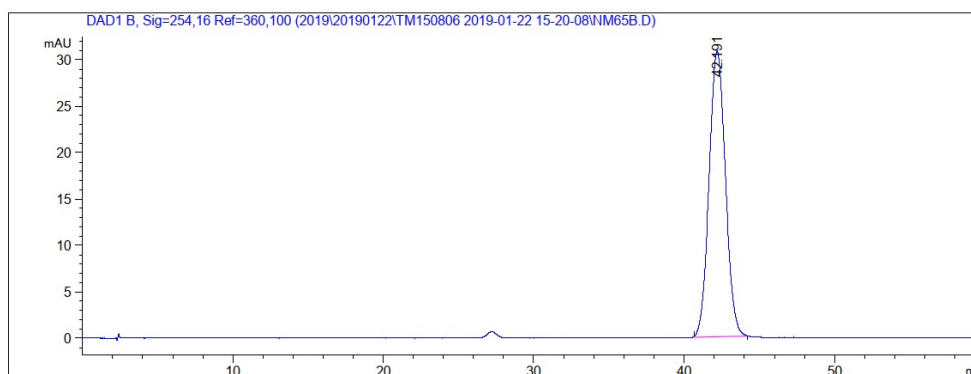
The ee was determined by an HPLC according to the Method D.

Mixture of (S) and (R)-4e



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	41.754	BB	1.1686	1.36491e4	183.32391	75.6859
2	47.126	BB	1.2799	4384.79004	52.41736	24.3141
Totals :				1.80339e4	235.74128	

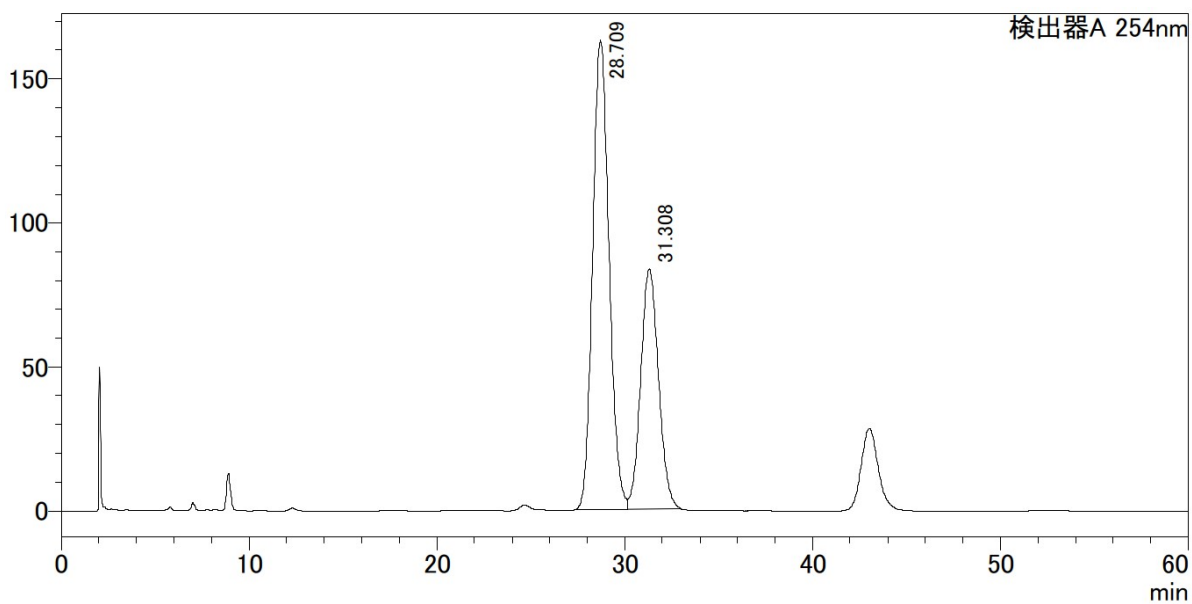
(S)-4e



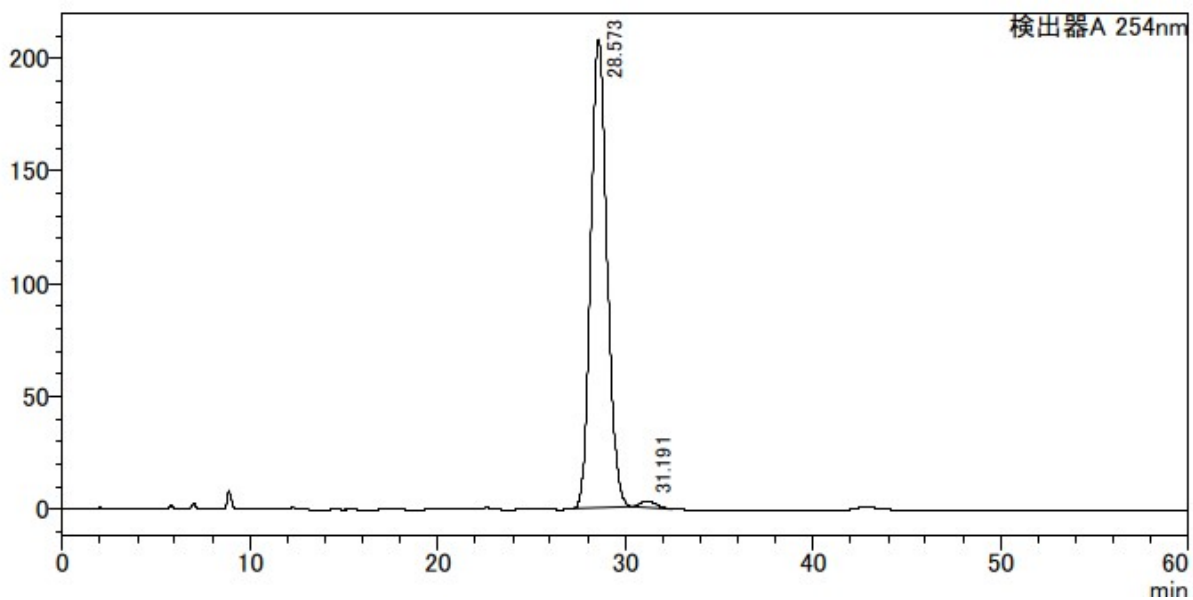
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	42.191	BB	1.1393	2325.09595	30.84879	100.0000
Totals :				2325.09595	30.84879	

The ee was determined by an HPLC according to the Method E.

Mixture of (S) and (R)-4f



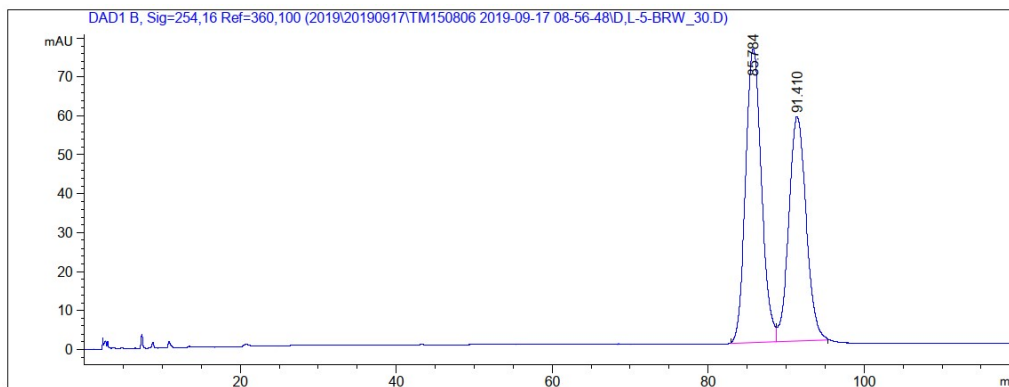
(S)-4f



Peak#	RetTime	Area	Area%
1	28.573	12548505	98.624
2	31.191	175109	1.376

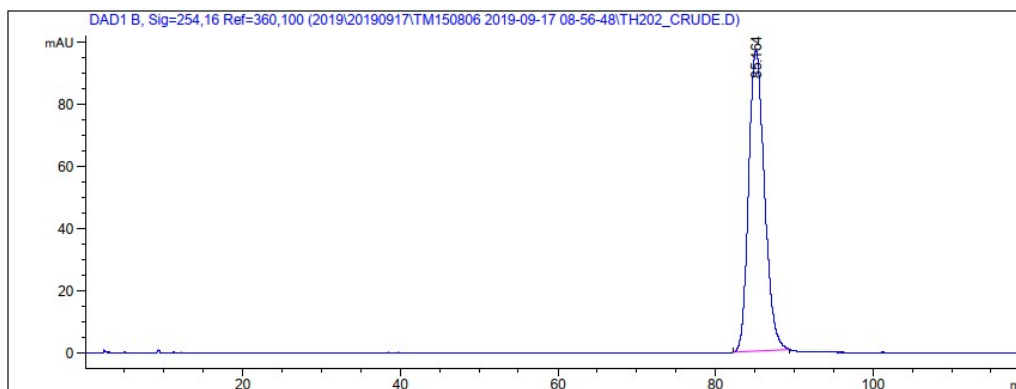
The ee was determined by an HPLC according to the Method D.

Mixture of (S) and (R)-4g



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	85.784	BV	2.1311	1.07463e4	75.47762	54.6429
2	91.410	VB	2.1271	8920.12109	57.58939	45.3571
Totals :				1.96664e4	133.06701	

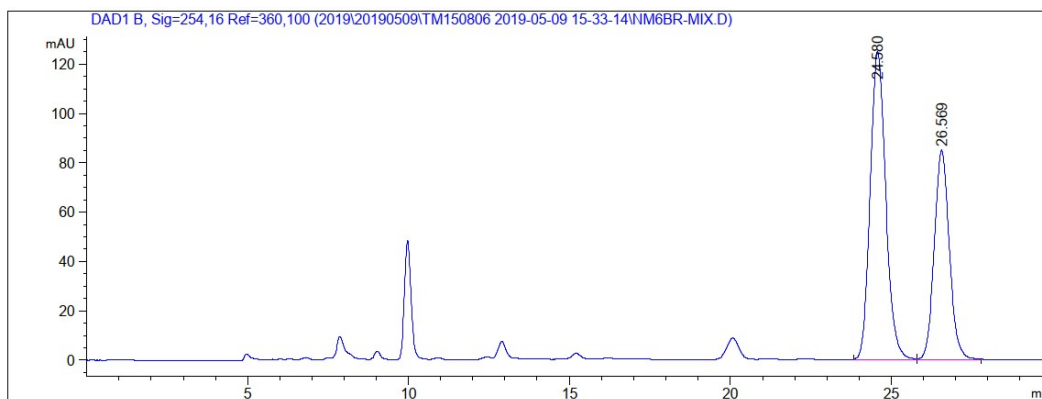
(S)-4g



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	85.164	BB	2.0604	1.35437e4	96.67652	100.0000
Totals :				1.35437e4	96.67652	

The ee was determined by an HPLC according to the Method F.

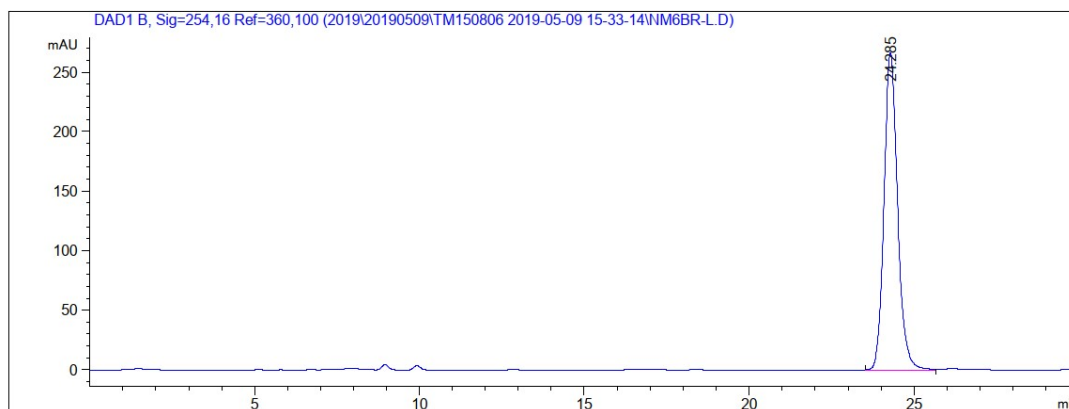
Mixture of (S) and (R)-4h



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	24.580	BV	0.5247	4203.69727	124.89906	60.3451
2	26.569	VB	0.4996	2762.39331	84.89160	39.6549

Totals : 6966.09058 209.79066

(S)-4h

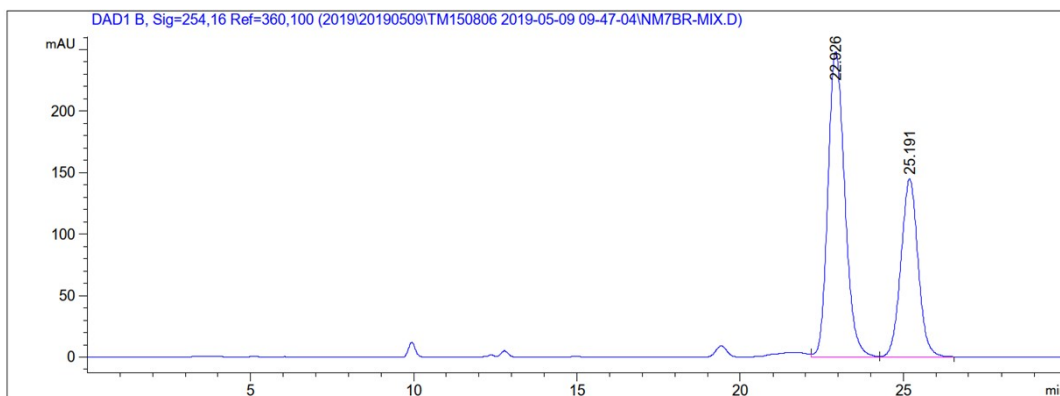


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	24.285	BB	0.4436	7620.62012	266.51480	100.0000

Totals : 7620.62012 266.51480

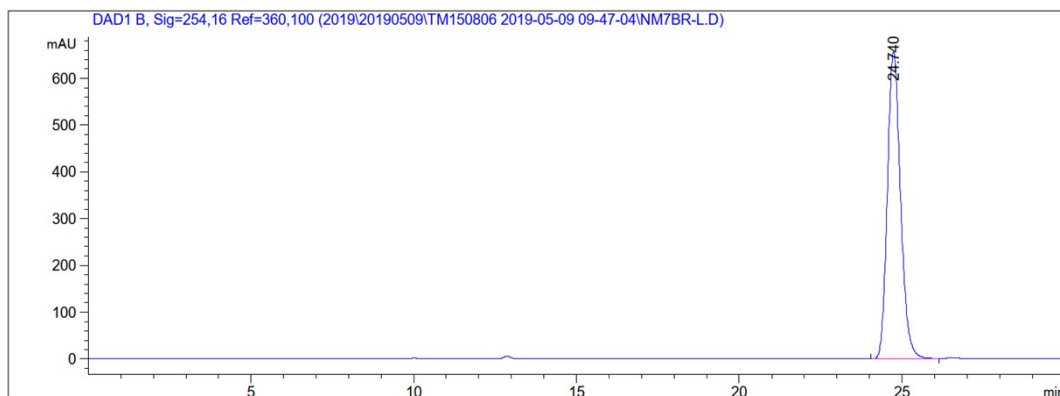
The ee was determined by an HPLC according to the Method G.

Mixture of (S) and (R)-4i



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	22.926	VV	0.5544	8920.86914	248.73927	62.7605
2	25.191	VB	0.5662	5293.27881	144.89851	37.2395
Totals :				1.42141e4	393.63779	

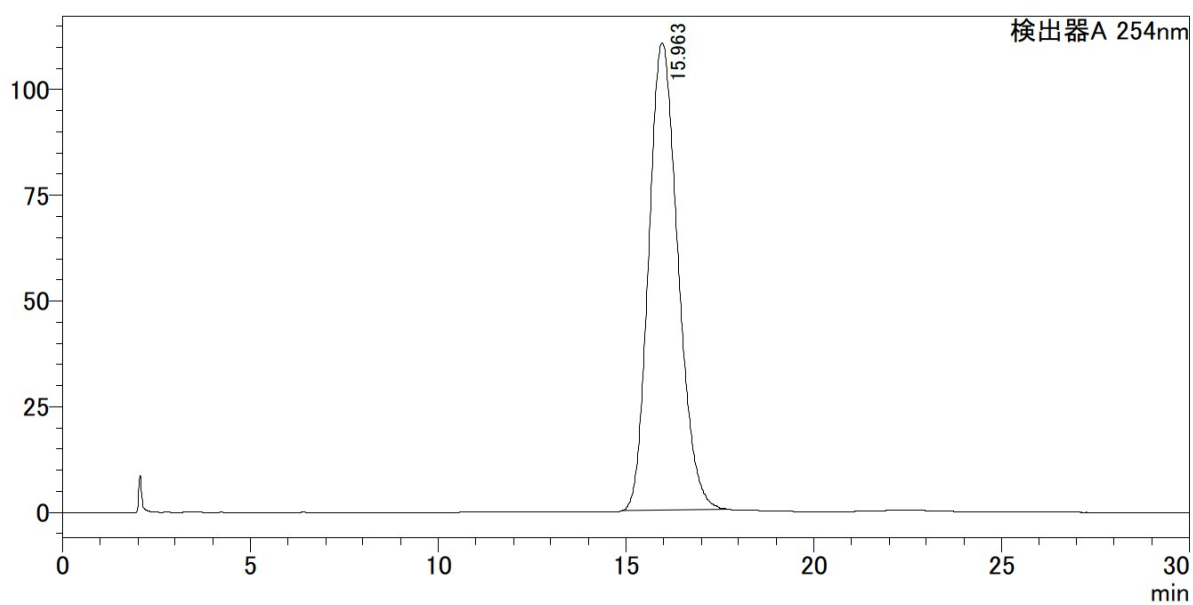
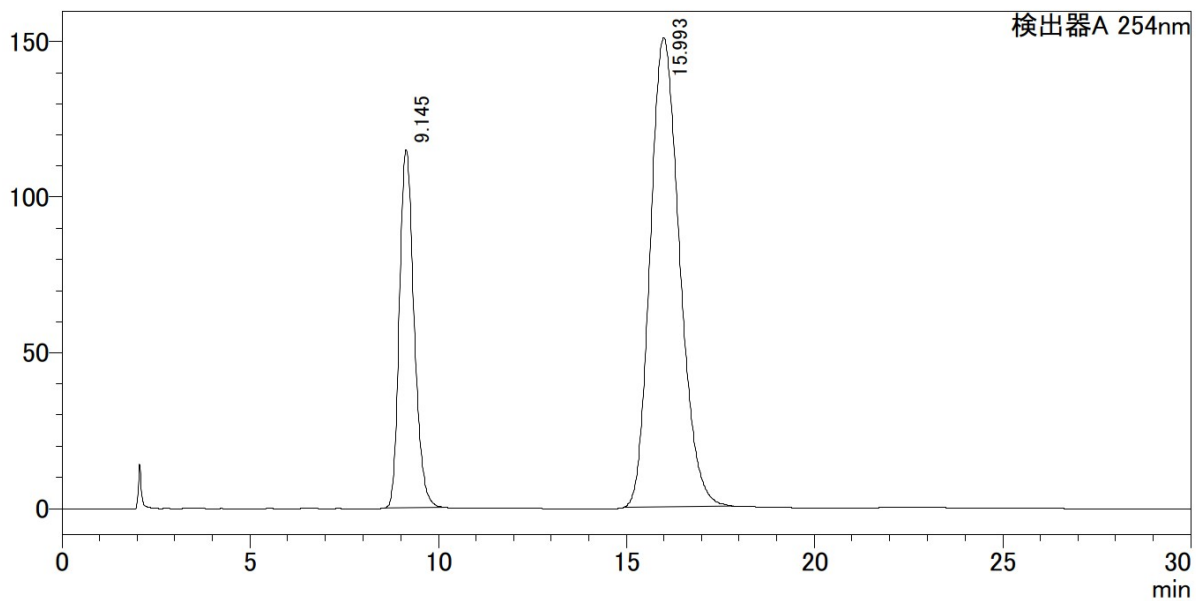
(S)-4i



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	24.740	BB	0.4303	1.84863e4	656.92871	100.0000
Totals :				1.84863e4	656.92871	

The ee was determined by an HPLC according to the Method B.

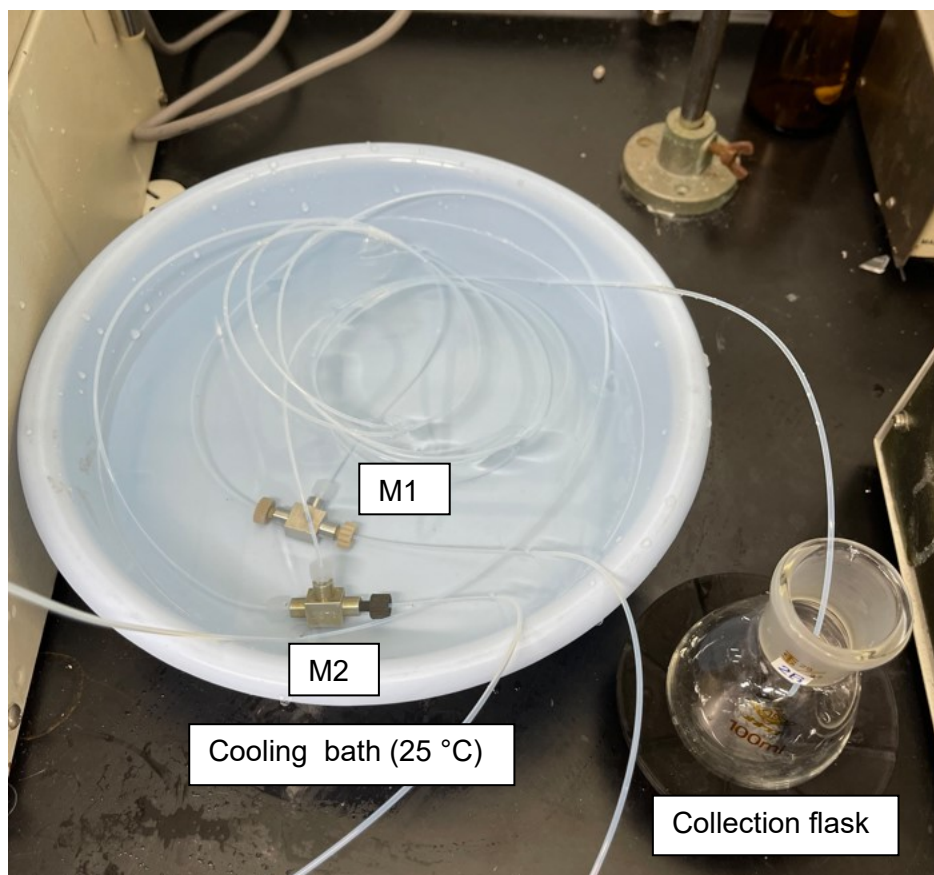
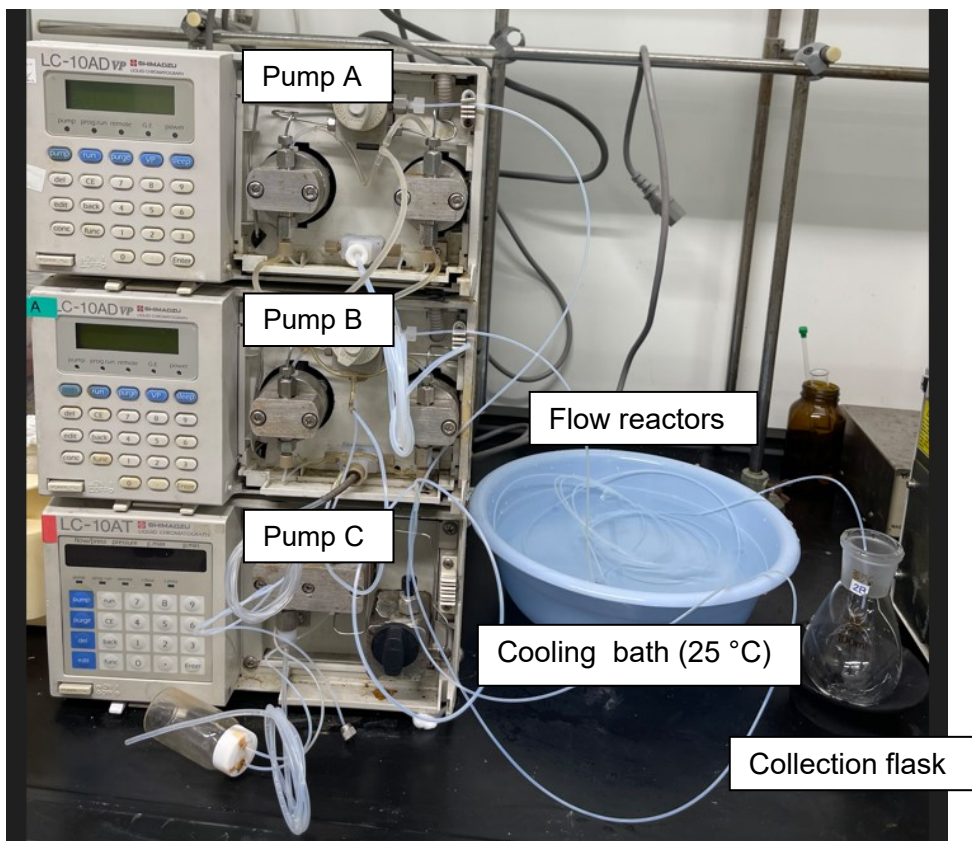
Mixture of (S) and (R)-4j



Peak#	RetTime	Area	Area%
1	15.963	5978423	100.000

The ee was determined by an HPLC according to the Method C.

Details of the continuous-flow reaction system in Table 5



Details of the continuous-flow reaction system in Table 6

