Development of an Enantioselective [3+2] Cycloaddition to Synthesize the Pyrrolidine Core of ABBV-3221 on Multi-kilogram Scale

Supporting Information

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HTP Catalyst Screen. Inside a glove-box, a 96-well plate was pre-loaded with ligands (0.22 µmol for bi-dentate (P-P) ligands and 0.44 µmol for mono-dentate (P) ligands, see legend on page S-3). To each well, a glass bead and stock solution of $[CuOTf]_2$*toluene complex (50µL, 0.1 µmol) were added. The plate was stirred by an orbital shaker at approx. 14°C for 15 min. Then stock solutions of imine **3** (50µL, 2.2 µmol), KOtBu (50µL, 1.6µmol), and nitro olefin **2** (50µL, 2.0µmol) were added, and the plate was stirred by orbital shaker at approx. 0°C for 18 h inside a glove-box. The plate was analyzed by RP-HPLC (conversion, d.e.) and chiral HPLC (e.e. *endo* product).

Conversion (%)

	1	2	3	4	5	6	7	8	9	10	11	12
A	98	99	99	99	75	99	80	99	98	98	99	69
B	100	99	100	98	97	100	99	0	72	96	1	99
C	99	100	100	99	99	77	99	98	99	54	98	98
D	98	97	98	99	52	83	99	99	98	62	100	75
E	99	100	100	100	96	96	99	99	99	98	99	98
F	100	94	98	99	58	51	99	99	99	78	99	100
G	99	99	57	87	96	99	99	73	77	99	98	81
H	100	99	69	78	99	79	99	99	100	100	99	99

e.e. *endo* (%)

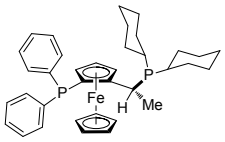
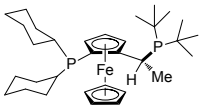
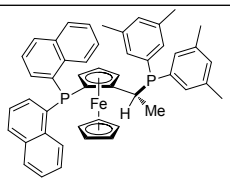
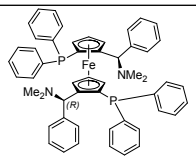
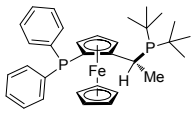
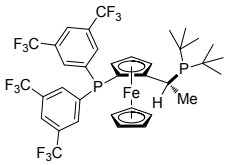
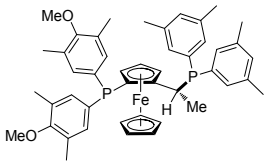
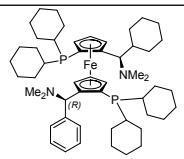
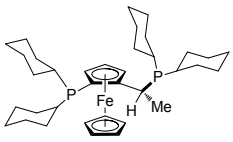
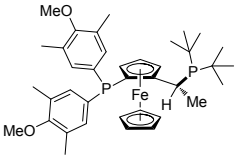
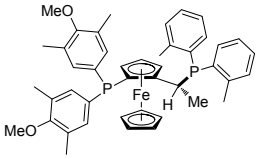
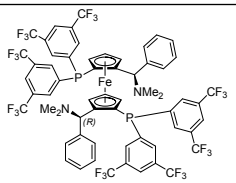
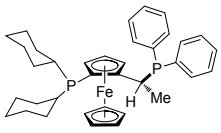
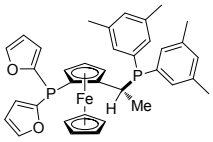
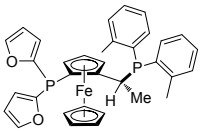
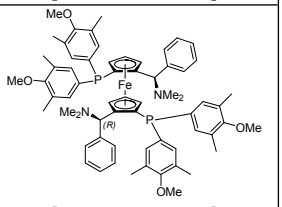
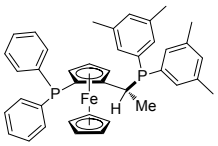
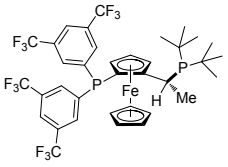
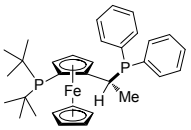
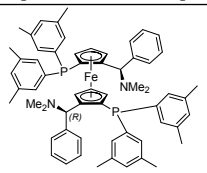
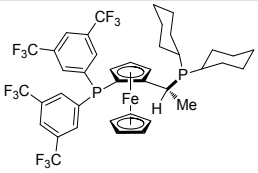
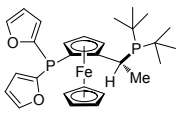
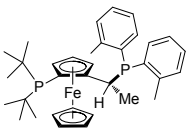
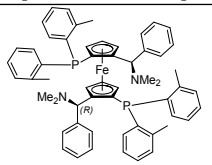
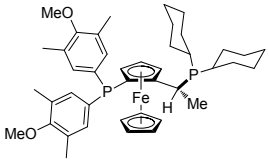
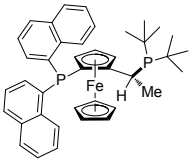
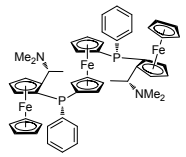
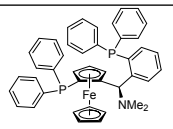
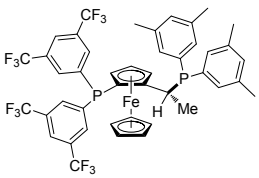
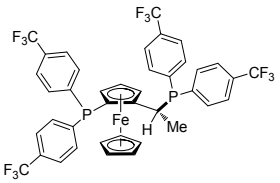
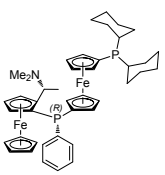
	1	2	3	4	5	6	7	8	9	10	11	12
A	56	17	-6	61	73	-35	-25	-10	30	-34	60	10
B	63	61	25	3	-23	-25	6	NA	-28	-39	ND	14
C	-41	53	52	-24	16	-59	-32	25	-15	78	-17	-16
D	-10	-20	34	34	60	-22	52	4	-14	52	44	-2
E	30	62	-26	50	0	20	-8	12	-46	88	-74	81
F	88	28	-30	88	42	-30	6	-48	-70	0	-38	-16
G	28	0	-18	-10	2	-20	2	40	82	-28	26	-2
H	80	24	14	-14	16	-79	-22	56	-64	99	-10	-16

90-100
80-90
70-80
60-70
50-60
40-50
30-40
20-30
10-20
0-10

d.e. (%)

	1	2	3	4	5	6	7	8	9	10	11	12
A	34	6	-10	68	86	-26	48	-34	-18	-6	98	98
B	4	26	-6	42	-28	-22	48	NA	-9	-22	ND	-28
C	38	20	18	99	26	24	48	76	22	93	24	40
D	-8	18	-38	-18	52	34	28	92	46	62	-64	94
E	-28	74	-16	26	16	2	-16	-22	-16	22	-14	-16
F	89	-16	45	23	92	16	-22	-18	-2	19	-38	12
G	21	47	92	-56	34	-15	-16	34	22	17	90	98
H	95	55	96	14	92	38	0	38	2	66	94	-4

80 – 100
60 – 80
40 – 60
20 – 40
0 – 20
0 – -20
-20 – -40
-40 – -60
-60 – -80
-80 – -100

Well	1	2	3	4
A	 [155806-35-2]	 [158923-11-6]	 [851308-40-2]	 [210842-74-3]
B	 [155830-69-6]	 [246231-79-8]	 [849924-45-4]	 [494227-35-9]
C	 [167416-28-6]	 [187733-50-2]	 [849924-49-8]	 [494227-36-0]
D	 [158923-09-2]	 [649559-65-9]	 [849924-73-8]	 [494227-37-1]
E	 [184095-69-0]	 J210-1	 [223120-71-6]	 [793718-16-8]
F	 [292638-88-1]	 [849924-41-0]	 [849924-76-1]	 [831226-37-0]
G	 [360048-63-1]	 [849924-43-2]	 [899811-43-9]	 [255884-98-1]
H	 [166172-63-0]	 [166172-60-7]	 [952586-19-5]	 [494227-38-2]

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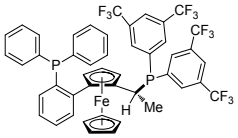
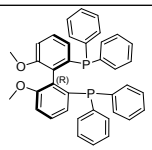
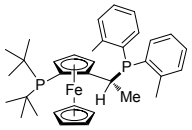
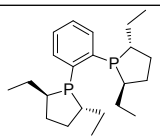
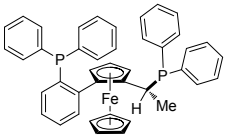
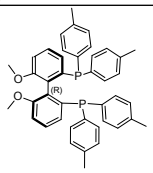
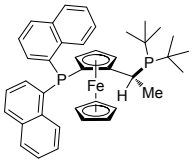
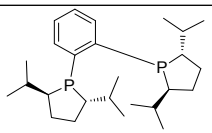
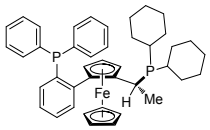
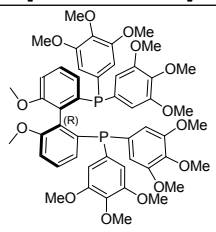
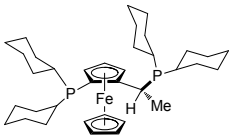
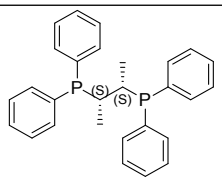
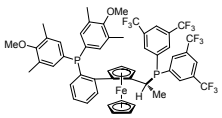
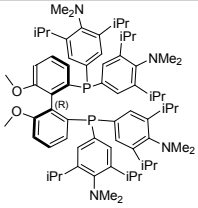
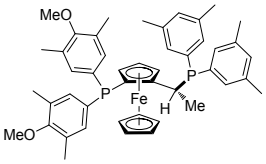
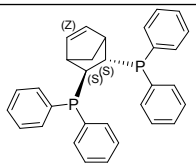
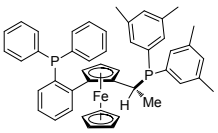
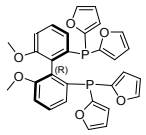
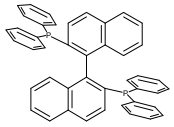
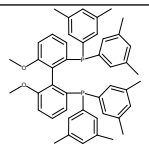
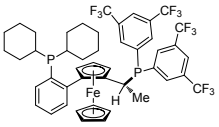
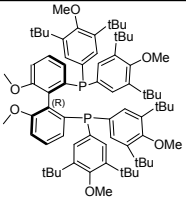
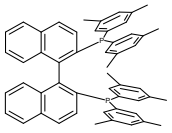
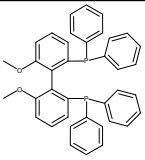
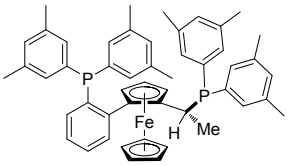
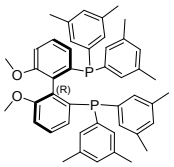
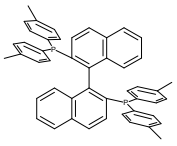
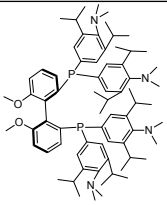
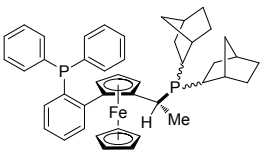
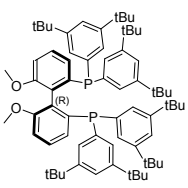
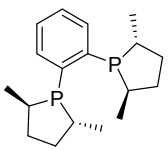
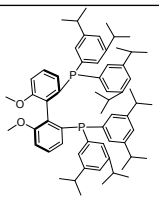
A	 [387868-06-6]	 [133545-16-1]	 [849924-76-1]	 [136705-64-1]
B	 [388079-58-1]	 [133545-24-1]	 [849924-43-2]	 [136705-65-2]
C	 [388079-60-5]	 [256390-47-3]	 [167416-28-6]	 [64896-28-2]
D	 [494227-30-4]	 [352655-40-4]	 [849924-45-4]	 [71042-54-1]
E	 [494227-31-5]	 [145214-57-9]	 [76189-55-4]	 [394248-45-4]
F	 [494227-32-6]	 [352655-61-9]	 [137219-86-4]	 [133545-16-1]
G	 [494227-33-7]	 [394248-45-4]	 [100165-88-6]	 [919338-66-2]
H	 [849925-29-7]	 [192138-05-9]	 [147253-67-6]	 [167709-31-1]

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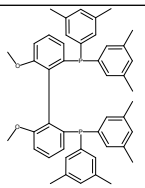
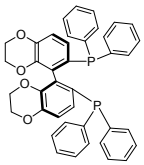
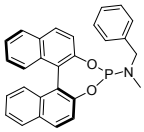
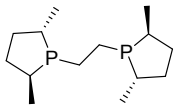
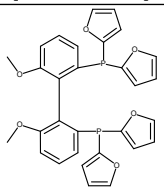
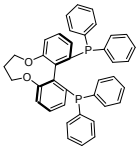
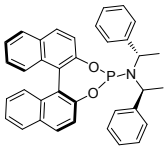
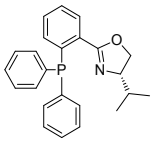
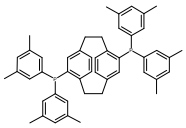
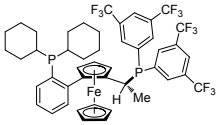
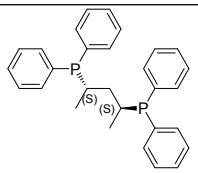
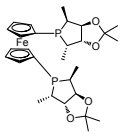
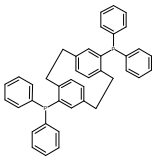
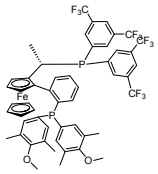
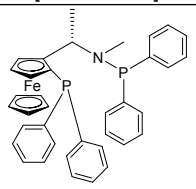
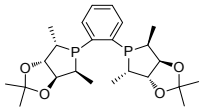
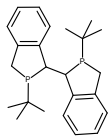
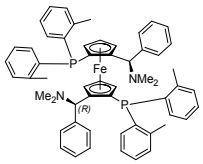
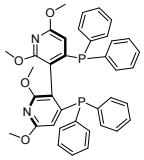
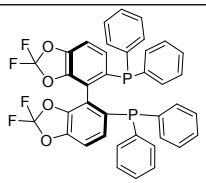
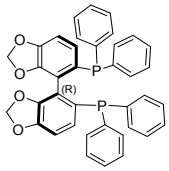
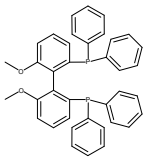
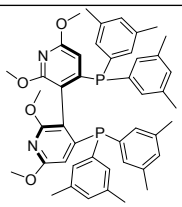
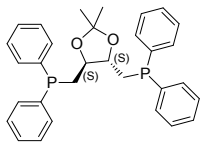
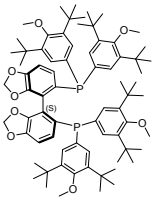
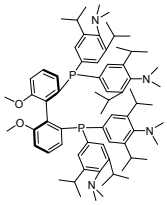
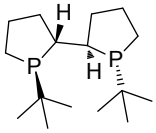
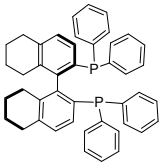
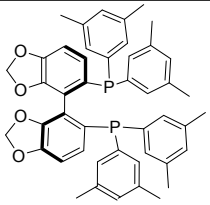
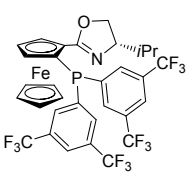
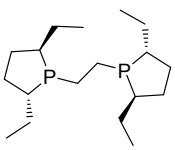
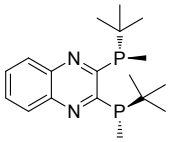
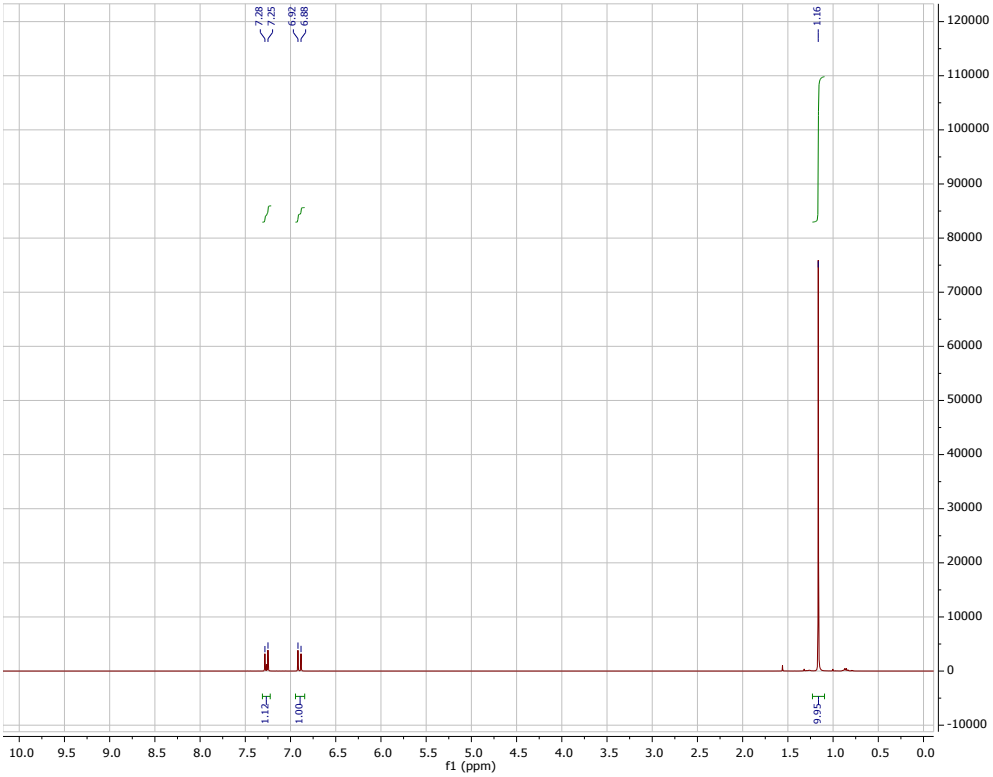
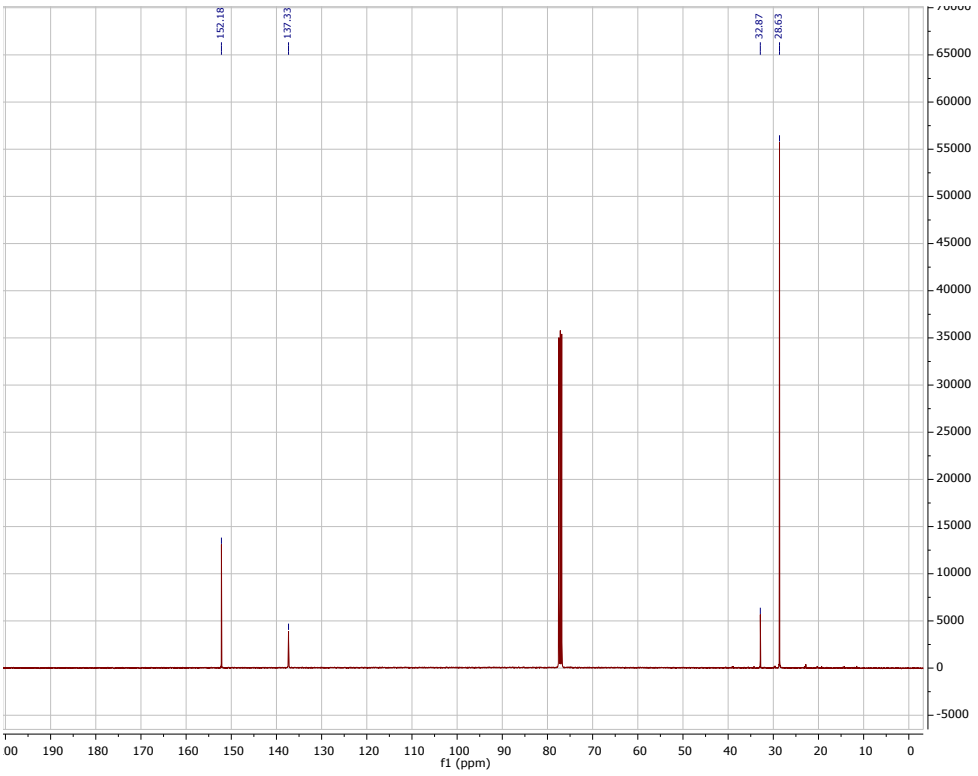
A	 [362634-22-8]	 [445467-61-8]	 [490023-37-5]	 [129648-07-3]
B	 [145214-59-1]	 [301847-89-2]	 [209482-27-9]	 [148461-14-7]
C	 [325168-89-6]	 [494227-32-6]	 [77876-36-2]	 [488760-58-3]
D	 [364732-88-7]	 [494227-30-4]	 [406681-09-2]	 [248244-33-9]
E	 [528814-26-8]	 [831226-37-0]	 [221012-82-4]	 [503538-70-3]
F	 [244261-66-3]	 [133545-16-1]	 [442905-33-1]	 [37002-48-5]
G	 [210169-40-7]	 [919338-66-2]	 [470480-32-1]	 [139139-86-9]
H	 [850253-53-1]	 [706814-27-9]	 [136779-27-6]	 [866081-62-1]

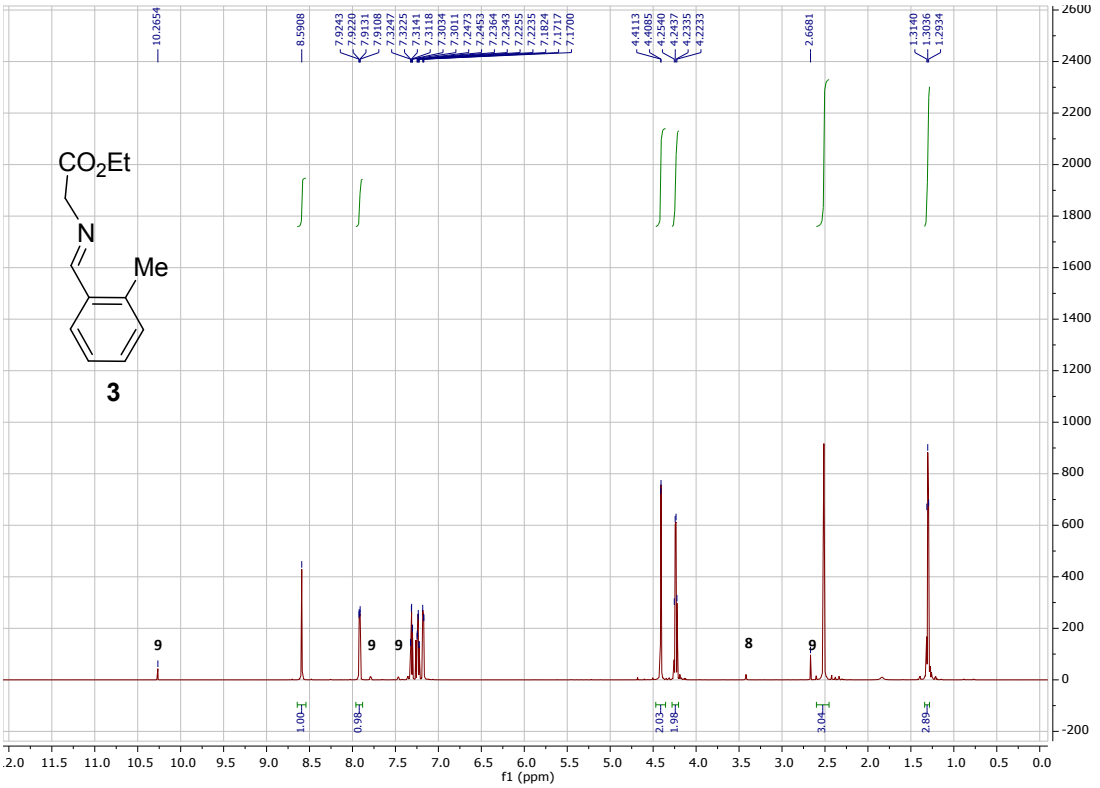
Compound **2** (^{1}H-NMR Spectrum):



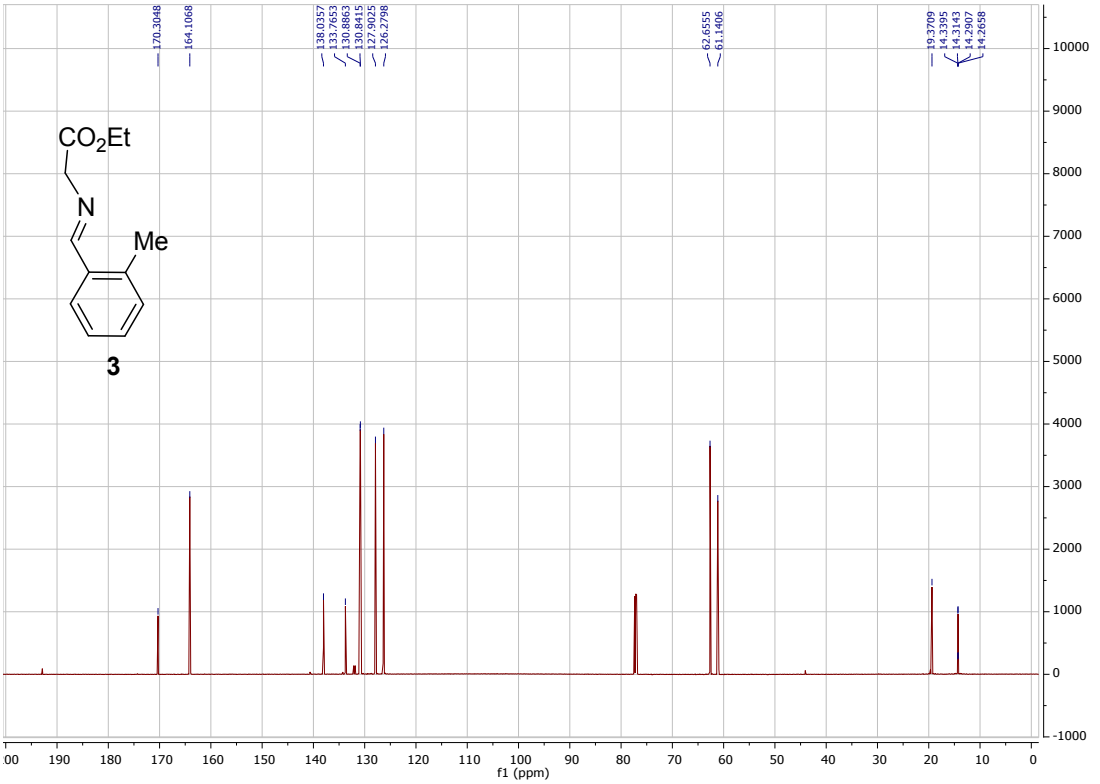
Compound **2** (^{13}C-NMR Spectrum):



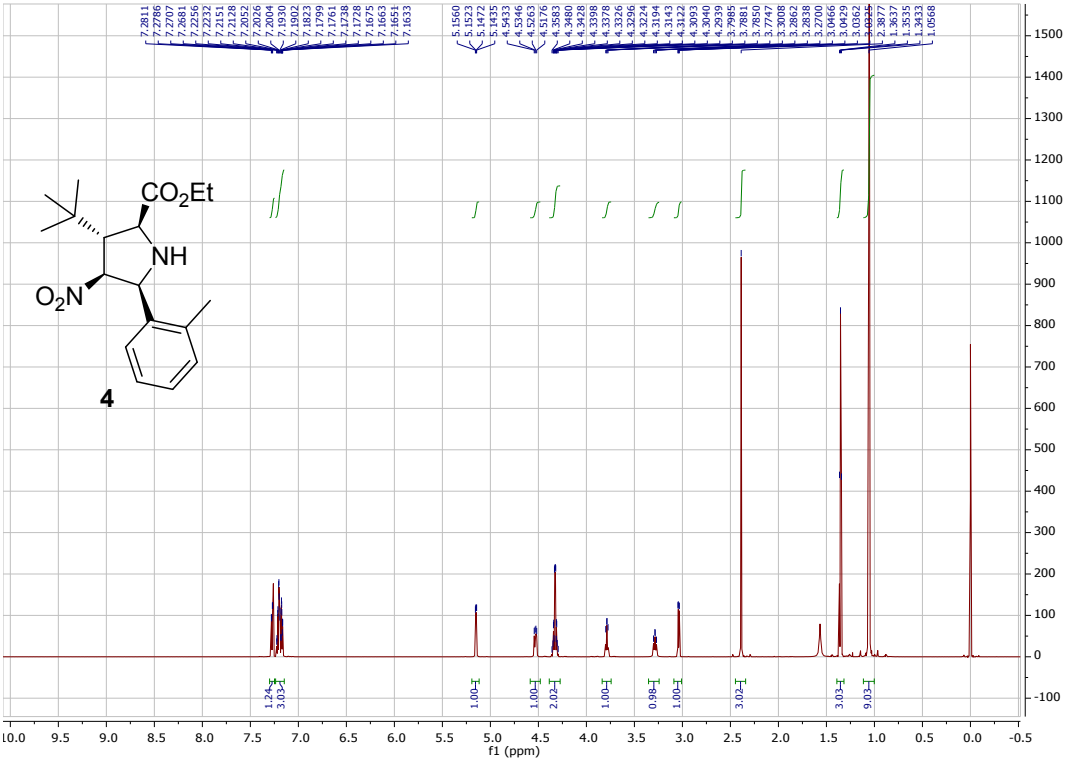
Compound **3** (^{1}H-NMR Spectrum; impurity signals annotated by compound number):



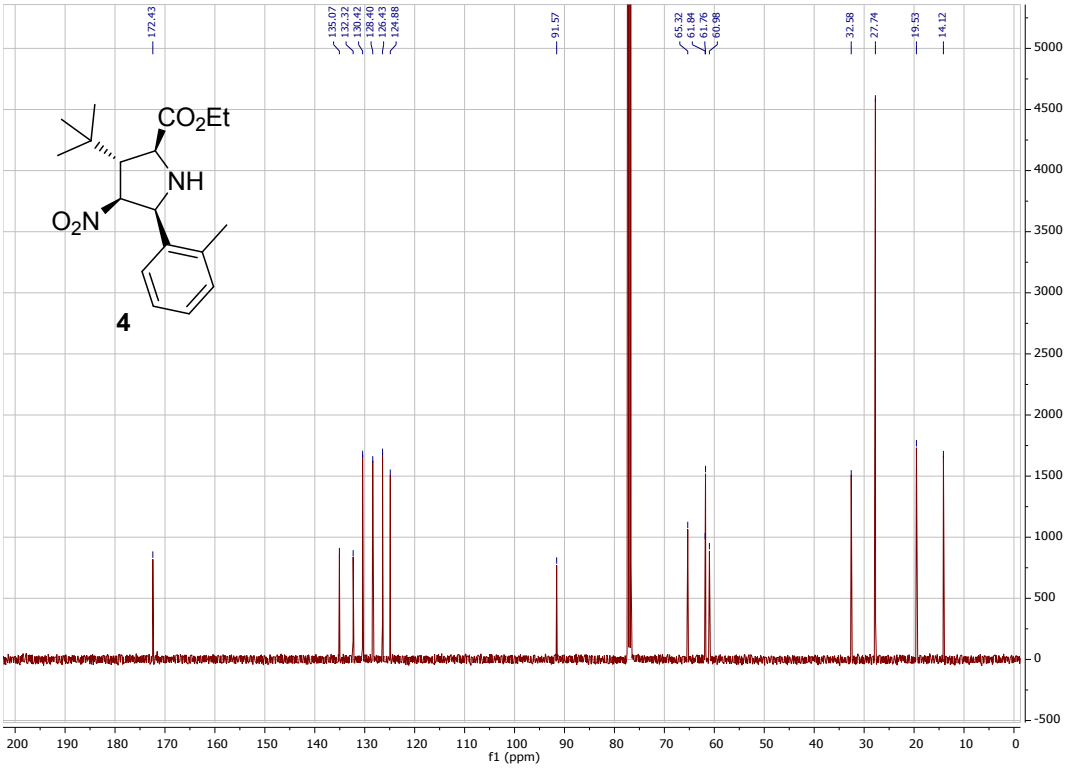
Compound **3** (^{13}C-NMR Spectrum):



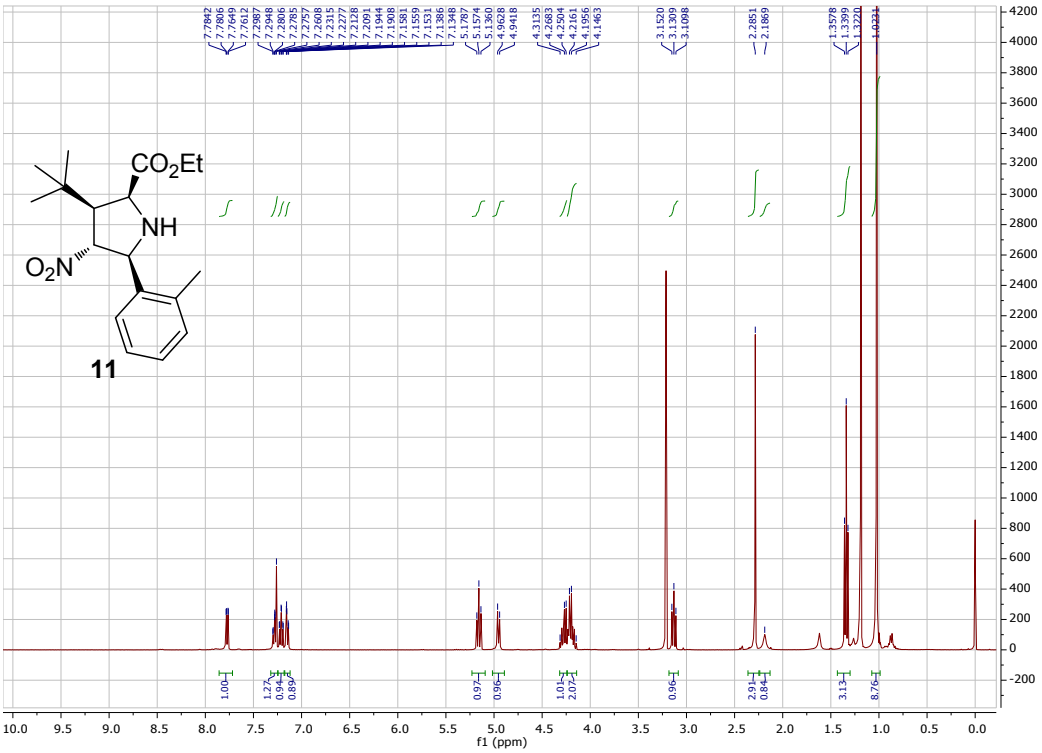
Compound **4** (^{1}H-NMR spectrum)



Compound **4** (^{13}C-NMR spectrum)



Compound **11** (^{1}H-NMR spectrum)

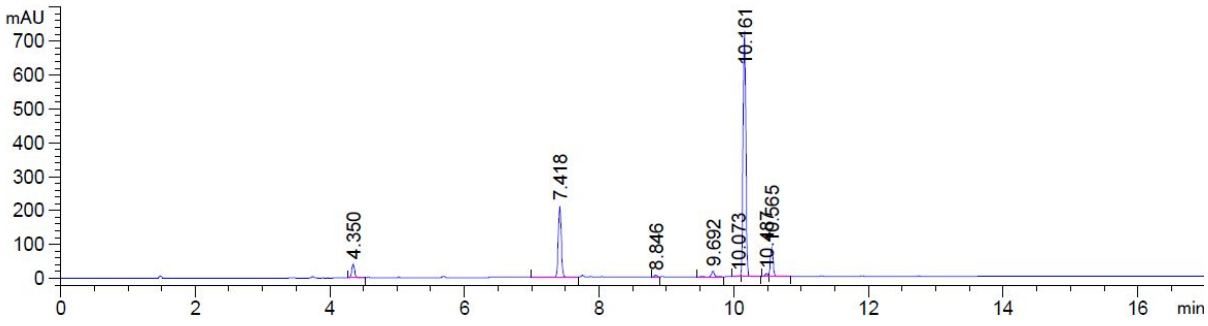


Analytical methods.

Crude reaction mixtures were analyzed by Agilent 1200 HPLC system comprising of an Agilent Binary pump, degasser, column compartment, autosampler and diode-array detector equipped with an Ascentis Express C18 (4.6 mm × 15 cm, 2.7 micron). Mobile phase A was 0.1% phosphoric acid in water and mobile phase B was acetonitrile. Flow rate was 1.0 mL/min with a column temperature of 35°C. The gradient was as follows: 0 min 10% B, 0-10 min 10-90% B, 10-16 min 90% B, 16-17 min 90-10% B. Starting material **2** has a retention time of 8.60 min, desired *endo* isomer **4** has a retention time of 10.16 min, *exo* isomer **11** has a retention time of 10.57 min.

Chiral purity was measured with a similar HPLC system equipped with a Chirapak IC column (4.6 mm x 15 cm, 5 micron). Mobile phase A was hexanes, mobile phase B was ethanol. An isocratic method (80:20 hexanes/ethanol) was used at 1.0 mL/min with an uncontrolled column temperature. Desired enantiomer **4** has a retention time of 5.48 min, undesired enantiomer **12** has a retention time of 8.07 min.

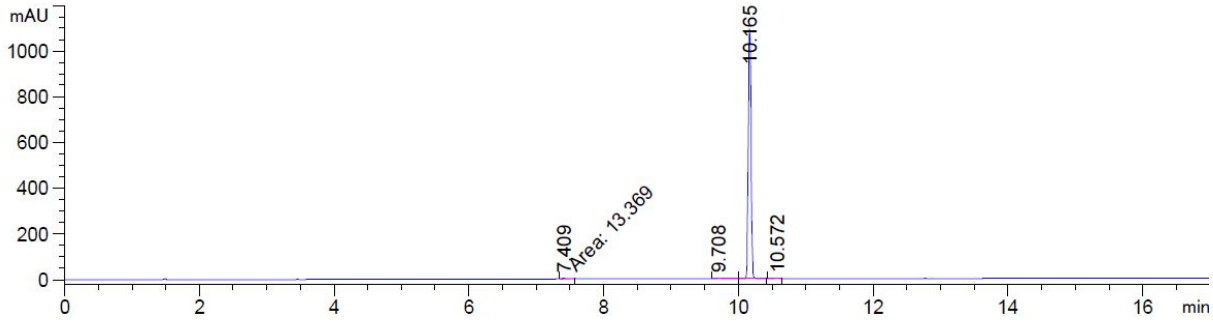
Representative Cycloaddition Reaction Mixture HPLC:



Signal 2: DAD1 B, Sig=210,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.350	BV	0.0499	122.66447	39.82179	3.8477
2	7.418	VV R	0.0478	643.23279	209.84764	20.1766
3	8.846	BV	0.0456	13.44294	4.66766	0.4217
4	9.692	VB R	0.0478	53.51948	17.42876	1.6788
5	10.073	BV E	0.0439	8.64203	2.97519	0.2711
6	10.161	VB R	0.0452	2066.17798	727.03284	64.8109
7	10.487	BV E	0.0419	24.16977	9.42365	0.7581
8	10.565	VV R	0.0475	256.16049	84.07521	8.0351
Totals :				3188.00995	1095.27274	

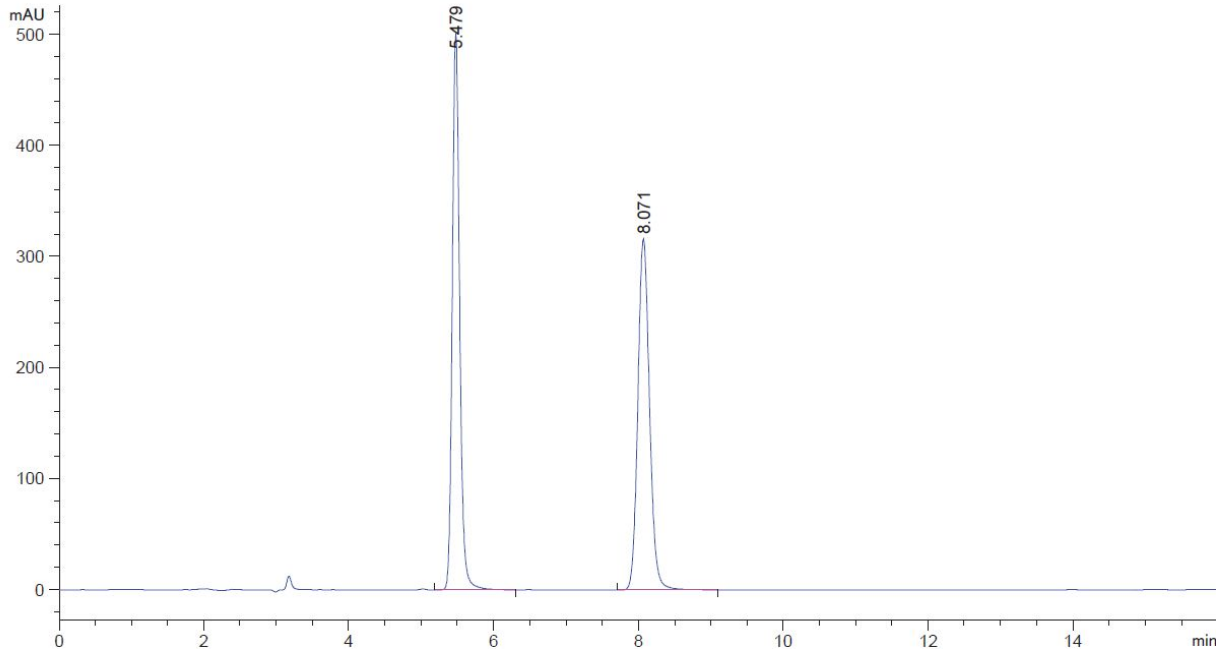
Representative Isolated **4** HPLC:



Signal 2: DAD1 B, Sig=210,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.409	FM	0.0552	13.36905	4.03864	0.4238
2	9.708	BB	0.0900	15.34104	2.35412	0.4863
3	10.165	VB R	0.0452	3115.51270	1094.90674	98.7522
4	10.572	VB R	0.0507	10.65787	3.21438	0.3378
Totals :				3154.88065	1104.51388	

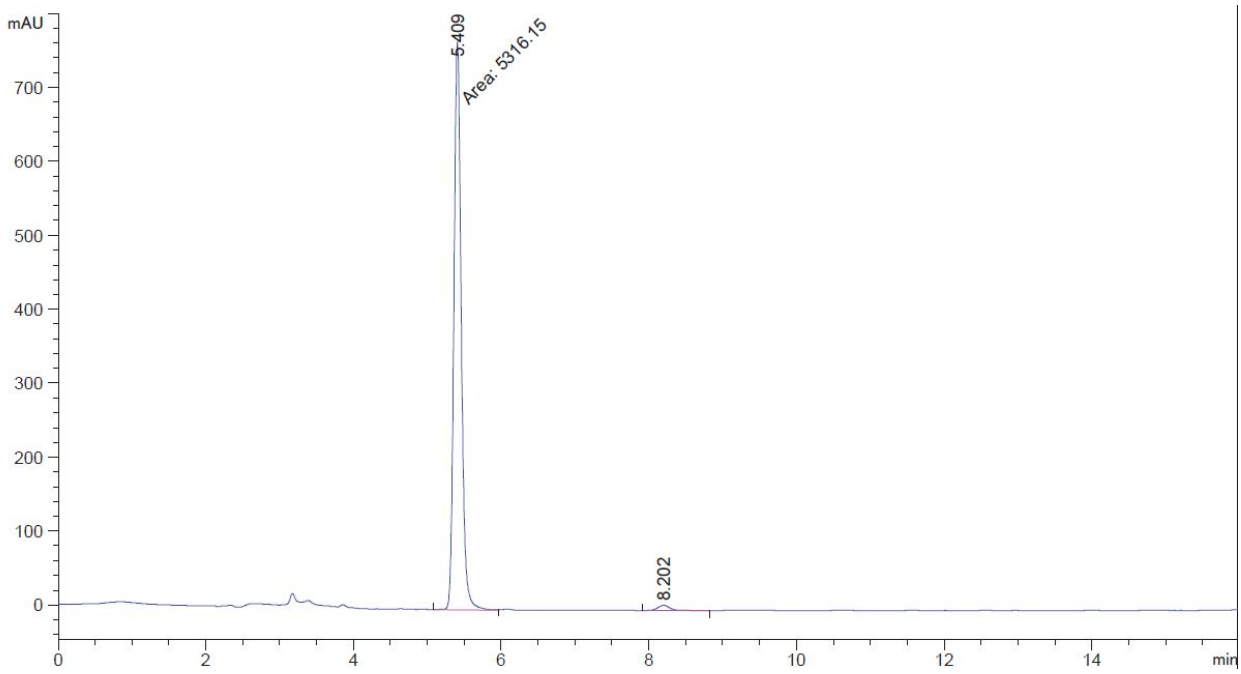
Chiral HPLC Trace of Racemic **4**:



Signal 1: VWD1 A, Wavelength=210 nm

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.479	BB	0.1086	3540.59497	501.05594	49.8446
2	8.071	BB	0.1738	3562.66553	315.97653	50.1554

Chiral HPLC Trace of Isolated **4** (98.5 : 1.5 e.r.):

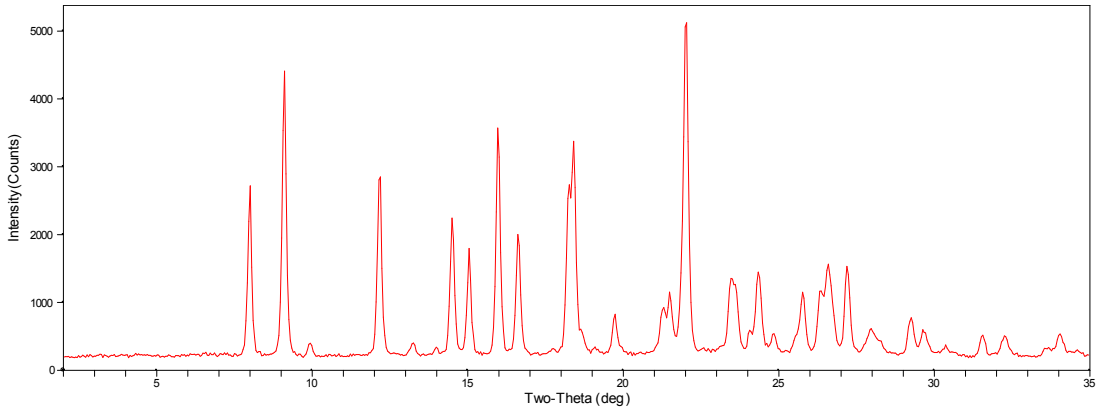


Signal 1: VWD1 A, Wavelength=210 nm

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.409	MF	0.1151	5316.14697	769.65570	98.5244
2	8.202	BB	0.1754	79.62177	6.97742	1.4756

Powder X-ray diffraction (PXRD) analysis. Samples for PXRD analysis were prepared by spreading the wet cake or sample powder in a thin layer on an aluminum sample holder and gently leveling with a glass microscope slide. The aluminum sample holder was then mounted on the rotating sample holder of the XRG 3000 diffractometer (Inel Corp., Artenay, France) and diffraction data is collected at ambient conditions. The XRG 3000 diffractometer was equipped with a curved position sensitive detector and parallel beam optics and was operated with a copper anode tube (1.5 kW fine focus) energized at 40 kV and 30 mA. An incident beam germanium monochromoter was utilized to provide monochromatic Kα1 radiation (λ=1.540562 Å). The diffractometer was calibrated using the attenuated direct beam at one-degree intervals. Calibration was checked using a silicon powder line position reference standard (NIST 640c). The instrument was controlled using the Symphonix 1.0 software (Inel Corp., Artenay, France) and the data was analyzed using MDI Jade software (version 9.0 Materials Data, Inc., Livermore, CA).

PXRD of **4** Racemate:



PXRD of Enantiopure **4**: