Supporting Information for:

Application of Catalytic Dynamic Resolution of *N*-Boc-2-lithiopiperidine to the Asymmetric Synthesis of 2-Aryl and 2-Vinyl Piperidines

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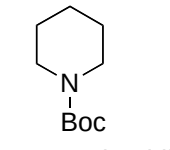
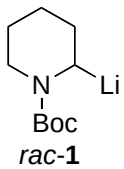


N-Boc-piperidine



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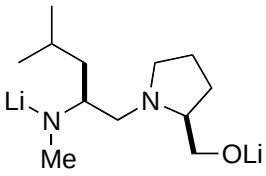

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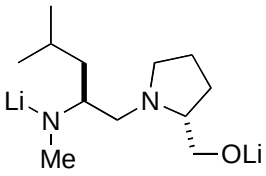

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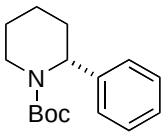

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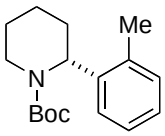

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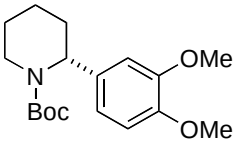

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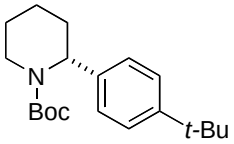

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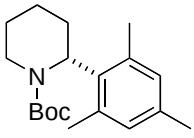

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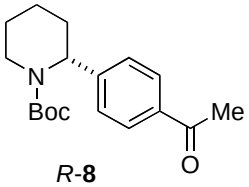

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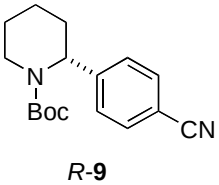

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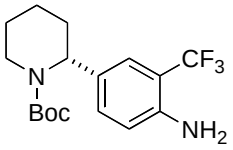

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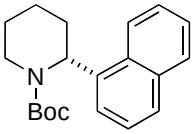

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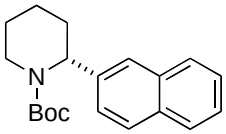

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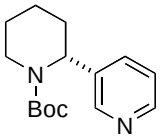

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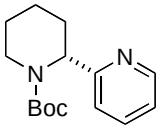

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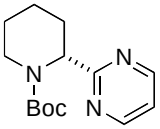

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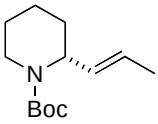

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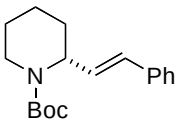

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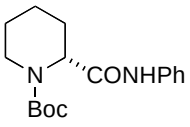


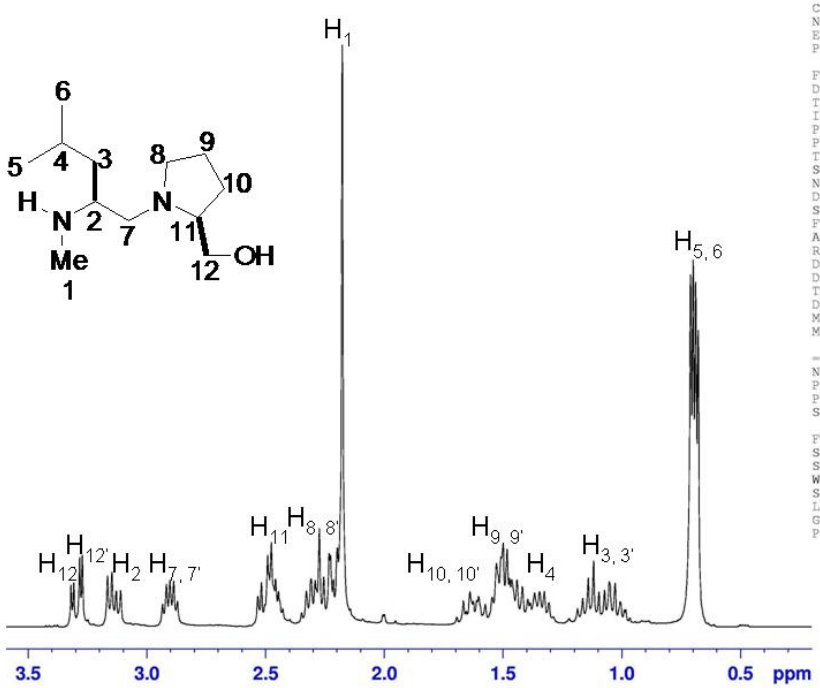
R-**17**

2. General/Typical Procedures

The experiments involving organolithium reagents were carried out under an inert atmosphere of argon. All solvents were freshly distilled. Tetrahydrofuran (THF) was predried over molecular sieves and distilled from sodium benzophenone ketyl. Diethyl ether (Et_2O) was distilled from sodium benzophenone ketyl. The ligands (*S*,*S*)-**2** and (*S*,*R*)-**2** were purified by Kugelrohr distillation. The concentration of commercial *s*-BuLi (solution in cyclohexane) was determined prior to use by No-D NMR spectroscopy[1] with 1,5-cyclooctadiene (COD) as the internal standard. Column chromatography was performed on silica gel (230-400 mesh). For all enantiomer ratio (er) analyses, authentic racemic compounds were used to establish the method of separation of the enantiomers. The enantiomer ratios were determined by CSP-SFC, monitoring at 210 and 254 nm. The following chiral columns were utilized: Regis Technologies Pirkle-Whelk-O-1, with a chiral stationary phase of 4-(3,5-dinitrobenzamido) tetrahydrophenanthrene, covalently bound to silica, and Daicel Chiralcel OD-H, with a chiral stationary phase of 4-Cellulose tris-(3,5-dimethylphenylcarbamate) coated on 5μm silica-gel. The temperature was controlled by a thermostatted cooling coil and all reported temperatures are internal to a reaction vessel. Unless otherwise indicated, ^1H, ^{13}C, DEPT-135, HMQC NMR spectra were acquired using $CDCl_3$ as solvent at room temperature. Chemical shifts are quoted in parts per million (ppm).

The alcohol precursors to ligands (*S*,*S*)-**2** and (*S*,*R*)-**2** were synthesized according to our previously reported method.[2a]

The full ^1H NMR assignments are provided below.

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F2 - Processing parameters
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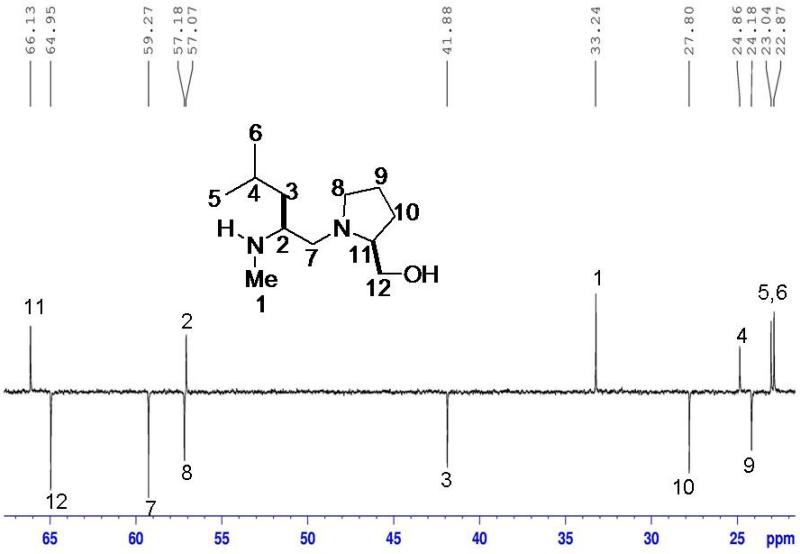
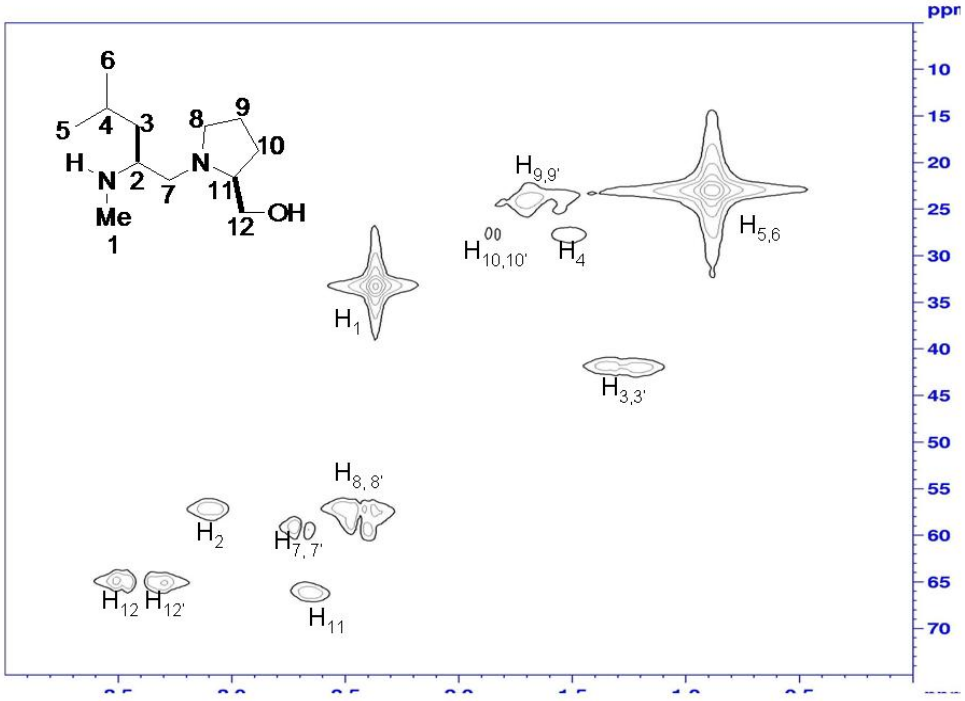
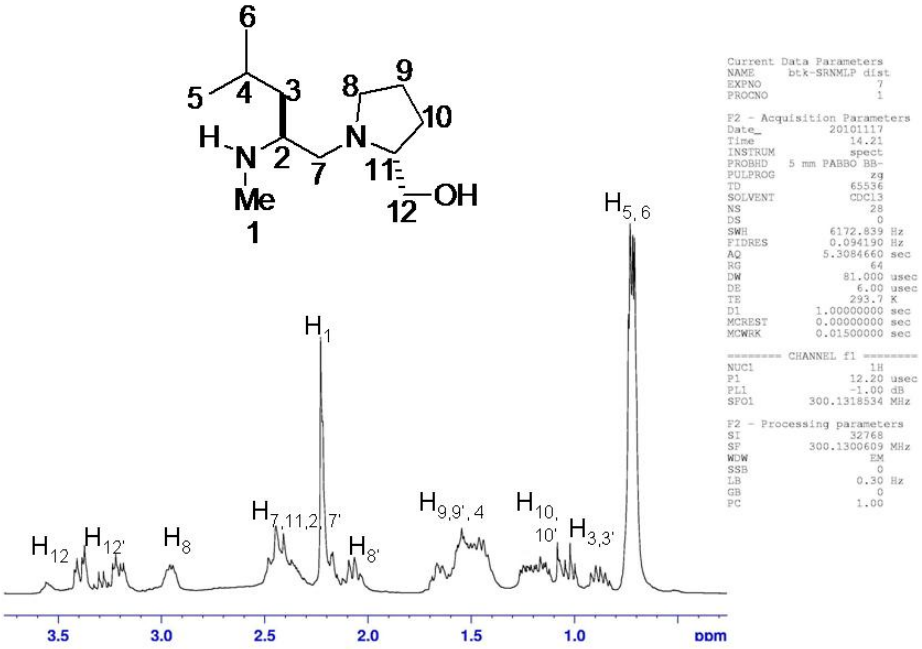
DEPT-135 spectrum

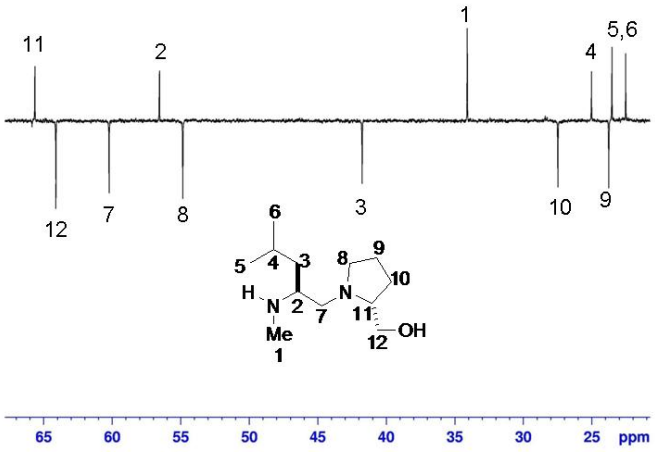


HMQC for alcohol precursor to (*S*,*S*)-**2**

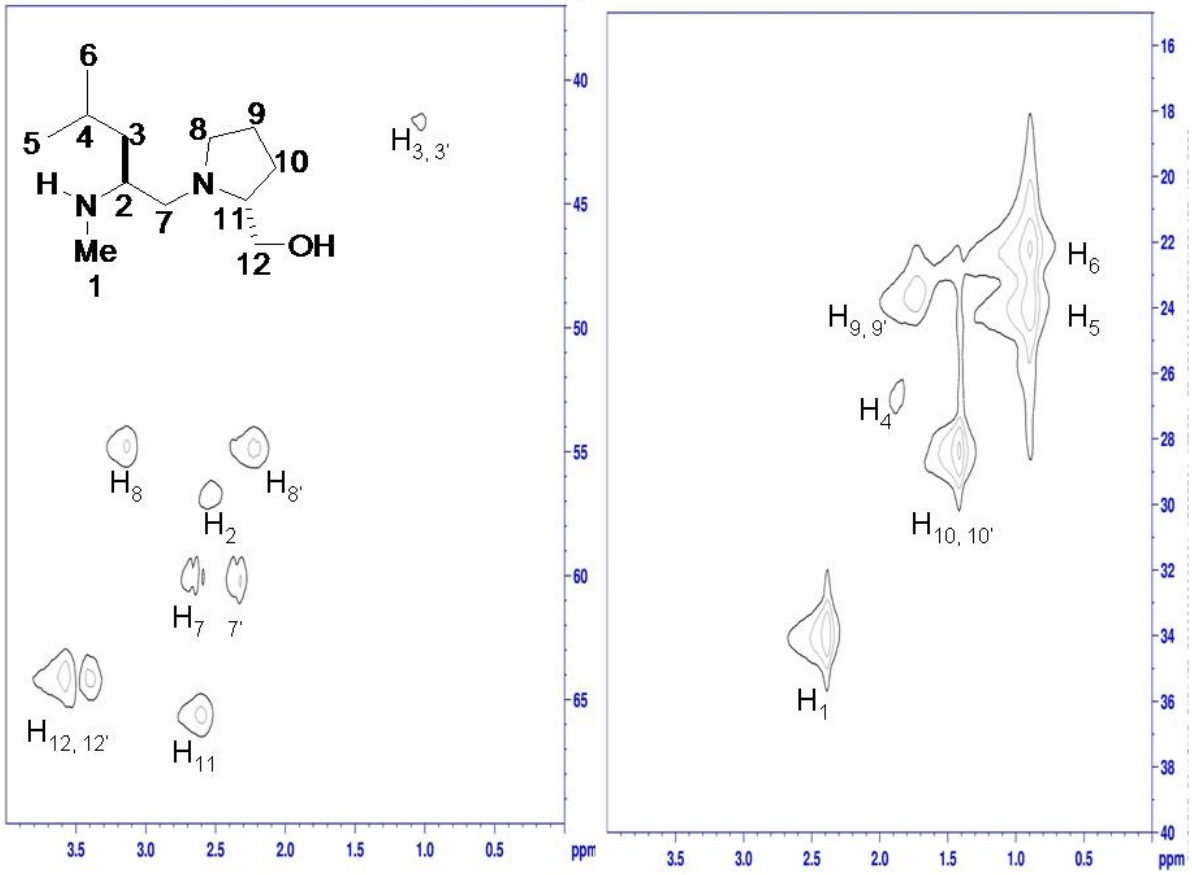


^{1}H NMR spectrum for the alcohol precursor to (*S*,*R*)-**2**





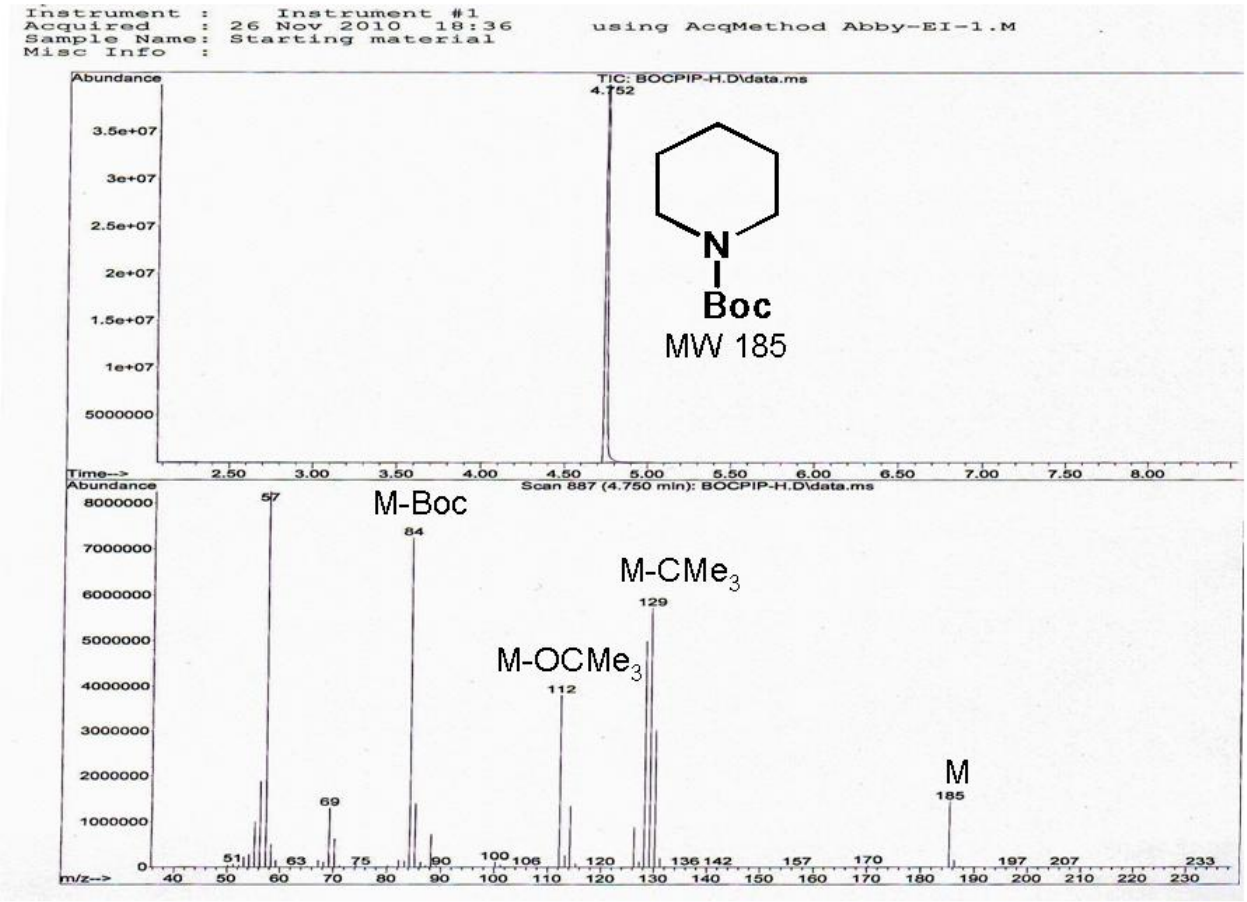
HMQC for the alcohol precursor to (*S*,*R*)-**2**



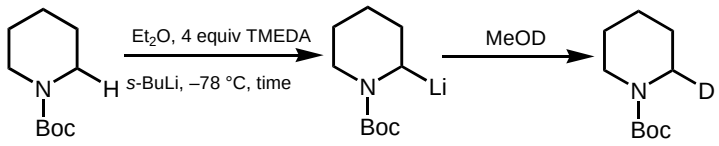
A. General Procedure for Catalytic Dynamic Resolution (CDR) of 2-lithio-*N*-Boc-piperidine followed by Transmetalation and Negishi Cross Coupling

In an oven-dried, septum-capped 25 mL round bottom flask equipped with a stir bar, *freshly* distilled *N*-Boc-piperidine (2 mmol, 1.0 equiv) and *freshly* distilled TMEDA (8 mmol, 4.0 equiv) were dissolved in *freshly* distilled Et_2O under argon. The solution was cooled to –78 °C and *s*-BuLi (2.4 mmol, 1.2 equiv) was added slowly by means of a syringe, down the side of the flask, over a ten minute period. The mixture was stirred for 3 h to effect deprotonation, affording *rac*-**1**·TMEDA. The extent of deprotonation was monitored by quenching an aliquot of the reaction mixture with methanol-d_1 (CH_3OD) and checking for deuterium incorporation by GC-MS. *Freshly* distilled dilithiated diamino alcohol, precursor of (*S*,*S*)-**2** (0.1 mmol, 5 mol %) in Et_2O was treated with *s*-BuLi (10 mol %). After complete deprotonation of *N*-Boc-piperidine as noted by GC-MS (there is a shift in the molecular ion peak from m/z 185 to m/z 186 after deuterium incorporation; see attached spectra below), the preformed alkoxide (*S*,*S*)-**2** was added and the flask was quickly transferred to a second thermostatted bath at –45 °C, and allowed to stir for 5 h. A solution of anhydrous $ZnCl_2$ (2.6 mmol in 2.6 mL THF, 1.0 M, 1.3 equiv), was added slowly over a ten minute period and the mixture was stirred for 30 minutes followed by warming to room temperature. After 30 minutes, $Pd(OAc)_2$ (0.08 mmol, 4 mol %), *t*-$Bu_3P{\cdot}HBF_4$ (0.16 mmol, 8 mol %) and the aryl bromide, for example bromobenzene (2.6 mmol, 1.3 equiv) were added sequentially. After stirring for 18 h at room temperature, NH_4OH (10 mL, 10% aqueous solution) was added dropwise and the mixture was stirred for 30 minutes. The resulting slurry was filtered through Celite and rinsed with 10 mL Et_2O. The filtrate was washed with 1 M $HCl_{(aq)}$ (20 mL), then with water (2 x 10 mL), dried over Na_2SO_4 and evaporated under reduced pressure to obtain the crude product. Purification by silica gel column chromatography was accompanied by er determination.

GC-MS of *N*-Boc-piperidine



Monitoring the extent of deprotonation of *N*-Boc-piperidine at –78 °C



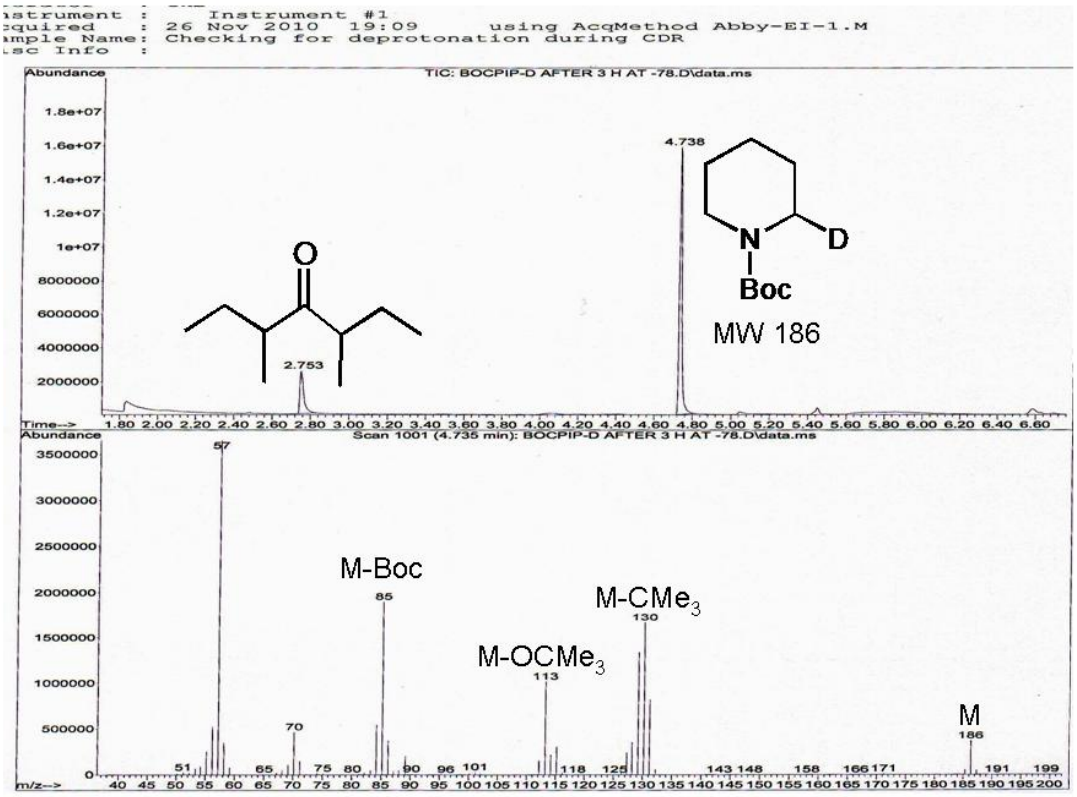
1

In an oven-dried, septum-capped 25 mL round bottom flask equipped with a stir bar, *freshly* distilled *N*-Boc-piperidine (2 mmol, 1.0 equiv) and *freshly* distilled TMEDA (8 mmol, 4.0 equiv) were dissolved in *freshly* distilled Et_2O under argon. The solution was cooled to –78 °C and *s*-BuLi (2.4 mmol, 1.2 equiv) was added slowly by means of a syringe, down the side of the flask, over a 10-min period. CH_3OD (0.1 mL), stored over molecular sieves, was placed in an oven-dried vial and the vial was capped rapidly. At various time intervals (every 60 min), an aliquot

(*ca* 0.1 mL) of the deprotonating mixture was drawn using a syringe equipped with an oven-dried needle, and rapidly placed in the vial containing the CH_3OD. The mixture was diluted with freshly distilled Et_2O (*ca* 1 mL). The ethereal layer was filtered through Celite. The sample was placed in a GC vial and analyzed by GC-MS for deuterium incorporation using electron impact ionization.

When the deprotonation is complete, there is a noticeable shift of the molecular ion peak from m/z 185 for *N*-Boc-piperidine to m/z 186 for the singly deuterated *N*-Boc-piperidine.

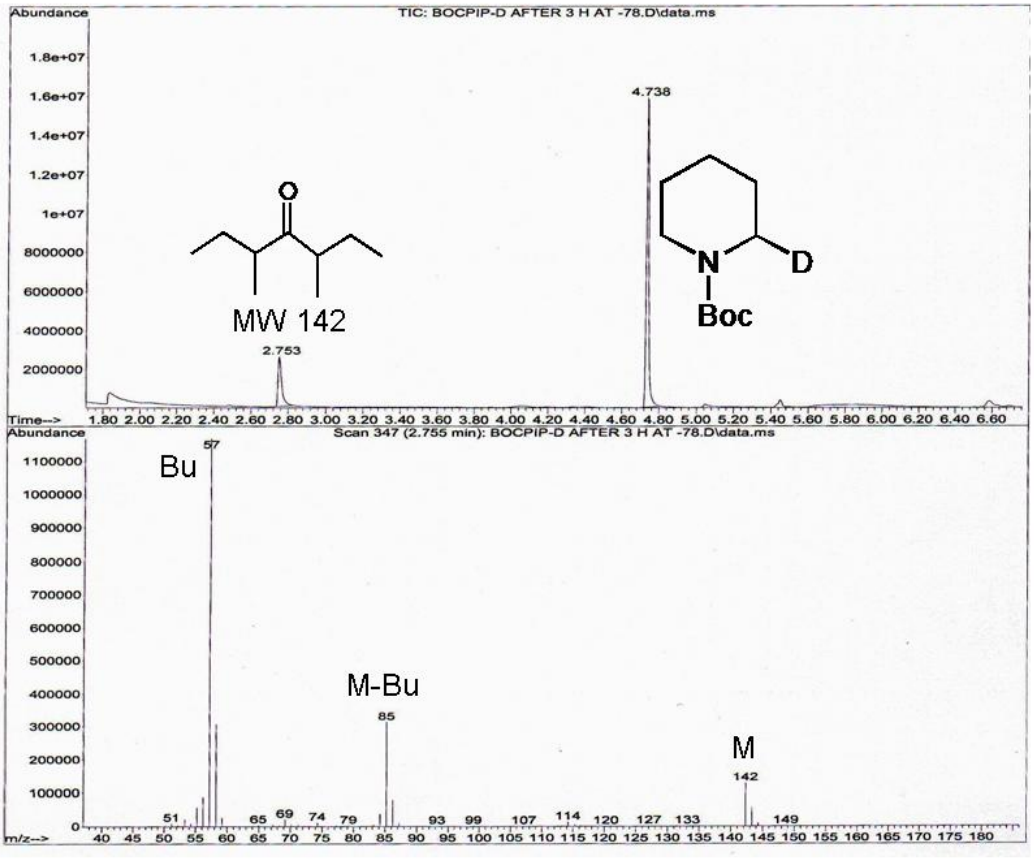
Checking for the extent of deprotonation of *N*-Boc-piperidine after 3 h at –78 °C



Note 1: We find that it is necessary to carry out the deprotonation at –78 °C, in order to minimize attack of the Boc-group by *s*-BuLi. We routinely detect this byproduct by GC-MS (peak at 2.75 min) when checking for the extent of deprotonation.

It is absolutely critical to ensure complete deprotonation of N-Boc-piperidine in order to maximize yield and enantioselectivity.

GC-MS of byproduct formed by attack of the Boc-group by *s*-BuLi during deprotonation of *N*-Boc-piperidine

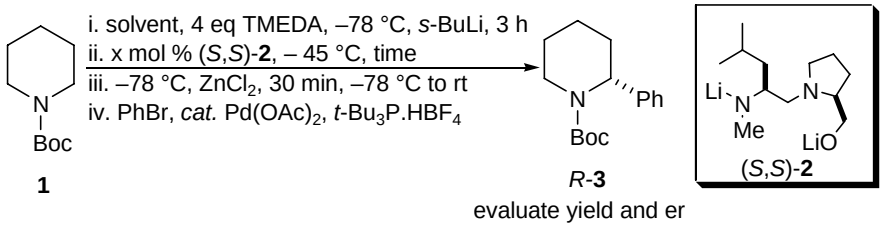


Note 2: The minimum requirement for a CDR to be operative is that the barrier to racemization must be significantly higher than the barrier to DTR.[2a,b] In collaboration with the Coldham group, we showed that the rates of racemization and DTR of *N*-Boc-2-lithiopiperidine **1** are both 1st-order in TMEDA up to one equivalent of the latter.[2c] Since excess TMEDA beneficially retards racemization and accelerates both DTR and CDR, we use four molar equivalents.

B. General Procedure for Catalytic Dynamic Resolution (CDR) of 2-lithio-*N*-Boc-piperidine followed by Transmetalation and Negishi Cross Coupling with Heteroaryl halides.

In an oven-dried, septum-capped 25 mL round bottom flask equipped with a stir bar, *freshly* distilled *N*-Boc-piperidine (2 mmol, 1.0 equiv) and *freshly* distilled TMEDA (8 mmol, 4.0 equiv) were dissolved in *freshly* distilled Et_2O under argon. The solution was cooled to –78 °C and *s*-BuLi (2.4 mmol, 1.2 equiv) was added slowly by means of a syringe, down the side of the flask, over a ten minute period. The mixture was stirred for 3 h to effect deprotonation, affording *rac*-**1**·TMEDA. The extent of deprotonation was monitored by quenching an aliquot of the reaction mixture with methanol-d_1 (CH_3OD) and checking for deuterium incorporation by GC-MS. *Freshly* distilled dilithiated diamino alcohol, precursor of (*S*,*S*)-**2** (0.1 mmol, 5 mol %) in Et_2O was treated with *s*-BuLi (10 mol %). After complete deprotonation of *N*-Boc-piperidine as noted by GC-MS, the preformed alkoxide (*S*,*S*)-**2** was added and the flask was quickly transferred to a second thermostatted bath at –45 °C, and allowed to stir for 5 h. A solution of anhydrous $ZnCl_2$ (2.6 mmol in 2.6 mL THF, 1.0 M, 1.3 equiv), was added slowly over a ten minute period and the mixture was stirred for 30 minutes followed by warming to room temperature. After 30 minutes, the heteroaryl bromide, for example 3-bromopyridine (2.6 mmol, 1.3 equiv), $Pd(OAc)_2$ (0.08 mmol, 4 mol %) and *t*-$Bu_3P{\cdot}HBF_4$ (0.16 mmol, 8 mol %) were added sequentially. After stirring for 22 h at 60 ^oC, the mixture was cooled to room temperature and NH_4OH (10 mL, 10% aqueous solution) was added dropwise and the mixture was stirred for 30 minutes. The resulting slurry was filtered through Celite and rinsed with 10 mL Et_2O. The filtrate was washed with 1 M $HCl_{(aq)}$ (20 mL), then with water (2 x 10 mL), dried over Na_2SO_4 and evaporated under reduced pressure to obtain the crude product. Purification by silica gel column chromatography was accompanied by er determination.

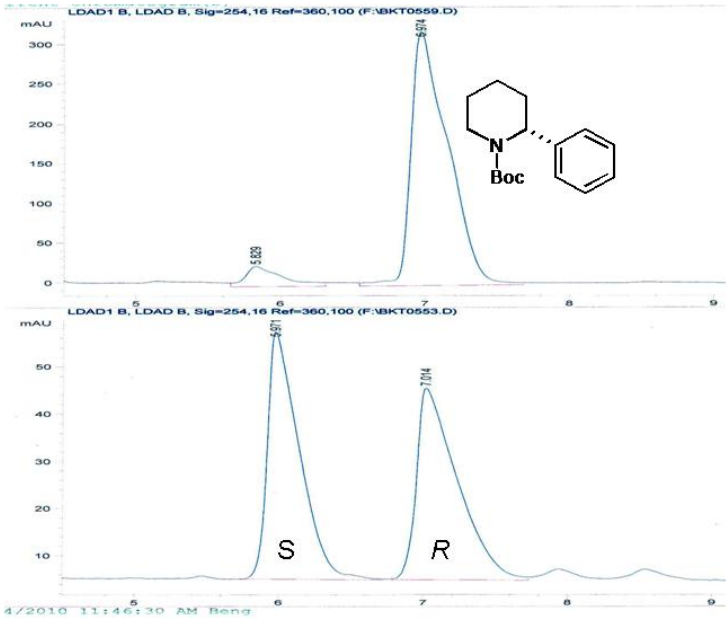
3. Optimization of the arylation of *N*-Boc-piperidine using bromobenzene



evaluate yield and er

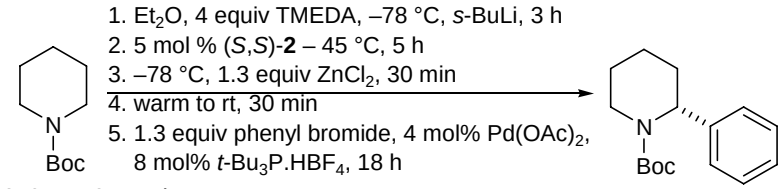
Entry	Amount of (*S*,*S*)-**2** (mol %)	Time (h)	Solvent	Yield (%) of **3**	er (*R*:*S*)
1	10	3	Et_2O	74	90:10
2	10	3	MTBE	65	86:14
3	5	3	Et_2O	70	93:7
4	5	5	Et_2O	68	96:4
5	5	5	MTBE	60	89:11
6	100	3	Et_2O	71	53:47

R-**3** (96:4 er) from optimized CDR



4.0. Variation of the Electrophile in the Arylation and Vinylation of *N*-Boc-piperidine

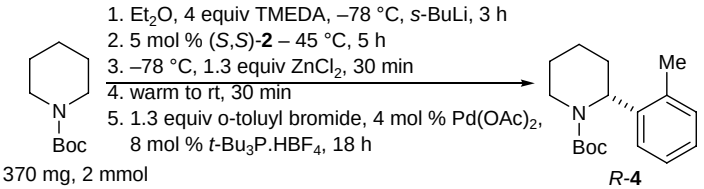
4.1. Electrophilic quench with phenyl bromide



R-**3**
68%, 96:4 er

Using **General Procedure A**, *N*-Boc-piperidine (370 mg, 2.0 mmol), TMEDA (1.2 mL, 8.0 mmol, 4.0 equiv), Et_2O (10 mL), *s*-BuLi (2.4 mL, 1.0 M, 2.4 mmol, 1.2 equiv), (*S*,*S*)-**2** (21.4 mg, 0.1 mmol, 5 mol%, in 0.40 mL Et_2O pretreated with freshly titrated *s*-BuLi), $ZnCl_2$ (355 mg, 2.6 mmol, 1.3 equiv) in THF (2 mL), phenyl bromide (0.30 mL, 2.6 mmol, 1.3 equiv), $Pd(OAc)_2$ (20 mg, 0.08 mmol, 4 mol%) and *t*-$Bu_3P{\cdot}HBF_4$ (46 mg, 0.16 mmol, 8 mol%) gave the crude product as an oil. Purification by silica gel column chromatography eluting with Hexane/EtOAc (94:6) afforded 355 mg of the pure product as an oil in 68% yield and 96:4 er; spectroscopic data as reported.[3] $[\alpha]_D^{22}$ +76.2 (*c* = 1, $CHCl_3$), lit[3b]. for *R*-**3**; $[\alpha]_D^{25}$ +83.7 (*c* = 0.98, $CHCl_3$).

4.2. Electrophilic quench with *o*-toluyl bromide

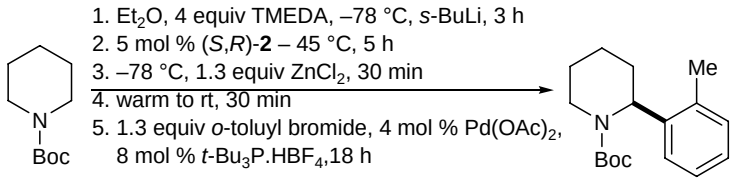


R-**4**
63%, 92:8 er

Using **General Procedure A**, *N*-Boc-piperidine (370 mg, 2.0 mmol), TMEDA (1.2 mL, 8.0 mmol, 4.0 equiv), Et_2O (10 mL), *s*-BuLi (2.4 mL, 1.0 M, 2.4 mmol, 1.2 equiv), (*S*,*S*)-**2** (21.4 mg, 0.1 mmol, 5 mol%, in 0.40 mL Et_2O pretreated with freshly titrated *s*-BuLi), $ZnCl_2$ (355 mg, 2.6 mmol, 1.3 equiv) in THF (2 mL), *o*-toluyl bromide (0.32 mL, 2.6 mmol, 1.3 equiv), $Pd(OAc)_2$ (20 mg, 0.08 mmol, 4 mol%) and *t*-$Bu_3P{\cdot}HBF_4$ (46 mg, 0.16 mmol, 8 mol%) gave the crude product as an oil. Purification by silica gel column chromatography eluting with Hexane/EtOAc (98:2) afforded 357 mg of the pure product as an oil in 63% yield and 92:8 er, $[\alpha]_D^{22}$ +114.2 (*c* = 1, $CHCl_3$). The er was determined by CSP-SFC as follows: **Column:** Pirkle-Whelk-O-1, **Flow Rate**: 2.0 mL/min, **Polarity Modifier %**: 2.0% EtOH, Outlet Pressure **= 150 psi**, **Oven Temperature** = 35 ^oC. The minor enantiomer elutes after ~3.9 min and the major enantiomer

elutes after ~4.5 min. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.23-7.07 (m, 4H), 5.15 (br, s, 1H), 4.08-3.95 (m, 1H), 3.3-2.22 (m, 5H), 1.94-1.51(m, 5H), 1.42 (s, 9H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 155.0, 142.5, 134.5, 130.5, 126.6, 125.4, 125.1, 79.4, 52.5, 41.2, 28.8, 28.4, 25.8, 19.3, 18.2.

4.2b. Synthesis of *S*-4

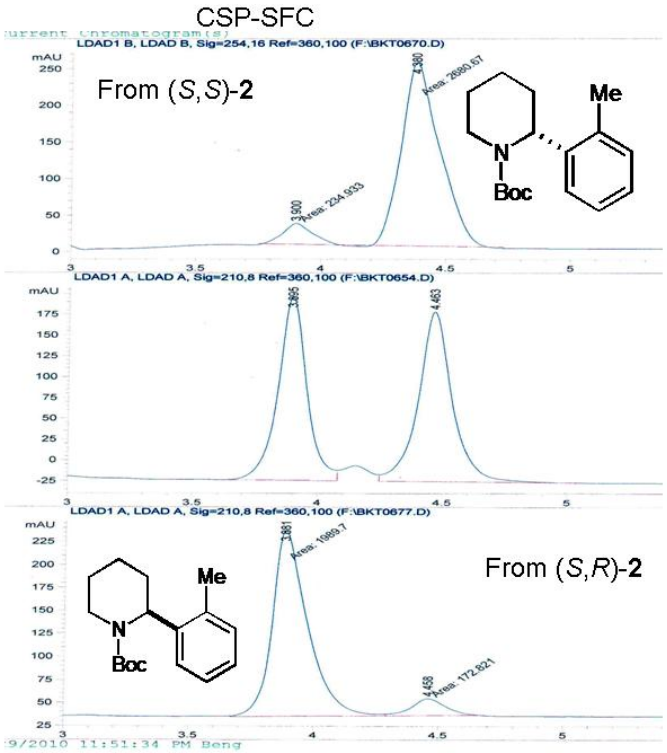


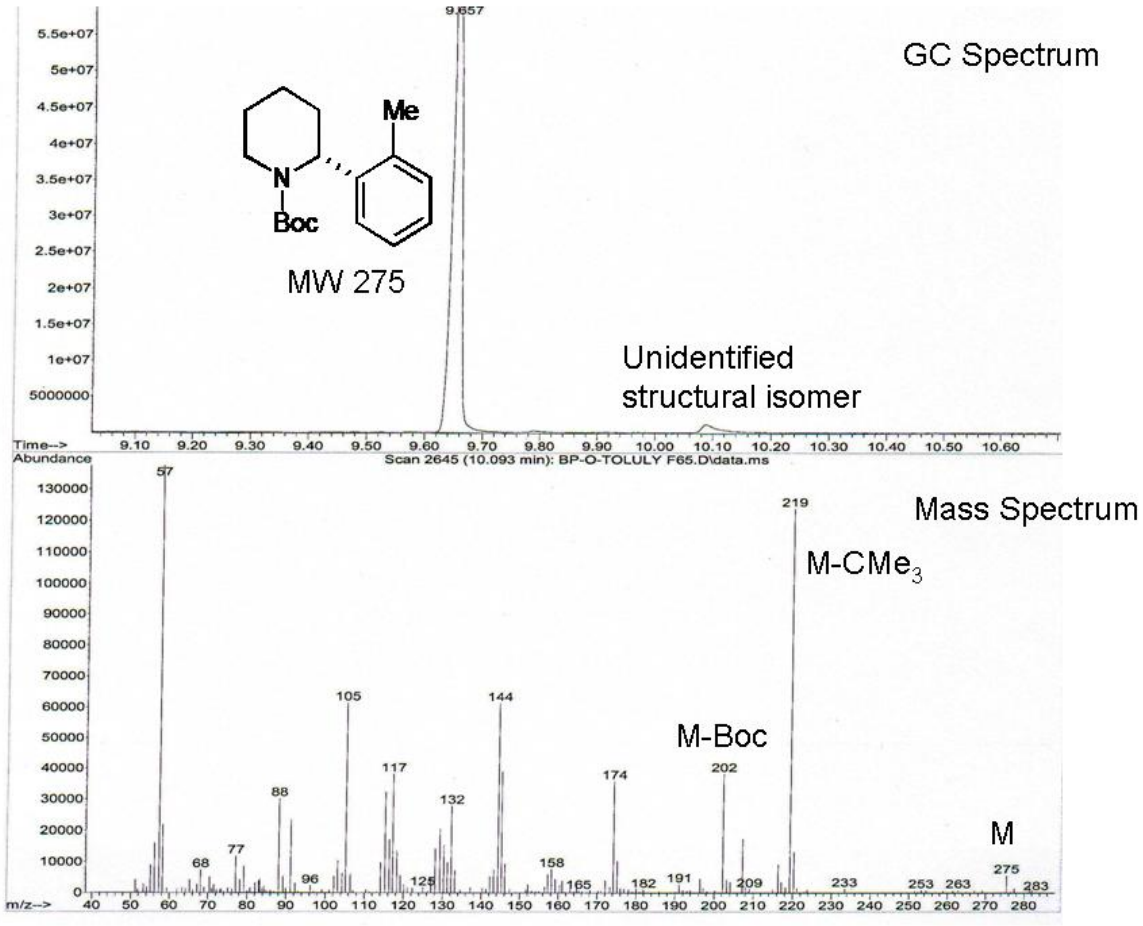
1.85 g, 10 mmol

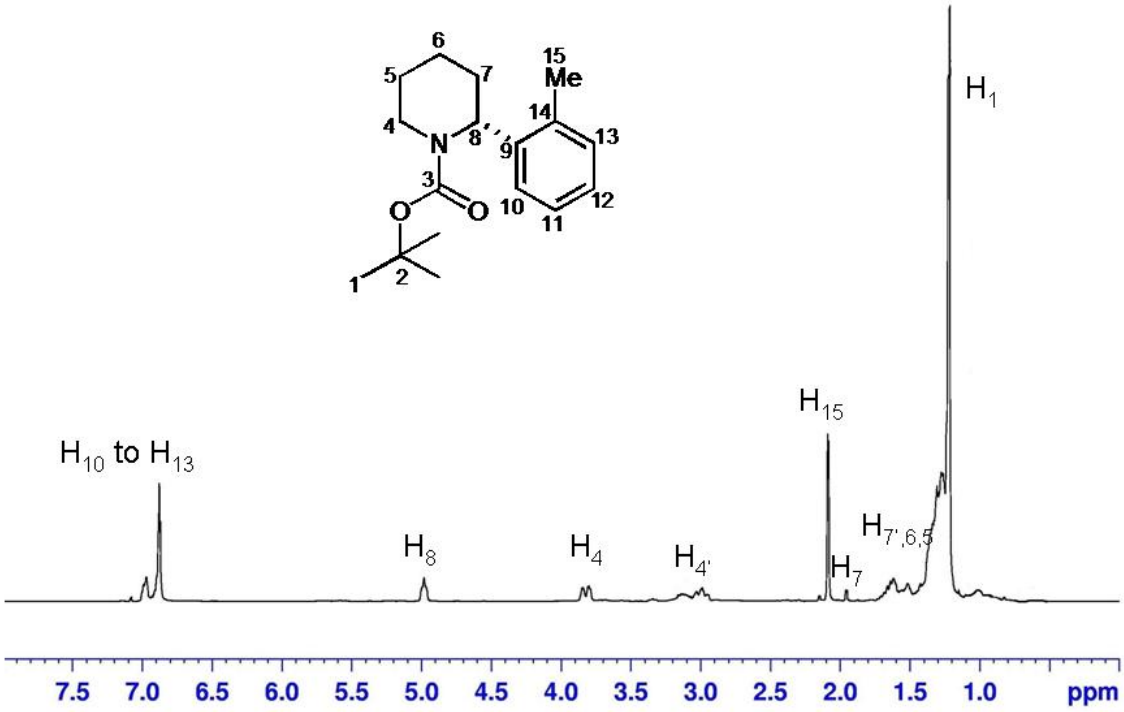
S-**4**

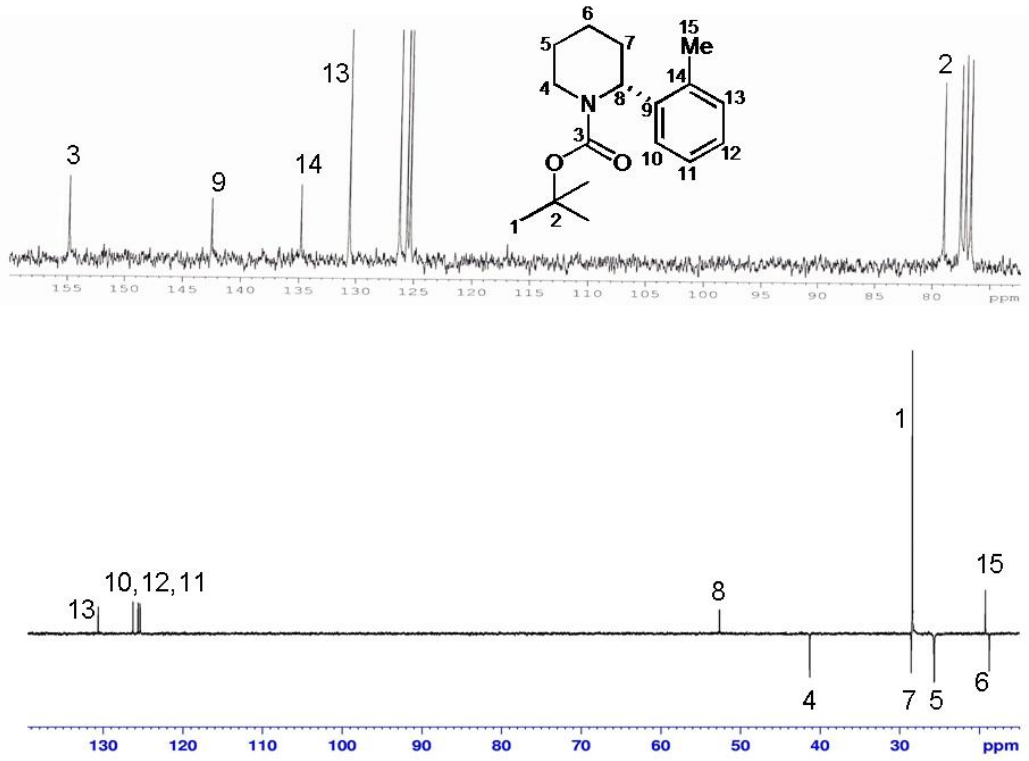
59%, 94:6 er

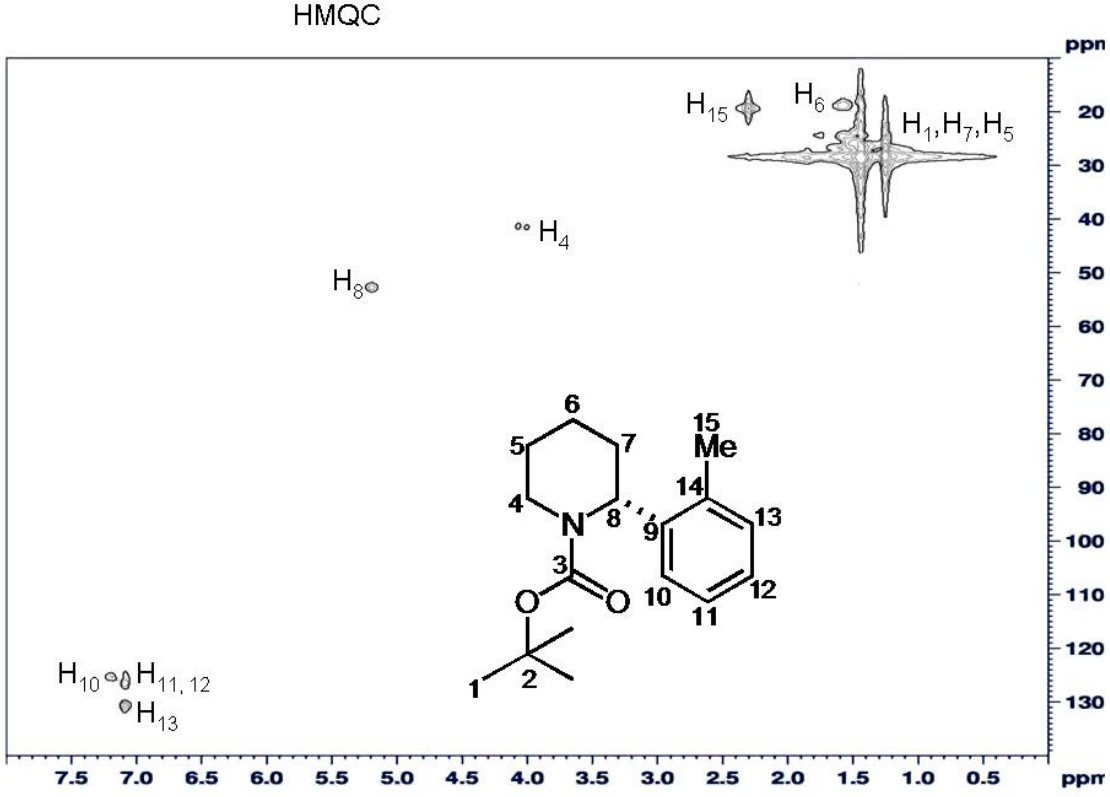
Using **General Procedure A**, *N*-Boc-piperidine (1.85 g, 10.0 mmol), TMEDA (6 mL, 40 mmol, 4.0 equiv), Et_2O (50 mL), *s*-BuLi (12 mL, 1.0 M, 12 mmol, 1.2 equiv), (*S*,*R*)-**2** (107 mg, 0.5 mmol, 5 mol %, in 2.0 mL Et_2O pretreated with freshly titrated *s*-BuLi), $ZnCl_2$ solution (13 mL, 1.0 M in Et_2O, 13 mmol, 1.3 equiv), *o*-toluyl bromide (1.6 mL, 12 mmol, 1.3 equiv), $Pd(OAc)_2$ (100 mg, 0.4 mmol, 4 mol %) and *t*-$Bu_3P{\cdot}HBF_4$ (230 mg, 0.8 mmol, 8 mol %) afforded 1.67 g of *S*-**4** as an oil in 59% yield and 94:6 er, $[\alpha]_D^{22}$ –118.6 (*c* = 1, $CHCl_3$).



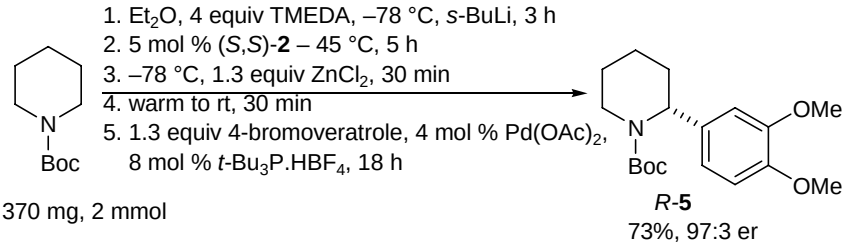

GC Spectrum
Me
N
Boc
MW 275
Unidentified
structural isomer
Mass Spectrum
M-CMe3
M-Boc
M


6
5
7
15
Me
4
N
8
14
13
9
3
O
O
10
12
11
1
2
H1
H15
H10 to H13
H7',6,5
H8
H4
H4'
H7
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
ppm


3
9
14
13
2
1
10,12,11
8
15
4
7
5
6
ppm

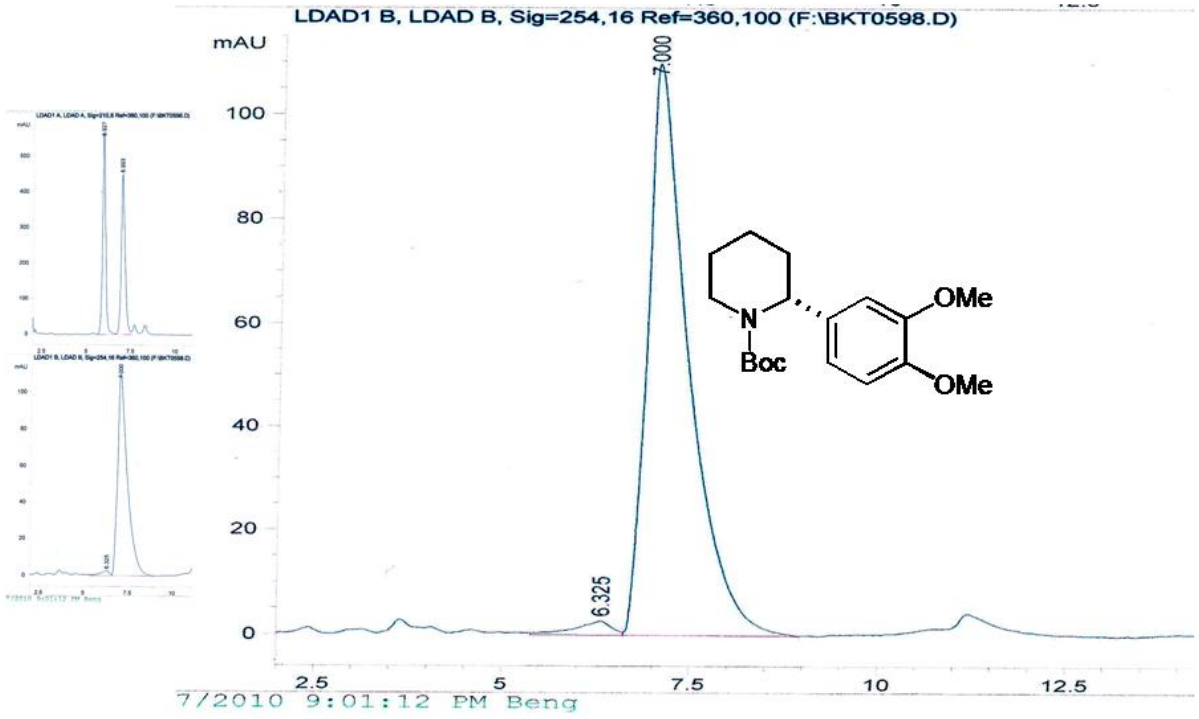

HMQC
H15
H6
H1,H7,H5
H4
H8
H10
H11, 12
H13
ppm

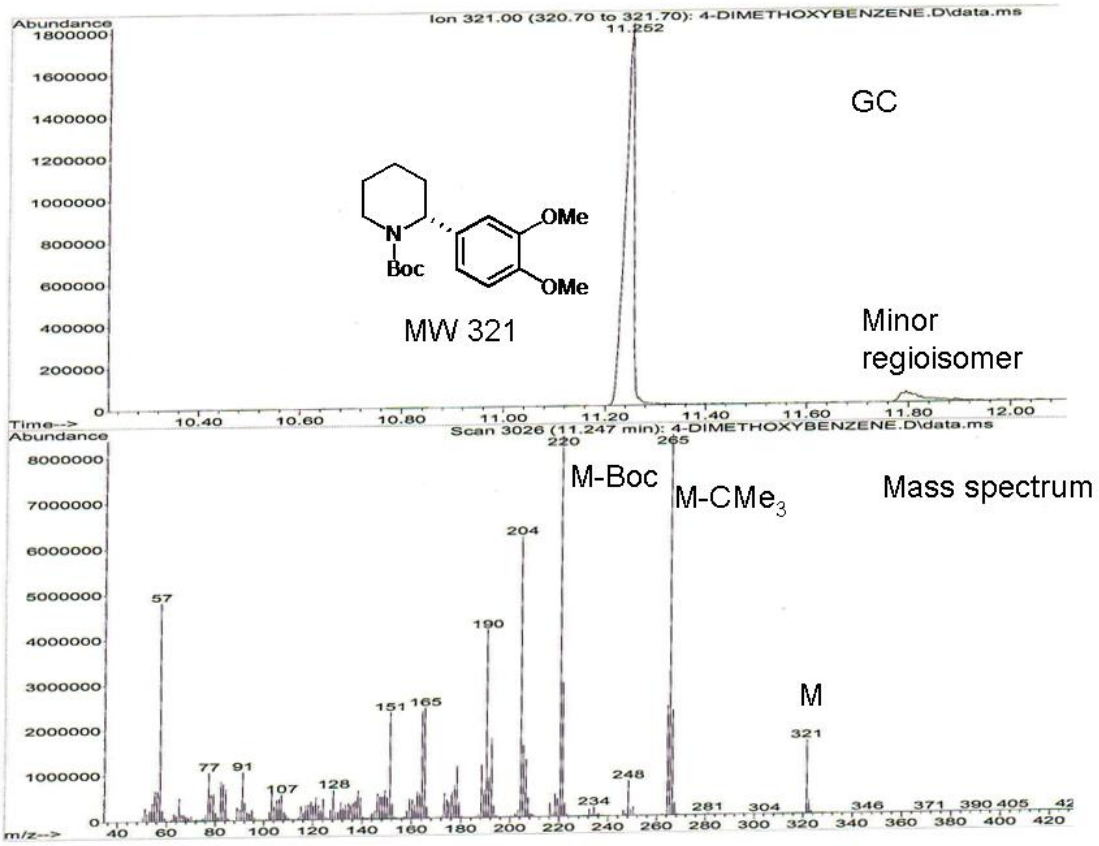
4.3. Electrophilic quench with 4-bromoveratrole: Synthesis of *R*-5

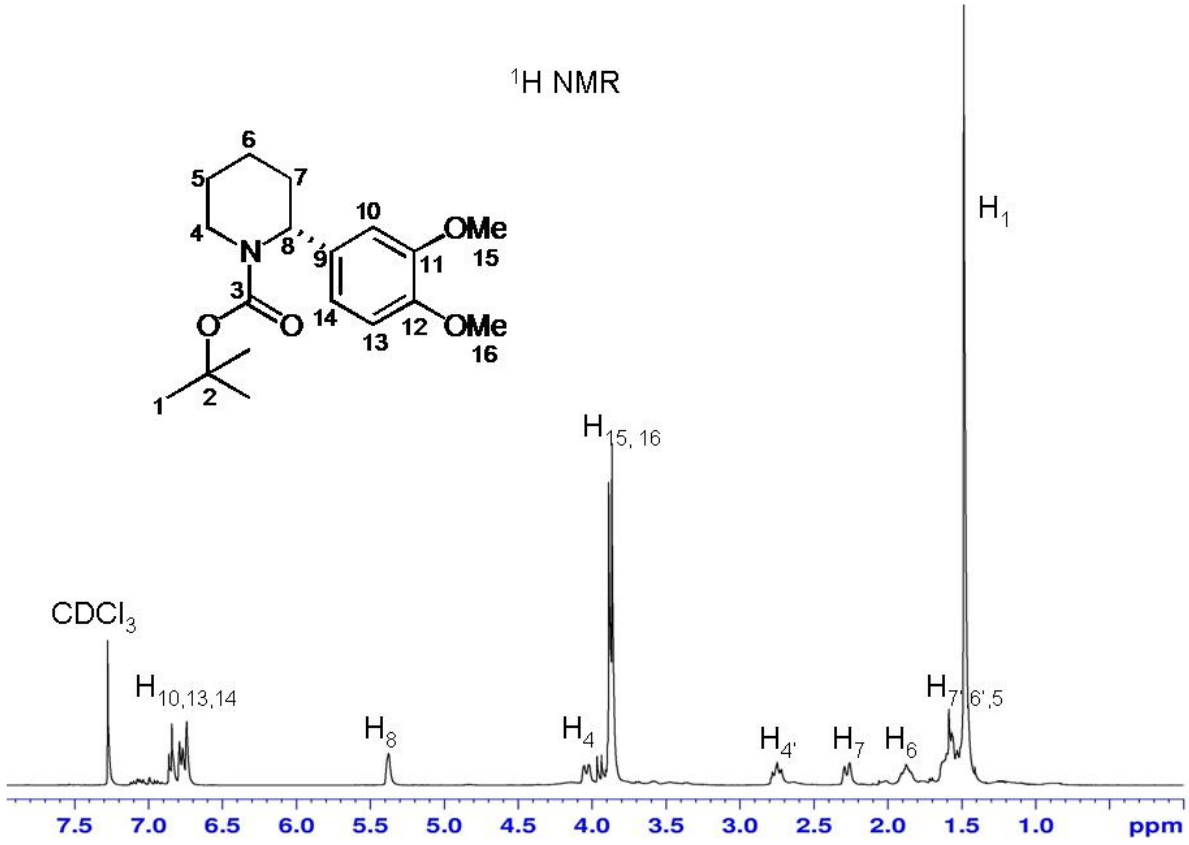


Using **General Procedure A**, *N*-Boc-piperidine (370 mg, 2.0 mmol), TMEDA (1.2 mL, 8.0 mmol, 4.0 equiv), Et_2O (10 mL), *s*-BuLi (2.4 mL, 1.0 M, 2.4 mmol, 1.2 equiv), (*S*,*S*)-**2** (21.4 mg, 0.1 mmol, 5 mol %, in 0.40 mL Et_2O pretreated with freshly titrated *s*-BuLi), $ZnCl_2$ (355 mg, 2.6 mmol, 1.3 equiv) in THF (2 mL), 4-bromoveratrole (0.38 mL, 2.6 mmol, 1.3 equiv), $Pd(OAc)_2$ (20 mg, 0.08 mmol, 4 mol %) and *t*-$Bu_3P{\cdot}HBF_4$ (46 mg, 0.16 mmol, 8 mol %) gave the crude product as an oil. Purification by silica gel column chromatography eluting with Hexane/EtOAc (85:15) afforded 482 mg of the pure product as an oil in 75% yield and 97:3 er; spectroscopic data as reported.[5] $[\alpha]_D^{22}$ +106.2 (*c* = 1.0, $CHCl_3$), lit[5]. for *S*-**5** of 82:18 er ($[\alpha]_D^{20}$ –49.6 (*c* = 0.275, $CHCl_3$). The er was determined by CSP-SFC as follows: **Column:** Pirkle-Whelk-O-1, **Flow Rate**: 3.0 mL/min, **Polarity Modifier %**: 3.0% EtOH, Outlet Pressure **= 150 psi**, **Oven Temperature** = 35 ^oC. The minor enantiomer elutes after ~6.2 min and the major enantiomer elutes after ~7.2 min. ^1H NMR (300 MHz, $CDCl_3$) δ 6.85-6.70 (m, 3H), 5.35 (br, s, 1H), 4.08-3.99 (m, 1H), 3.88-3.86 (m, 6H), 2.65 (m, 1H), 2.33-2.22 (m, 1H), 1.94-1.81 (m, 1H), 1.66-1.52 (m, 4H), 1.48 (s, 9H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 155.6, 149.1, 147.5, 132.8, 118.6, 111.0, 109.9, 79.5, 55.83, 55.77, 52.7, 40.0, 28.4, 27.9, 25.5, 19.4.

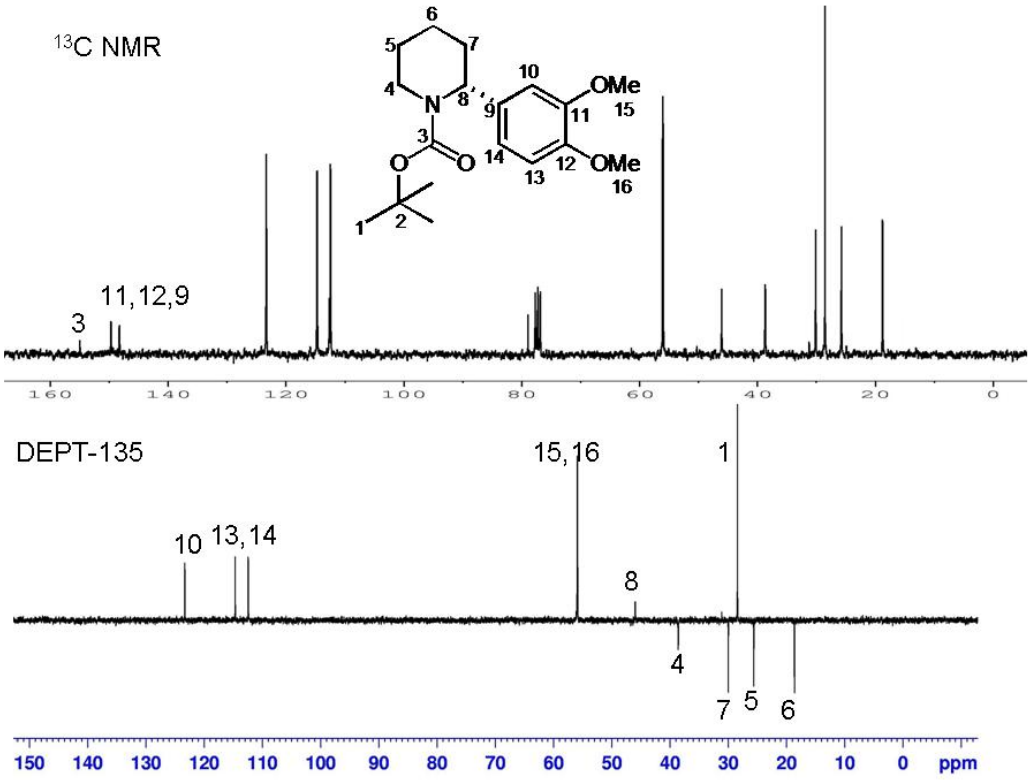
CSP-SFC

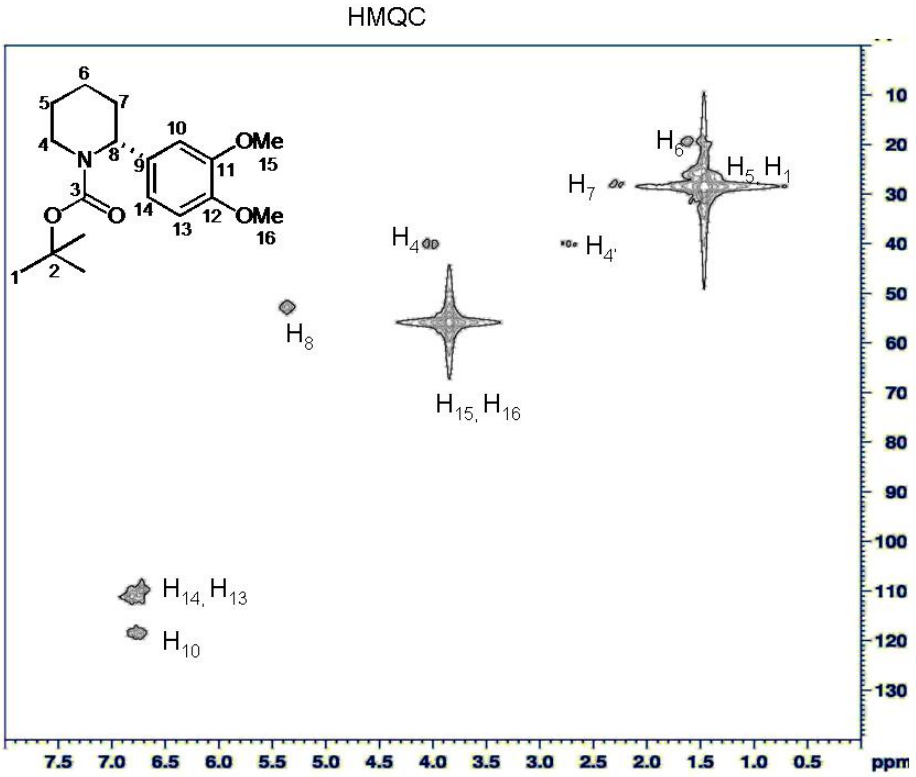

LDAD1 B, LDAD B, Sig=254,16 Ref=360,100 (F:\BKT0598.D)
mAU
100
80
60
40
20
0
7.000
6.325
N
Boc
OMe
OMe
2.5
5
7.5
10
12.5
7/2010 9:01:12 PM Beng


Ion 321.00 (320.70 to 321.70): 4-DIMETHOXYBENZENE.D\data.ms
11.252
GC
OMe
N
Boc
OMe
MW 321
Minor
regioisomer
Abundance
Time-->
Scan 3026 (11.247 min): 4-DIMETHOXYBENZENE.D\data.ms
M-Boc
M-CMe3
Mass spectrum
M
m/z-->

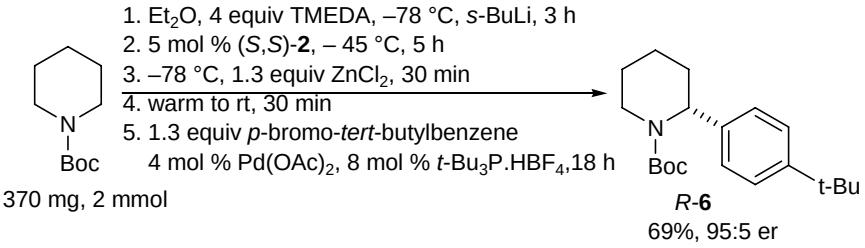


See full assignments on HMQC


13C NMR
11,12,9
3
DEPT-135
15,16
1
10
13,14
8
4
7
5
6
ppm


HMQC
H6
H5, H1
H7
H4'
H4
H8
H15, H16
H14, H13
H10
ppm

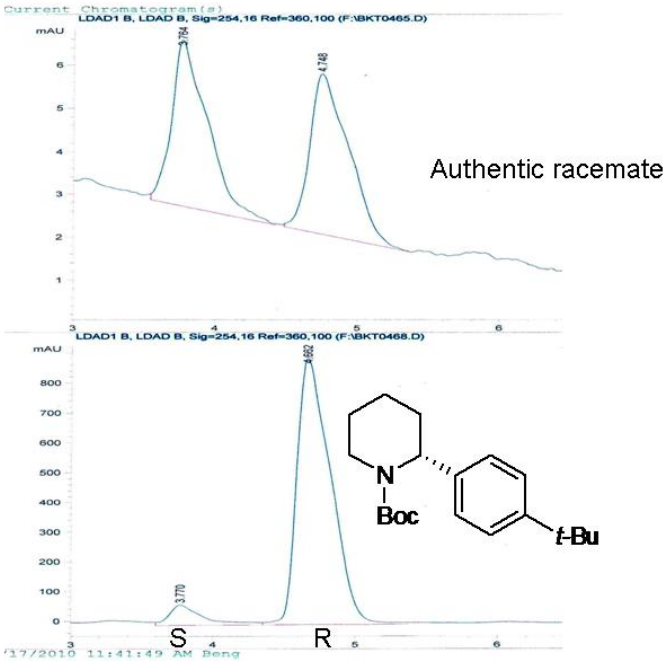
4.4. Electrophilic quench with *p*-bromo-*tert*-butylbenzene: Synthesis of *R*-6

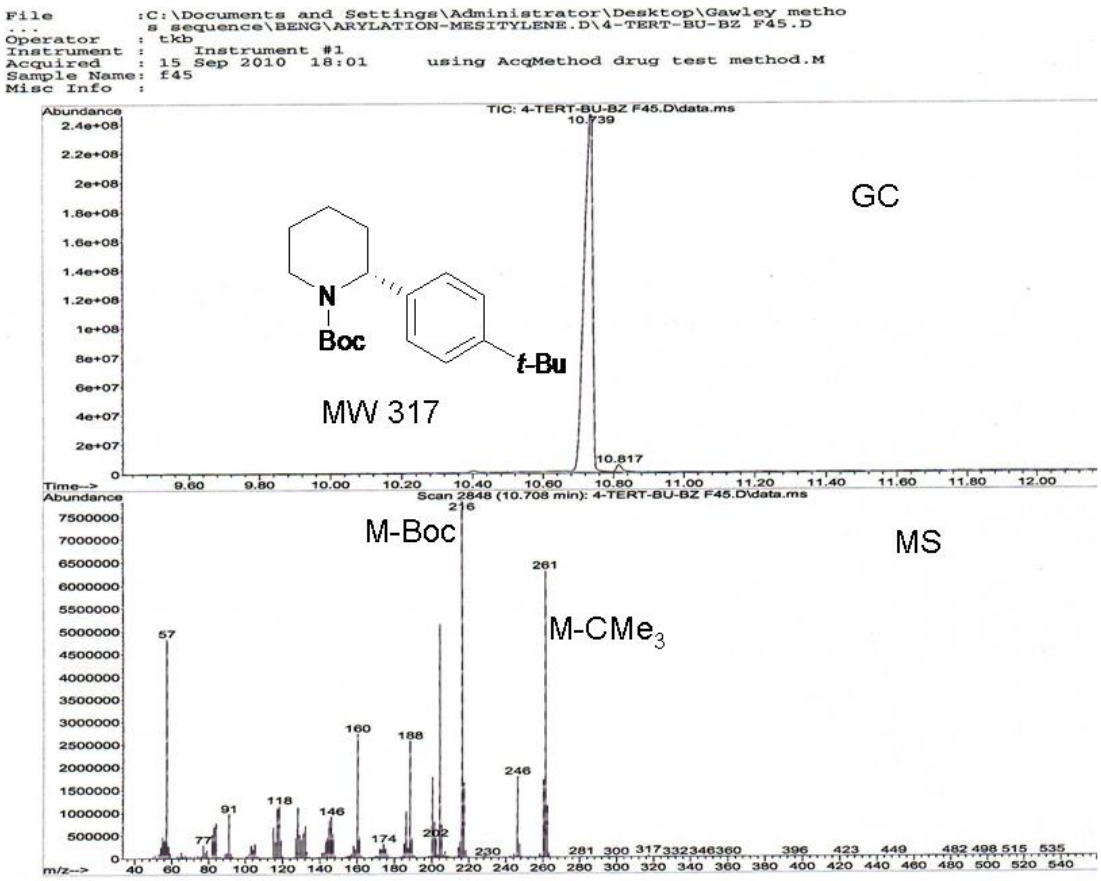


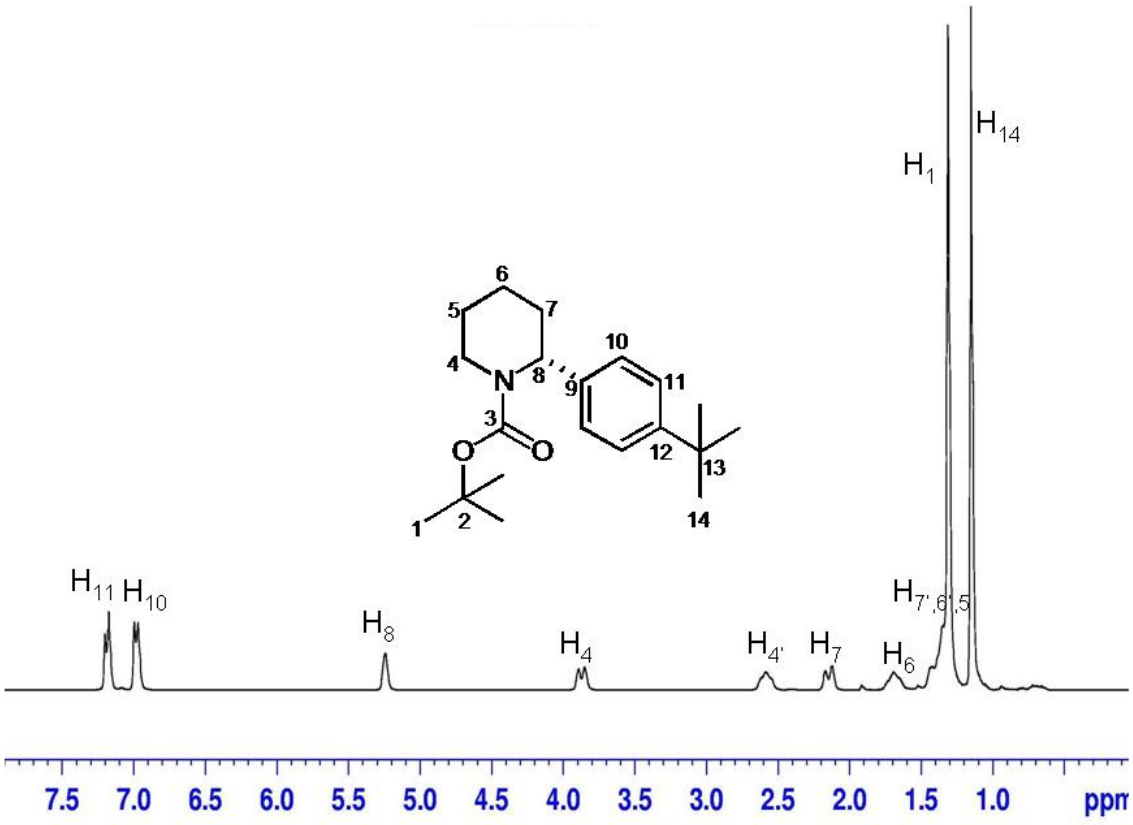
Using **General Procedure A**, *N*-Boc-piperidine (370 mg, 2.0 mmol), TMEDA (1.2 mL, 8.0 mmol, 4.0 equiv), Et_2O (10 mL), *s*-BuLi (2.4 mL, 1.0 M, 2.4 mmol, 1.2 equiv), (*S*,*S*)-**2** (21.4 mg, 0.1 mmol, 5 mol %, in 0.40 mL Et_2O pretreated with freshly titrated *s*-BuLi), $ZnCl_2$ (355 mg, 2.6 mmol, 1.3 equiv) in THF (2 mL), *p*-bromo-*tert*-butylbenzene (0.43 mL, 2.6 mmol, 1.3 equiv), $Pd(OAc)_2$ (20 mg, 0.08 mmol, 4 mol %) and *t*-$Bu_3P{\cdot}HBF_4$ (46 mg, 0.16 mmol, 8 mol %) gave the crude product as an oil. Purification by silica gel column chromatography eluting with Hexane/EtOAc (99:1) afforded 437 mg of the pure product as an oil in 69% yield and 95:5 er; $[\alpha]_D^{22}$ +104.4 (*c* = 1, $CHCl_3$). The er was determined by CSP-SFC as follows: **Column:** Daicel Chiralcel OD-H, **Flow Rate** = 2.0 mL/min, **Polarity Modifier** = 3.0% EtOH. The minor enantiomer elutes after ~3.8 min and the major enantiomer elutes after ~4.7 min. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.4-7.3 (d, 2H), .7.2-7.1 (d, 2H), 5.4 (br, s, 1H), 4.1-3.98 (m, 1H), 2.85-2.7 (m, 1H), 2.34-2.25 (m, 1H), 1.92-1.57 (m, 5H) 1.48 (s, 9H), 1.25 (s, 9H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 155.6, 149.1, 137.1, 126.2, 125.4, 79.4, 52.9, 40.0, 34.3, 31.4, 28.5, 27.9, 25.6, 19.5.

CAUTION: *p*-bromo-*tert*-butylbenzene has a very strong odor.

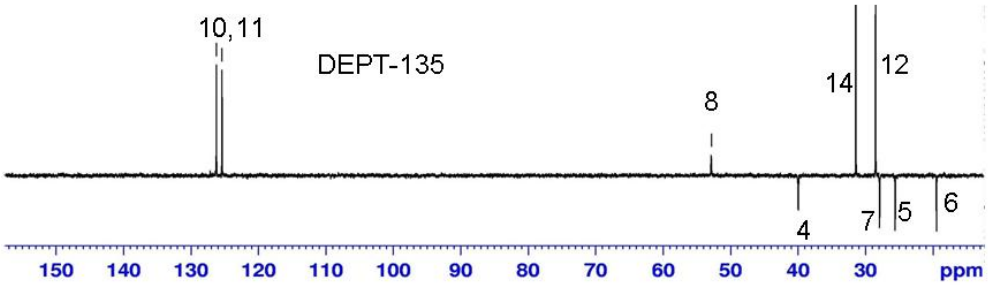
CSP-SFC

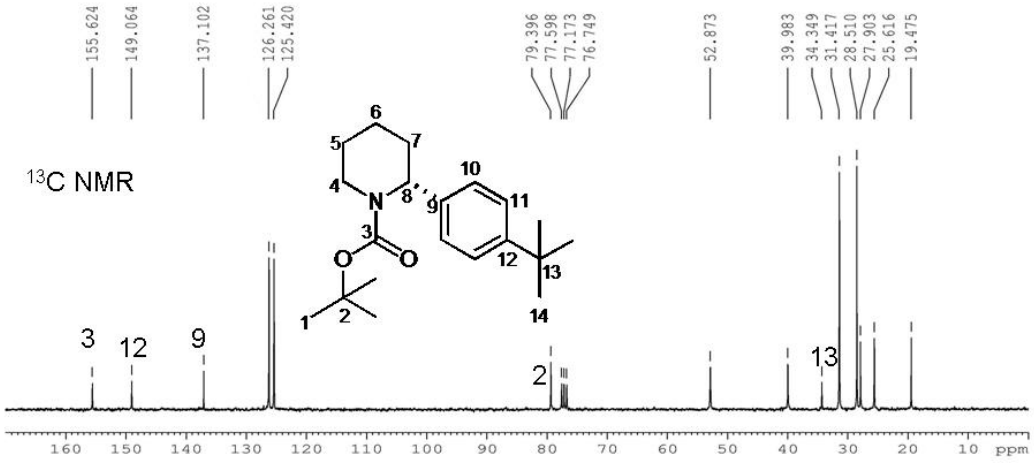

Current Chromatogram(s)
LDAD1 B, LDAD B, Sig=254,16 Ref=360,100 (F:\BKT0465.D)
mAU
3.764
4.748
Authentic racemate
LDAD1 B, LDAD B, Sig=254,16 Ref=360,100 (F:\BKT0468.D)
mAU
4.602
3.770
N
Boc
t-Bu
S
R
'17/2010 11:41:49 AM Beng


File :C:\Documents and Settings\Administrator\Desktop\Gawley metho
... s sequence\BENG\ARYLATION-MESITYLENE.D\4-TERT-BU-BZ F45.D
Operator : tkb
Instrument : Instrument #1
Acquired : 15 Sep 2010 18:01 using AcqMethod drug test method.M
Sample Name: f45
Misc Info :
TIC: 4-TERT-BU-BZ F45.D\data.ms
10.739
10.817
GC
N
Boc
t-Bu
MW 317
Abundance
Time-->
Scan 2848 (10.708 min): 4-TERT-BU-BZ F45.D\data.ms
M-Boc
M-CMe3
MS
216
261
57
160
188
246
91
118
146
77
174
202
230
m/z-->

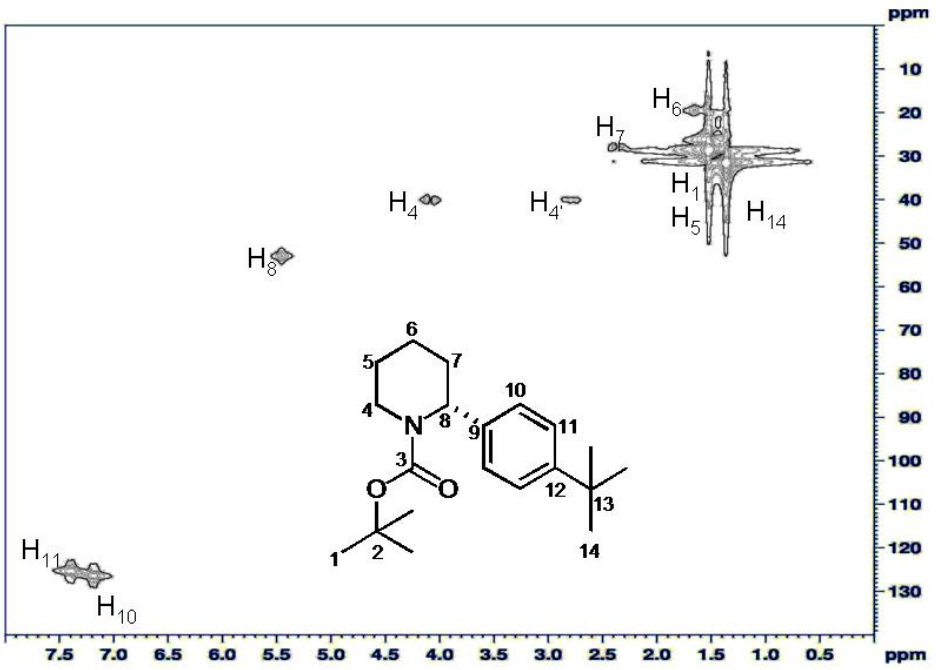


See full assignments on HMQC

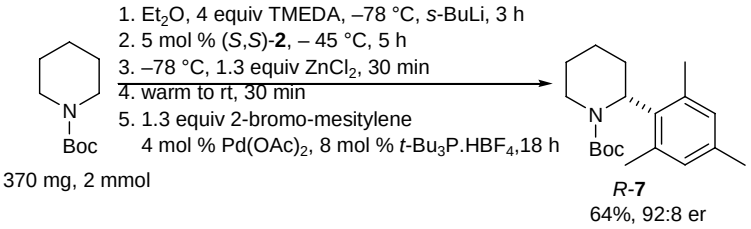

10,11
DEPT-135
8
14
12
4
7
5
6
150 140 130 120 110 100 90 80 70 60 50 40 30 ppm


155.624
149.064
137.102
126.261
125.420
79.396
77.598
77.173
76.749
52.873
39.983
34.349
31.417
28.510
27.903
25.616
19.475
13C NMR
3
12
9
2
13
160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

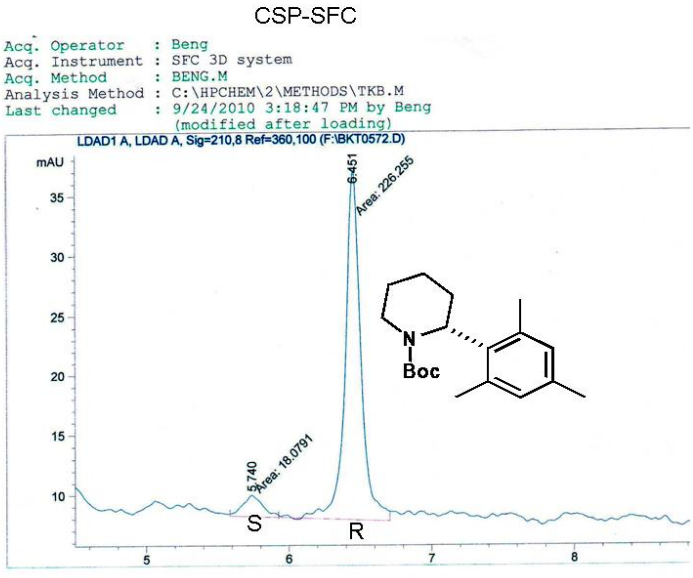
HMQC

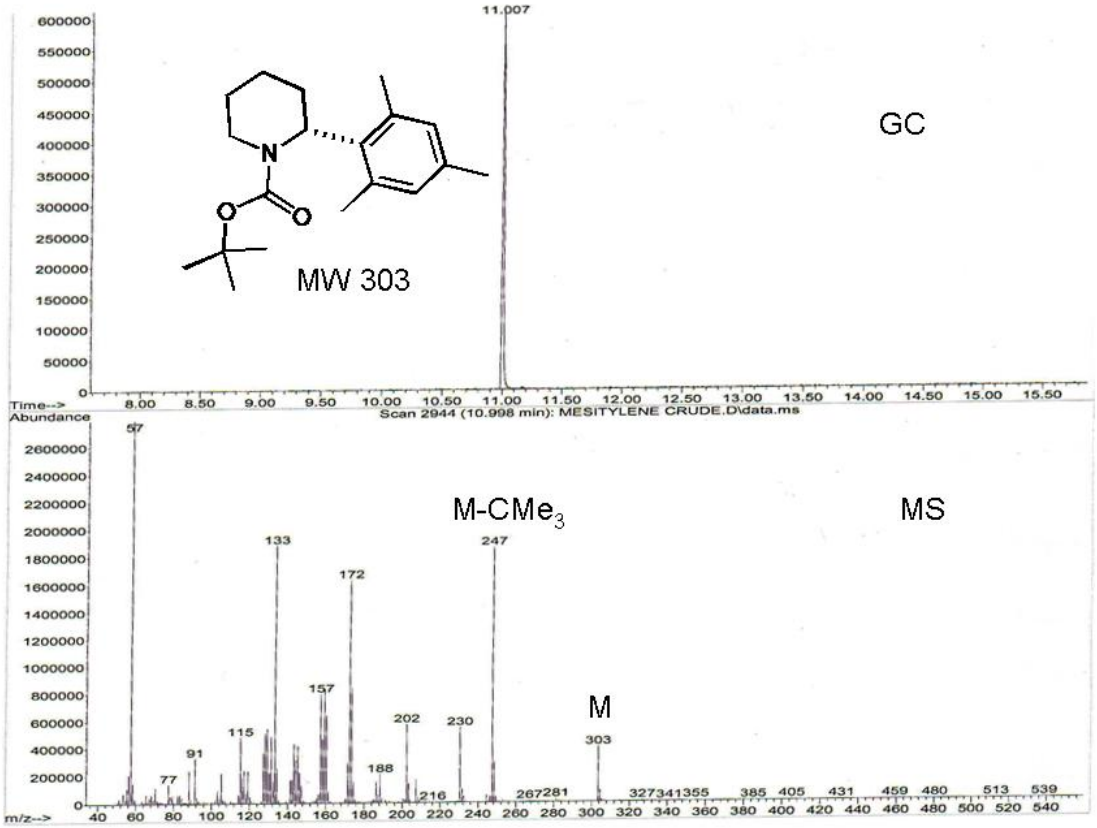

ppm
H6
H7
H1
H5
H14
H4
H4'
H8
H11
H10
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm

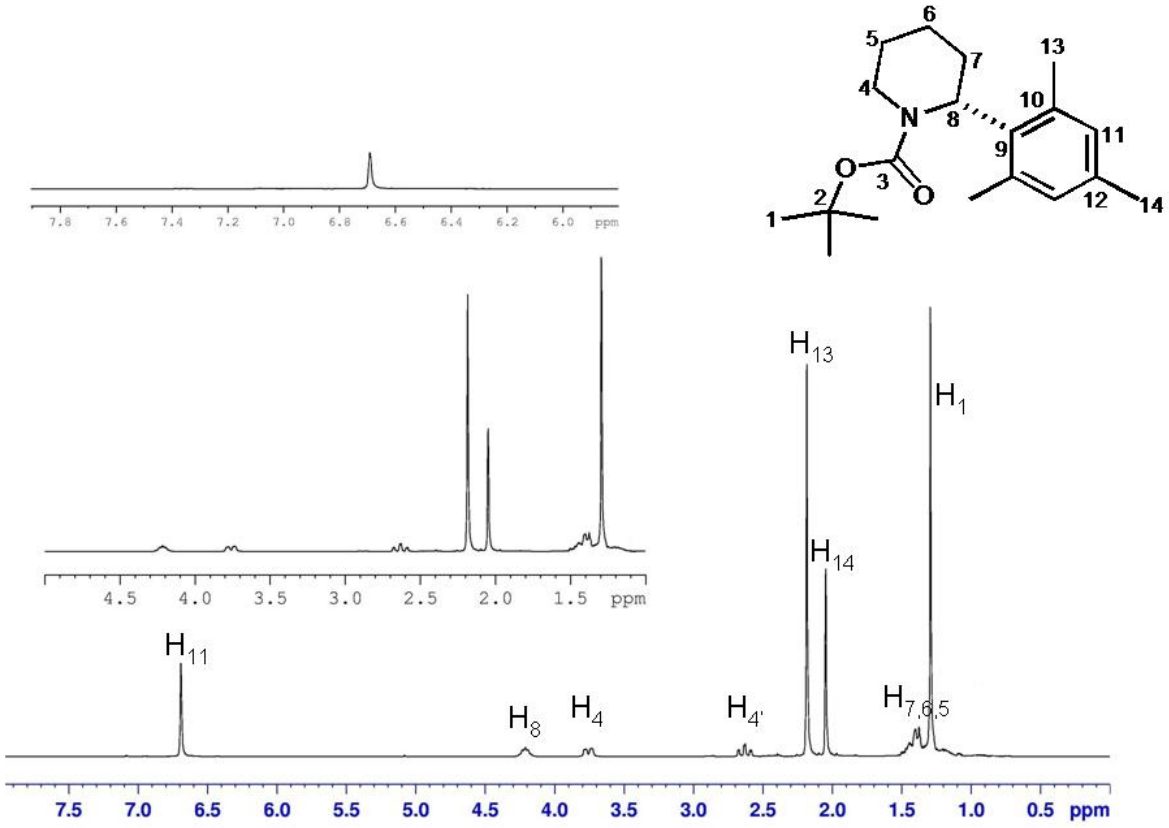
4.5. Electrophilic quench with 2-bromomesitylene: Synthesis of *R*-7

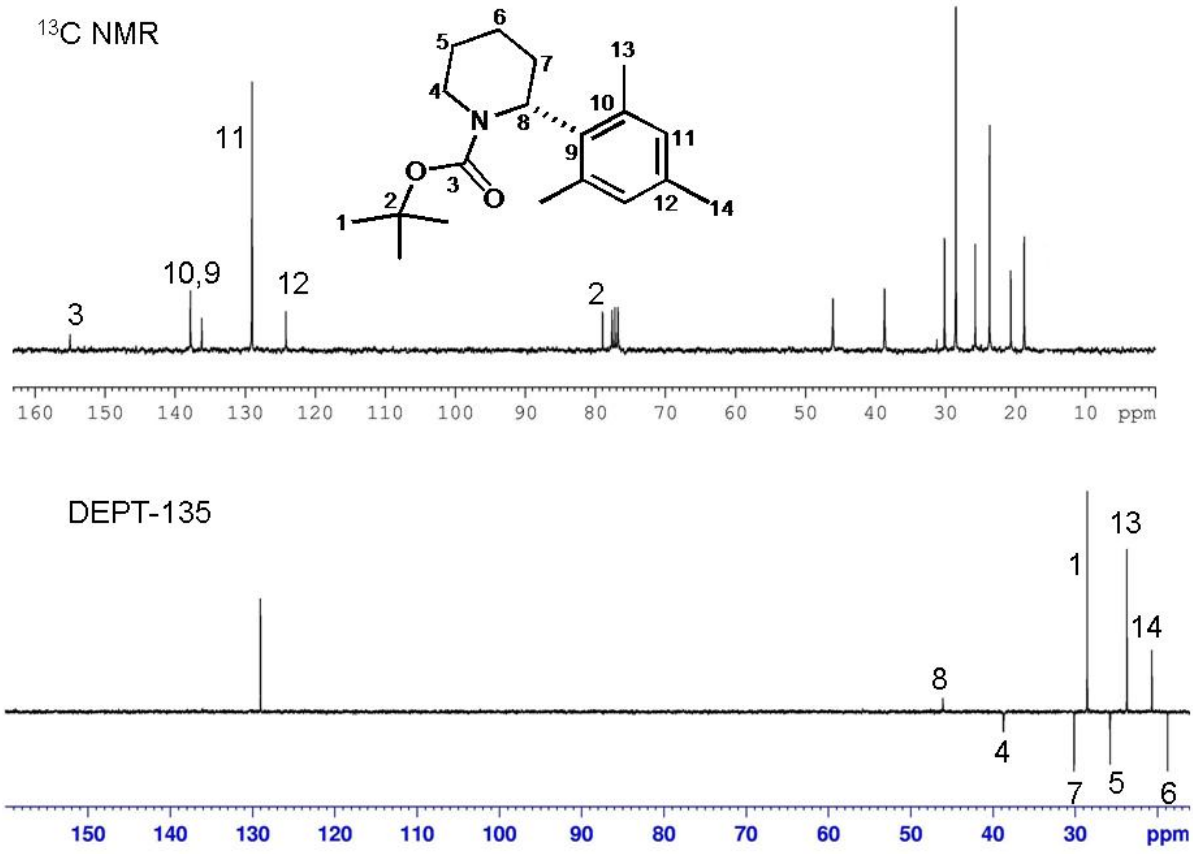


Using **General Procedure A**, *N*-Boc-piperidine (370 mg, 2.0 mmol), TMEDA (1.2 mL, 8.0 mmol, 4.0 equiv), Et_2O (10 mL), *s*-BuLi (2.4 mL, 1.0 M, 2.4 mmol, 1.2 equiv), (*S*,*S*)-**2** (21.4 mg, 0.1 mmol, 5 mol %, in 0.40 mL Et_2O pretreated with freshly titrated *s*-BuLi), $ZnCl_2$ (355 mg, 2.6 mmol, 1.3 equiv) in THF (2 mL), 2-bromomesitylene (517 mg, 2.6 mmol, 1.3 equiv), $Pd(OAc)_2$ (20 mg, 0.08 mmol, 4 mol %) and *t*-$Bu_3P{\cdot}HBF_4$ (46 mg, 0.16 mmol, 8 mol %) gave the crude product as an oil. Purification by silica gel column chromatography eluting with Hexane/EtOAc (85:15) afforded 388 mg of the pure product as an oil in 64% yield and 92:8 er; $[\alpha]_D^{22}$ +97.1 (*c* = 1, $CHCl_3$) The er was determined by CSP-SFC as follows: **Column:** Pirkle-Whelk-O-1, **Flow Rate**: 2.0 mL/min, **Polarity Modifier %**: 2.0% EtOH, Outlet Pressure = **150 psi**, **Oven Temperature** = 35 °C. The minor enantiomer elutes after ~5.7 min and the major enantiomer elutes after ~6.5 min.

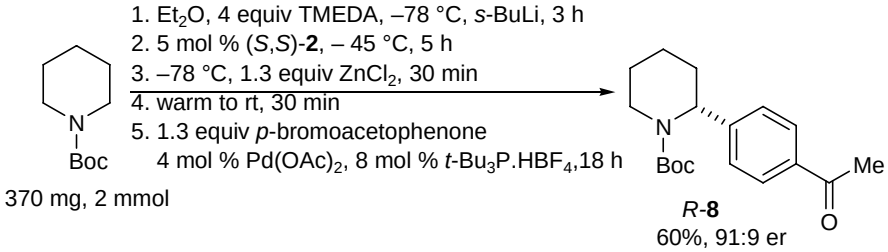



11.007
GC
MW 303
Time-->
Abundance
Scan 2944 (10.998 min): MESITYLENE CRUDE.D\data.ms
M-CMe3
MS
M
303
247
133
172
157
57
91
115
77
188
202
230
216
m/z-->


6
5
7
13
4
N
8
10
11
9
O
3
O
2
12
14
1
7.8 7.6 7.4 7.2 7.0 6.8 6.6 6.4 6.2 6.0 ppm
4.5 4.0 3.5 3.0 2.5 2.0 1.5 ppm
H13
H1
H14
H11
H8
H4
H4'
H7,6,5
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 ppm

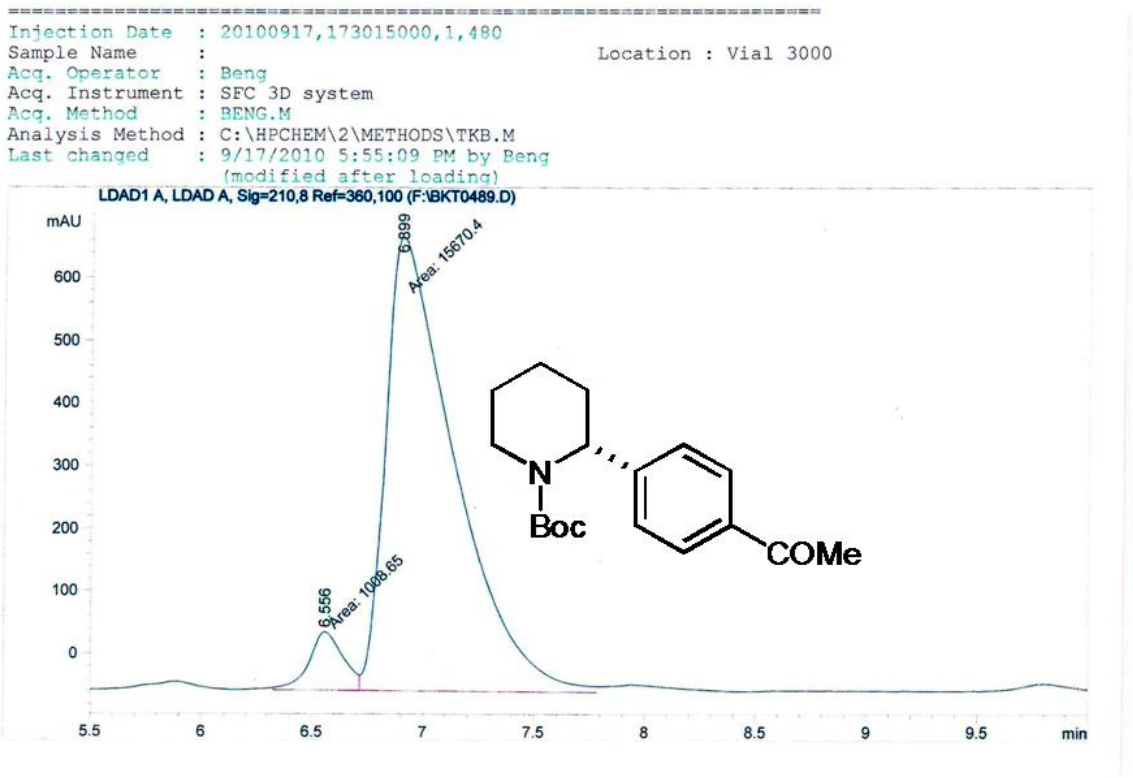


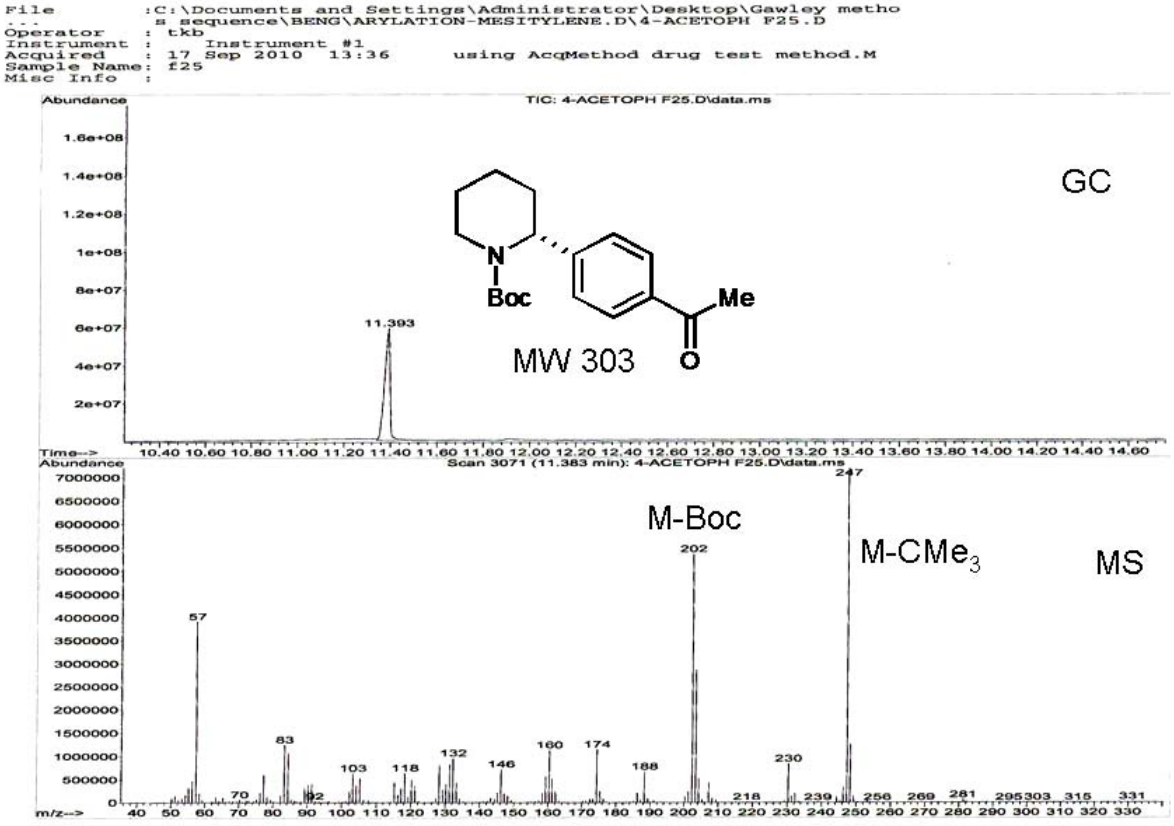
4.6. Electrophilic quench with *p*-bromoacetophenone: Synthesis of *R*-8



Using **General Procedure A**, *N*-Boc-piperidine (370 mg, 2.0 mmol), TMEDA (1.2 mL, 8.0 mmol, 4.0 equiv), Et_2O (10 mL), *s*-BuLi (2.4 mL, 1.0 M, 2.4 mmol, 1.2 equiv), (*S*,*S*)-**2** (21.4 mg, 0.1 mmol, 5 mol %, in 0.40 mL Et_2O pretreated with freshly titrated *s*-BuLi), $ZnCl_2$ (355 mg, 2.6 mmol, 1.3 equiv) in THF (2 mL), 4-bromoacetophenone (517 mg, 2.6 mmol, 1.3 equiv), $Pd(OAc)_2$ (20 mg, 0.08 mmol, 4 mol %) and *t*-$Bu_3P{\cdot}HBF_4$ (46 mg, 0.16 mmol, 8 mol %) gave the crude product as an oil. Purification by silica gel column chromatography eluting with Hexane/EtOAc (80:20) afforded 364 mg of the pure product as an oil in 60% yield and 91:9 er; $[\alpha]_D^{22}$ +126.5 (*c* = 1, $CHCl_3$) The er was determined by CSP-SFC as follows: **Column:** Pirkle-

Whelk-O-1, **Flow Rate**: 3.0 mL/min, **Polarity Modifier %**: 3.0% EtOH, Outlet Pressure = **150 psi**, **Oven Temperature** = 35 ^{o}C. The minor enantiomer elutes after ~6.5 min and the major enantiomer elutes after ~7.0 min. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.95-7.90 (d, 2H), .7.83-7.78 (d, 2H), 5.45 (br, s, 1H), 4.15-4.08 (m, 1H), 2.82-2.71 (m, 1H), 2.60 (s, 3H); 2.32-2.27 (m, 1H), 1.92-1.57 (m, 5H) 1.48 (s, 9H), ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 197.5, 155.6, 146.5, 135.4, 128.7, 126.7, 79.9, 53.4, 40.3, 28.4, 28.3, 26.6, 25.2, 19.4.




File :C:\Documents and Settings\Administrator\Desktop\Gawley metho
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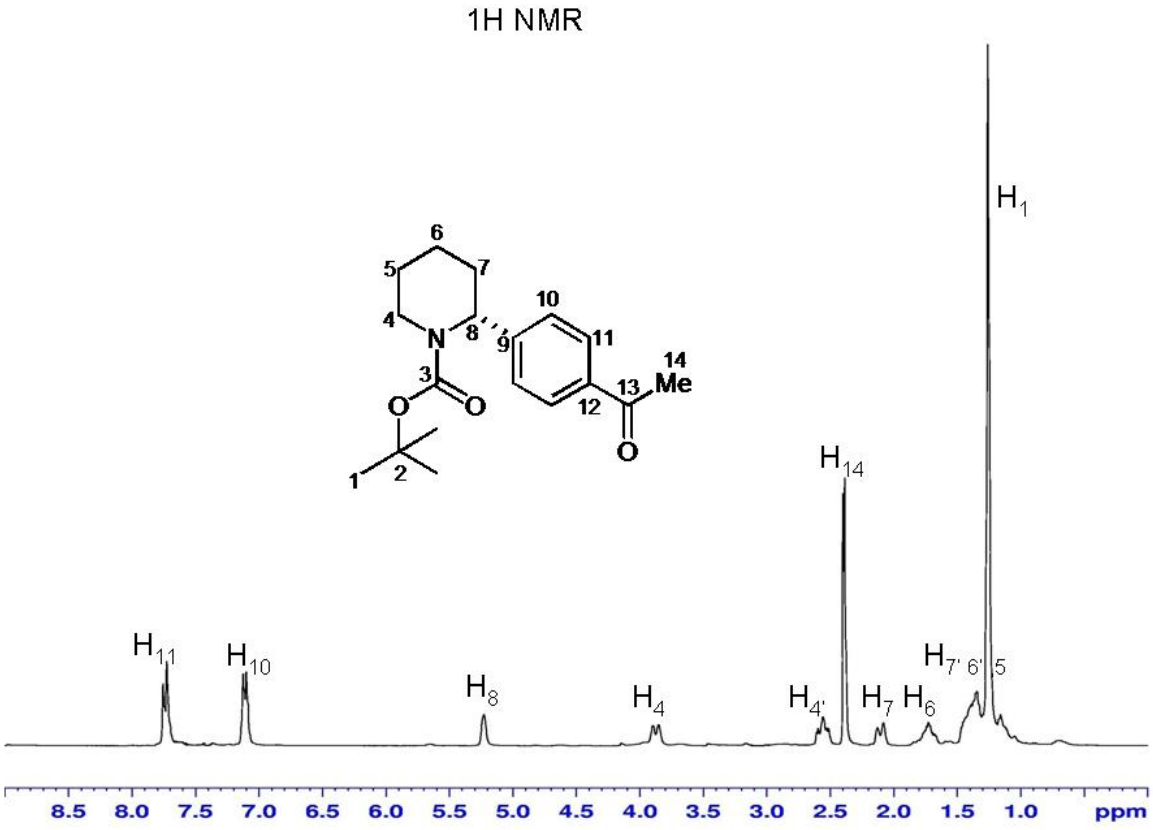
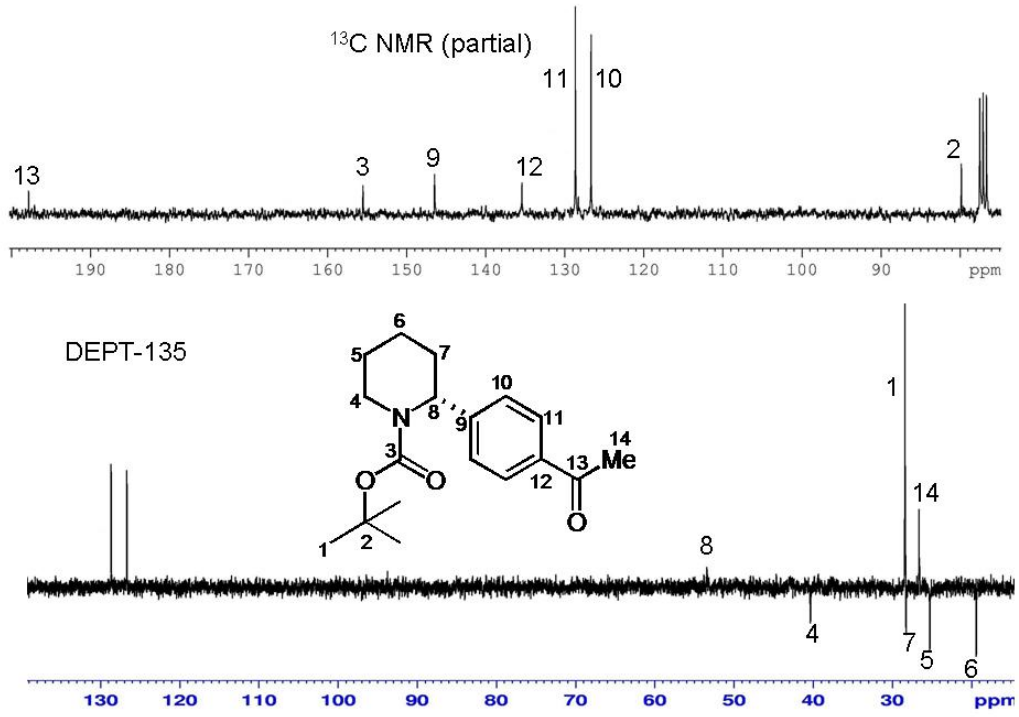
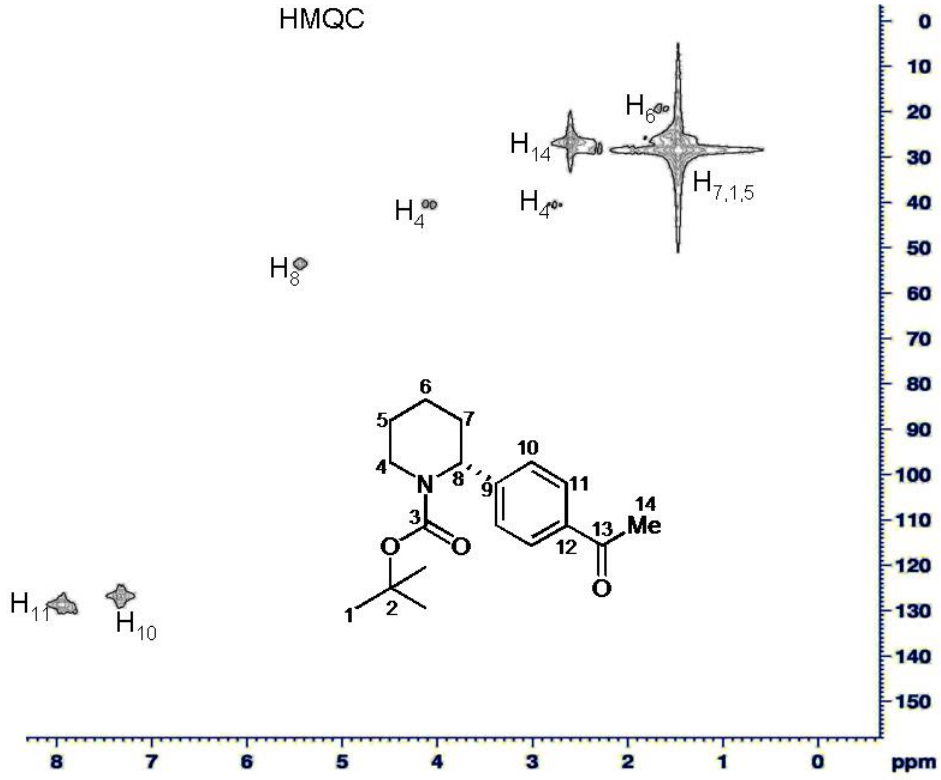
Instrument : Instrument #1
Acquired : 17 Sep 2010 13:36 using AcqMethod drug test method.M
Sample Name: f25
Misc Info :
Abundance
TIC: 4-ACETOPH F25.D\data.ms
GC
N
Boc
Me
O
MW 303
11.393
Time-->
Abundance
Scan 3071 (11.383 min): 4-ACETOPH F25.D\data.ms
M-Boc
M-CMe3
MS
247
202
57
83
103
118
132
146
160
174
188
230
m/z-->

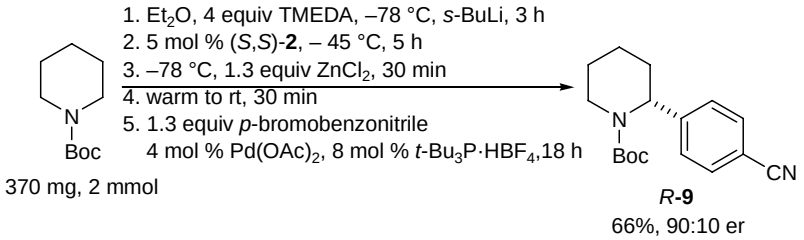


See full assignments on HMQC

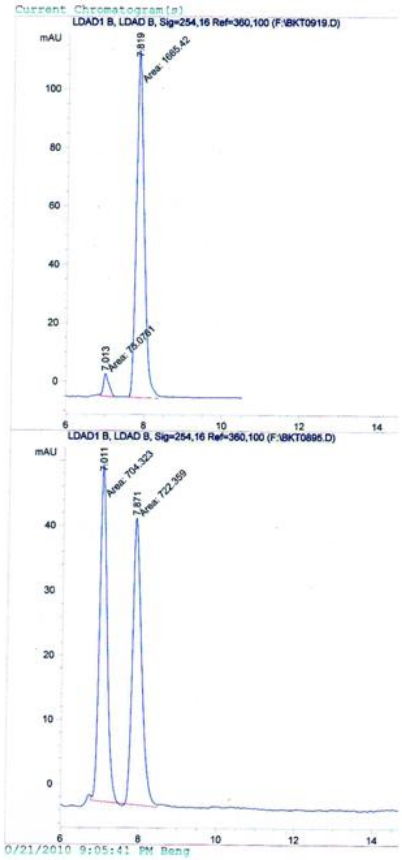

13C NMR (partial)
13
3
9
12
11
10
2
190
180
170
160
150
140
130
120
110
100
90
ppm
DEPT-135
1
14
8
4
7
5
6
130
120
110
100
90
80
70
60
50
40
30
ppm


HMQC
H6
H14
H7,1,5
H4
H4
H8
H11
H10
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
8
7
6
5
4
3
2
1
0
ppm

4.7. Electrophilic quench with *p*-bromobenzonitrile: Synthesis of *R*-9



Using **General Procedure A**, *N*-Boc-piperidine (370 mg, 2.0 mmol), TMEDA (1.2 mL, 8.0 mmol, 4.0 equiv), Et_2O (10 mL), *s*-BuLi (2.4 mL, 1.0 M, 2.4 mmol, 1.2 equiv), (*S*,*S*)-**2** (21.4 mg, 0.1 mmol, 5 mol %, in 0.40 mL Et_2O pretreated with freshly titrated *s*-BuLi), $ZnCl_2$ (355 mg, 2.6 mmol, 1.3 equiv) in THF (2 mL), 4-bromobenzonitrile (471 mg, 2.6 mmol, 1.3 equiv), $Pd(OAc)_2$ (20 mg, 0.08 mmol, 4 mol %) and *t*-$Bu_3P{\cdot}HBF_4$ (46 mg, 0.16 mmol, 8 mol %) gave the crude product as an oil. Purification by silica gel column chromatography eluting with Hexane/EtOAc (90:10) afforded 378 mg of the pure product as an oil in 66% yield and 90:10 er; , $[\alpha]_D^{22}$ +147.8 (*c* = 1, $CHCl_3$) The er was determined by CSP-SFC as follows: **Column:** Pirkle-Whelk-O-1, **Flow Rate**: 2.0 mL/min, **Polarity Modifier %**: 2.0% EtOH, Outlet Pressure = **150 psi**, **Oven Temperature** = 35 ^oC. The minor enantiomer elutes after ~7.0 min and the major enantiomer elutes after ~7.8 min. ^1H NMR (300 MHz, $CDCl_3$) δ 7.60 (d, 2H), 7.30 (d, 2H), 5.25 (br, s, 1H), 3.87 (m, 1H), 2.55-2.48 (m, 1H), 2.10-2.05 (m, 1H), 1.92-1.57 (m, 5H) 1.48 (s, 9H), ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 155.4, 146.6, 132.4, 127.3, 118.9 110.3, 80.0, 53.4, 40.4, 28.4, 28.1, 25.1, 19.3.

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Injection Date  : 20101021,203914000,1,480
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Acq. Operator   : Beng
Acq. Instrument : SFC 3D system
Acq. Method     : BENG.M
Analysis Method : C:\HPCHEM\2\METHODS\TKB.M
Last changed    : 10/21/2010 9:09:24 PM by Beng
                  (modified after loading)
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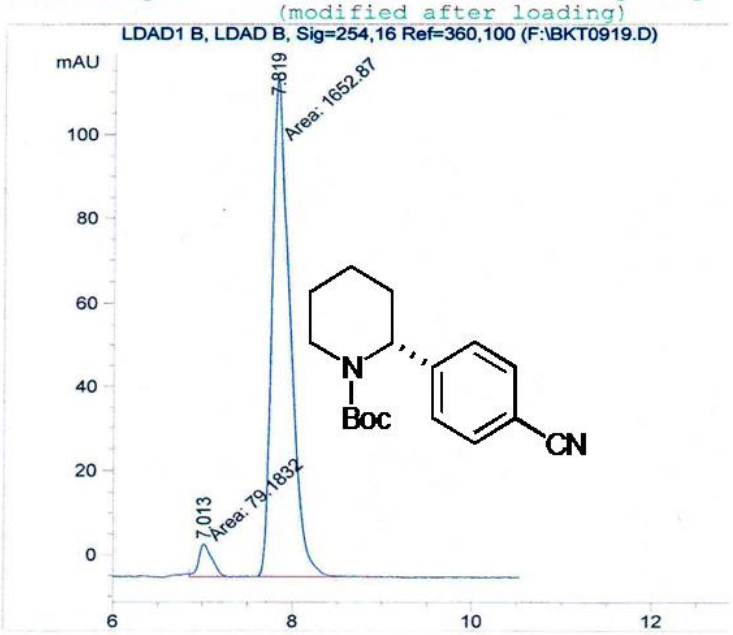

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...            1.D
Instrument :      Instrument #1
Operator   : tkb
Acquired   : 20 Oct 2010  21:07      using AcqMethod drug test method.M
Sample Name: f41
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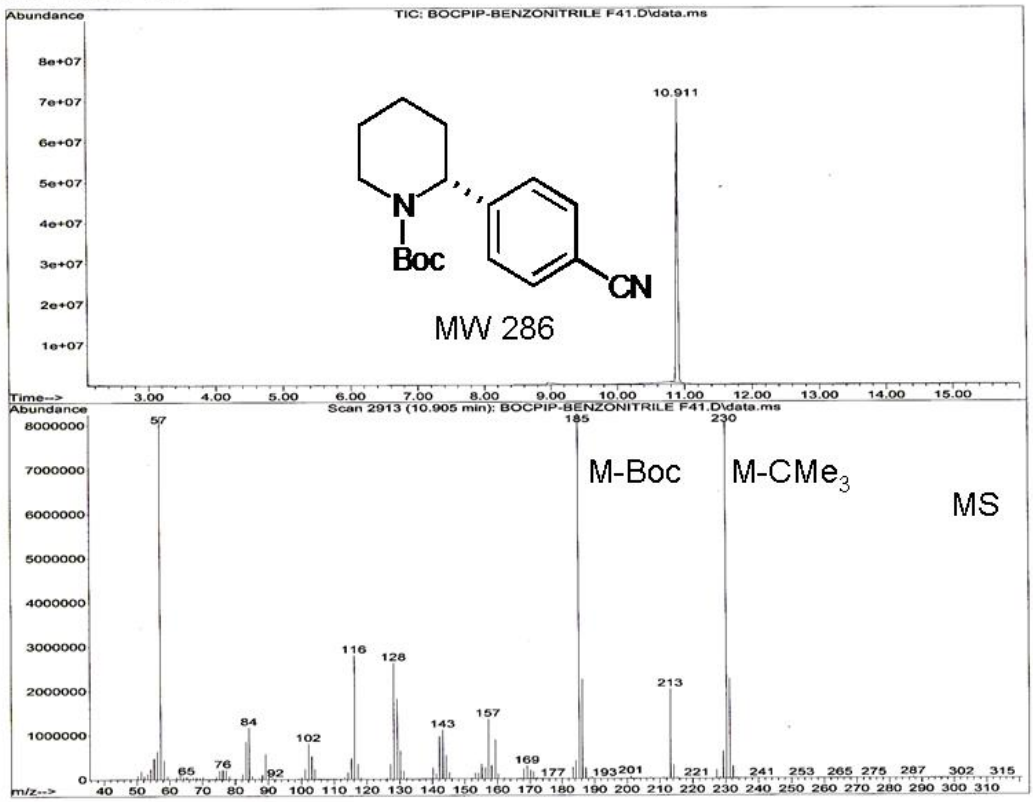

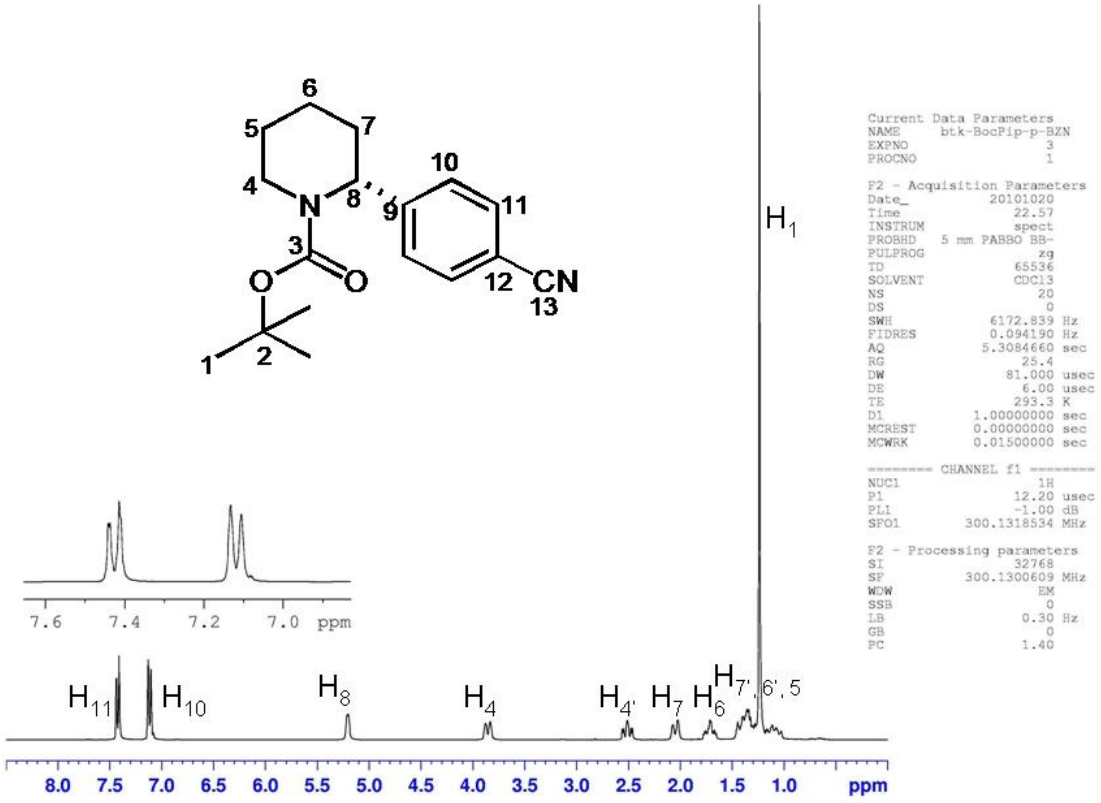


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Current Data Parameters
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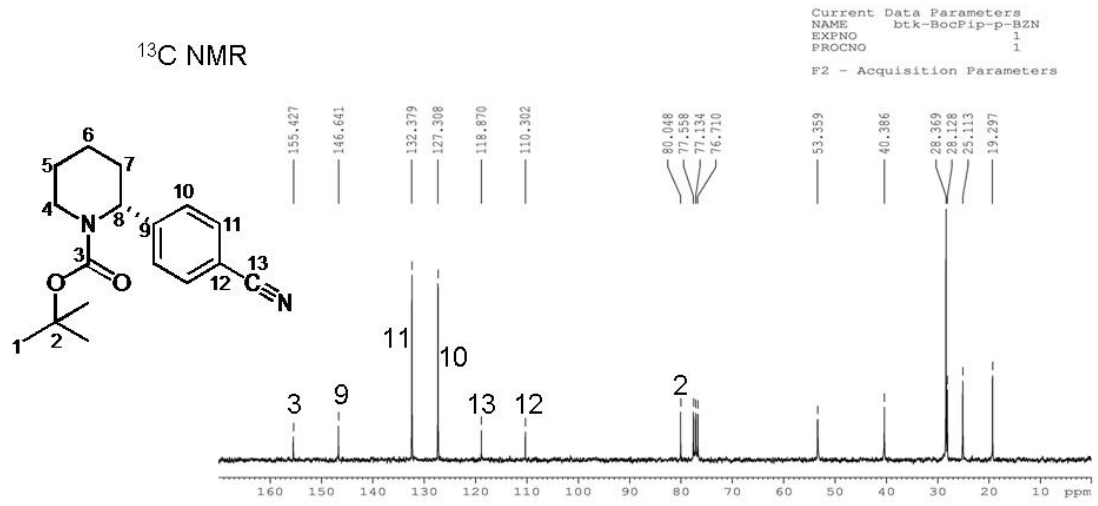
EXPNO                    3
PROCNO                   1

F2 - Acquisition Parameters
Date_             20101020
Time                 22.57
INSTRUM              spect
PROBHD    5 mm PABBO BB-
PULPROG                 zg
TD                   65536
SOLVENT              CDCl3
NS                      20
DS                       0
SWH               6172.839 Hz
FIDRES               0.094190 Hz
AQ                5.3084660 sec
RG                    25.4
DW                  81.000 usec
DE                   6.00 usec
TE                  293.3 K
D1              1.00000000 sec
MCREST          0.00000000 sec
MCWRK           0.01500000 sec

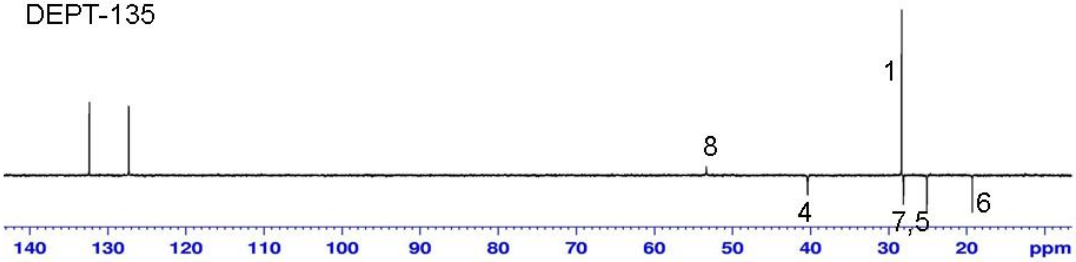
======== CHANNEL f1 ========
NUC1                     1H
P1                   12.20 usec
PL1                  -1.00 dB
SFO1           300.1318534 MHz

F2 - Processing parameters
SI                       32768
SF             300.1300609 MHz
WDW                        EM
SSB                         0
LB                       0.30 Hz
GB                          0
PC                       1.40
```

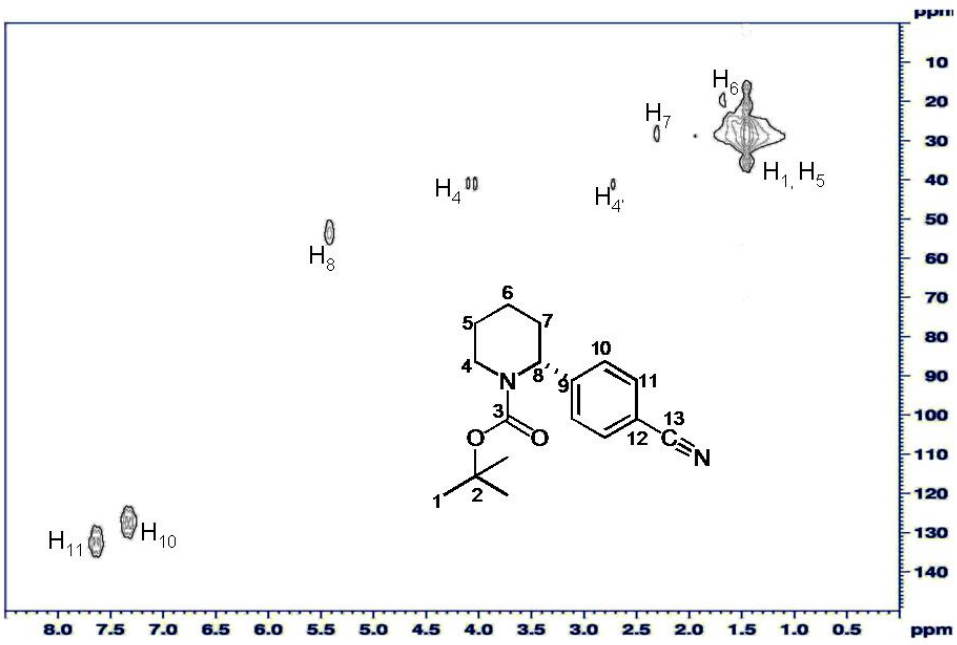
^{13}C NMR



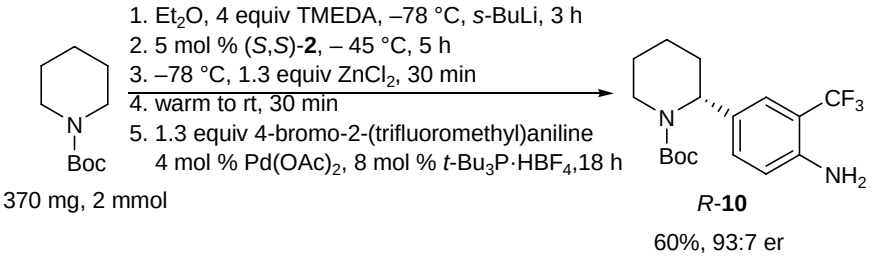
DEPT-135



HMQC

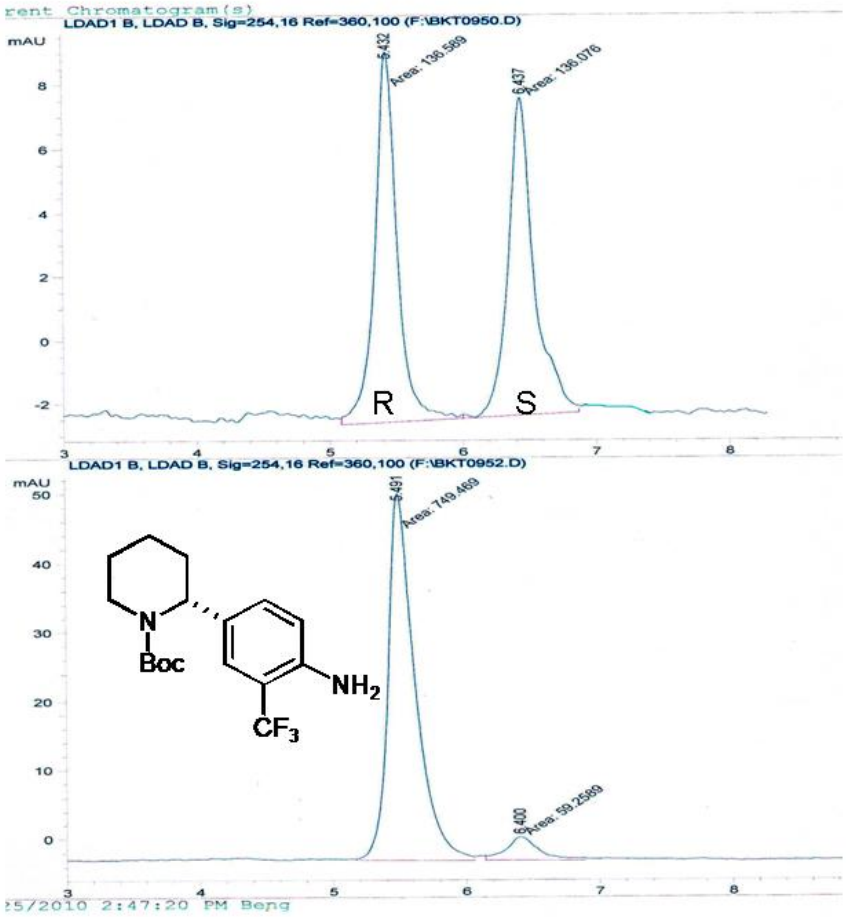


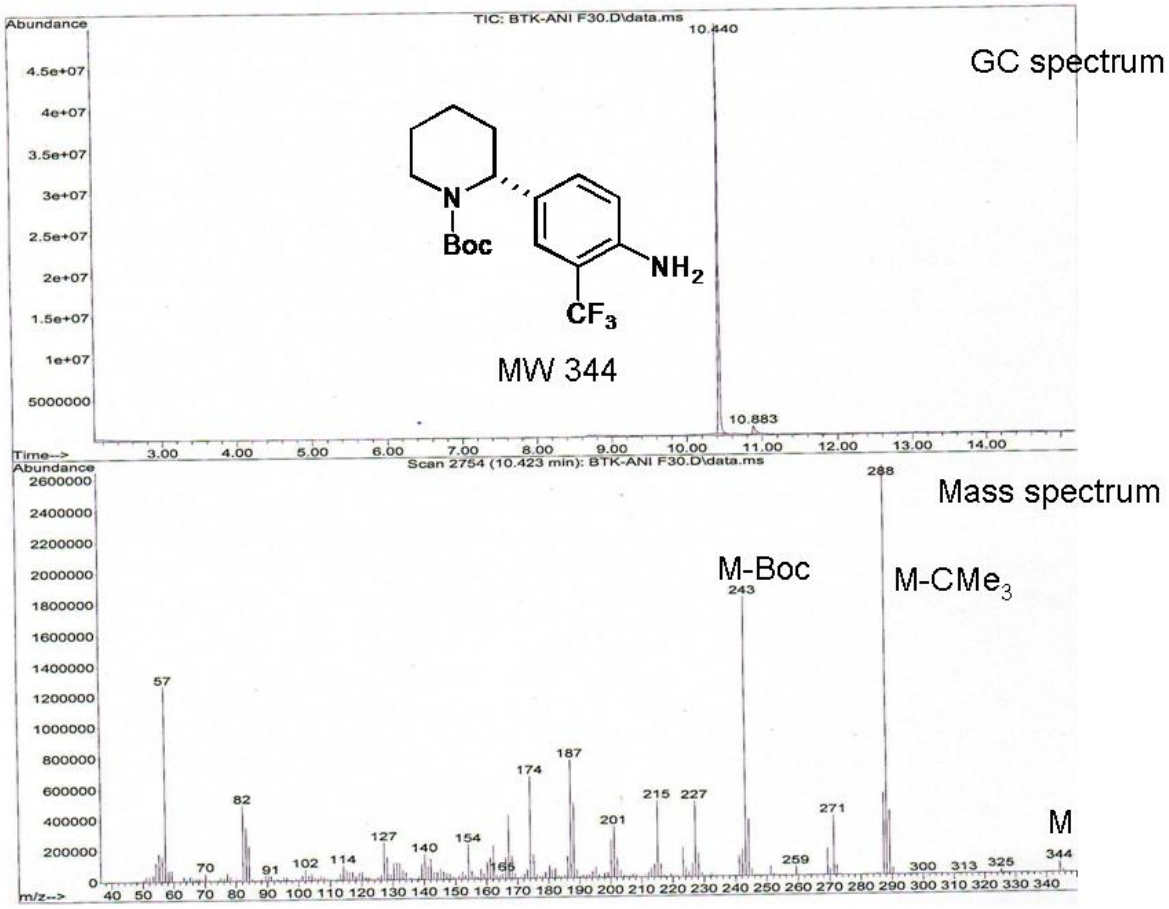
4.8. Electrophilic quench with 4-bromo-2-trifluoromethyl aniline: Synthesis of *R*-10



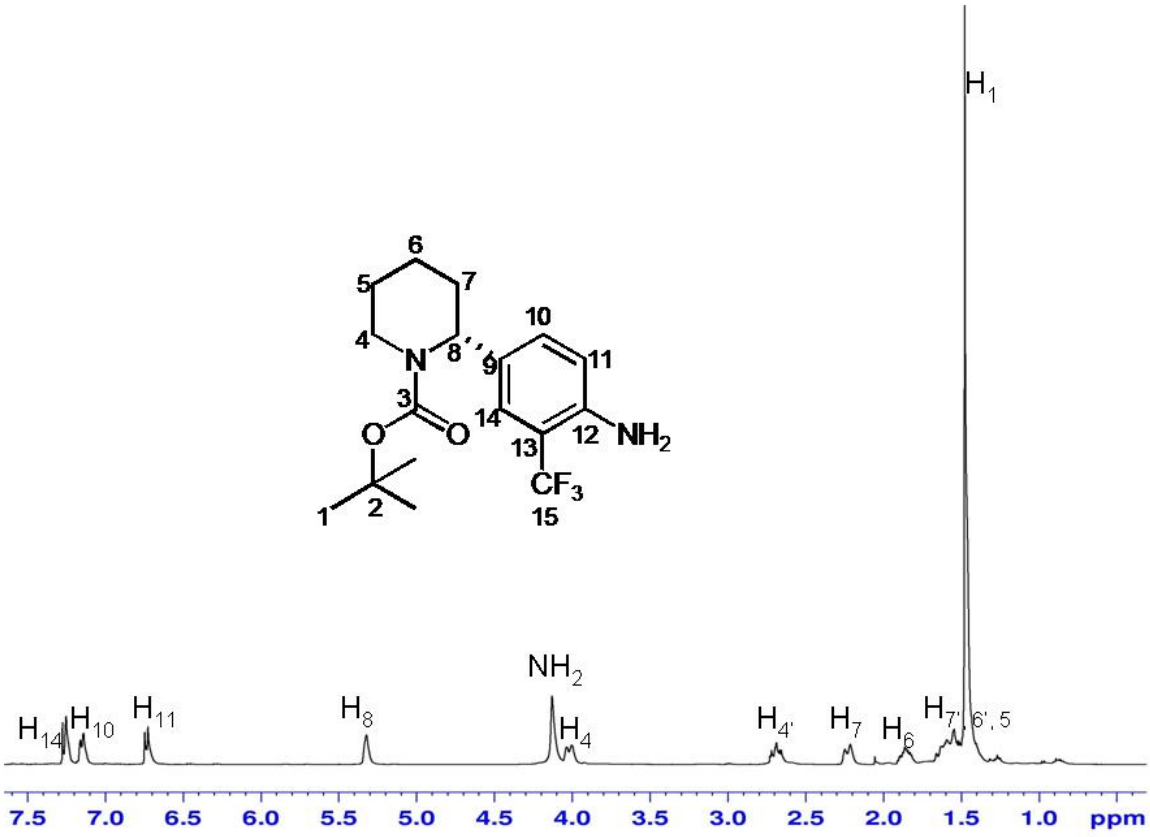
Using **General Procedure A**, *N*-Boc-piperidine (370 mg, 2.0 mmol), TMEDA (1.2 mL, 8.0 mmol, 4.0 equiv), Et_2O (10 mL), *s*-BuLi (2.4 mL, 1.0 M, 2.4 mmol, 1.2 equiv), (*S*,*S*)-**2** (21.4 mg, 0.1 mmol, 5 mol %, in 0.40 mL Et_2O pretreated with freshly titrated *s*-BuLi), $ZnCl_2$ (355 mg, 2.6 mmol, 1.3 equiv) in THF (2 mL), 4-bromo-2-trifluoromethylaniline (621 mg, 2.6 mmol, 1.3 equiv), $Pd(OAc)_2$ (20 mg, 0.08 mmol, 4 mol %) and *t*-$Bu_3P{\cdot}HBF_4$ (46 mg, 0.16 mmol, 8 mol %) gave the crude product as an oil. Purification by silica gel column chromatography eluting with Hexane/EtOAc (90:10) afforded 413 mg of the pure product as an oil in 60% yield and 93:7 er; , $[\alpha]_D^{22}$ +101.6 (*c* = 1, $CHCl_3$) The er was determined by CSP-SFC as follows: **Column:** Pirkle-Whelk-O-1, **Flow Rate**: 2.5 mL/min, **Polarity Modifier %**: 2.5% EtOH, Outlet Pressure = **150 psi**, **Oven Temperature** = 35 ^oC. The major enantiomer elutes after ~5.4 min and the minor enantiomer elutes after ~6.4 min. ^1H NMR (300 MHz, $CDCl_3$) δ 7.25 (s, 1H), 7.15 (d, 1H), 6.75 (d, 1H), 5.35 (br, s, 1H), 4.15-3.99 (m, 3H), 2.68 (m, 1H), 2.28-2.22 (m, 1H), 1.91-1.78 (m, 1H), 1.66-1.48 (m, 13H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 155.6, 143.0, 131.2, 129.4, 124.5, 117.6, 114.2, 79.7, 52.3, 39.9, 28.4, 27.7, 25.4, 19.3.

CSP-SFC

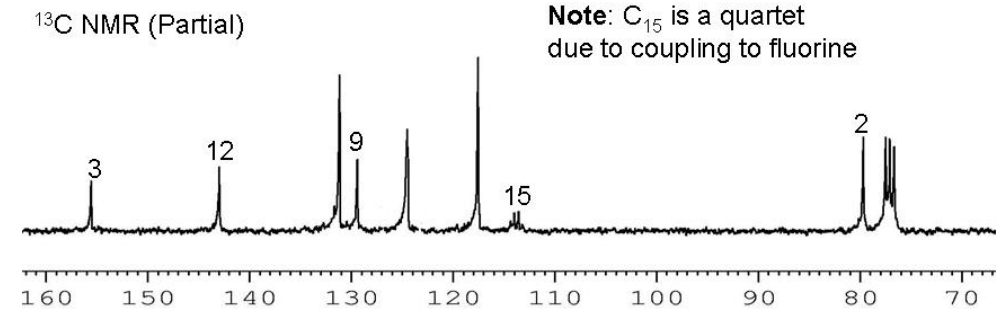

rent Chromatogram(s)
LDAD1 B, LDAD B, Sig=254,16 Ref=360,100 (F:\BKT0950.D)
mAU
6.432
Area: 136.589
6.437
Area: 136.076
R
S
LDAD1 B, LDAD B, Sig=254,16 Ref=360,100 (F:\BKT0952.D)
mAU
5.491
Area: 749.469
6.400
Area: 59.2589
N
Boc
NH2
CF3
25/2010 2:47:20 PM Beng

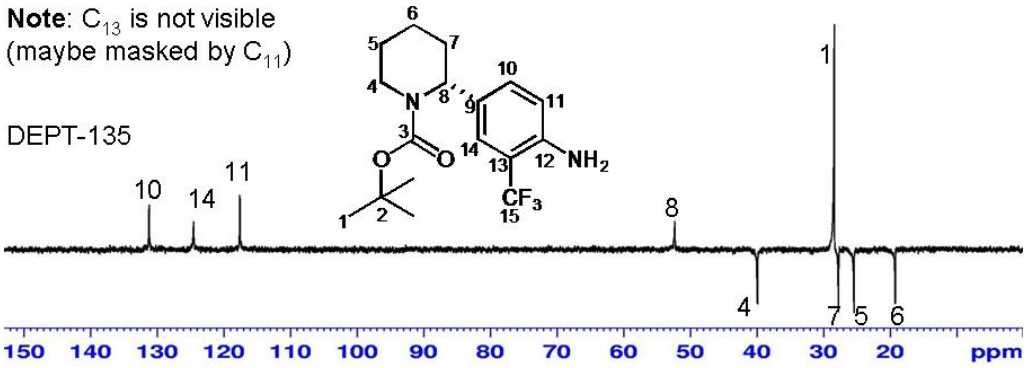


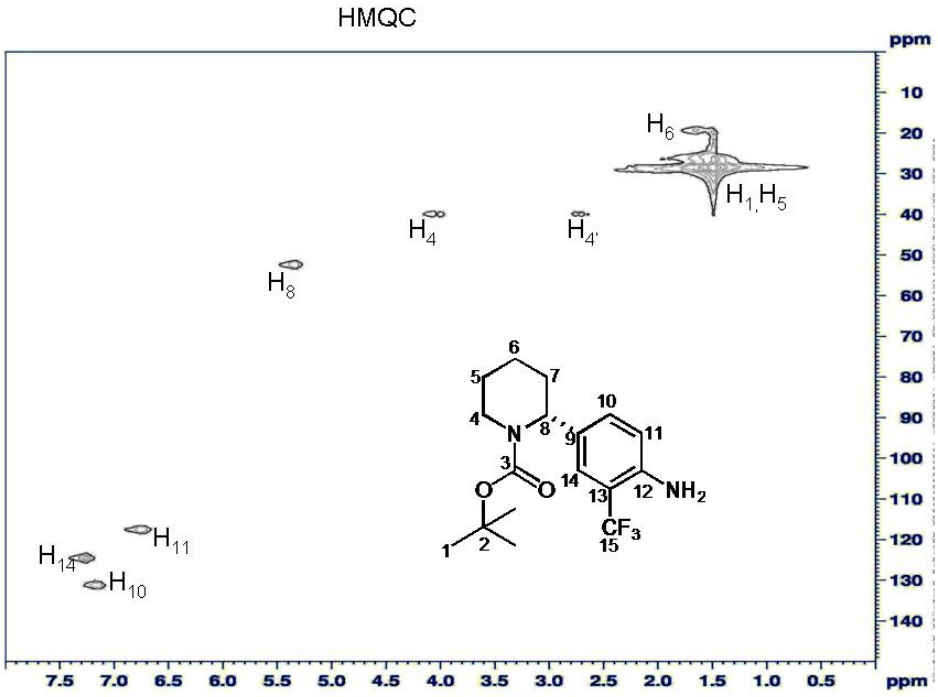
Note: The minor peak at 10.88 min corresponds to an unidentified structural isomer.



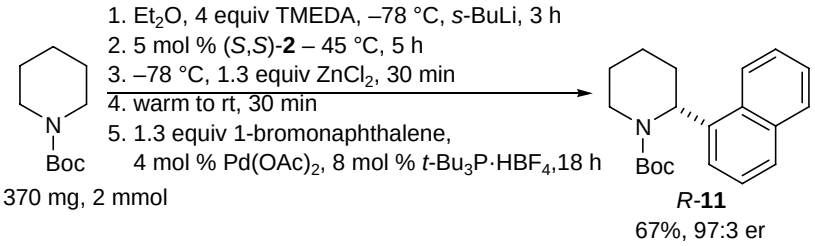
See full assignments on HMQC


^{13}C NMR (Partial)
Note: C_{15} is a quartet due to coupling to fluorine
3
12
9
15
2
160 150 140 130 120 110 100 90 80 70


Note: C_{13} is not visible (maybe masked by C_{11})
DEPT-135
10
14
11
8
1
4
7
5
6
150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm

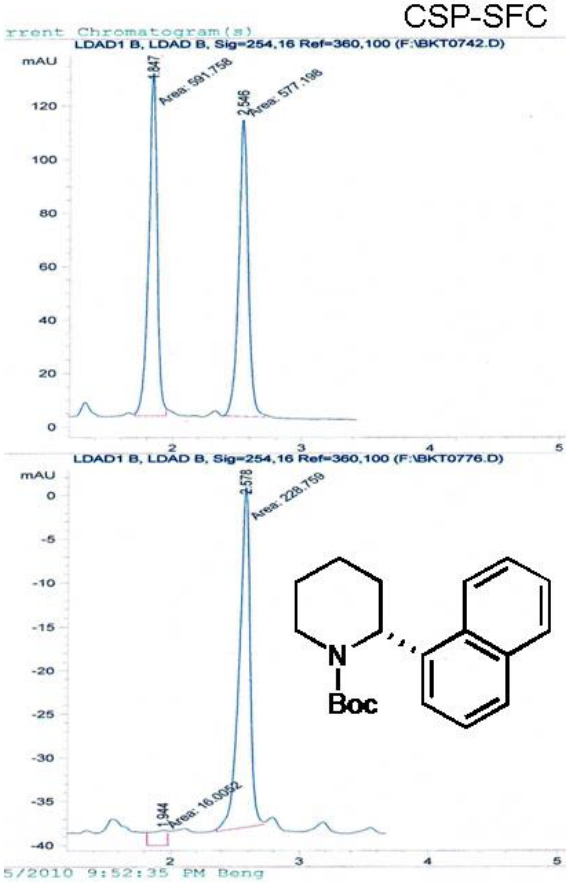

HMQC
H_6
H_1,H_5
H_4
$H_{4'}$
H_8
H_{11}
H_{14}
H_{10}
ppm
10 20 30 40 50 60 70 80 90 100 110 120 130 140
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm

4.9. Electrophilic quench with 1-Bromonaphthalene: Synthesis of *R*-11



Using **General Procedure A**, *N*-Boc-piperidine (370 mg, 2.0 mmol), TMEDA (1.2 mL, 8.0 mmol, 4.0 equiv), Et_2O (10 mL), *s*-BuLi (2.4 mL, 1.0 M, 2.4 mmol, 1.2 equiv), (*S*,*S*)-**2** (21.4 mg, 0.1 mmol, 5 mol %, in 0.40 mL Et_2O pretreated with freshly titrated *s*-BuLi), $ZnCl_2$ (355 mg, 1.3 mmol, 1.3 equiv) in THF (2 mL), 1-bromonaphthalene (532 mg, 0.36 mL, 2.6 mmol, 1.3 equiv), $Pd(OAc)_2$ (20 mg, 0.08 mmol, 4 mol %) and *t*-$Bu_3P{\cdot}HBF_4$ (46 mg, 0.16 mmol, 8 mol %) gave the crude product as an oil. Purification by silica gel column chromatography eluting with Hexane/EtOAc (60:40) afforded 417 mg of the pure product as an amorphous solid in 67% yield and 97:3 er; spectroscopic data as reported.[3] The er was determined by CSP-SFC as follows: **Column:** Pirkle-Whelk-O-1, **Flow Rate**: 3.0 mL/min, **Polarity Modifier %**: 10.0% EtOH, Outlet Pressure = **150 psi**, **Oven Temperature** = 35 ^{o}C. The minor enantiomer elutes after ~1.8 min and the major enantiomer elutes after ~2.5 min. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.34–7.37 (m, 6H), 6.05–5.89 (t, 1H), 4.22–4.07 (m, 1H), 3.33–3.19 (m, 1H), 2.24–2.09 (m, 2H), 1.84–1.75 (m, 1H), 1.71–1.54 (m, 4H), 1.46 (s, 9H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 155.6, 139.1, 134.0, 128.9, 127.3, 125.8, 125.4, 124.9, 123.5, 123.2, 79.5, 52.1, 41.7, 29.5, 28.3, 24.7, 19.4

CSP-SFC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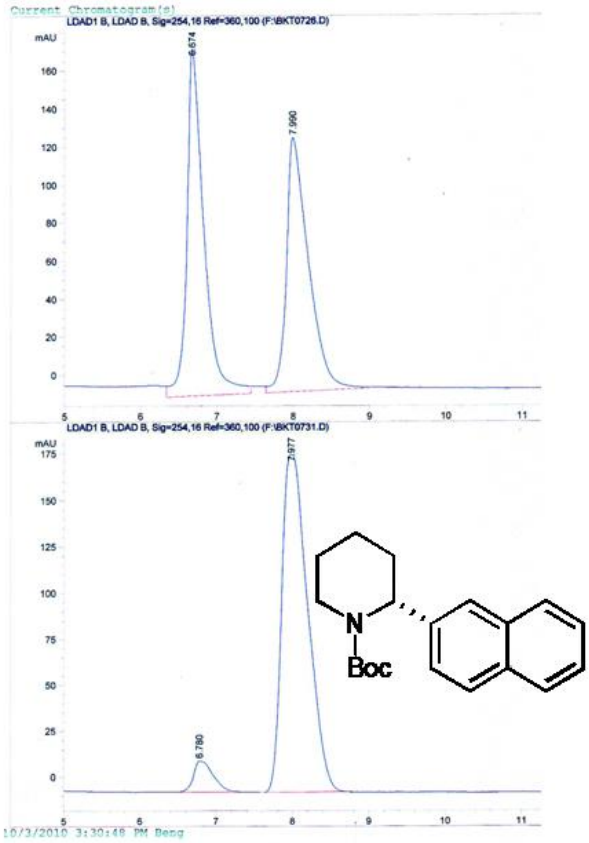
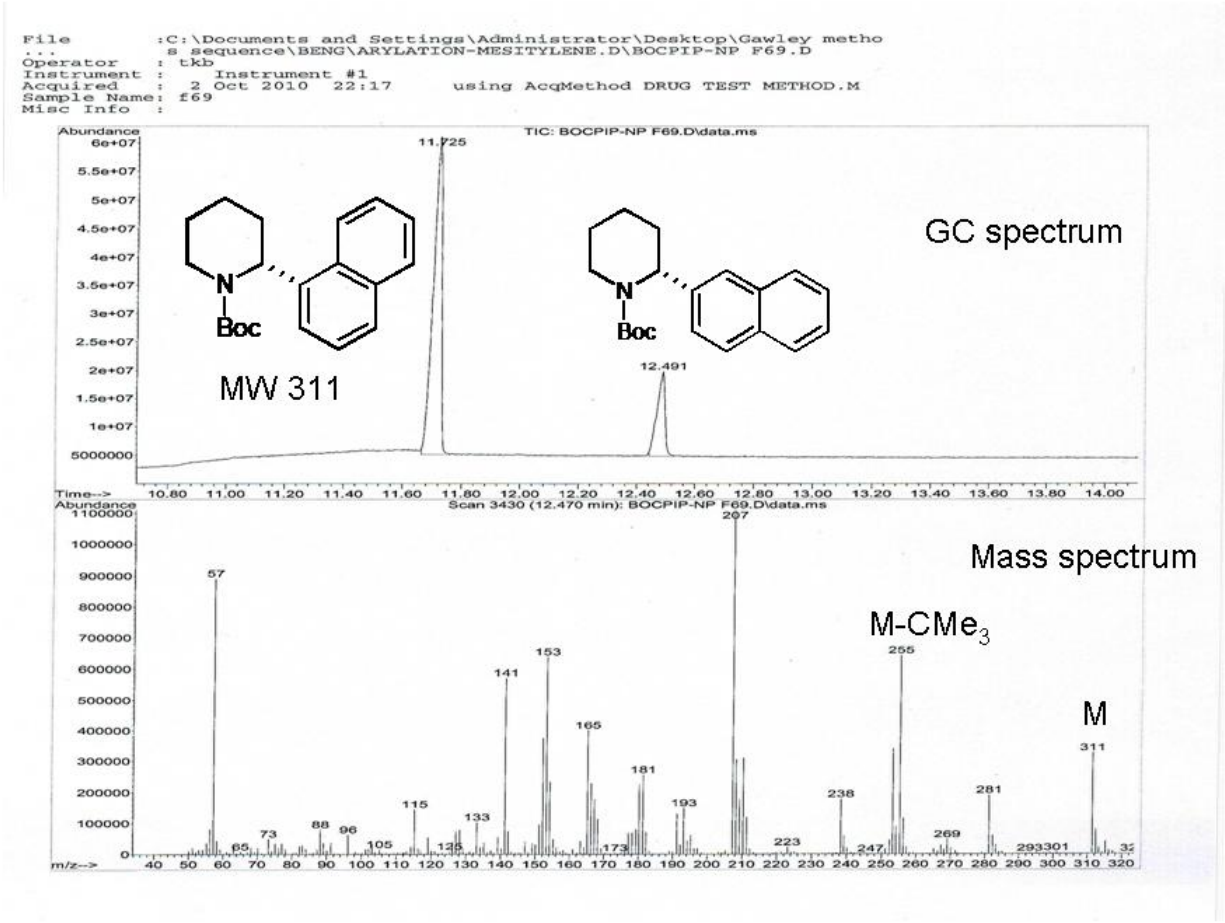
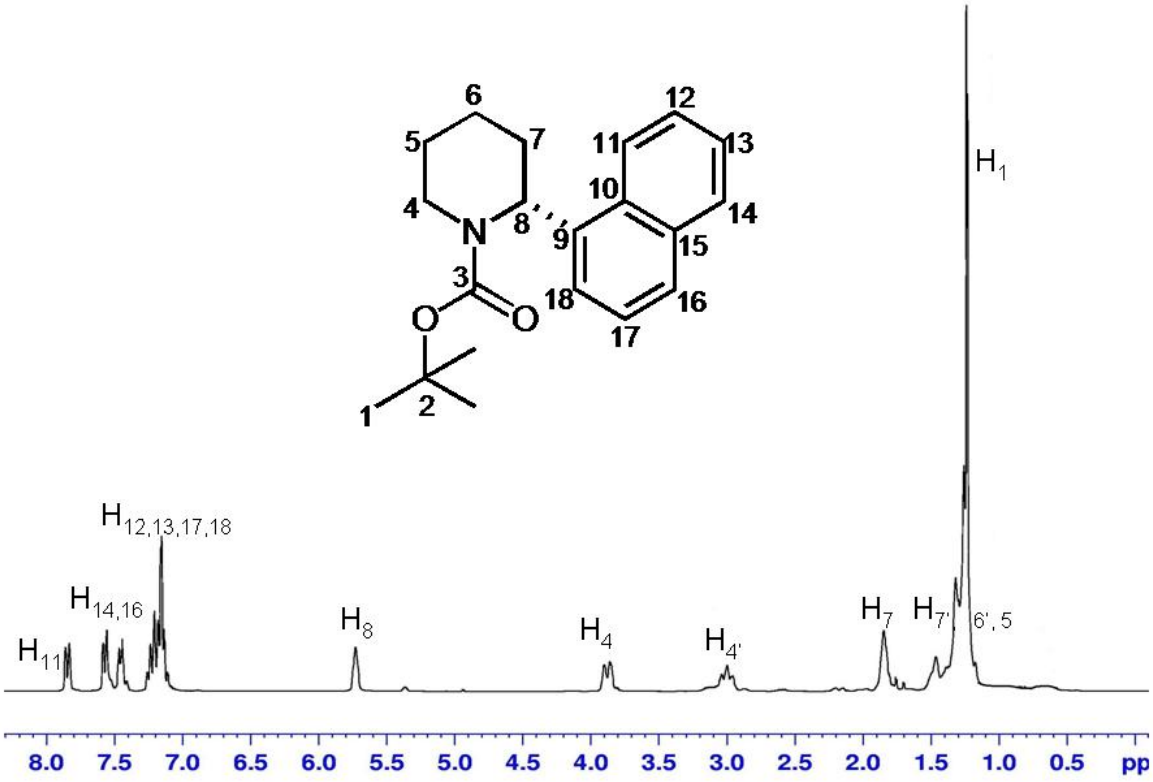
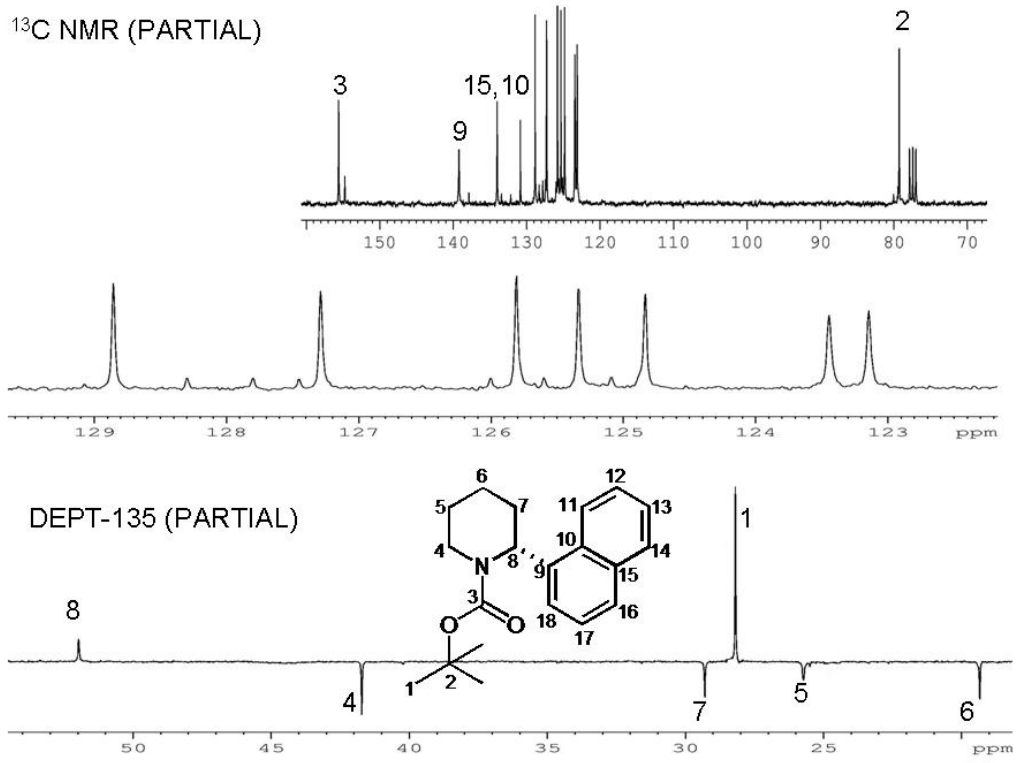
mAU
1.847
Area: 591.758
2.546
Area: 577.198
LDAD1 B, LDAD B, Sig=254,16 Ref=360,100 (F:\BKT0776.D)
2.578
Area: 228.759
1.944
Area: 16.0092
N
Boc
5/2010 9:52:35 PM Beng

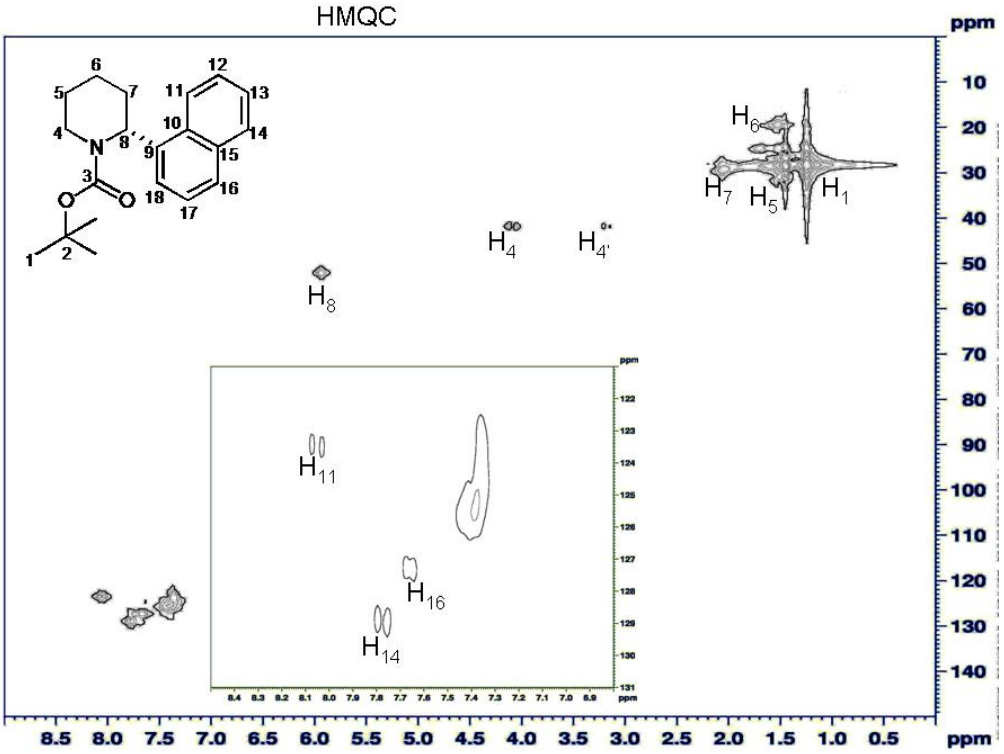

Current Chromatogram(s)
LDAD1 B, LDAD B, Sig=254,16 Ref=360,100 (F:\BKT0726.D)
mAU
6.674
7.990
LDAD1 B, LDAD B, Sig=254,16 Ref=360,100 (F:\BKT0731.D)
7.977
6.780
N
Boc
10/3/2010 3:30:48 PM Beng



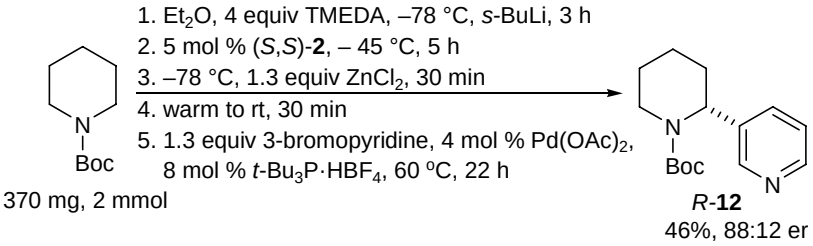
Note: During the synthesis of *R*-**11**, the aryl bromide contained small amounts of 2-bromonaphthalene, as such *R*-**11** was prepared in 95:5 er (see SFC trace above). The er was determined by CSP-SFC as follows: **Column:** Regis Technologies Pirkle-Whelk-O-1, **Flow Rate**: 2.0 mL/min, **Polarity Modifier %**: 3.0% EtOH, Outlet Pressure = **150 psi**, **Oven Temperature** = 35 ^{o}C. The minor enantiomer elutes after ~6.7 min and the major enantiomer elutes after ~8.0 min. The above GC-MS is from one of the fractions during column chromatography. It doesn't reflect the exact ratio of the two regioisomers.


6
5
7
4
N
8
9
3
O
O
1
2
12
11
13
10
14
15
18
16
17
H1
H12,13,17,18
H14,16
H11
H8
H4
H4'
H7
H7'
6', 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
pp


13C NMR (PARTIAL)
3
15,10
9
2
150 140 130 120 110 100 90 80 70
129 128 127 126 125 124 123 ppm
DEPT-135 (PARTIAL)
8
4
7
5
6
1
50 45 40 35 30 25 ppm


HMQC
H8
H4
H4'
H6
H7
H5
H1
H11
H16
H14
ppm
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 ppm

4.10. Electrophilic quench with 3-Bromopyridine: synthesis of *R*-12



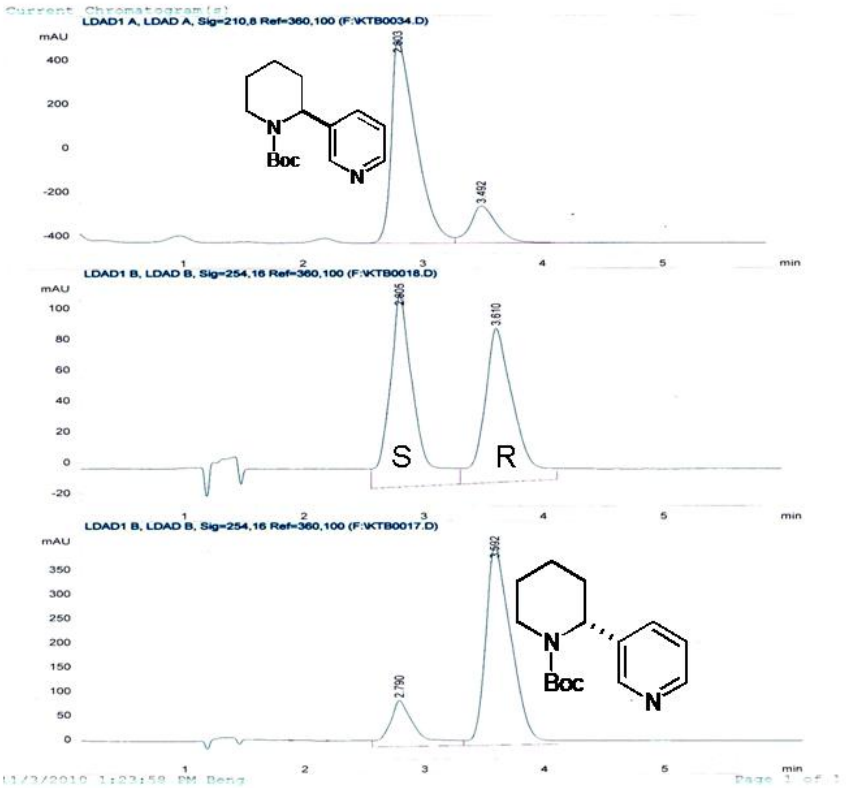
370 mg, 2 mmol

R-**12**

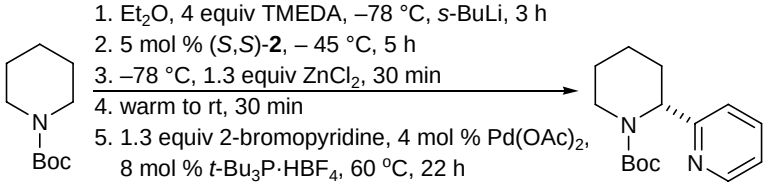
46%, 88:12 er

Using **General Procedure B**, *N*-Boc-piperidine (370 mg, 2.0 mmol), TMEDA (1.2 mL, 8.0 mmol, 4.0 equiv), Et_2O (10 mL), *s*-BuLi (2.4 mL, 1.0 M, 2.4 mmol, 1.2 equiv), (*S*,*S*)-**2** (21.4 mg, 0.1 mmol, 5 mol %, in 0.40 mL Et_2O pretreated with freshly titrated *s*-BuLi), $ZnCl_2$ (355 mg, 2.6 mmol, 1.3 equiv) in THF (2 mL), 3-bromopyridine (0.25 mL, 2.6 mmol, 1.3 equiv), $Pd(OAc)_2$ (20 mg, 0.08 mmol, 4 mol %) and *t*-$Bu_3P{\cdot}HBF_4$ (46 mg, 0.16 mmol, 8 mol %) gave the crude product as an oil. Purification by silica gel column chromatography eluting with Hexane/EtOAc (70:30) afforded 241 mg of the pure product as an oil in 46% yield and 88:12 er, $[\alpha]_D^{22}$ +88.6 (*c* = 1, $CHCl_3$) spectroscopic data as reported.[12] ^1H NMR (300 MHz, $CDCl_3$) δ = 8.51 (br, s, 2H), 7.54 (t, 1H), 7.32–7.21 (m, 1H), 5.47 (br, s, 1H), 4.1 (d, 1H), 2.87–2.68 (m, 1H), 2.29 (d, 1H), 1.99–1.87 (m, 1H), 1.71–1.33 (m, 13H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 155.7, 148.3, 147.0, 136.4, 134.9, 123.9, 80.1, 47.1, 40.6, 28.8, 28.2, 25.7, 19.7

CSP-SFC



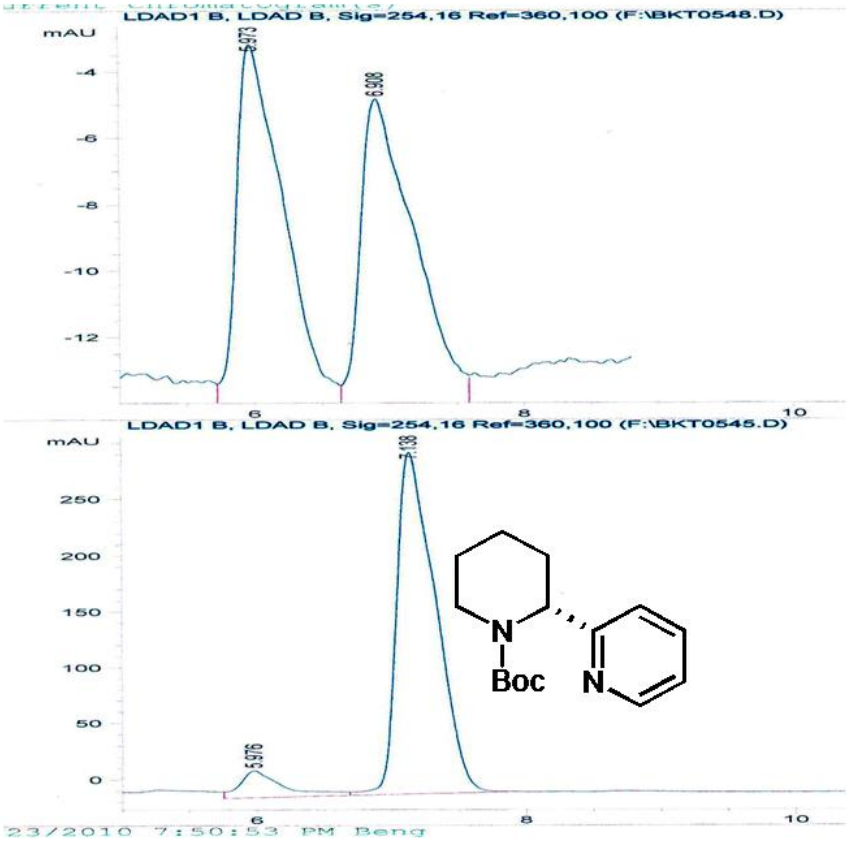
4.11. Electrophilic quench with 2-Bromopyridine: Synthesis of *R*-13

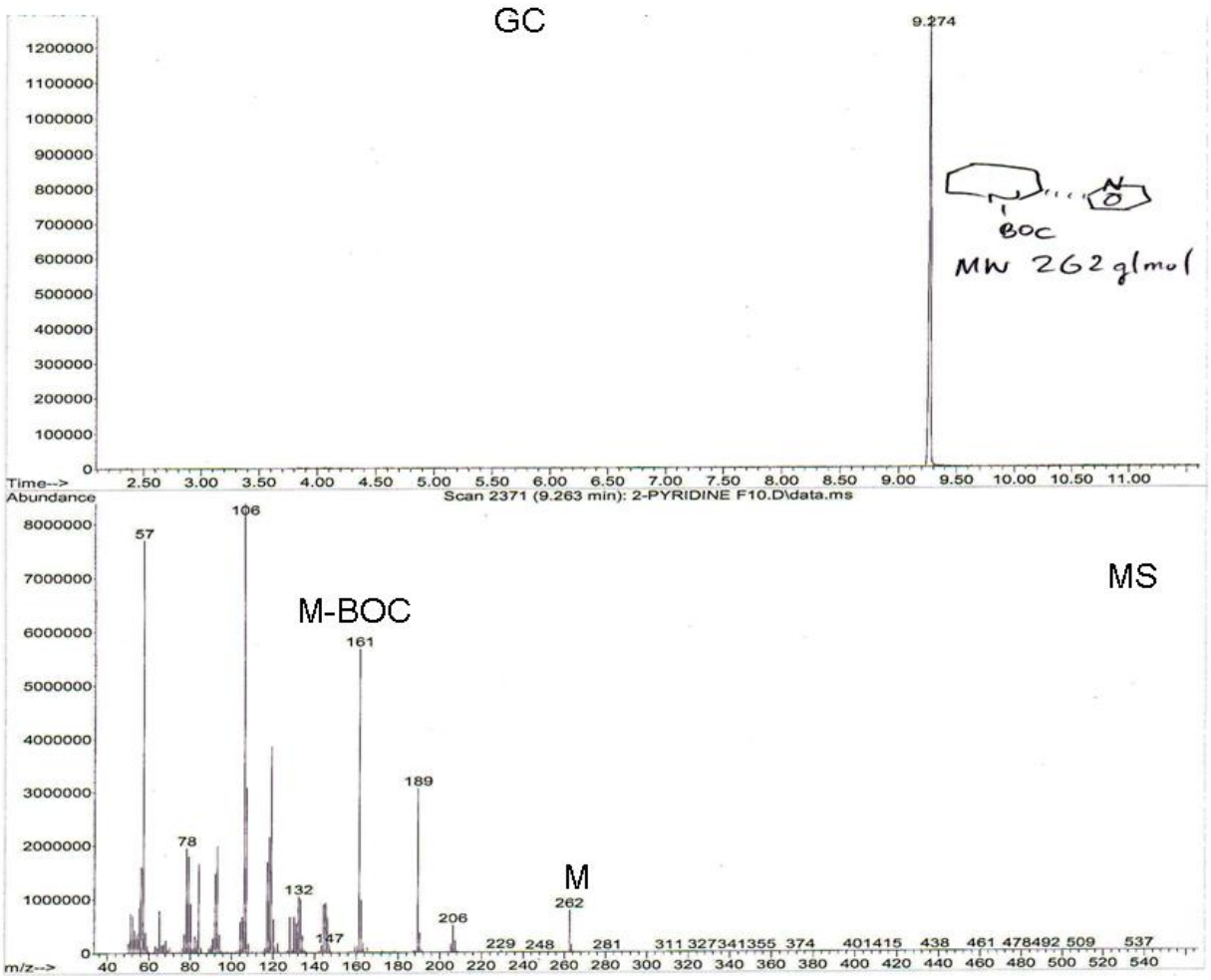


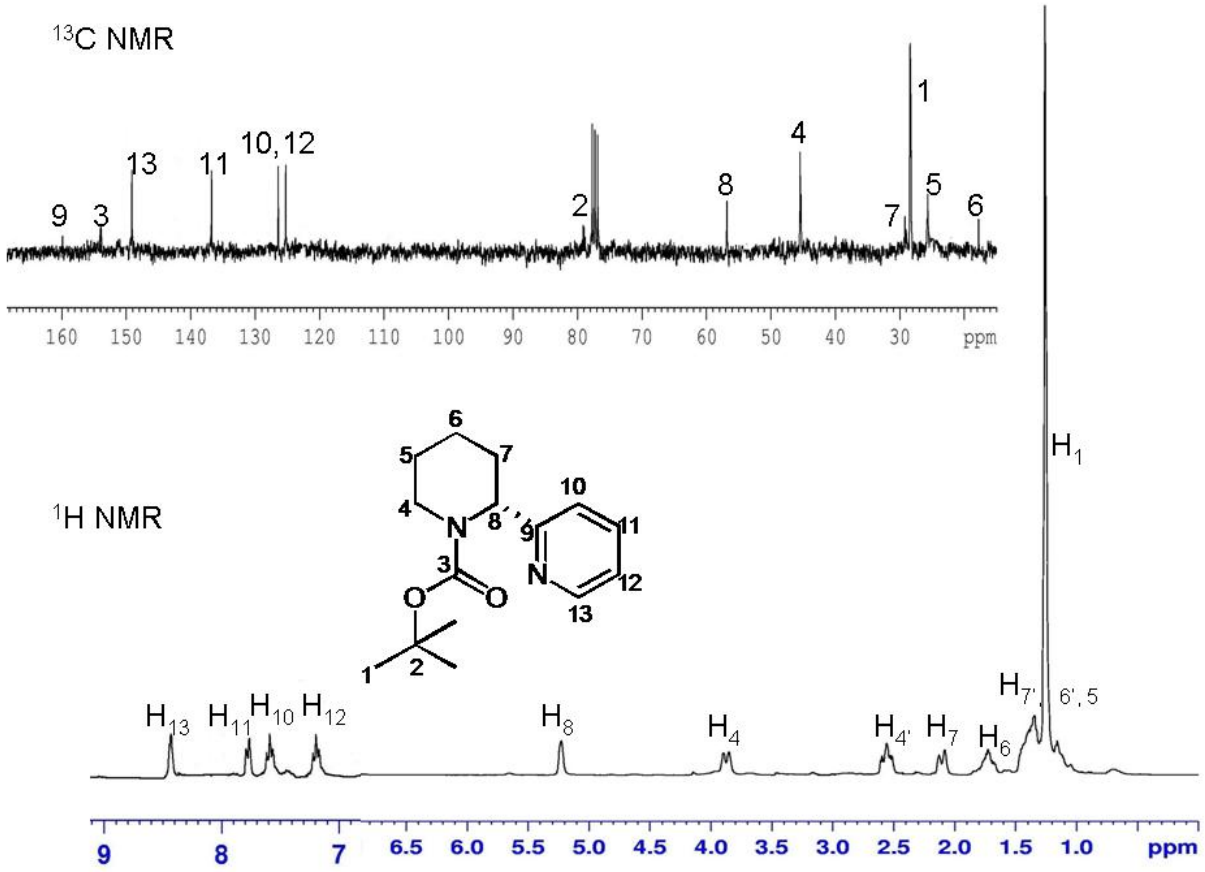
Using **General Procedure B**, *N*-Boc-piperidine (370 mg, 2.0 mmol), TMEDA (1.2 mL, 8.0 mmol, 4.0 equiv), Et_2O (10 mL), *s*-BuLi (2.4 mL, 1.0 M, 2.4 mmol, 1.2 equiv), (*S*,*S*)-**2** (21.4 mg, 0.1 mmol, 5 mol %, in 0.40 mL Et_2O pretreated with freshly titrated *s*-BuLi), $ZnCl_2$ (355 mg, 2.6 mmol, 1.3 equiv) in THF (2 mL), 2-bromopyridine (0.25 mL, 2.6 mmol, 1.3 equiv), $Pd(OAc)_2$ (20 mg, 0.08 mmol, 4 mol %) and *t*-$Bu_3P{\cdot}HBF_4$ (46 mg, 0.16 mmol, 8 mol %) gave the crude product as an oil. Purification by silica gel column chromatography eluting with Hexane/EtOAc (70:30) afforded 262 mg of the pure product as an oil in 50% yield and 93:7 er; $[\alpha]_D^{22}$ +93.1 (*c* =

1, $CHCl_3$) The er was determined by CSP-SFC as follows: **Column:** Daicel Chiralcel OD-H, **Flow Rate** = 2.0 mL/min, **Polarity Modifier** = 2.0% EtOH. The minor enantiomer elutes after ~6 min and the major enantiomer elutes after 7 min.

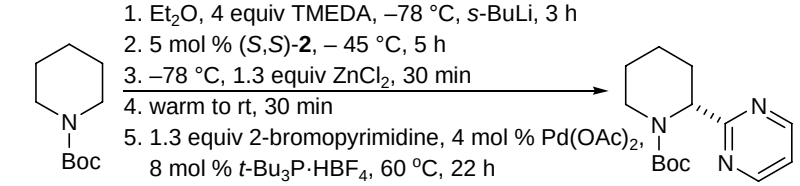
CSP-SFC




GC
9.274
BOC
MW 262 g/mol
Time-->
Abundance
Scan 2371 (9.263 min): 2-PYRIDINE F10.D\data.ms
MS
M-BOC
M
106
57
161
189
78
132
206
262
147
m/z-->



4.12. Electrophilic quench with 2-Bromopyrimidine: Synthesis of *R*-14

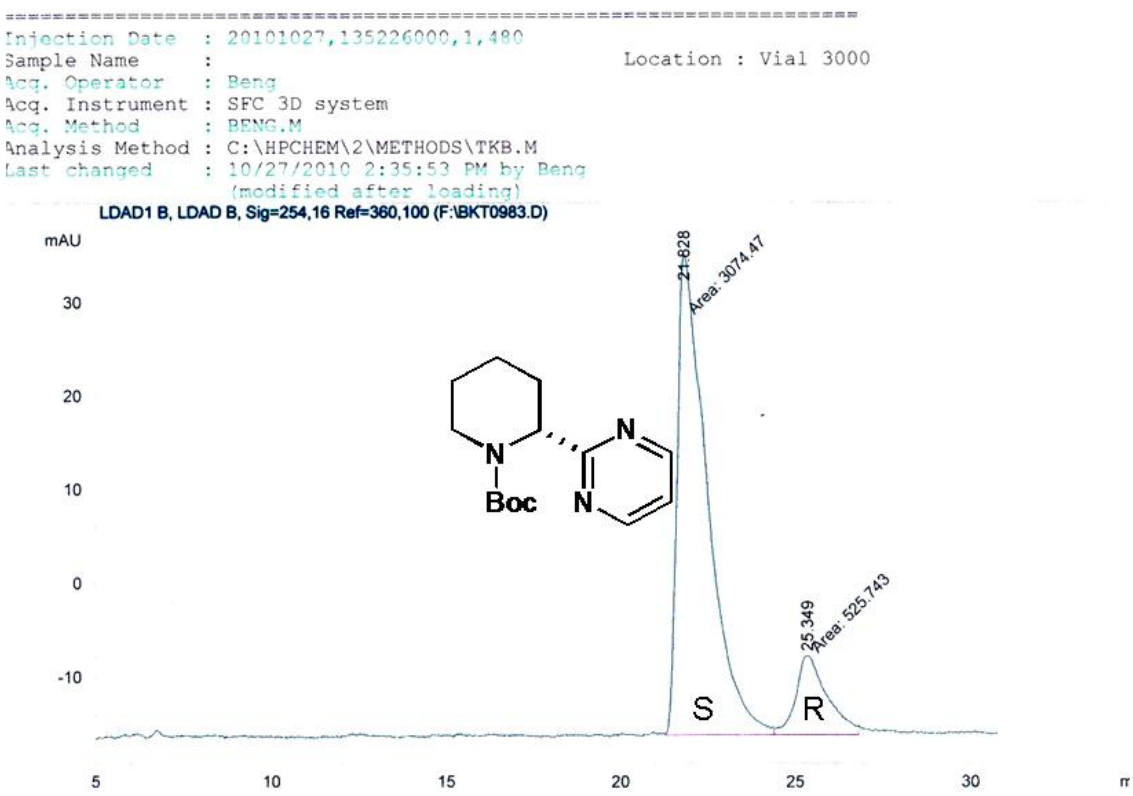


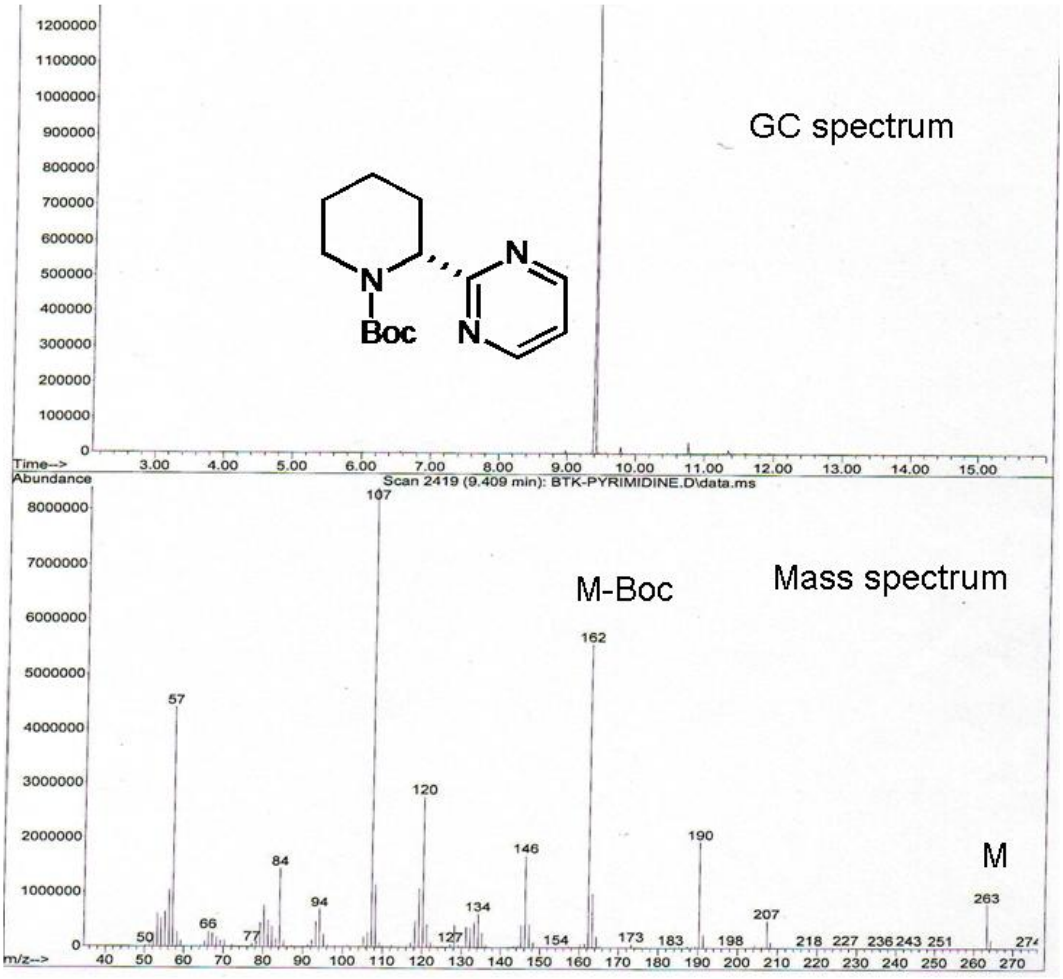
R-**14**
53%, 85:15 er

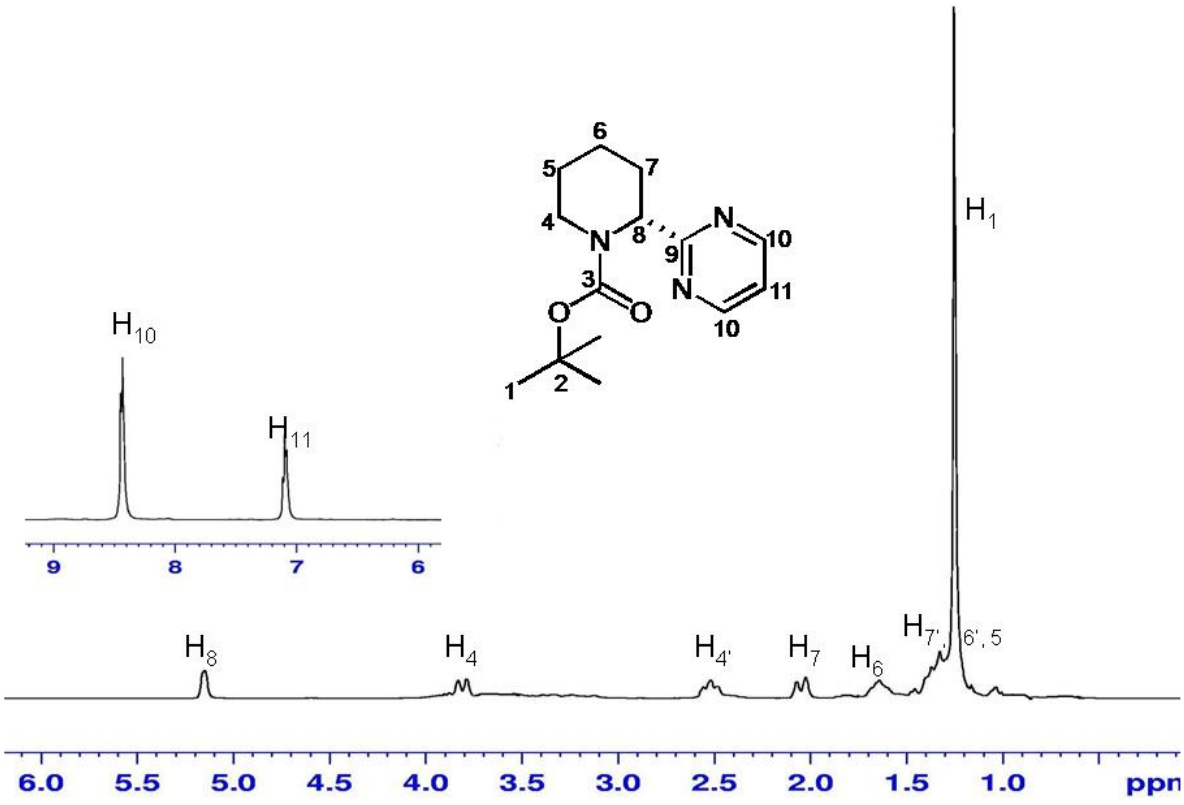
Using **General Procedure B**, *N*-Boc-piperidine (370 mg, 2.0 mmol), TMEDA (1.2 mL, 8.0 mmol, 4.0 equiv), Et_2O (10 mL), *s*-BuLi (2.4 mL, 1.0 M, 2.4 mmol, 1.2 equiv), (*S*,*S*)-**2** (21.4 mg, 0.1 mmol, 5 mol %, in 0.40 mL Et_2O pretreated with freshly titrated *s*-BuLi), $ZnCl_2$ (355 mg, 2.6 mmol, 1.3 equiv) in THF (2 mL), 2-bromopyrimidine (413 mg, 2.6 mmol, 1.3 equiv), $Pd(OAc)_2$ (20 mg, 0.08 mmol, 4 mol %) and *t*-$Bu_3P{\cdot}HBF_4$ (46 mg, 0.16 mmol, 8 mol %) gave the crude product as an oil. Purification by silica gel column chromatography eluting with Hexane/EtOAc (60:40) afforded 278 mg of the pure product as an oil in 53% yield and 85:15 er; $[\alpha]_D^{22}$ +75.6 (*c*

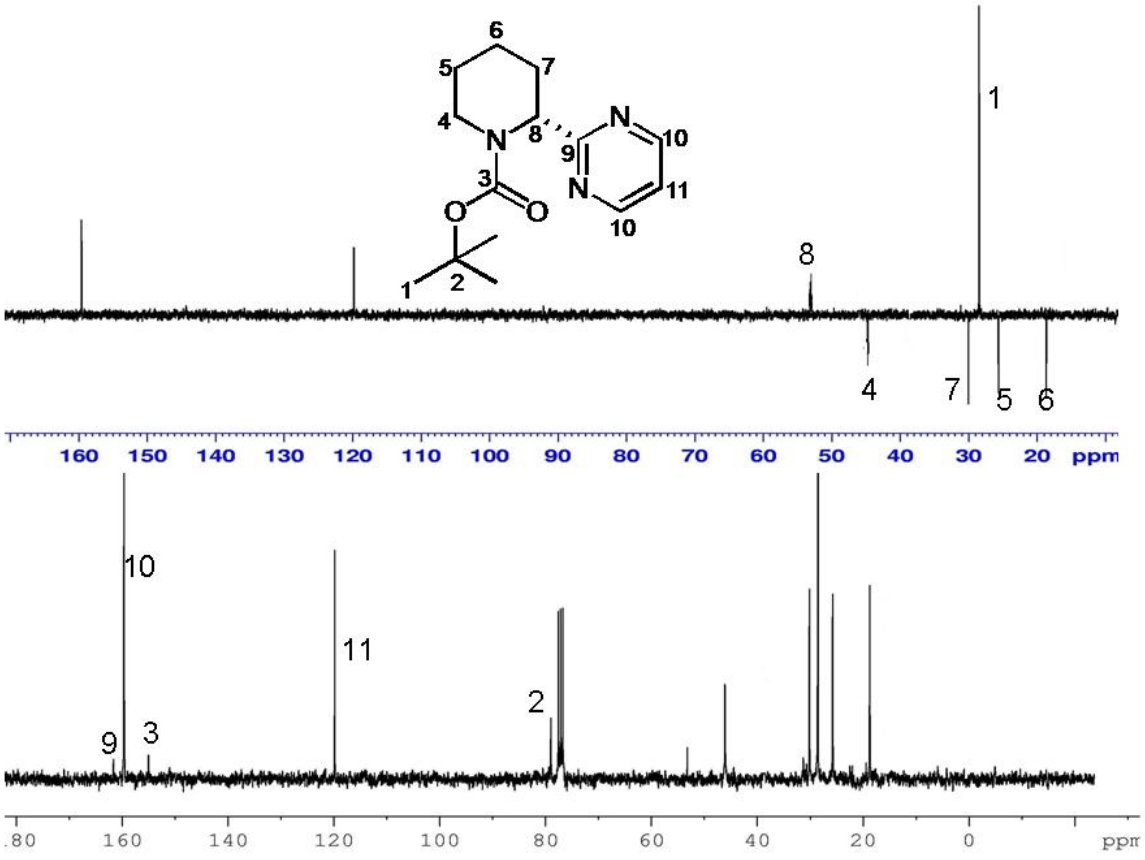
= 1, $CHCl_3$) The er was determined by CSP-SFC as follows: **Column:** Pirkle-Whelk-O-1, **Flow Rate**: 1.0 mL/min, **Polarity Modifier %**: 1.0% EtOH, Outlet Pressure **= 150 psi**, **Oven Temperature** = 35 ^{o}C. The major enantiomer elutes after ~21.8 min and the minor enantiomer elutes after ~25.3 min.

CSP-SFC




GC spectrum
Boc
N
N
Time-->
Abundance
Scan 2419 (9.409 min): BTK-PYRIMIDINE.D\data.ms
Mass spectrum
M-Boc
M
m/z-->


H10
H11
9
8
7
6
6
5
7
4
N
8''
N
10
9
N
11
3
O
O
10
1
2
H1
H8
H4
H4'
H7
H6
H7'
6',5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm



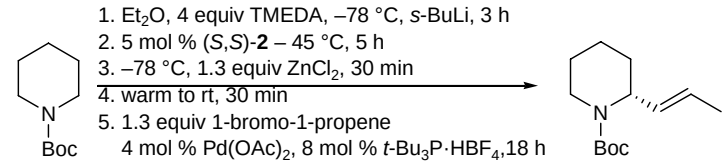
5. Synthesis of (*S*)-anabasine

To *N*-Boc-(*S*)-(-)-anabasine of 90:10 er (150 mg, 0.58 mol) dissolved in CH_2Cl_2 (3.0 mL), was added CF_3CO_2H (0.25 mL) under argon at room temperature. The mixture was stirred for 10 h at this temperature and concentrated in vacuo to obtain the salt. The salt was basified to pH 10 – 12 with 20% $NaOH_{(aq)}$. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 5 mL). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure to give 92 mg of (*S*)-(-)-anabasine in 100% yield. $[\alpha]_D^{22}$ −73.4 (*c* = 1.0, MeOH), lit.[16d] $[\alpha]_D^{20}$ −80 (*c* = 0.91, MeOH); all other spectroscopic data as reported.[16] ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.57 (1H, s), 8.47 (1H, d), 7.77 (1H, d), 7.32–7.15 (1H, m), 3.62 (1H, d), 3.19 (1H, d), 2.79 (1H, t), 2.12–1.42 (6H, m); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 148.6, 140.6, 134.2, 123.5, 59.8, 47.6, 34.8, 25.7, 25.2.

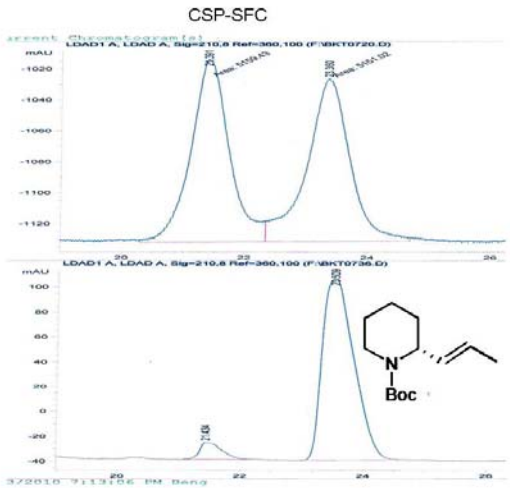
Note: (*R*)-(+)-anabasine was synthesized in the same was as the *S*-enantiomer; $[\alpha]_D^{22}$ −70.9 (*c* = 1.0, MeOH)

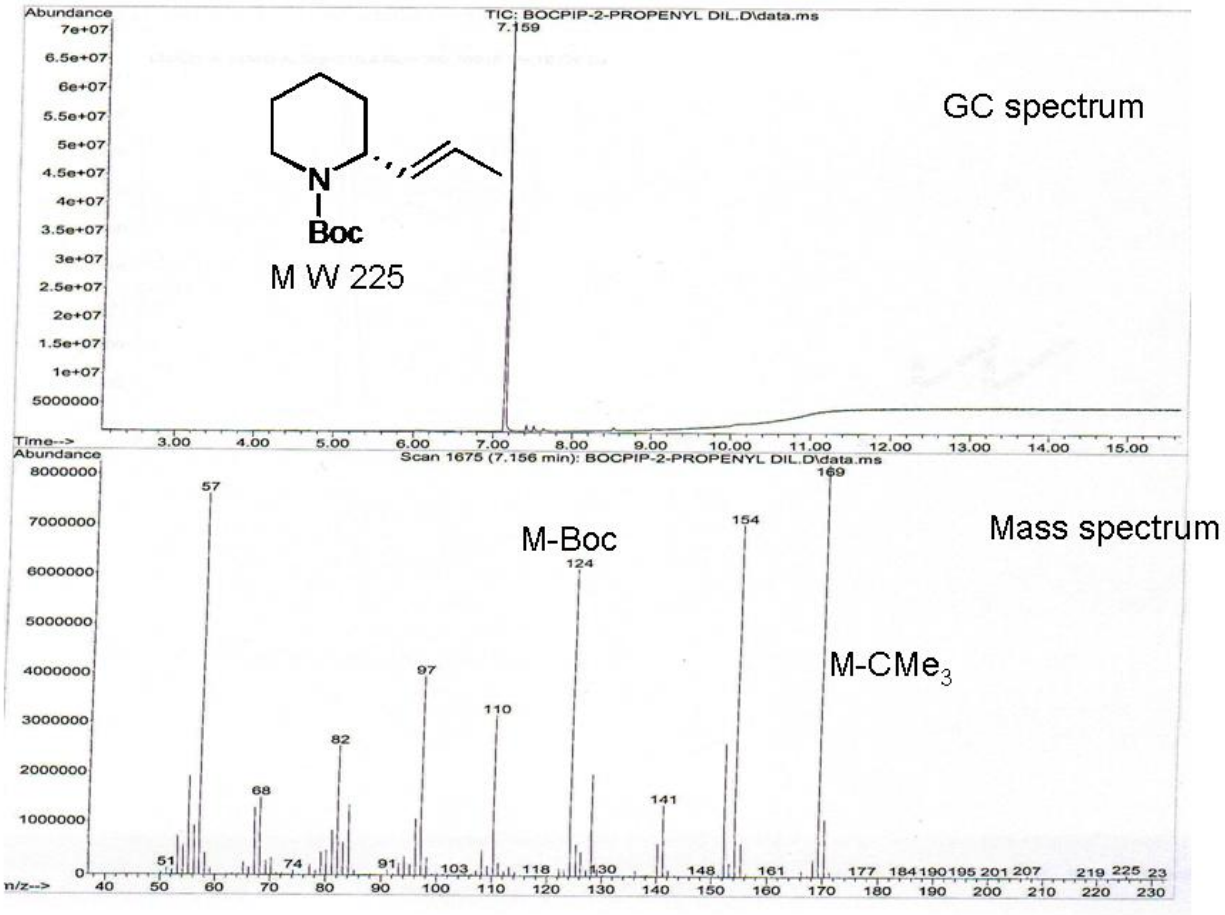
6.0. Vinylation of *N*-Boc-piperidine

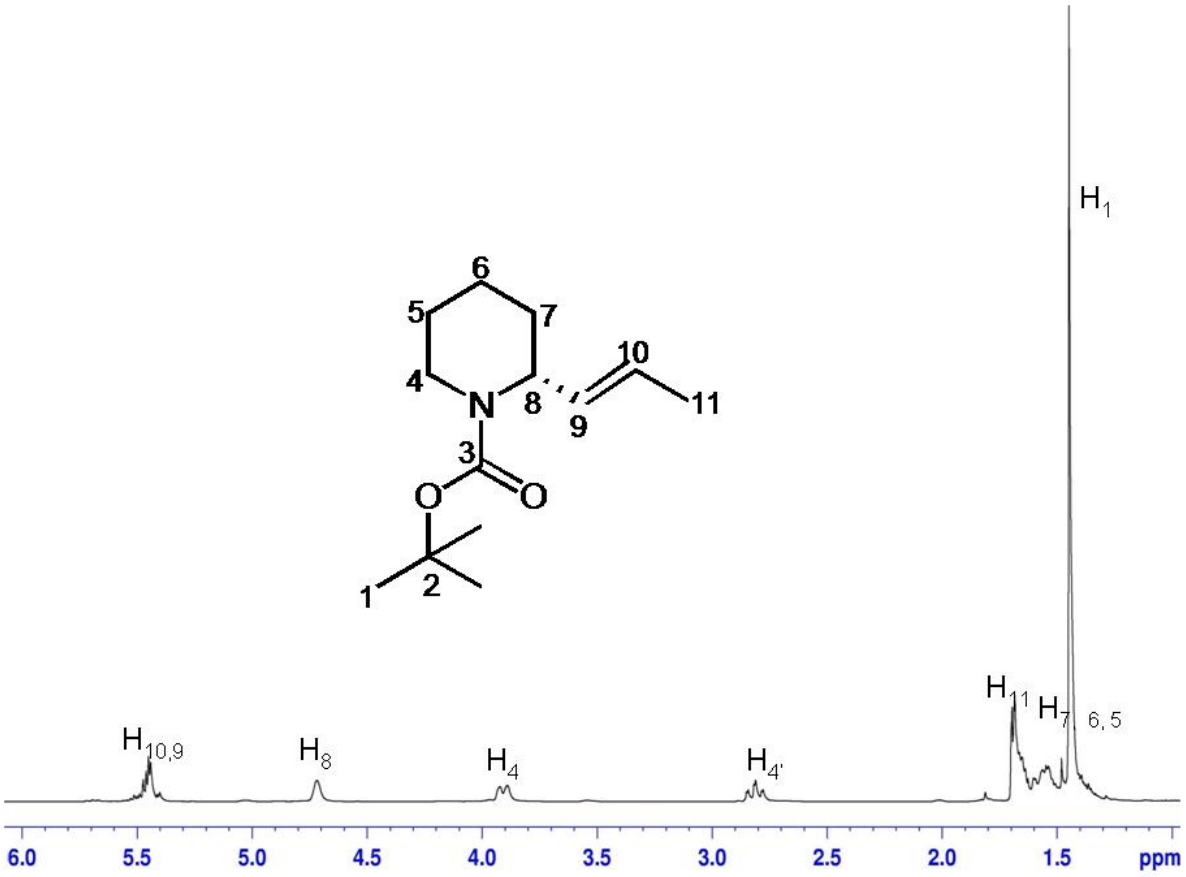
6.1. Electrophilic quench with 1-bromo-1-propene: Synthesis of *R*-15

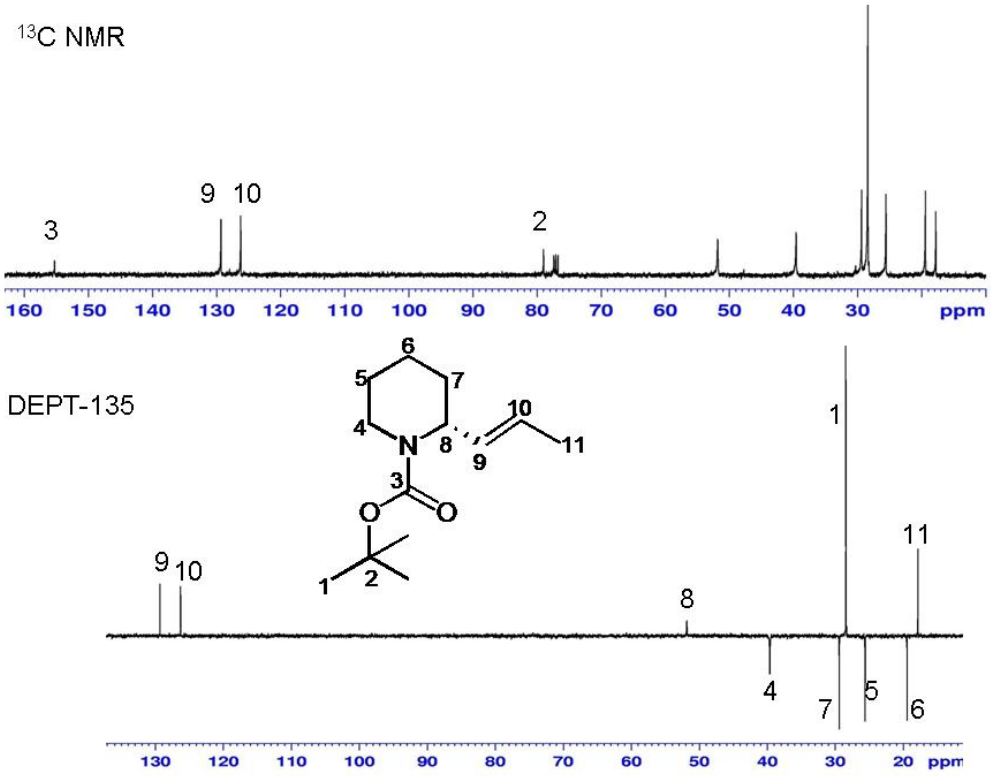


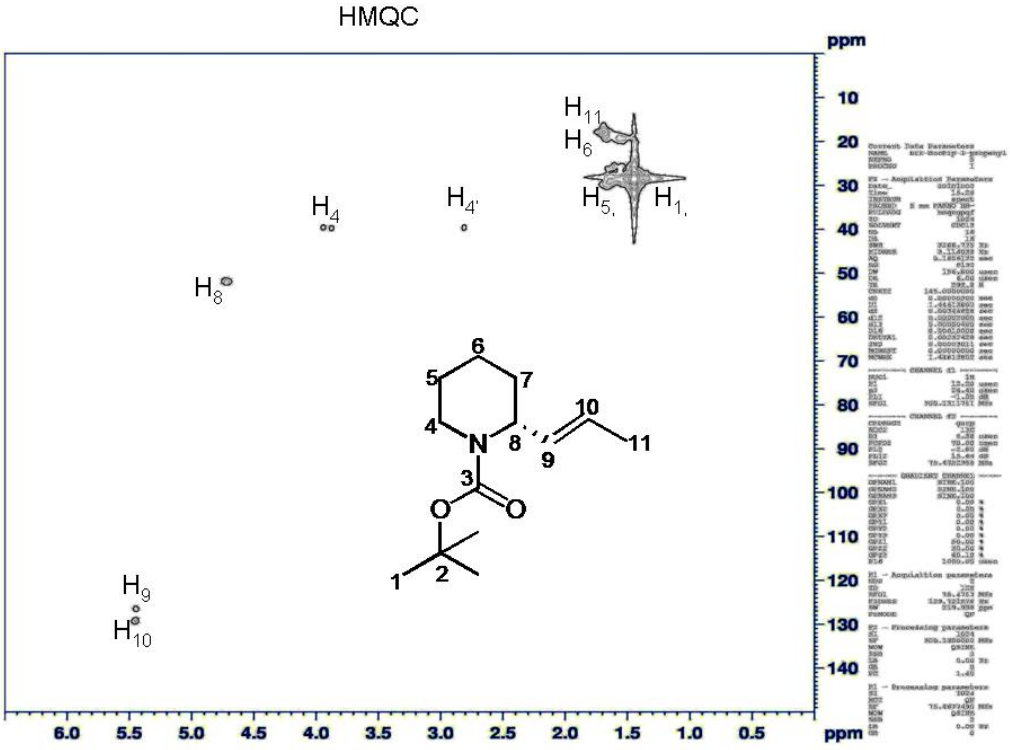
Using **General Procedure A**, *N*-Boc-piperidine (370 mg, 2.0 mmol), TMEDA (1.2 mL, 8.0 mmol, 4.0 equiv), Et_2O (10 mL), *s*-BuLi (2.4 mL, 1.0 M, 2.4 mmol, 1.2 equiv), (*S*,*S*)-**2** (21.4 mg, 0.1 mmol, 5 mol %, in 0.40 mL Et_2O pretreated with freshly titrated *s*-BuLi), $ZnCl_2$ (355 mg, 2.6 mmol, 1.3 equiv) in THF (2 mL), 1-bromo-1-propene (315 mg, 0.22 mL, 2.6 mmol, 1.3 equiv), $Pd(OAc)_2$ (20 mg, 0.08 mmol, 4 mol %) and *t*-$Bu_3P{\cdot}HBF_4$ (46 mg, 0.16 mmol, 8 mol %) gave the crude product as an oil. Purification by silica gel column chromatography eluting with Hexane/EtOAc (98:2) afforded 284 mg of the pure product as an oil in 63% yield and 92:8 er; spectroscopic data as reported.[16] $[\alpha]_D^{22}$ 10.1 (*c* = 0.3, $CHCl_3$). The er was determined by CSP-SFC as follows: **Column:** Pirkle-Whelk-O-1, **Flow Rate**: 0.5 mL/min, **Polarity Modifier %**: 1.0% EtOH, Outlet Pressure = **150 psi**, **Oven Temperature** = 35 °C. The minor enantiomer elutes after ~21.4 min and the major enantiomer elutes after ~23.4 min. ^{1}H NMR (300 MHz; see HMQC for exact shifts): δ 5.53-5.45 (m, 2H), 4.72-4.70 (br, s, 1H), 3.75-3.70 (m, 1H), 2.78-2.74 (m, 1H), 1.65-1.38 (m, 9H), 1.45 (s, 9H); ^{13}C NMR (75.5 MHz): δ 155.6, 129.6, 126.5, 79.0, 51.3, 39.8, 29.3, 28.4 (3C), 25.5, 19.5, 13.1;



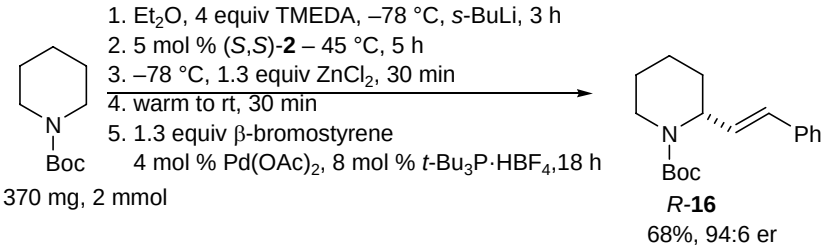

Abundance
TIC: BOCPIP-2-PROPENYL DIL.D\data.ms
7.159
GC spectrum
N
Boc
M W 225
Time-->
Abundance
Scan 1675 (7.156 min): BOCPIP-2-PROPENYL DIL.D\data.ms
Mass spectrum
M-Boc
M-CMe3
m/z-->


H1
6
5
7
10
4
N
8
11
9
3
O
O
1
2
H11
H7, 6, 5
H10,9
H8
H4
H4'
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
ppm


13C NMR
3
9 10
2
160 150 140 130 120 110 100 90 80 70 60 50 40 30 ppm
DEPT-135
1
11
9 10
8
4
7
5
6
130 120 110 100 90 80 70 60 50 40 30 20 ppm

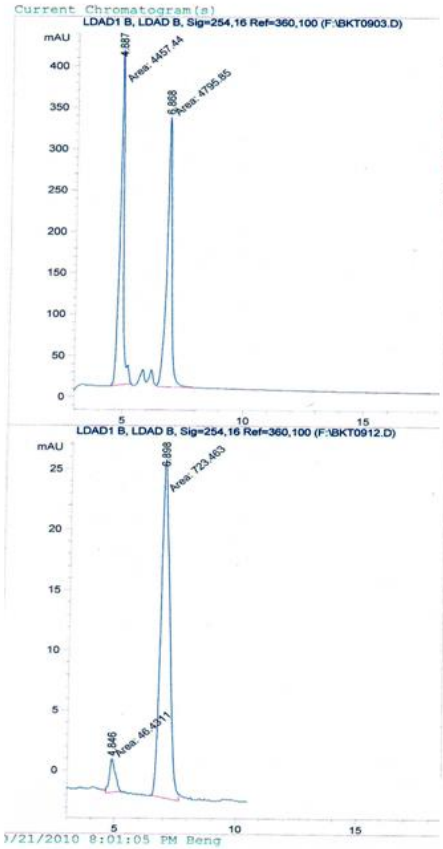

HMQC
ppm
H11
H6
H4
H4'
H5,
H1,
H8
H9
H10
6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm

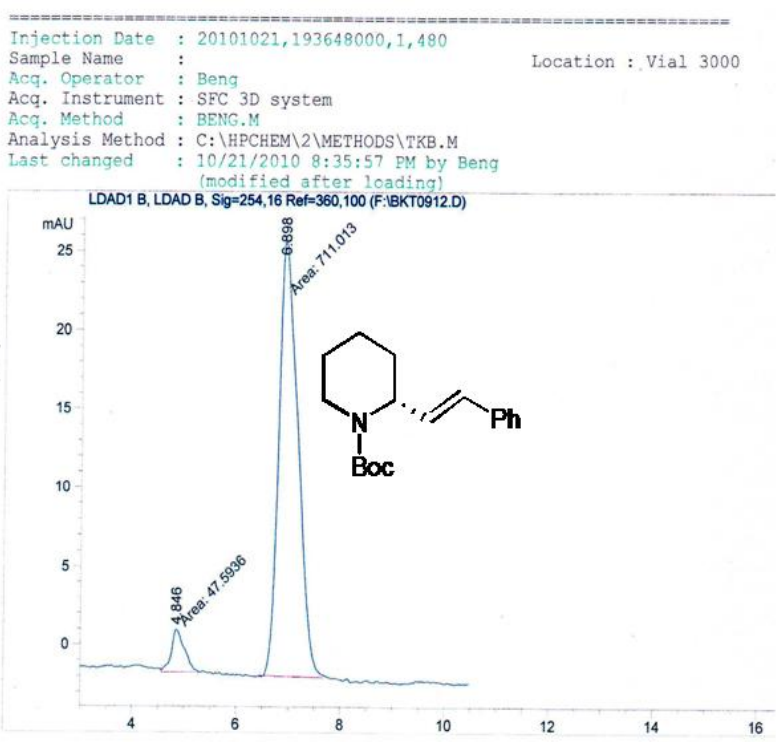
6.2. Electrophilic quench with β-bromostyrene: Synthesis of *R*-16



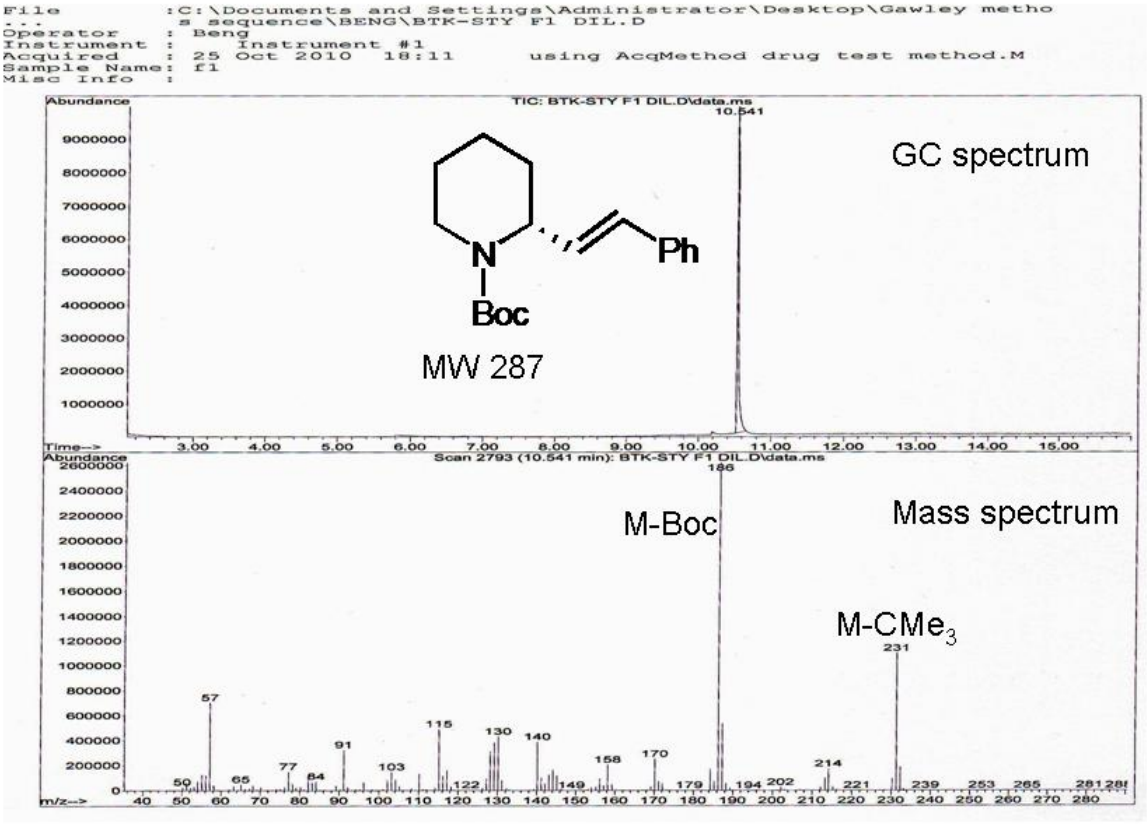
Using **General Procedure A**, *N*-Boc-piperidine (370 mg, 2.0 mmol), TMEDA (1.2 mL, 8.0 mmol, 4.0 equiv), Et_2O (10 mL), *s*-BuLi (2.4 mL, 1.0 M, 2.4 mmol, 1.2 equiv), (*S*,*S*)-**2** (21.4 mg, 0.1 mmol, 5 mol %, in 0.40 mL Et_2O pretreated with freshly titrated *s*-BuLi), $ZnCl_2$ (355 mg, 2.6 mmol, 1.3 equiv) in THF (2 mL), β-bromostyrene (476 mg, 0.35 mL, 2.6 mmol, 1.3 equiv), $Pd(OAc)_2$ (20 mg, 0.08 mmol, 4 mol %) and *t*-$Bu_3P{\cdot}HBF_4$ (46 mg, 0.16 mmol, 8 mol %) gave the crude product as an oil. Purification by silica gel column chromatography eluting with Hexane/EtOAc (98:2) afforded 390 mg of the pure product as an oil in 68% yield and 94:6 er; spectroscopic data as reported.[16] $[\alpha]_D^{22}$ 108.5 (*c* = 0.3, $CHCl_3$), lit[16] for *S*-**16** ($[\alpha]_D^{25}$ –116.9 (*c* = 0.3, $CHCl_3$). The er was determined by CSP-SFC as follows: **Column:** Regis Technologies Pirkle-Whelk-O-1, **Chiral Stationary Phase**: 4-(3,5-dinitrobenzamido) tetrahydrophenanthrene, covalently bound to silica, **Flow Rate**: 2.0 mL/min, **Polarity Modifier %**: 2.0% EtOH, Outlet Pressure **= 150 psi**, **Oven Temperature** = 35 °C. The minor enantiomer elutes after ~4.8 min and the major enantiomer elutes after ~6.9 min. ^{1}H NMR (300 MHz; exact chemical shifts obtained from HMQC): δ 7.38-7.15 (m, 5H), 6.39 (dd, 1H), 6.18 (dd, 1H), 4.95 (br, s, 1H), 3.98 (d, br, 1H), 2.95-2.88 (m, 1H), 1.82-1.52 (m, 6H), 1.46 (s, 9H); ^{13}C NMR (75.5 MHz): δ 155.5, 137.0, 130.7, 128.7, 128.5 (2C), 127.3, 126.2 (2C), 79.4, 52.2, 39.8, 29.5, 28.4 (3C), 25.5, 19.6.

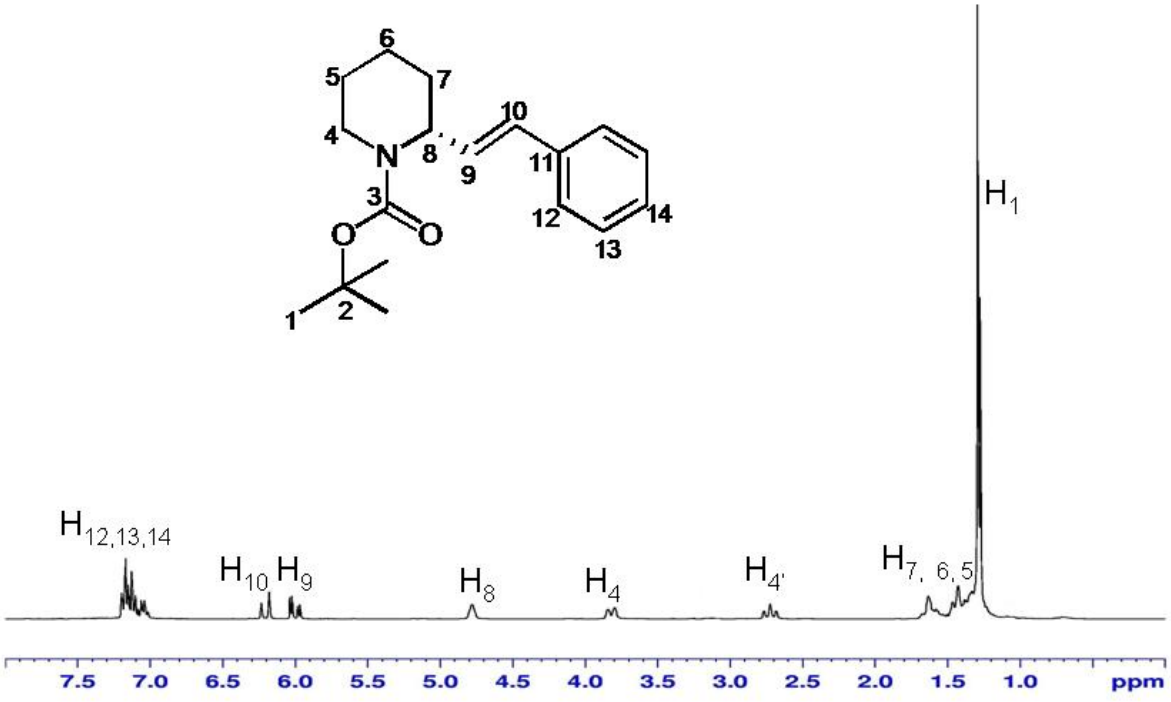
CSP-SFC


Current Chromatogram(s)
LDAD1 B, LDAD B, Sig=254,16 Ref=360,100 (F:\BKT0903.D)
mAU
4.887
Area: 4457.44
6.898
Area: 4795.85
LDAD1 B, LDAD B, Sig=254,16 Ref=360,100 (F:\BKT0912.D)
mAU
6.898
Area: 723.463
4.846
Area: 46.4311
/21/2010 8:01:05 PM Beng

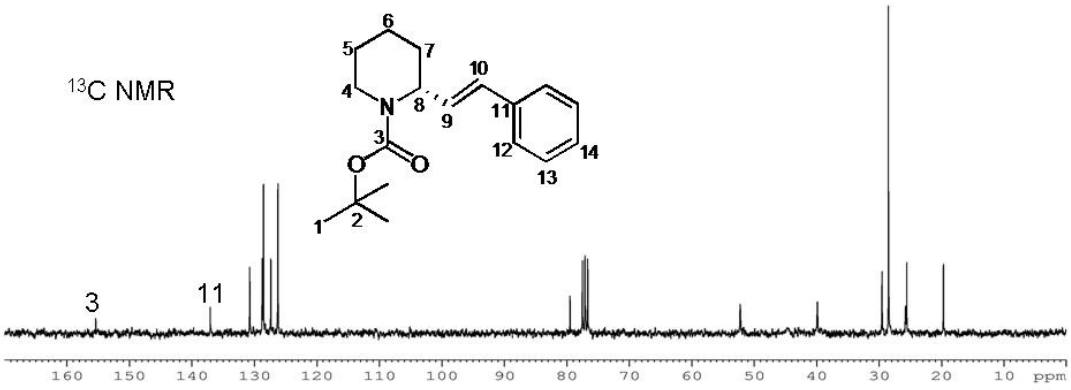

Injection Date : 20101021,193648000,1,480
Sample Name :
Location : Vial 3000
Acq. Operator : Beng
Acq. Instrument : SFC 3D system
Acq. Method : BENG.M
Analysis Method : C:\HPCHEM\2\METHODS\TKB.M
Last changed : 10/21/2010 8:35:57 PM by Beng
(modified after loading)
LDAD1 B, LDAD B, Sig=254,16 Ref=360,100 (F:\BKT0912.D)
mAU
6.898
Area: 711.013
4.846
Area: 47.5936
N
Boc
Ph

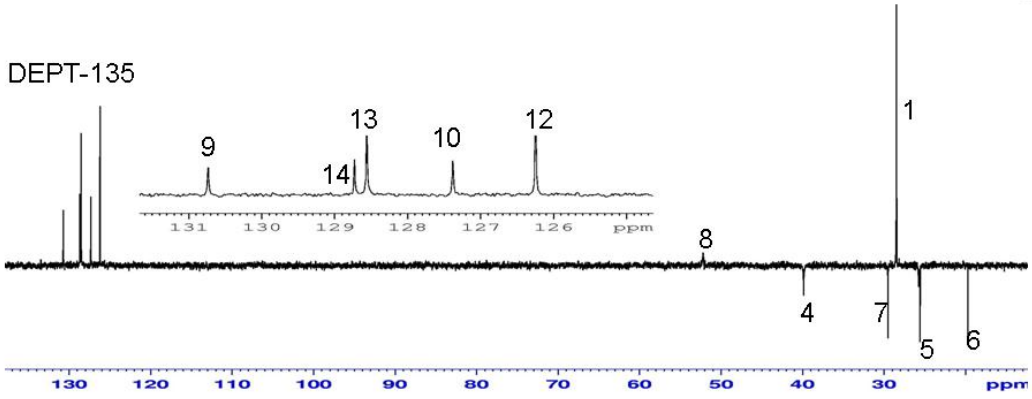
GC-MS

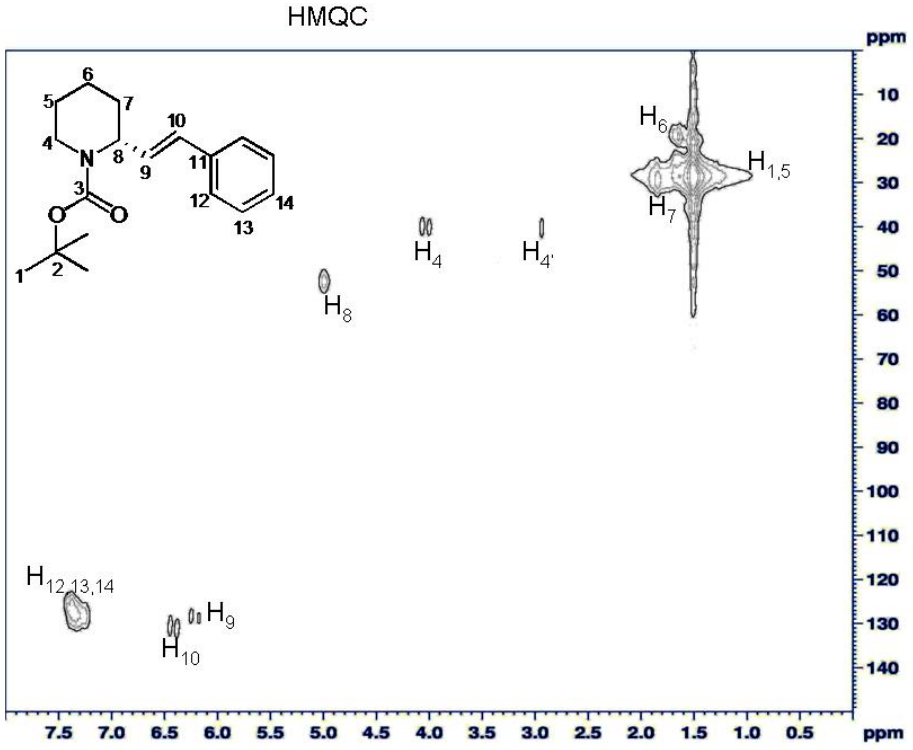

File :C:\Documents and Settings\Administrator\Desktop\Gawley metho
... s sequence\BENG\BTK-STY F1 DIL.D
Operator : Beng
Instrument : Instrument #1
Acquired : 25 Oct 2010 18:11 using AcqMethod drug test method.M
Sample Name: f1
Misc Info :
TIC: BTK-STY F1 DIL.D\data.ms
10.541
GC spectrum
N
Ph
Boc
MW 287
Scan 2793 (10.541 min): BTK-STY F1 DIL.D\data.ms
186
M-Boc
Mass spectrum
M-CMe3
231
Abundance
m/z-->



See full assignments on HMQC


^{13}C NMR
3
11
160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


DEPT-135
9
13
14
10
12
1
8
4
7
5
6
131 130 129 128 127 126 ppm
130 120 110 100 90 80 70 60 50 40 30 ppm


HMQC
H_6
$H_{1,5}$
H_7
H_4
$H_{4'}$
H_8
$H_{12,13,14}$
H_9
H_{10}
ppm
10 20 30 40 50 60 70 80 90 100 110 120 130 140
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 ppm

4.20. References

No-D NMR Spectroscopy

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2-Bromotoluene quench: *R*- and *S*-4

(4) None

4-Bromoveratrole quench: *R*-5

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(6) None

2-Bromomesitylene quench: *R*-7

(7) None

***p*-Bromoacetophenone quench: *R*-8**

(8) None

***p*-Bromobenzonitrile quench: *R*-9**

(9) None

4-Bromo-2-trifluoromethyl aniline quench: *R*-10

(10) None

1-Bromonaphthalene quench: *R*-11

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3-Bromopyridine quench: *R*-12

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2-Bromopyridine quench: *R*-13

(13) None

2-Bromopyrimidine quench: *R*-14

(14) None

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