

Supporting Information for:

Synthetic Applications and Inversion Dynamics of Configurationally Stable 2-Lithio-2-aryl-
Pyrrolidines and -Piperidines

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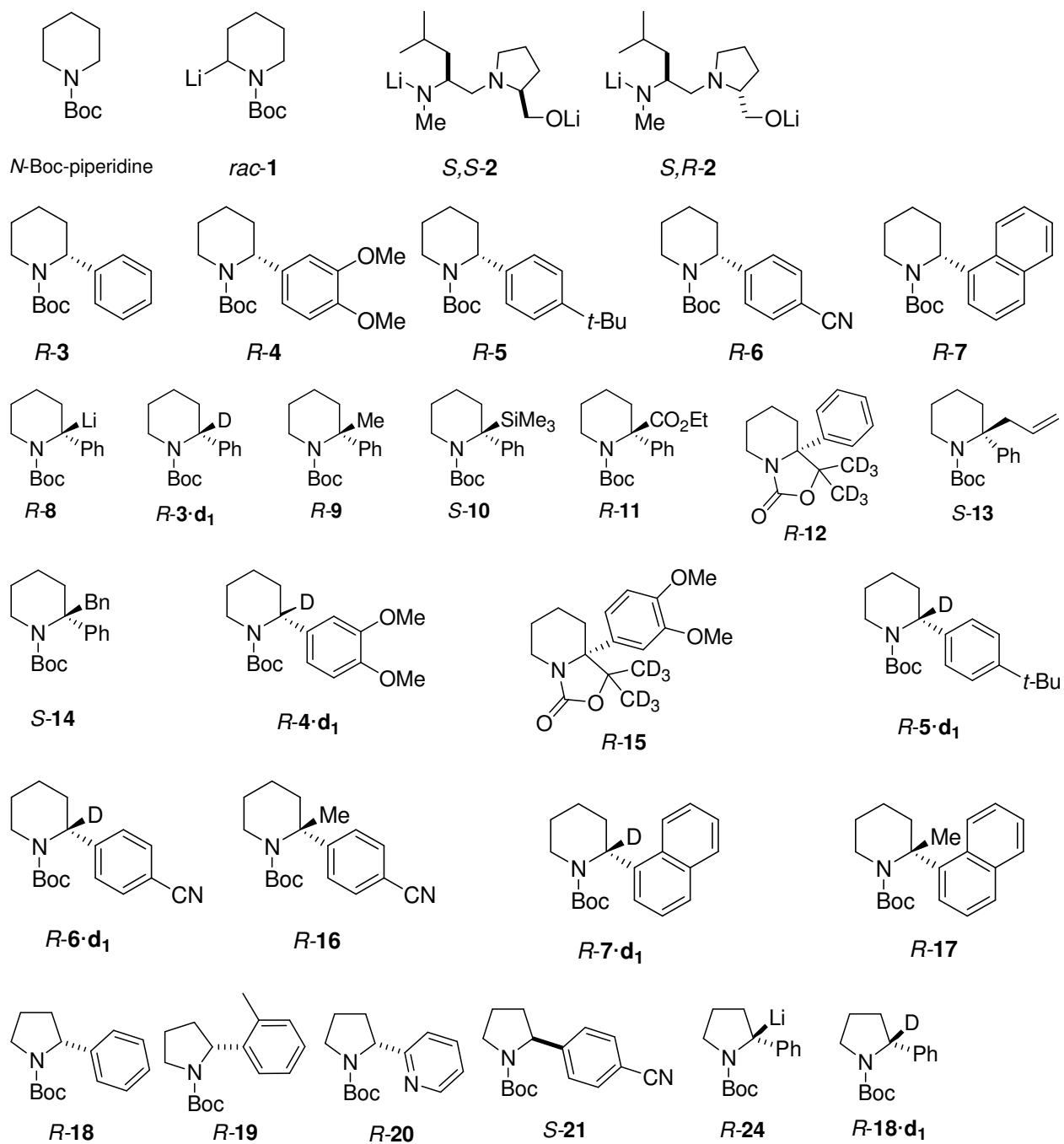
bgawley@uark.edu

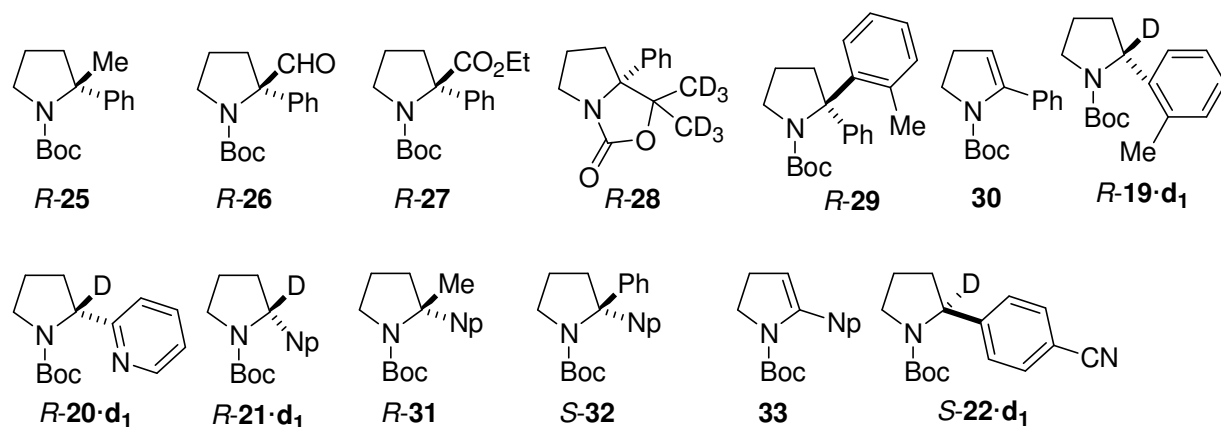
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1. Structures





2. Experimental Section

All experiments involving organolithium reagents were carried out under an inert atmosphere of argon or nitrogen and using freshly distilled solvents. Et₂O and THF were distilled from sodium benzophenone ketyl. TMEDA and the conjugate acid of (*S,S*)-**2** was purified by Kugelrohr distillation from CaH₂. Solutions of ZnCl₂ (1 M in Et₂O or THF) were obtained from commercial sources. Solid ZnCl₂, CuCN, LiCl were flame-dried under vacuum prior to use. The concentration of commercial *s*-BuLi (solution in cyclohexane) and *n*-BuLi were determined prior to use by No-D NMR spectroscopy.¹ All electrophiles that were not newly purchased were distilled immediately before use. Newly purchased electrophiles with less than 98.5% purity were also distilled immediately before use. Column chromatography was performed on silica gel (230-400 mesh). Thin-layer chromatography (TLC) was performed on silica plates. Visualization of the TLC plates was aided by UV irradiation at 254 nm or by KMnO₄ staining. For enantiomer ratio (er) analyses, authentic racemic compounds were used to establish the method of separation of the enantiomers. The temperature was controlled by a thermostatted cooling coil and all reported temperatures were internal to a reaction vessel. The enantiomer ratios were determined by CSP-SFC. The following chiral columns were utilized; Regis Technologies Pirkle-Whelk-O-1 and Daicel Chiralcel OD-H. In some cases the enantiomer ratios were determined by CSP-GC on a β-cyclodextrin-permethylated 120 fused silica capillary column [30 m × 0.25 mm i.d., 20% permethylated β-cyclodextrin in SPB-35 poly(35% diphenyl/65% dimethyl)siloxane. Unless otherwise indicated, ¹H, ¹³C, DEPT-135, COSY 45, and HMQC NMR spectra were acquired using CDCl₃ as solvent at ambient temperature. Chemical shifts are quoted in parts per million (ppm).

N-Boc-piperidine, the alcohol precursors to ligands (*S,S*)-**2** and (*S,R*)-**2** were synthesized according to previously reported methods.^{2,3}

2.1. General Procedure A: Catalytic Dynamic Resolution (CDR) of 2-lithio-*N*-Boc-piperidine followed by Transmetalation and Palladium-catalyzed Arylation

In an oven-dried, septum-capped 25 mL round bottom flask equipped with a stir bar, freshly distilled *N*-Boc-piperidine (1 mmol, 1.0 equiv) and freshly distilled TMEDA (4 mmol, 4.0 equiv) were dissolved in freshly distilled Et₂O under argon. The solution was cooled to –80 °C and *s*-BuLi (1.2 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 freshly distilled diamino alcohol, precursor of (*S,S*)-**2** (0.05 mmol, 5 mol%) in Et₂O was treated with *s*-BuLi (10 mol%). After complete deprotonation of *N*-Boc-piperidine as noted by 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. The mixture was cooled to –80 °C and a solution of ZnCl₂ (0.6 mL, 1.0 M solution in Et₂O, 0.6 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 (0.04 mmol, 4 mol%), *t*-Bu₃P·HBF₄ (0.08 mmol, 8 mol%) and the aryl bromide (1.1 mmol, 1.1 equiv) were added sequentially. After stirring for 18 h at room temperature, NH₄OH (5 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 5 mL Et₂O. The filtrate was washed with 1 M HCl_(aq) (10 mL), then with water (2 x 5 mL), dried over Na₂SO₄ and evaporated under reduced pressure to obtain the crude product. The er was determined before and after purification by column chromatography.

Note: The purity of reagents (especially the *chiral ligand*) is critical to achieving a resolution under either catalytic or stoichiometric conditions! We occasionally face this challenge as well.

2.2. General Procedure B: Lithiation of (*R*)-*N*-Boc-2-arylpiperidine or pyrrolidine followed by direct trapping with the electrophile

To an oven-dried, septum-capped round bottom flask equipped with a stir bar, was added freshly distilled TMEDA (4.0 equiv) and Et₂O under argon. The solution was cooled to –80 °C and a solution of *s*-BuLi in cyclohexane (1.0 equiv) was added (note 1). A precooled solution of the *N*-Boc-2-arylpiperidine (1.0 equiv) in Et₂O was added to the flask containing the TMEDA/*s*-BuLi mixture. After 30 min at this temperature, the mixture was quenched with the electrophile (~1.1

to 1.5 equiv). After 2 – 16 h, MeOH (note 2) was added and the mixture was stirred for 5 min. After warming to room temperature, 2 M HCl was added. The layers were separated and the aqueous layer was extracted with Et₂O. The combined organic layers were dried over MgSO₄ and evaporated to obtain the crude product. The er was determined before and after purification by column chromatography.

Note 1: Cooling the *s*-BuLi before substrate addition obviates the need for slow addition. Using GC-MS analysis, we detect very small amounts (if any) of the byproducts formed by attack of *s*-BuLi on the Boc-group.

Note 2: In some cases, MeOH was added after warming to room temperature.

2.3. General Procedure C: Lithiation of (*R*)-*N*-Boc-2-arylpiperidine followed by Copper-Mediated Allylation or Benzylation

To an oven-dried, septum-capped round bottom flask equipped with a stir bar, was added freshly distilled TMEDA (4.0 equiv) and Et₂O under argon. The solution was cooled to –80 °C and a solution of *s*-BuLi in cyclohexane (1.0 equiv) was added. A precooled solution of the *N*-Boc-2-arylpiperidine (1.0 equiv) in Et₂O was added to the flask containing the TMEDA/*s*-BuLi mixture. After 30 min, a solution of ZnCl₂ (1.3 equiv, 1.0 M in Et₂O) was added slowly. After 30 min, a solution of CuCN·2LiCl [prepared from CuCN (1.2 equiv) and LiCl (2.5 equiv)] in THF was added. After 30 min, allyl bromide or benzyl bromide (1.1 equiv) was added. The mixture was allowed to stir for 10 h at this temperature prior to addition of MeOH and warming to room temperature. A solution of NH₄Cl was added and the aqueous layer was extracted with Et₂O. The combined organic layers were dried over Na₂SO₄ and evaporated to give the crude product. The er was determined before and after purification by column chromatography.

2.4. General Procedure D: Lithiation of *N*-Boc-protected arylpiperidine with MeOD (or other electrophile): Screening reactions where only GC conversions are reported.

To an oven-dried, septum-capped 5 mL vial equipped with a stir bar, was added freshly distilled TMEDA (0.5 mL, 0.24 M solution in Et₂O, 4.0 equiv), *N*-Boc-2-arylpiperidine (0.5 mL, 0.06 M solution in Et₂O, 1.0 equiv) under argon. It was cooled to –80 °C and a solution of *s*-BuLi in cyclohexane (1.0 equiv) was added slowly. After 30 min, 0.10 mL of CH₃OD (or the desired screening electrophile) was added. The mixture was diluted with freshly distilled Et₂O (*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 chemical ionization (in some cases

electron impact ionization was utilized due to technical difficulties with the CI source). When the deprotonation is complete, there is a noticeable shift of the protonated molecular ion peak from MH^+ to MH^++1 . In most cases, the base peak was utilized for analytical purposes. The sample was also analyzed by CSP-SFC for er evaluation.

2.5. General Procedure E: Preparation of *N*-Boc-(arylmethyl)-(3-chloro) propylamines.⁴

To a suspension of NaH (800 mg, 60% dispersion in mineral oil), washed with three portions of hexane, in THF (40 mL) was added *N*-Boc-3-chloropropylamine (2.06 g, 10 mmol 1.0 equiv) in THF (10 mL) and the arylmethyl bromide (15 mmol). The suspension was heated at reflux for 8 h. Water (20 mL) was added, and the solution was extracted with Et₂O (3 x 40 mL). The combined organic layers were washed with water (20 mL), dried over MgSO₄, and evaporated to give the crude product, which was purified by chromatography.

2.6. General Procedure F: Lithiation-cyclization of *N*-Boc-(arylmethyl)-(3-chloro) propylamines in the presence of (–)-sparteine: Synthesis of (*S*)-*N*-Boc-2-arylpyrrolidines.⁴

To an oven-dried, septum-capped round bottom flask equipped with a stir bar, was added freshly distilled (–)-sparteine (1.5 equiv) and freshly distilled toluene under argon. The solution was cooled to –80 °C and a solution of *s*-BuLi in cyclohexane (1.5 equiv) was added. A precooled solution of the *N*-Boc-(arylmethyl)-(3-chloro) propylamine (1.0 equiv) in toluene was added to the flask containing the sparteine/*s*-BuLi mixture. After 7 h at this temperature, H₂O and Et₂O were added sequentially. The layers were separated and the aqueous layer was extracted with Et₂O. The combined organic layers were washed with 5% H₃PO₄ and with H₂O, dried over MgSO₄ and evaporated under reduced pressure to obtain the crude product. The er was determined before and after purification by column chromatography.

Note: A similar procedure was used to synthesize racemic *N*-Boc-2-arylpyrrolidines for facilitation of er analysis by CSP-SFC. In such cases TMEDA was used in place of (–)-sparteine and the reaction time was shortened to 3 h.

2.7. General Procedure G: Lithiation-Substitution of *N*-Boc-protected arylpyrrolidine with MeOD: Screening reactions where only GC conversions are reported.

To an oven-dried, septum-capped 5 mL vial equipped with a stir bar, was added freshly distilled TMEDA (0.5 mL, 0.06 M solution in Et₂O, 1.0 equiv), the desired aryl pyrrolidine (0.5 mL, 0.06 M solution in Et₂O, 1.0 equiv) under argon. It was cooled to –60 °C and a pre-titrated (by No-D NMR) solution of *n*-BuLi in hexanes (2.00 M, 1.0 equiv) was added down the side of the vial by

means of a microlitre syringe. After 3 h, 0.10 mL of CH₃OD, stored over molecular sieves, was added. The mixture was diluted with freshly distilled Et₂O (*ca* 1 mL). The ethereal layer was filtered through Celite, placed in a GC vial and analyzed by GC-MS for deuterium incorporation using chemical ionization (in some cases electron impact ionization was utilized due to technical difficulties with the CI source). The crude mixture was also analyzed by CSP-SFC for er evaluation. When the deprotonation is complete, there is a noticeable shift of the protonated molecular ion peak from MH⁺ to MH⁺+1. In most cases, the base peak was utilized for analytical purposes.

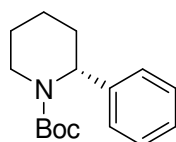
2.8. General Procedure H: Lithiation of (*R*)-*N*-Boc-2-arylpiperidine followed by direct trapping with the electrophile

To an oven-dried, septum-capped round bottom flask equipped with a stir bar, was added freshly distilled TMEDA (1.0 equiv) and Et₂O under argon. The mixture was cooled to -60 °C and a solution of *n*-BuLi in hexanes (1.0 equiv) was added. A precooled solution of the *N*-Boc-2-arylpiperidine (1.0 equiv) in Et₂O was added to the flask containing the TMEDA/*n*-BuLi mixture. After 3 h at -60 °C, the mixture was quenched with the electrophile (~1.1 to 1.5 equiv). After 2 – 16 h, depending on the electrophile, MeOH was added and the mixture was stirred for 5 min. After warming to room temperature, 2 M HCl was added. The layers were separated and the aqueous layer was extracted with Et₂O. The combined organic layers were dried over MgSO₄ and evaporated to obtain the crude product. The er was determined before and after column chromatography.

3. Synthesis of (*R*)-*N*-Boc-2-arylpiperidines

In the wake of recent publications from O'Brien et al⁵ and from Knochel and coworkers⁶, we have slightly modified the previously reported procedure for the enantioselective arylation of *N*-Boc-piperidine. The minor change is the decrease in the amounts of ZnCl₂ and the aryl bromide.

3.1. (*R*)-*N*-Boc-2-phenylpiperidine

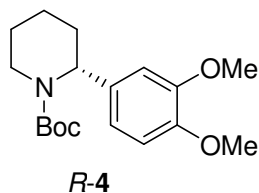


R-3

Using **General Procedure A**, *N*-Boc-piperidine (3700 mg, 20 mmol), TMEDA (12 mL, 80.0 mmol, 4.0 equiv), Et₂O (100 mL), *s*-BuLi (24 mL, 1.0 M, 24 mmol, 1.2 equiv), the alcohol

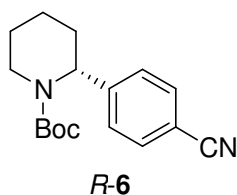
precursor of (*S,S*)-**2** (214 mg, 1.0 mmol, 5 mol%, in 4.0 mL Et₂O pretreated with freshly titrated *s*-BuLi), ZnCl₂ (12 mL, 1 M solution in Et₂O, 0.6 equiv), phenyl bromide (2.6 mL, 22 mmol, 1.1 equiv), Pd(OAc)₂ (200 mg, 0.8 mmol, 4 mol%) and *t*-Bu₃P·HBF₄ (460 mg, 1.6 mmol, 8 mol%) gave the crude product as an oil. Purification by silica gel column chromatography eluting with hexane-EtOAc (94:6) afforded 3.7 g of the pure product as an oil in 71% yield and 96:4 er; spectroscopic data as previously reported.³

3.2. (*R*)-*N*-Boc-2-(3,4-dimethoxy)phenylpiperidine



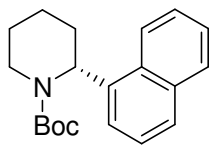
Using **General Procedure A**, *N*-Boc-piperidine (740 mg, 4 mmol), TMEDA (2.4 mL, 16.0 mmol, 4.0 equiv), Et₂O (20 mL), *s*-BuLi (3.4 mL, 1.4 M, 4.8 mmol, 1.2 equiv), the alcohol precursor of (*S,S*)-**2** (43 mg, 0.2 mmol, 5 mol%, in 1.0 mL Et₂O pretreated with freshly titrated *s*-BuLi), ZnCl₂ (2.4 mL, 1 M solution in Et₂O, 0.6 equiv), 4-bromoveratrole (0.64 mL, 4.4 mmol, 1.1 equiv), Pd(OAc)₂ (40 mg, 0.16 mmol, 4 mol%) and *t*-Bu₃P·HBF₄ (92 mg, 0.32 mmol, 8 mol%) gave the crude product as an oil. Purification by silica gel column chromatography eluting with hexane-EtOAc (85:15) afforded 990 mg of the pure product as an oil in 73% yield and 97:3 er; spectroscopic data as previously reported.³

3.3. (*R*)-*N*-Boc-2-(4-cyano)phenylpiperidine



Using **General Procedure A**, *N*-Boc-piperidine (740 mg, 4 mmol), TMEDA (2.4 mL, 16.0 mmol, 4.0 equiv), Et₂O (20 mL), *s*-BuLi (4.0 mL, 1.2 M, 4.8 mmol, 1.2 equiv), the alcohol precursor of (*S,S*)-**2** (43 mg, 0.2 mmol, 5 mol%, in 1.0 mL Et₂O pretreated with freshly titrated *s*-BuLi), ZnCl₂ (2.4 mL, 1 M solution in Et₂O, 0.6 equiv), 4-bromobenzonitrile (797 mg, 4.4 mmol, 1.1 equiv), Pd(OAc)₂ (40 mg, 0.16 mmol, 4 mol%) and *t*-Bu₃P·HBF₄ (92 mg, 0.32 mmol, 8 mol%) gave the crude product as an oil. Purification by silica gel column chromatography eluting with hexane-EtOAc (90:10) afforded 790 mg of the pure product as an oil in 69% yield and 91:9 er; spectroscopic data as previously reported.³

3.4. (*R*)-*N*-Boc-2-(1-naphthyl)piperidine

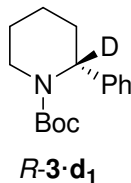


R-7

Using **General Procedure A**, *N*-Boc-piperidine (740 mg, 4 mmol), TMEDA (2.4 mL, 16.0 mmol, 4.0 equiv), Et₂O (20 mL), *s*-BuLi (4.8 mL, 1.0 M, 4.8 mmol, 1.2 equiv), the alcohol precursor of (*S,S*)-**2** (43 mg, 0.2 mmol, 5 mol%, in 1.0 mL Et₂O pretreated with freshly titrated *s*-BuLi), ZnCl₂ (2.4 mL, 1 M solution in Et₂O, 0.6 equiv), 1-bromonaphthalene (0.6 mL, 4.4 mmol, 1.1 equiv), Pd(OAc)₂ (40 mg, 0.16 mmol, 4 mol%) and *t*-Bu₃P·HBF₄ (92 mg, 0.32 mmol, 8 mol%) gave the crude product as an oil. Purification by silica gel column chromatography eluting with hexane-EtOAc (60:40) afforded 871 mg of the pure product as an amorphous solid in 70% yield and 97:3 er; spectroscopic data as previously reported.³

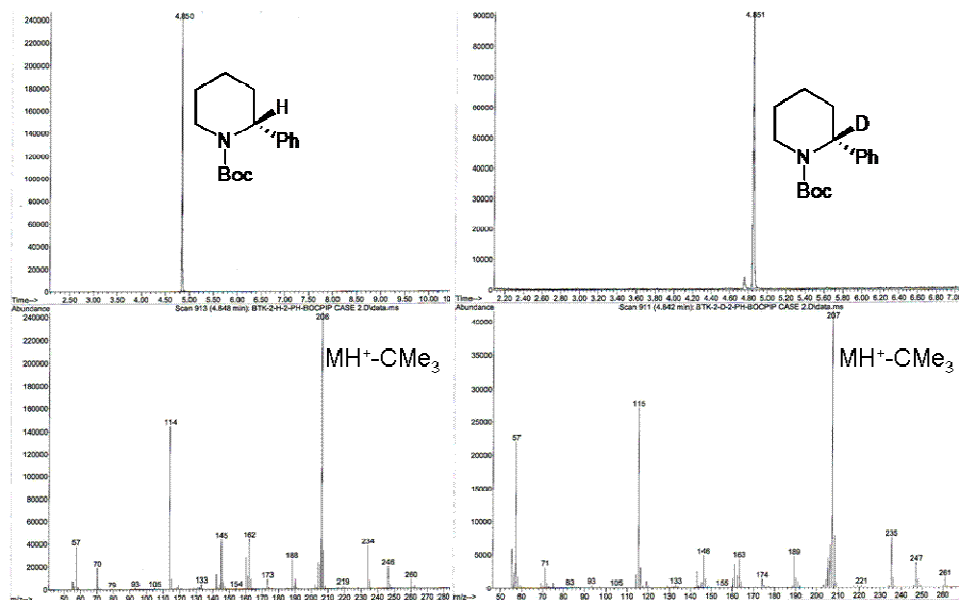
4. Lithiation-substitution of (*R*)-*N*-Boc-2-phenylpiperidine with several electrophiles

4.1. With MeOD



R-3-*d*₁

Using **General Procedure D**, *R*-3 of 96:4 er and 0.1 mL MeOD showed complete deuteration. There is a noticeable shift of the protonated base peak from *m/z* 206 for **3** to *m/z* 207 for **3**·*d*₁.

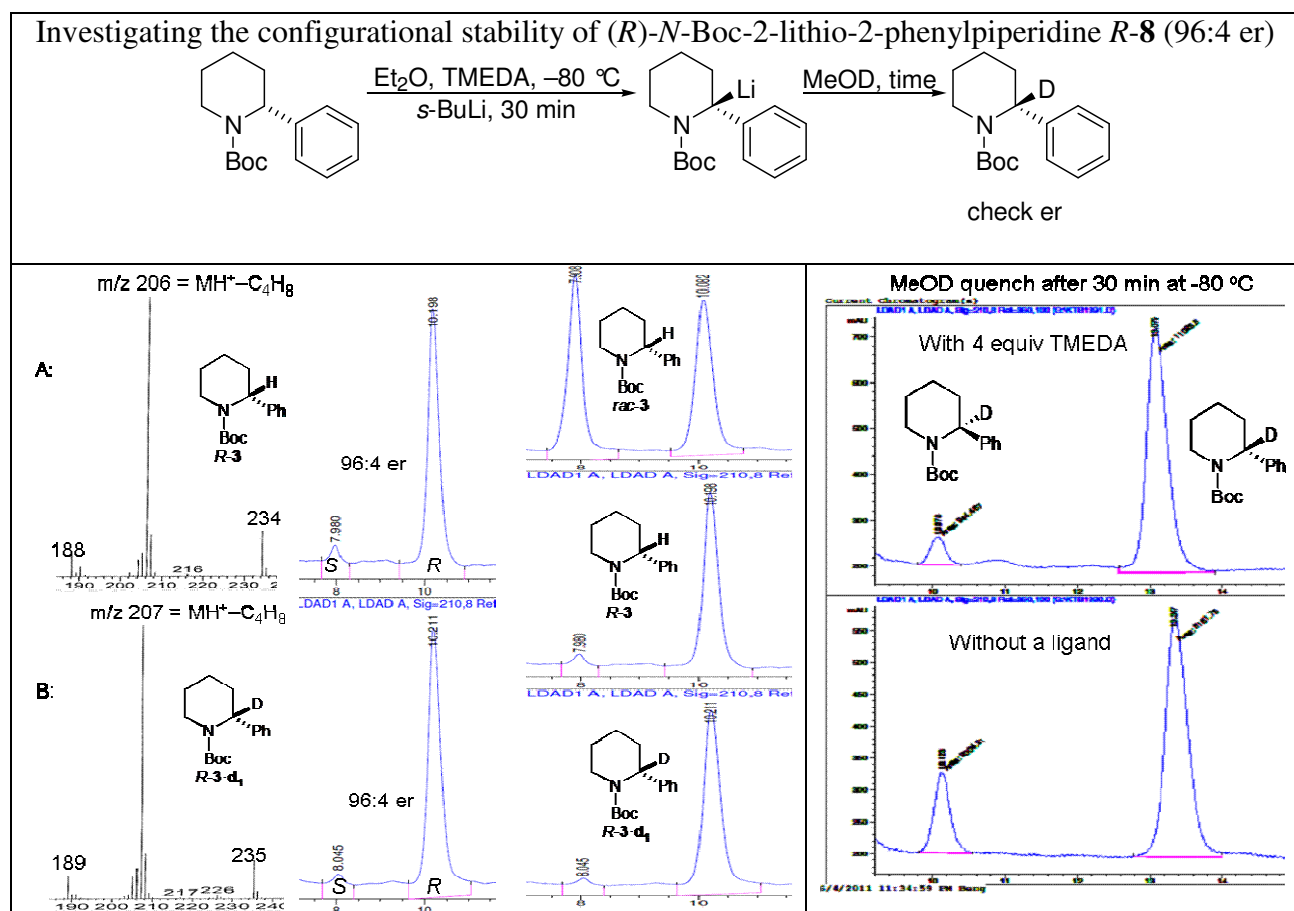


Note 1: Although, we observed complete formation of organolithium **8** in the absence of a ligand after 60 min at $-80\text{ }^{\circ}\text{C}$, we add excess TMEDA to enhance the configurational stability of the benzylic organolithium (see Figure below) and to speed up the lithiation.

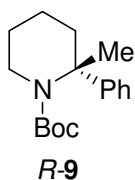
Note 2: It is absolutely necessary to minimize the amount of excess *s*-BuLi in order to avoid undesirable lithiation at C-6. The absence of a byproduct with *m/z* 208 clearly means that no simultaneous deuteration at C-2 and C-6 occurred under the reaction conditions.

Note 3: Lithiation at higher temperatures resulted in a complex mixture due to the possibility of attack on the Boc-group by *s*-BuLi and due to enhanced possibility of lithiation at C-6.

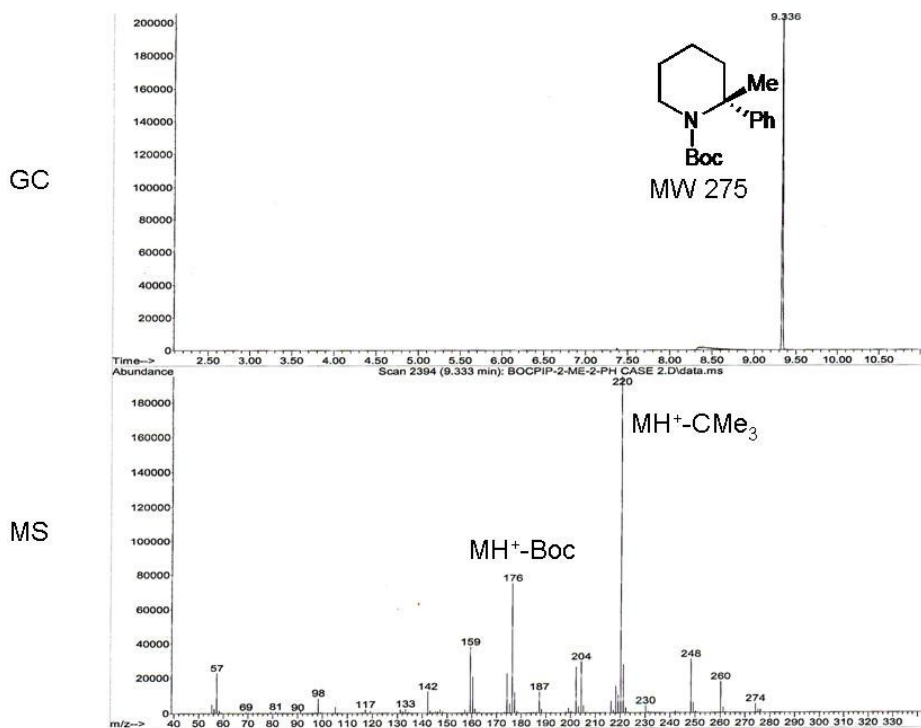
Note 4: The lithiation can be carried out using *n*-BuLi at $-80\text{ }^{\circ}\text{C}$ but longer reaction times ($>2\text{ h}$) or higher temperatures are required.

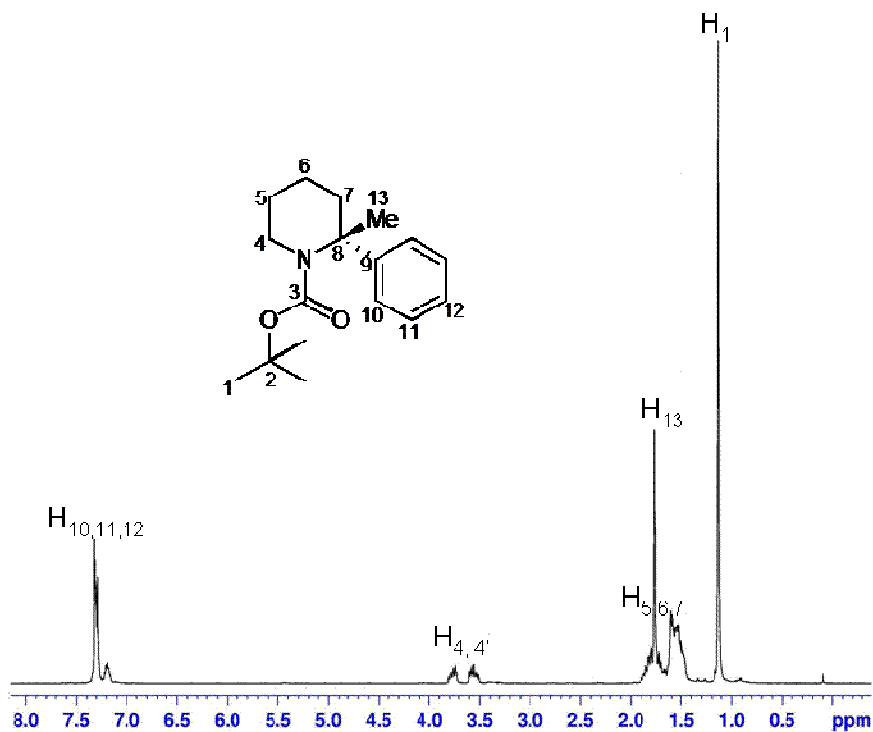
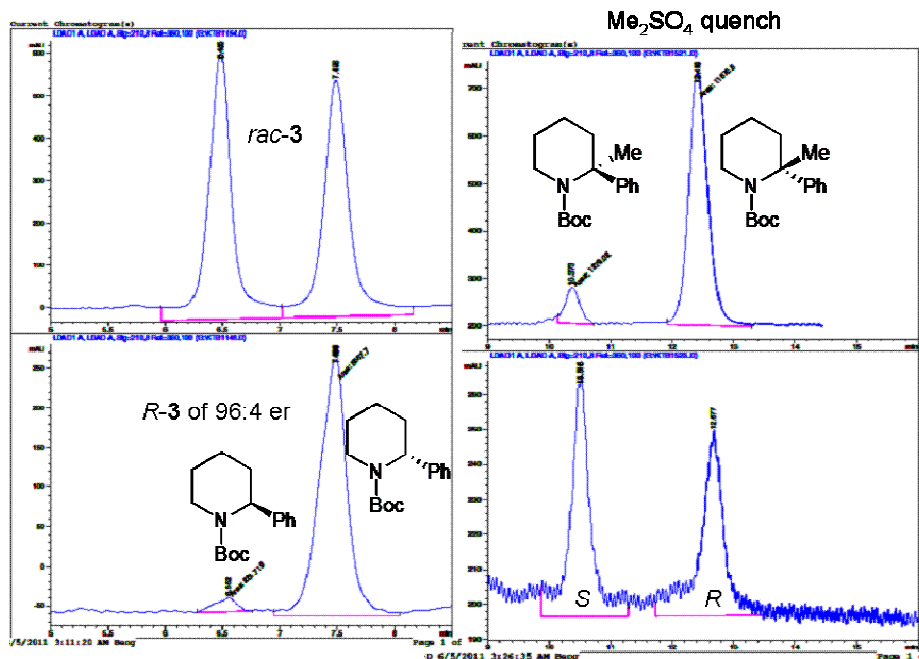


4.2. With Me₂SO₄



Using **General Procedure B**, *R-3* of 96:4 er (261 mg, 1.0 mmol), TMEDA (0.6 mL, 4.0 mmol, 4.0 equiv), Et₂O (10 mL), *s*-BuLi (1.0 mL, 1.0 mmol, 1.0 M, 1.0 equiv), Me₂SO₄ (0.15 mL, 1.5 mmol, 1.5 equiv) for 18 h prior to addition of 2 mL MeOH, gave the crude product as an oil. Purification by silica gel chromatography eluting with hexane-EtOAc (93:7) afforded 217 mg of *R-9* as an oil in 79% yield and 95:5 er. All other spectroscopic data as reported for *rac-9*.⁷ The enantiomer ratio was evaluated by CSP-SFC, monitoring at 210 nm, by comparison with an authentic racemic sample, under the following column conditions: **Column:** Pirkle Whelk-O-1, **Flow Rate** = 1.0 mL/min, **Polarity Modifier** = 3.0% EtOH. The minor enantiomer elutes after ~10.4 min and the major elutes after ~12.4 min.



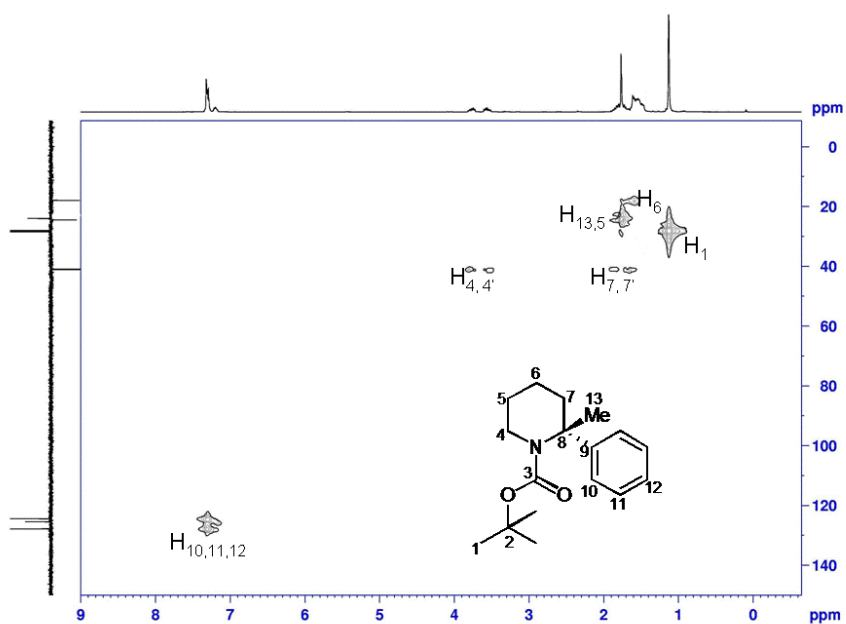
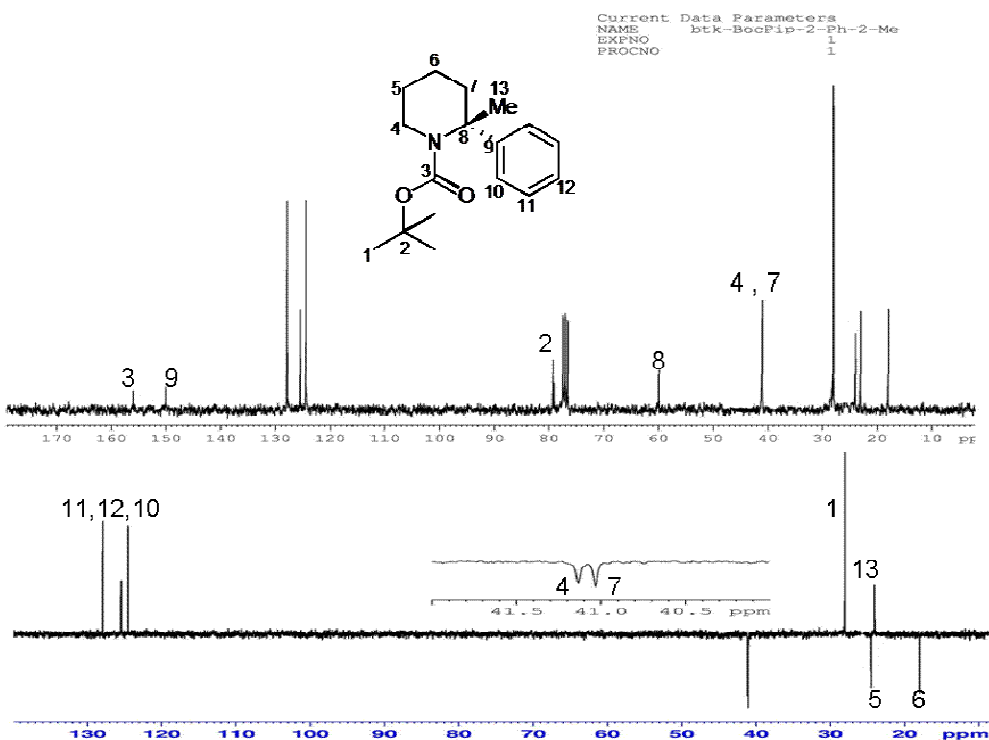


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 MCREST: 0.0000000 sec
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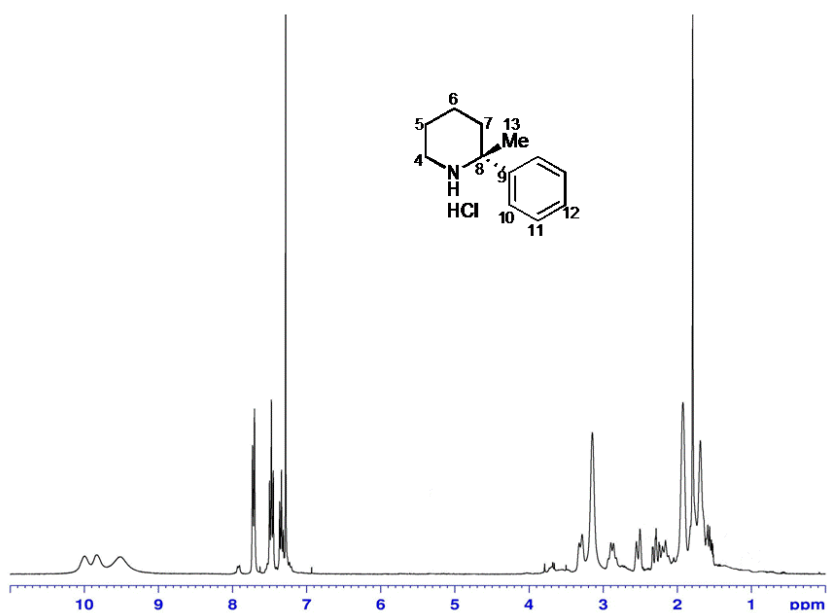
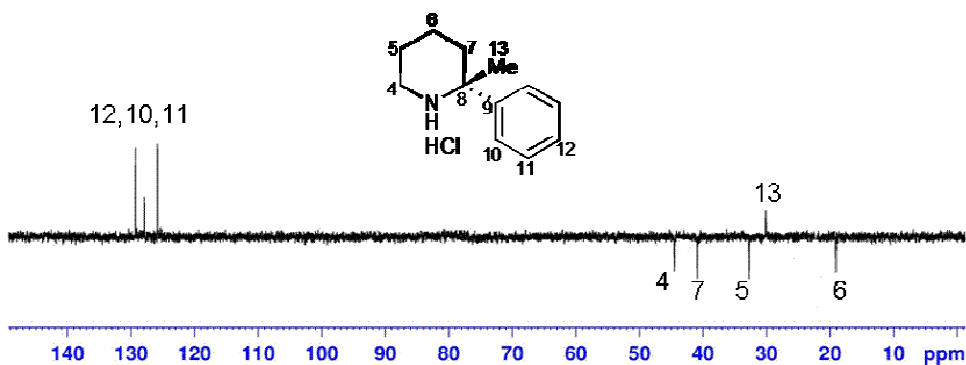
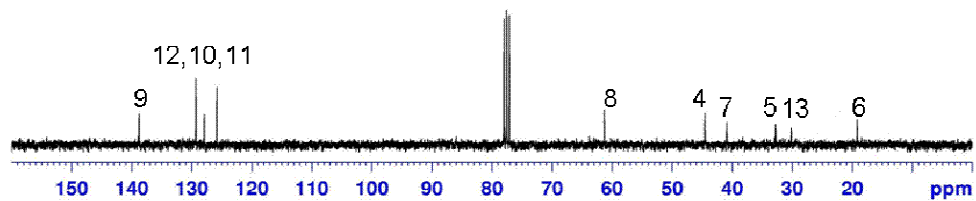
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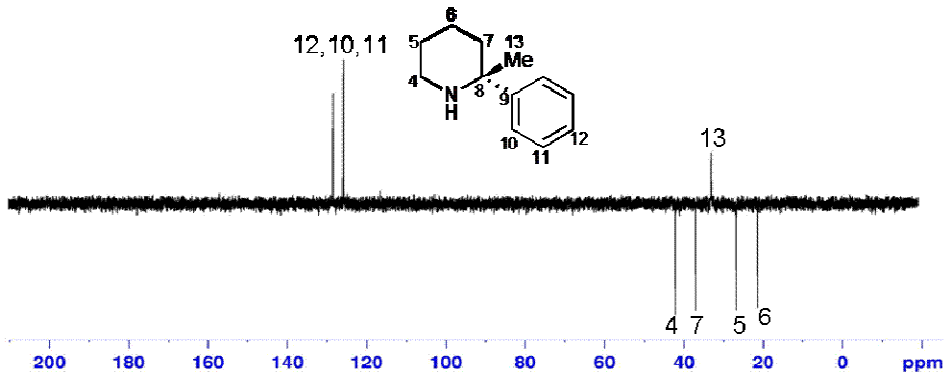
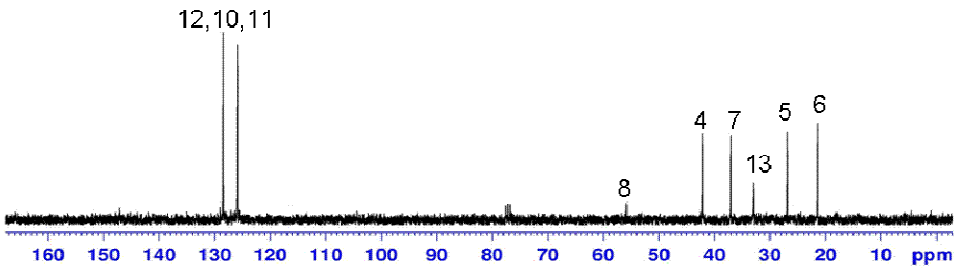
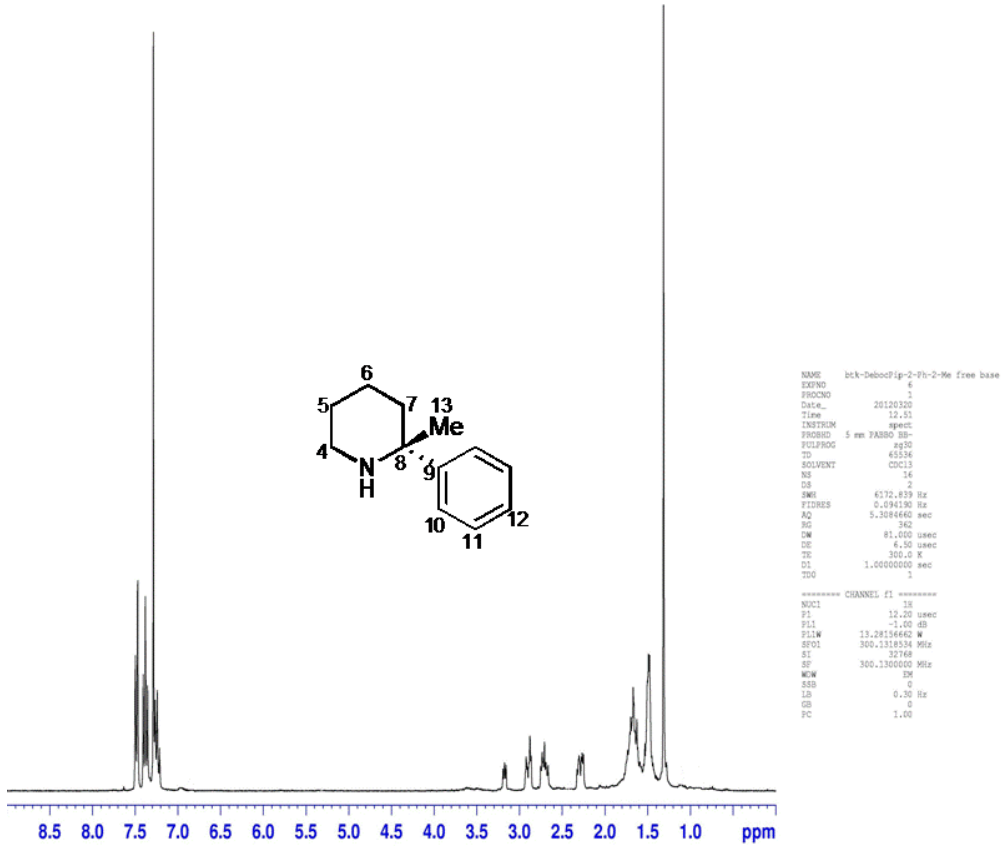
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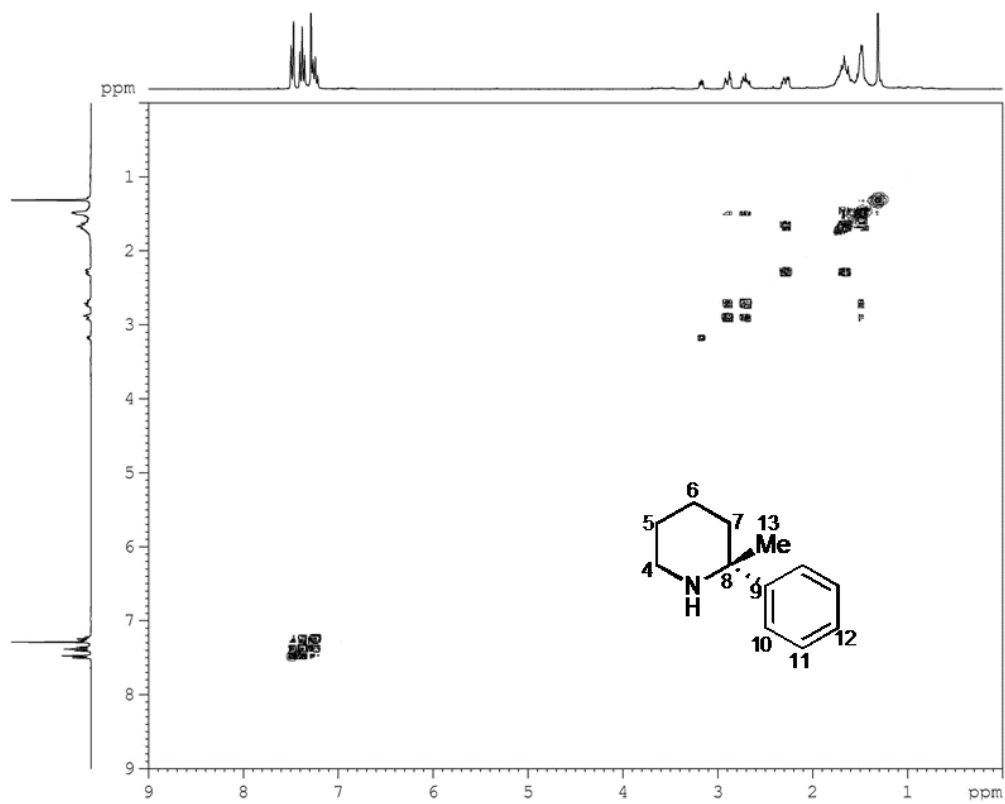
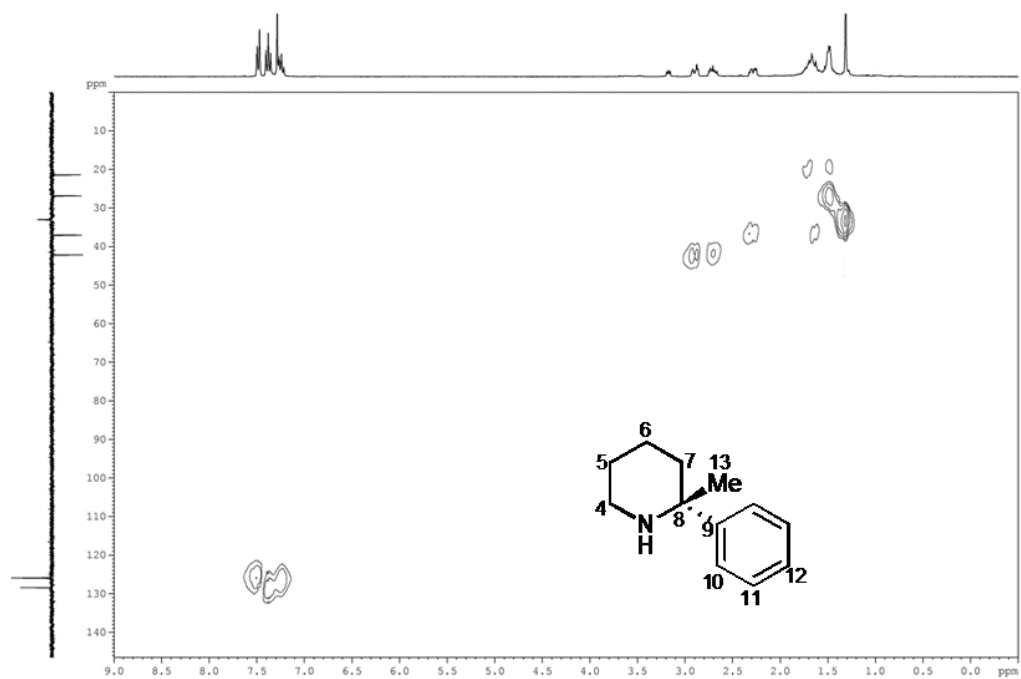
To a solution of *R*-**9** (138 mg, 0.5 mmol, 1.0 equiv) in anhydrous MeOH (2 mL) at 0 °C, was added SOCl₂ (0.1 mL) dropwise. The mixture was stirred for 6 h and then concentrated under high vacuum to give the desired product as the hydrochloride salt. It was then basified to pH 12

with 2 M NaOH(aq) and extracted with CH₂Cl₂, (3 x 5 mL), dried over Na₂SO₄ and evaporated to give 83 g of the free amine in 94% yield, $[\alpha]_D^{22} -21$ ($c=0.5$, CH₂Cl₂), lit⁸. for enantiopure deprotected *R*-**9** $[\alpha]_D^{22} -18$ (c 0.33, CH₂Cl₂), all other data as reported.⁸

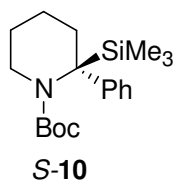


Spectral data for the free base:

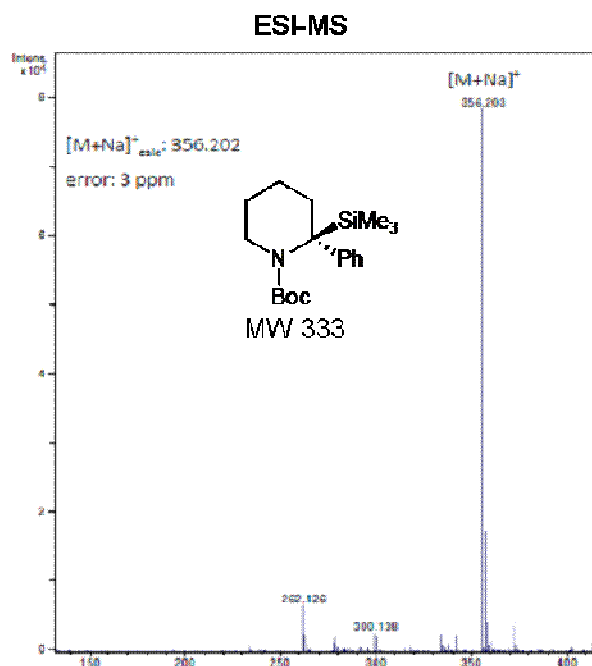


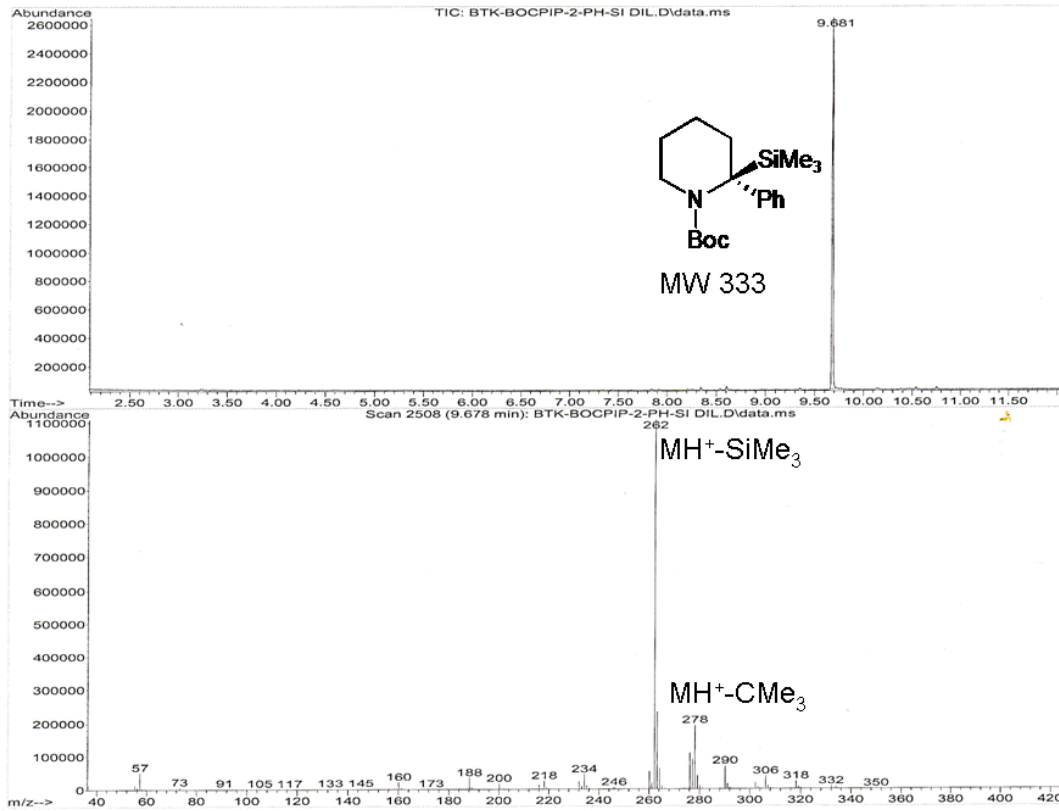


4.3. With TMSCl

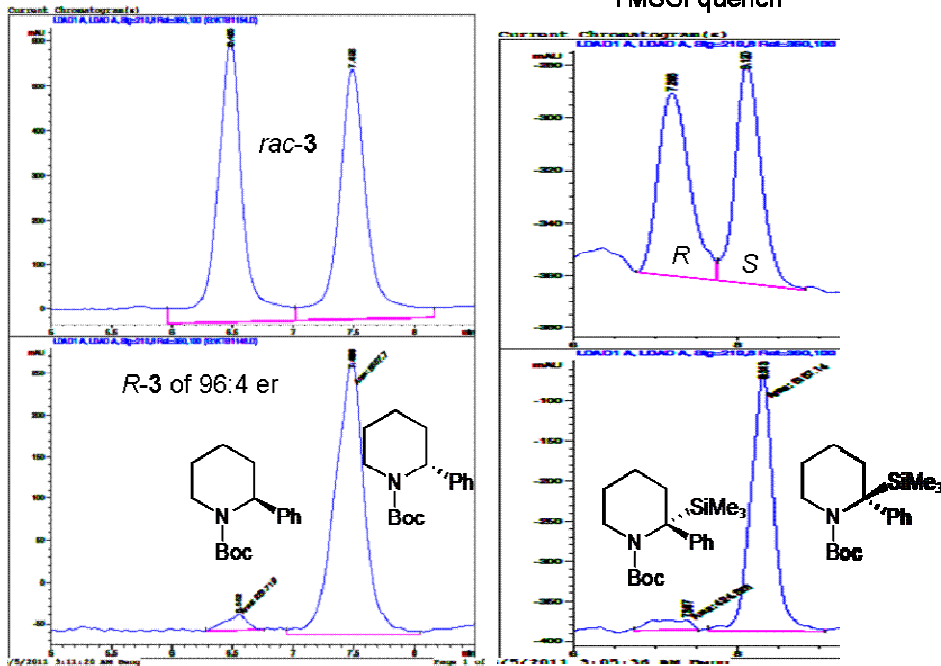


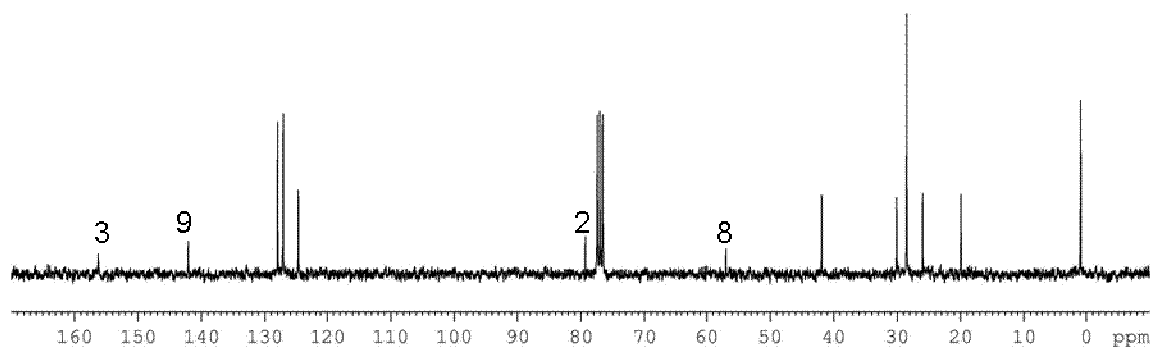
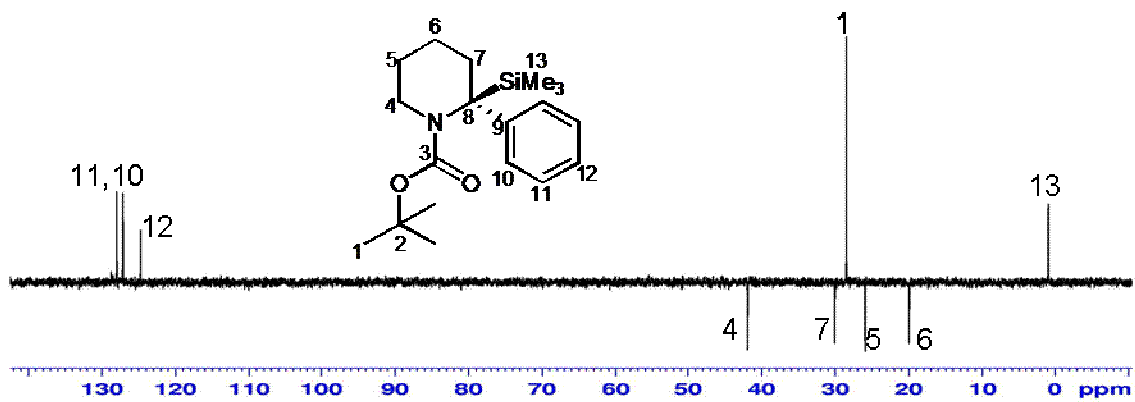
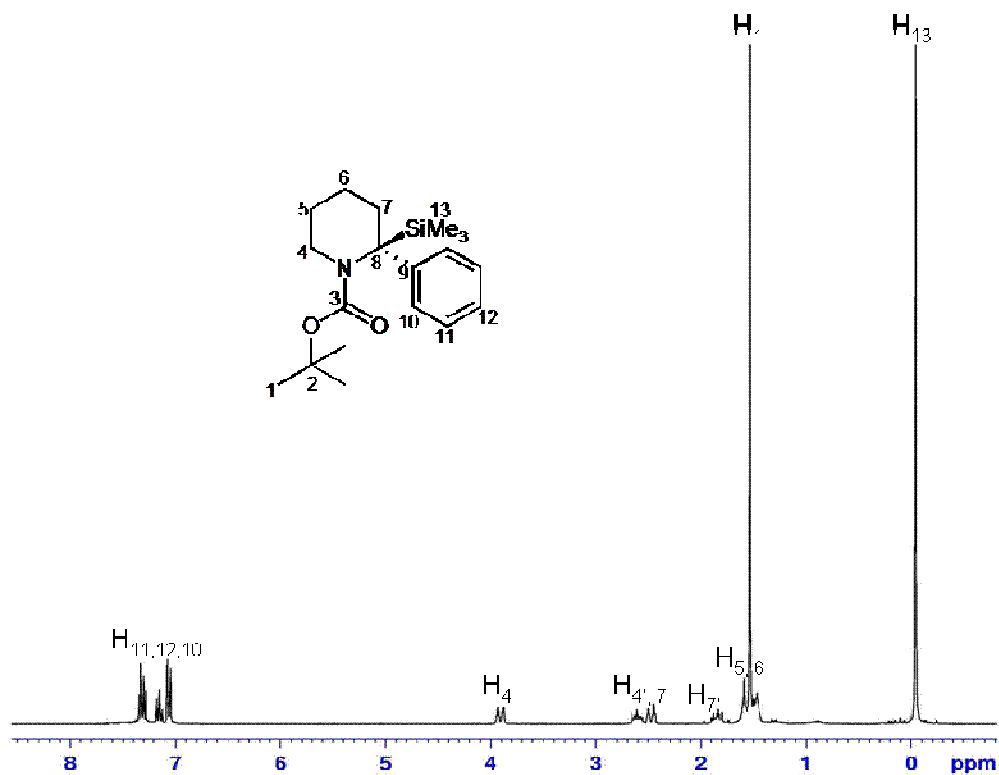
Using **General Procedure B**, *R-3* of 96:4 er (261 mg, 1.0 mmol), TMEDA (0.6 mL, 4.0 mmol, 4.0 equiv), Et₂O (10 mL), *s*-BuLi (1.0 mL, 1.0 mmol, 1.0 M, 1.0 equiv), Me₃SiCl (144 mg, 1.2 mmol, 1.2 equiv) for 4 h prior to addition of 2 mL MeOH and warming to rt, gave the crude product as an oil. Purification by silica gel chromatography eluting with hexane-EtOAc (90:10) afforded 293 mg of *S-10* as an oil in 88% yield and 96:4 er. ¹H NMR (300 MHz, CDCl₃) δ 7.63–7.05 (5H, m, Ph), 3.95 (1H, br, NCH), 2.77–2.45 (3H, m), 1.95–1.22 (13H, m), 0.21 (9H, s, 3 x CH₃) ¹³C NMR (75.5 MHz, CDCl₃) δ = 156.3 (C=O), 142.1 (C), 128.0 (CH), 127.1 (CH), 124.7 (CH), 79.3 (C), 57.0 (C), 41.9 (CH₂), 30.1 (CH₂), 28.5 (3 x CH₃), 26.0 (CH₂), 20.0 (CH₂) and 0.9 (3 x CH₃). The enantiomer ratio was evaluated by CSP-SFC, monitoring at 210 nm, by comparison with an authentic racemic sample, under the following column conditions: **Column:** Pirkle Whelk-O-1, **Flow Rate** = 1.5 mL/min, **Polarity Modifier** = 1.5% EtOH. The minor enantiomer elutes after ~7.3 min and the major elutes after ~8.2 min.

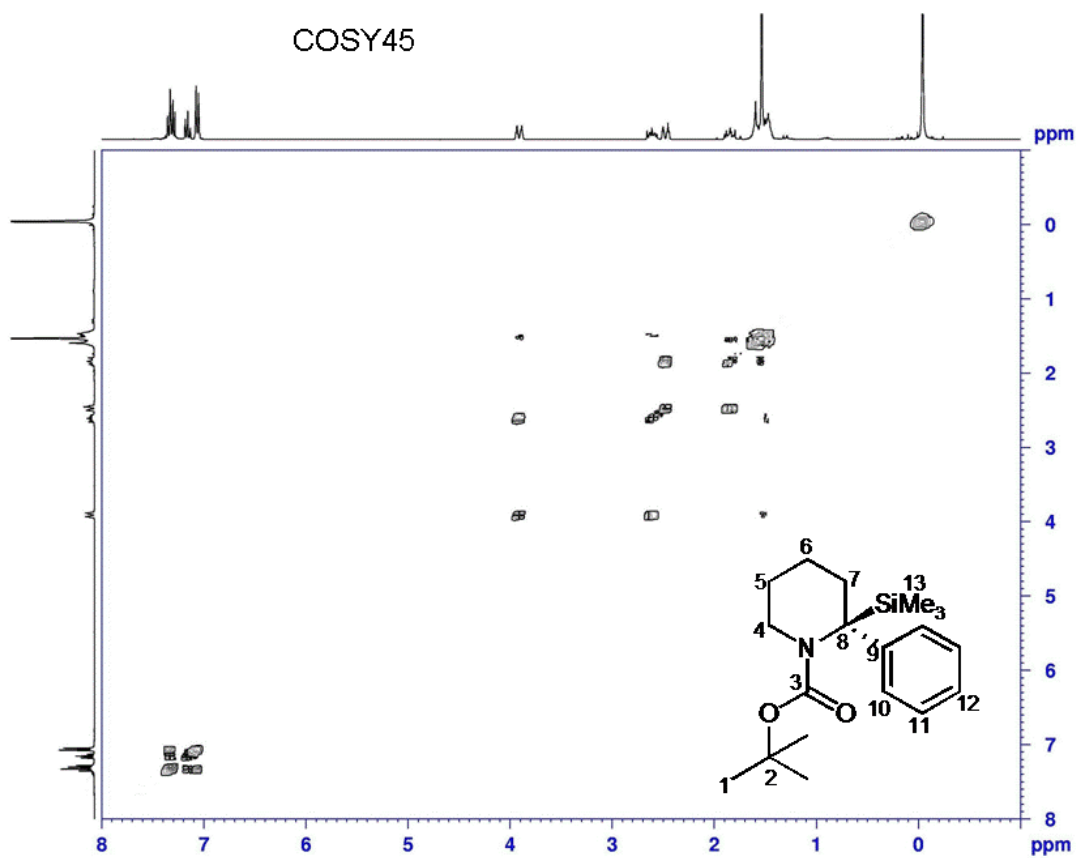
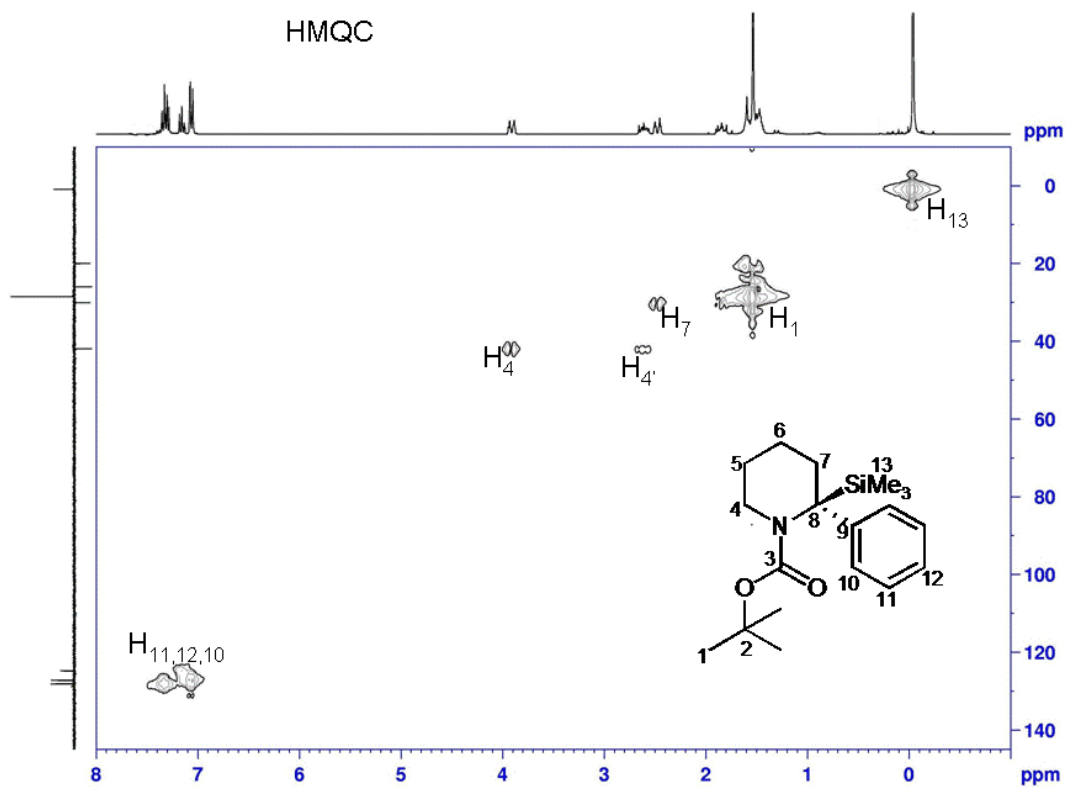




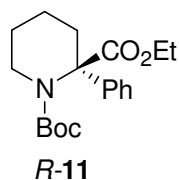
TMSCl quench



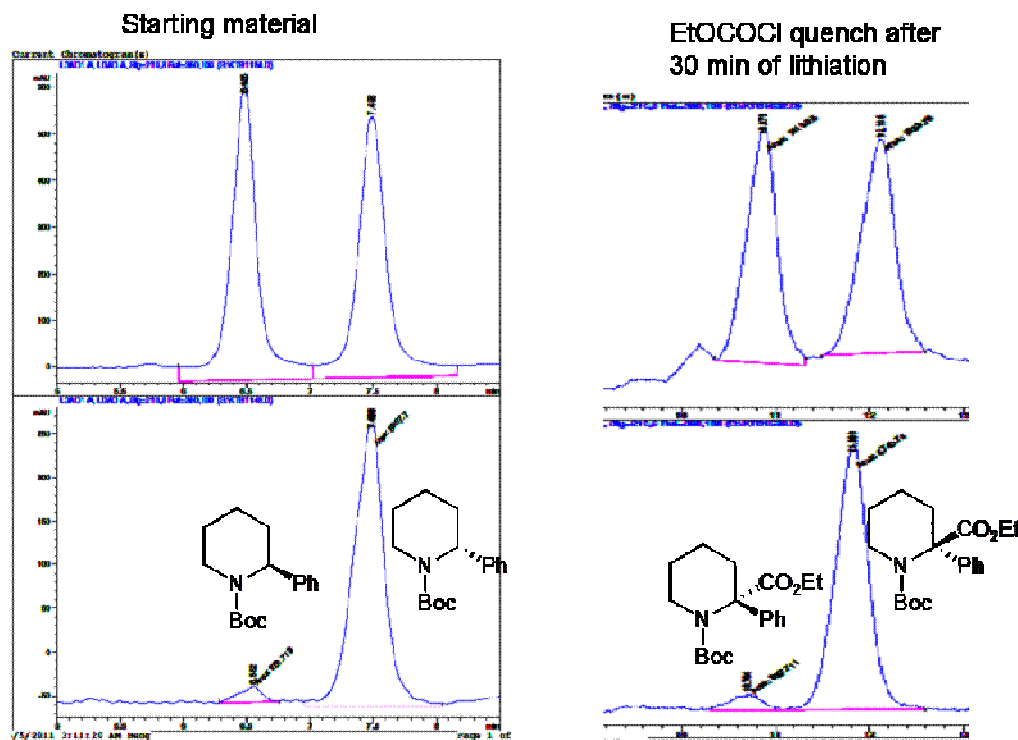


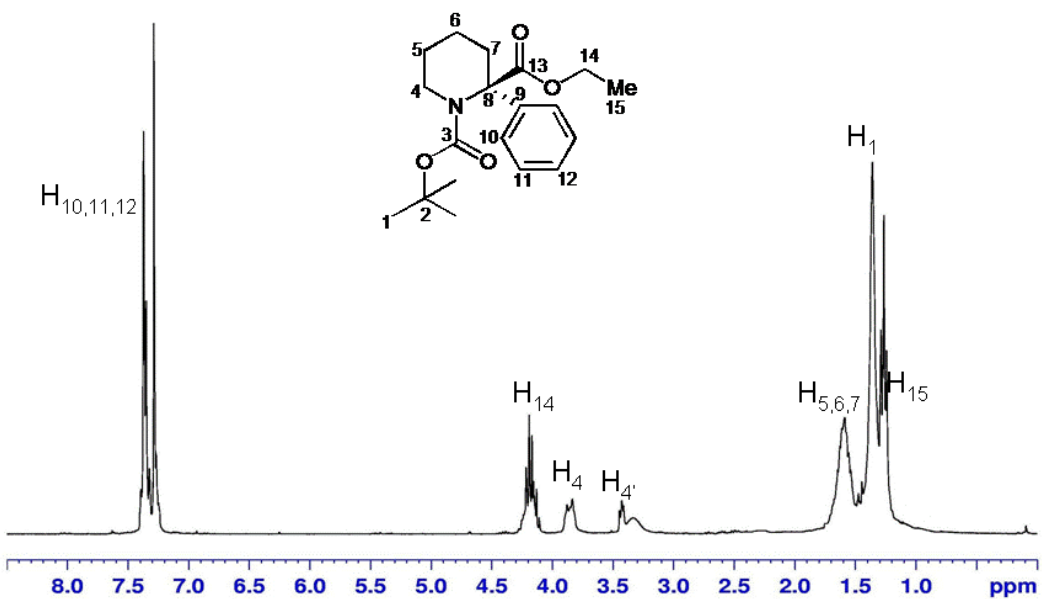
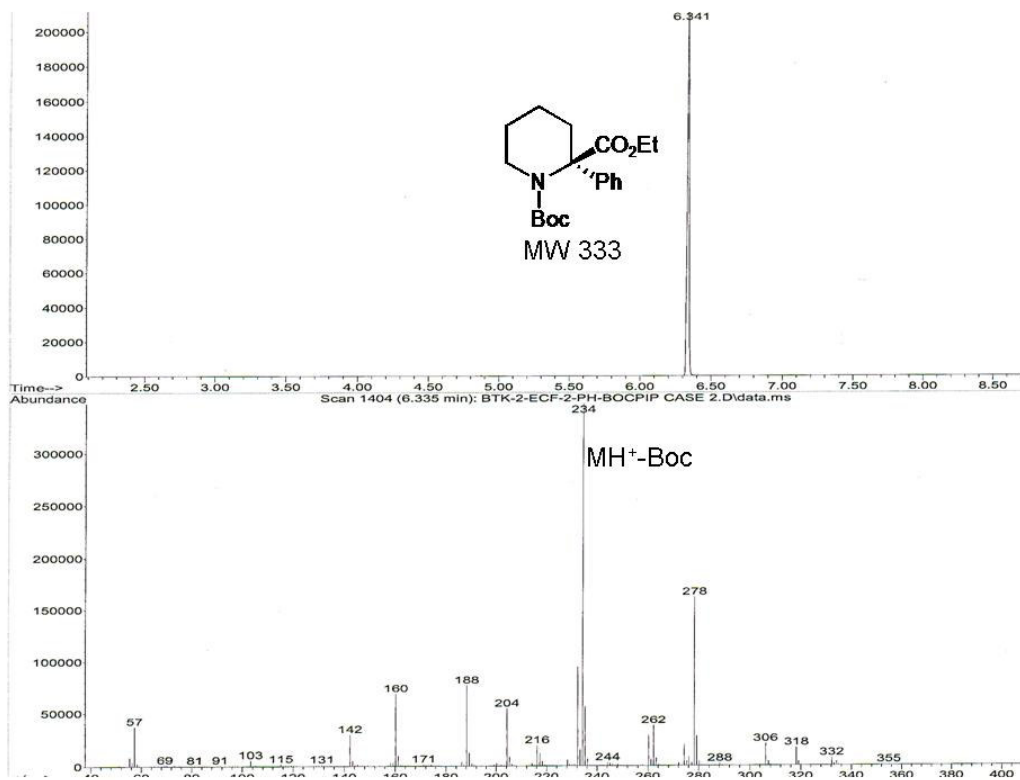


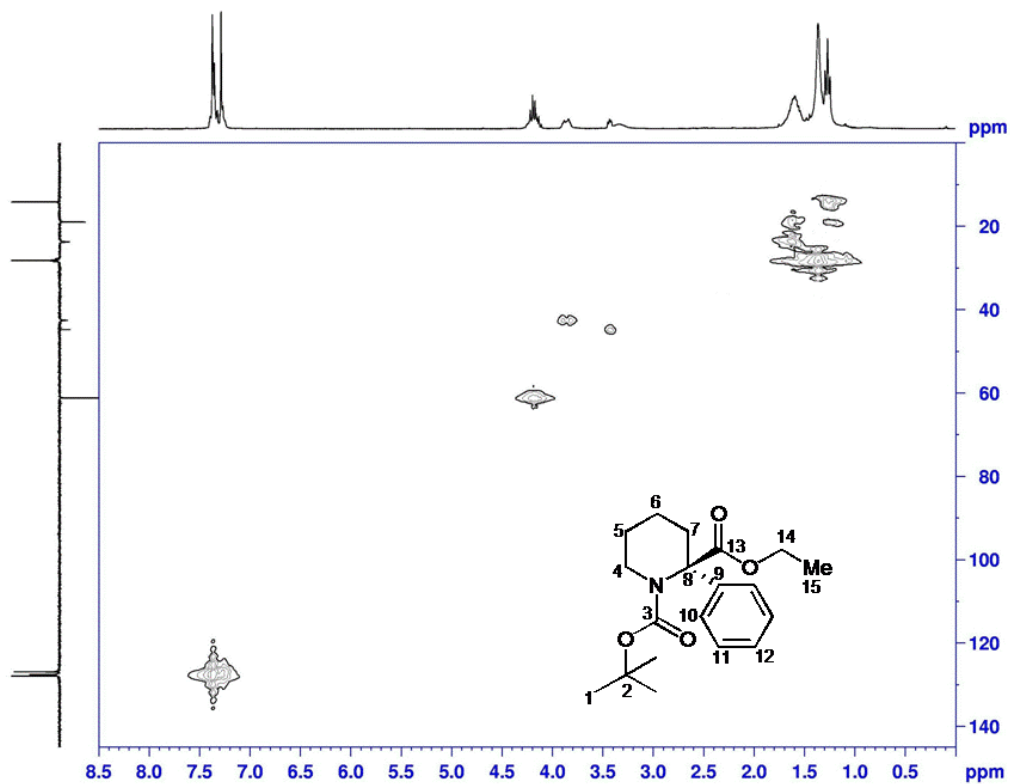
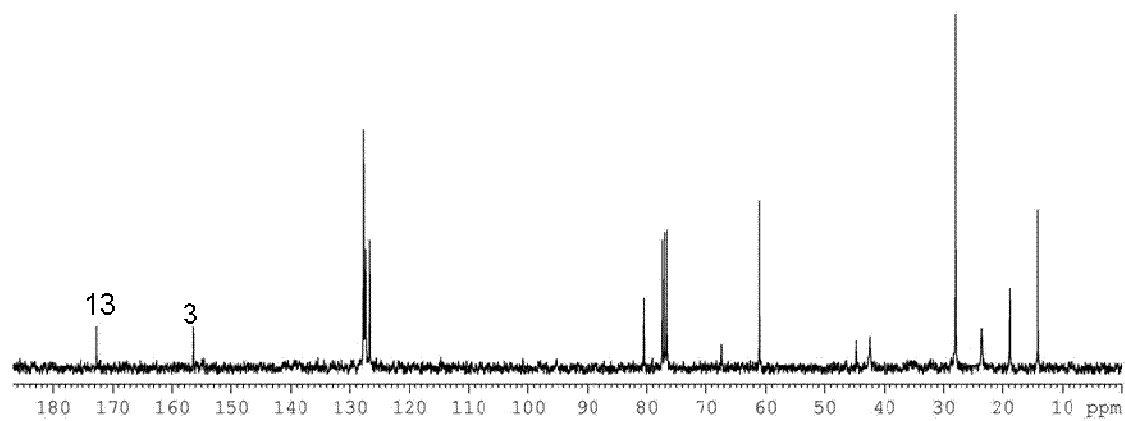
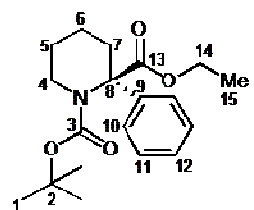
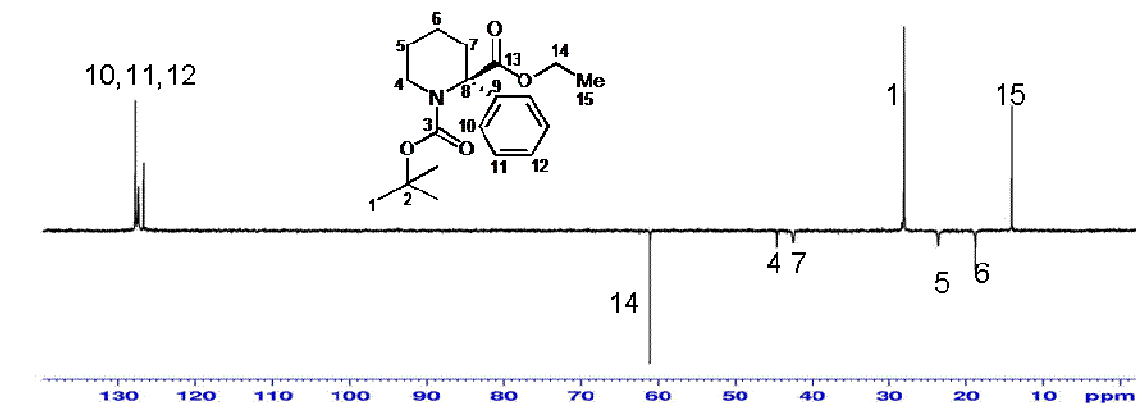
4.4. With EtOCOCl

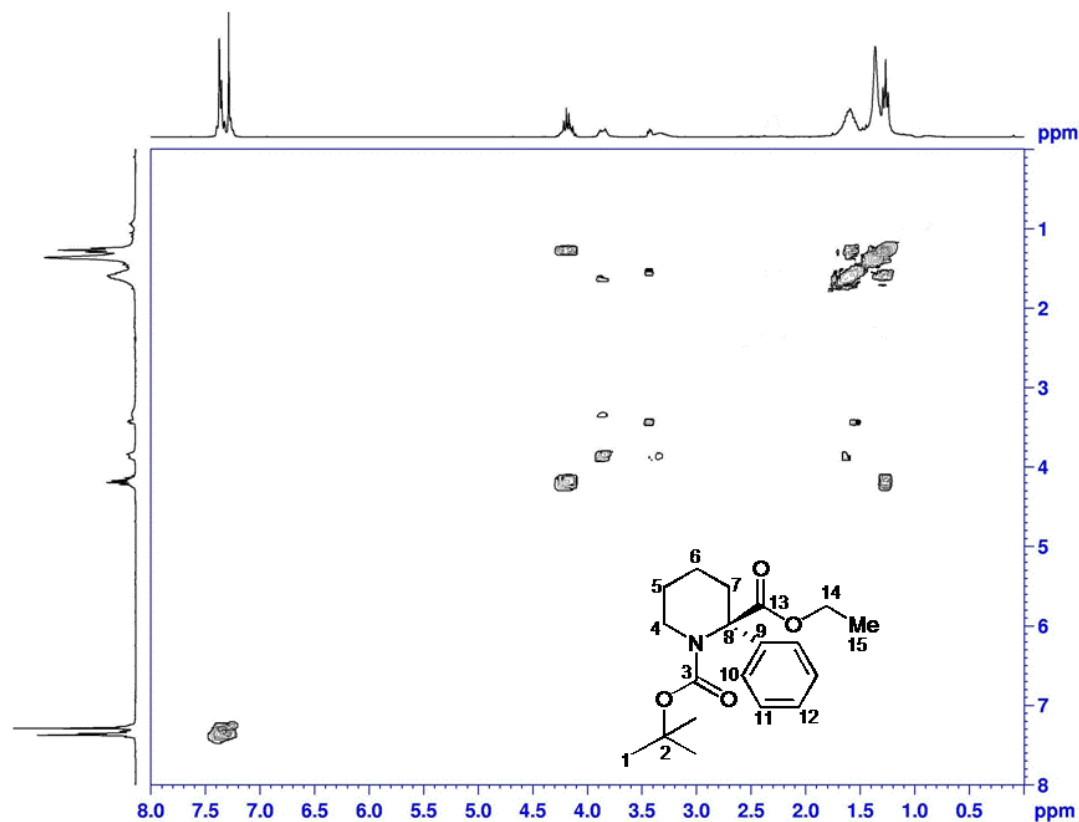


Using **General Procedure B**, *R-3* of 96:4 er (261 mg, 1.0 mmol), TMEDA (0.6 mL, 4.0 mmol, 4.0 equiv), Et₂O (10 mL), *s*-BuLi (1.0 mL, 1.0 mmol, 1.0 M, 1.0 equiv), EtOCOCl (0.13 mL, 1.5 mmol, 1.5 equiv) for 2 h prior to addition of 2 mL MeOH and warming to rt, gave the crude product as an oil. Purification by silica gel chromatography eluting with hexane-EtOAc (85:15) afforded 283 mg of *R-11* as an oil in 85% yield and 96:4 er. ¹H NMR (300 MHz, CDCl₃) δ 7.43–7.21 (5H, m, Ph), 4.27–4.03 (2H, quartet, CH₂), 3.86 (1H, br, NCH), 3.44 (1H, br, NCH), 1.72–0.96 (18H, m). ¹³C NMR (75.5 MHz, CDCl₃) δ = 172.2 (C=O of ester), 156.3 (C=O), 142.1 (C), 127.8 (CH), 125.1 (CH), 126.8 (CH), 80.5 (C), 67.5 (C), 61.1 (CH₂), 44.7 (CH₂), 44.5 (CH₂), 28.1 (3 x CH₃), 23.7 (CH₂), 18.8 (CH₂) and 14.1 (CH₃). The enantiomer ratio was evaluated by CSP-SFC, monitoring at 210 nm, by comparison with an authentic racemic sample, under the following column conditions: **Column:** Pirkle Whelk-O-1, **Flow Rate** = 1.0 mL/min, **Polarity Modifier** = 3.0% EtOH. The minor enantiomer elutes after ~10.7 min and the major elutes after ~11.9 min.

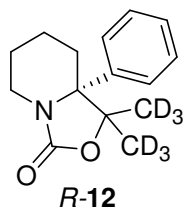






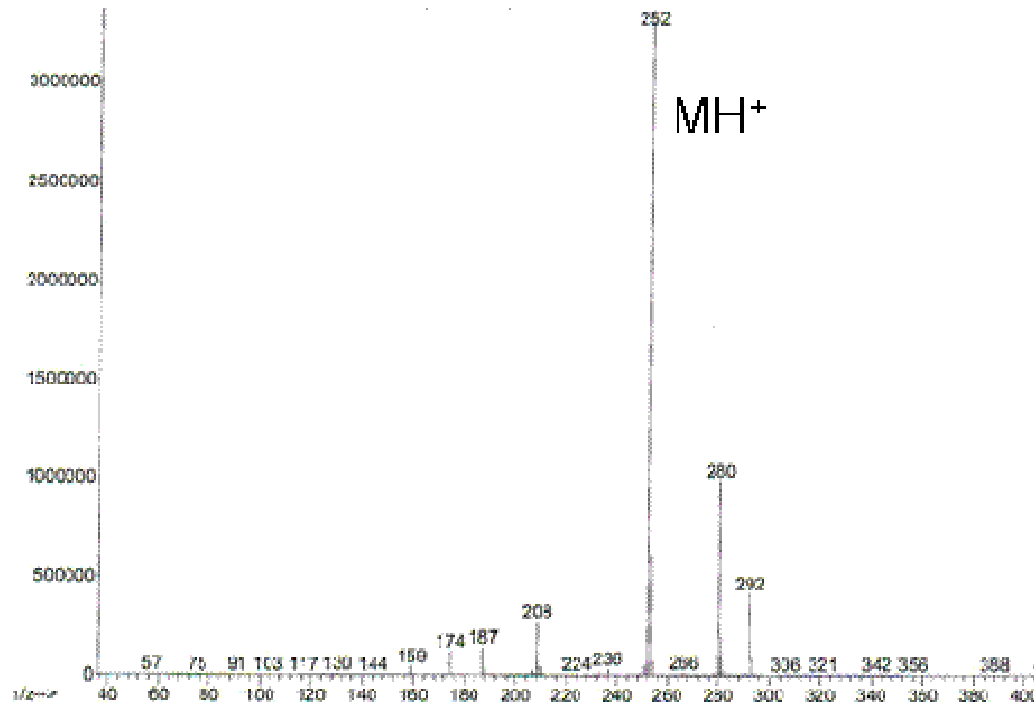
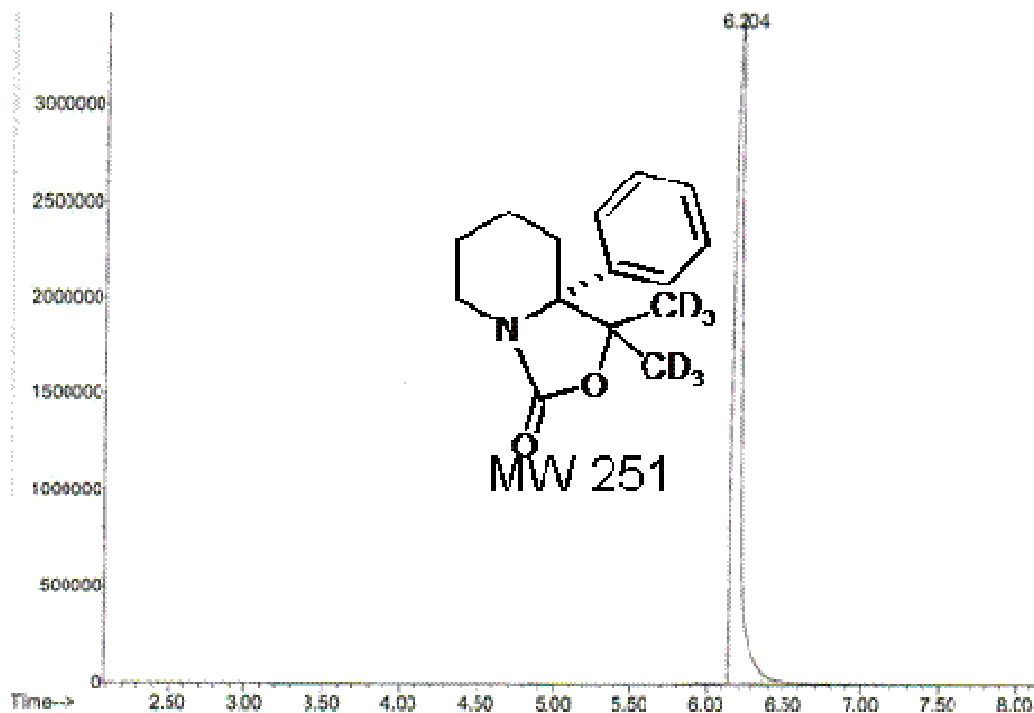


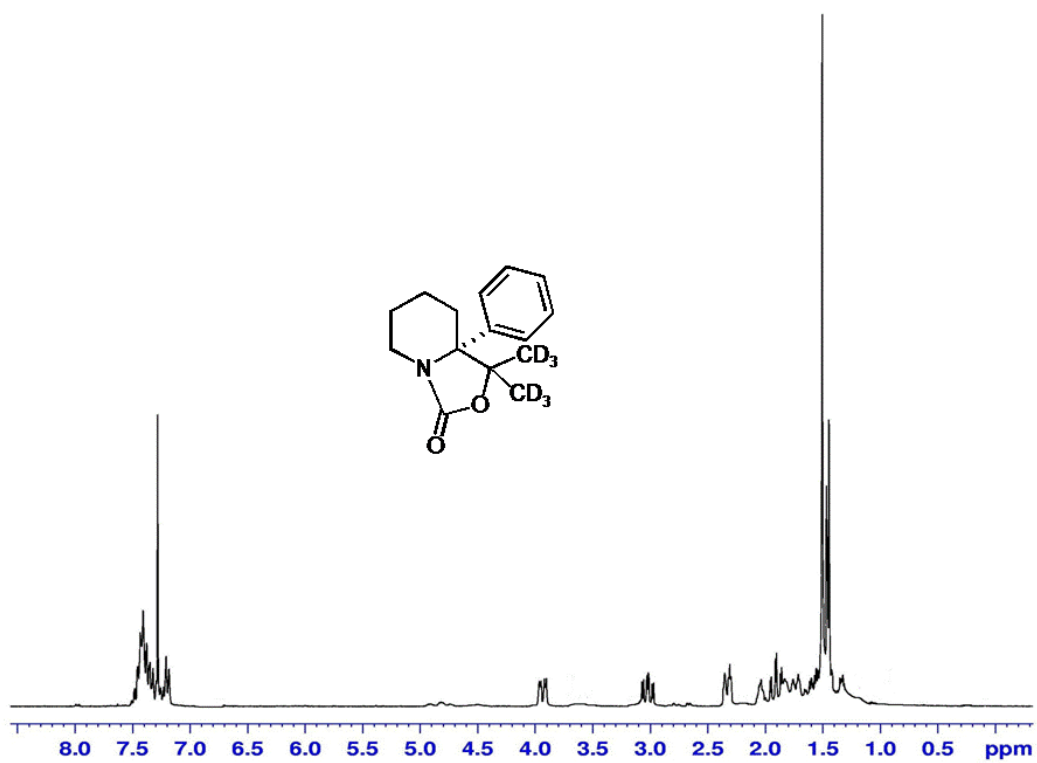
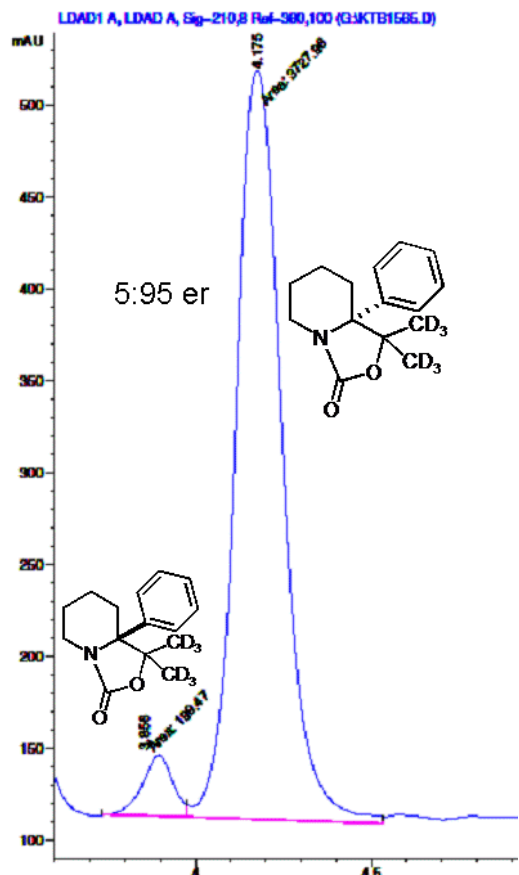
4.5. With acetone- d_6

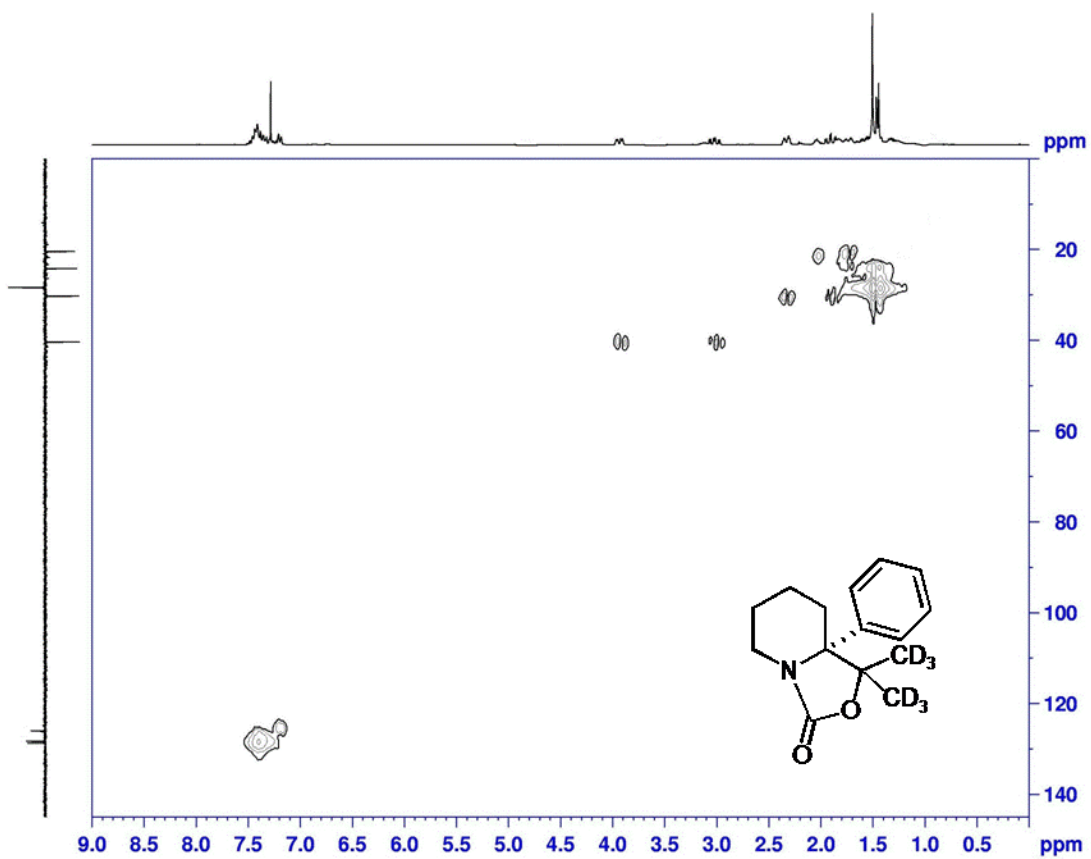
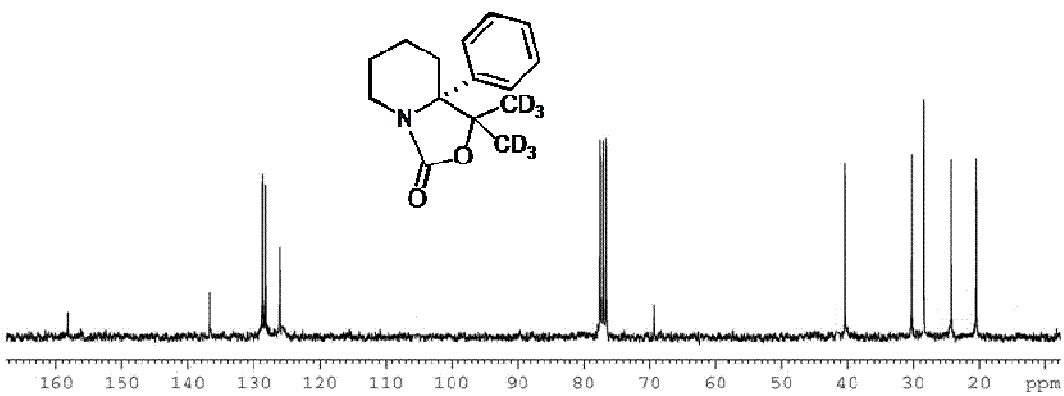
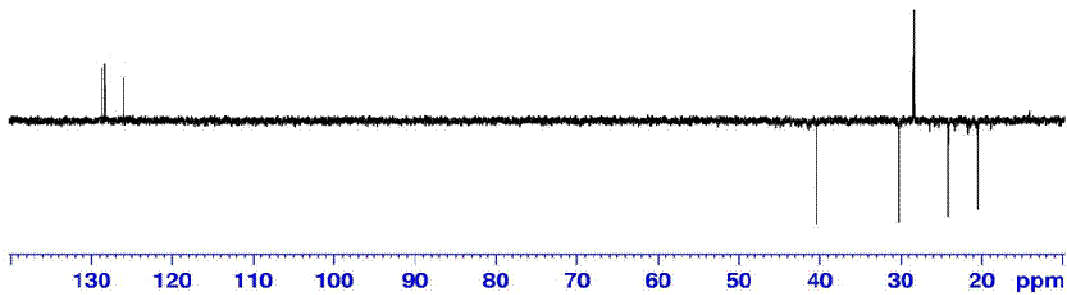


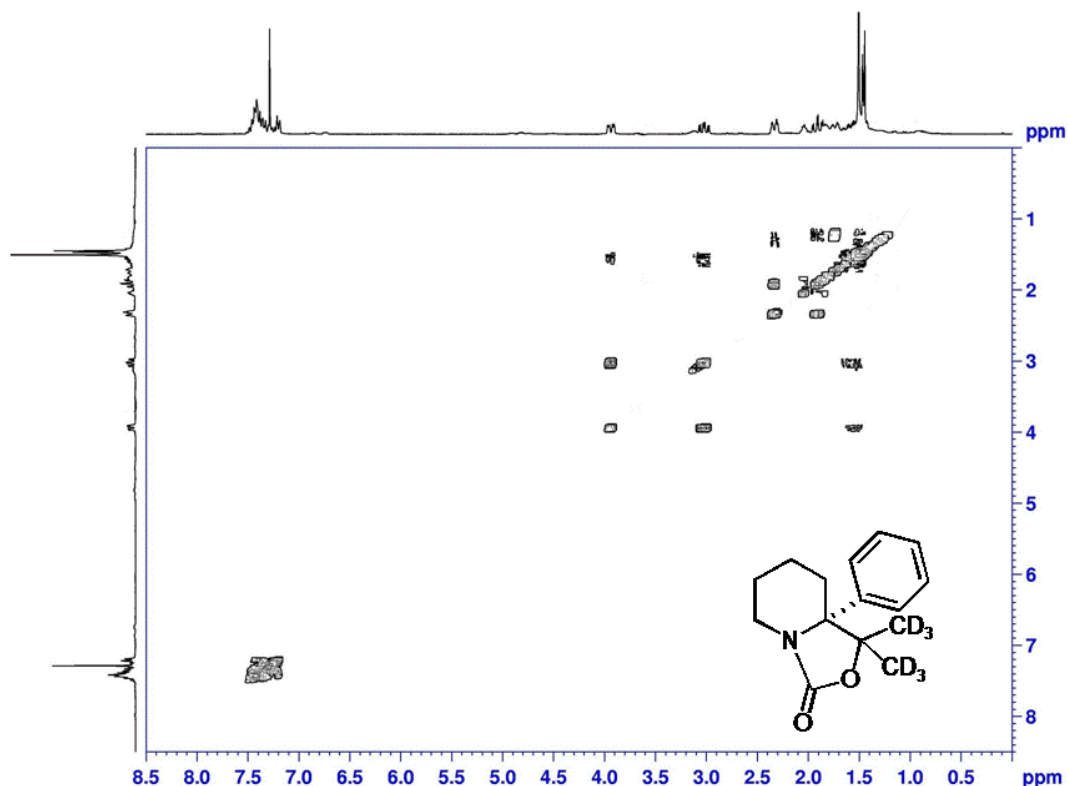
Using **General Procedure B**, *R-3* of 96:4 er (261 mg, 1.0 mmol), TMEDA (0.6 mL, 4.0 mmol, 4.0 equiv), Et₂O (10 mL), *s*-BuLi (1.0 mL, 1.0 mmol, 1.0 M, 1.0 equiv), (CD₃)₂CO (96 mg, 1.5 mmol, 1.5 equiv) for 2 h prior to warming to rt and addition of 2 mL MeOH gave the crude product as an oil. Purification by silica gel chromatography eluting with hexane-EtOAc (60:40) afforded 229 mg of the oxazolidinone *R-12* as an amorphous solid in 90% yield and 95:5 er. ¹H NMR (400 MHz, CDCl₃) δ = 7.55–7.15 (5H, m), 3.96 (1H, dd), 3.05 (1H, dt), 2.35 (1H, dd), 2.22–1.31 (5H and 6D, m). ¹³C NMR (75.5 MHz, CDCl₃) δ = 158.2 (C=O), 136.6 (C), 128.7 (CH), 127.7 (CH), 126.0 (CH), 77.2 (C), 69.4 (C), 40.4 (CH₂), 30.3 (CH₂), 28.3 (2 x CD₃), 24.2 (CH₂), 20.5 (CH₂). The enantiomer ratio was evaluated by CSP-SFC, under the following

column conditions: **Column:** Pirkle Whelk-O-1, **Flow Rate** = 1.0 mL/min, **Polarity Modifier** = 10% EtOH. The minor enantiomer elutes after ~3.9 min and the major elutes after ~4.2 min.

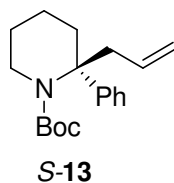




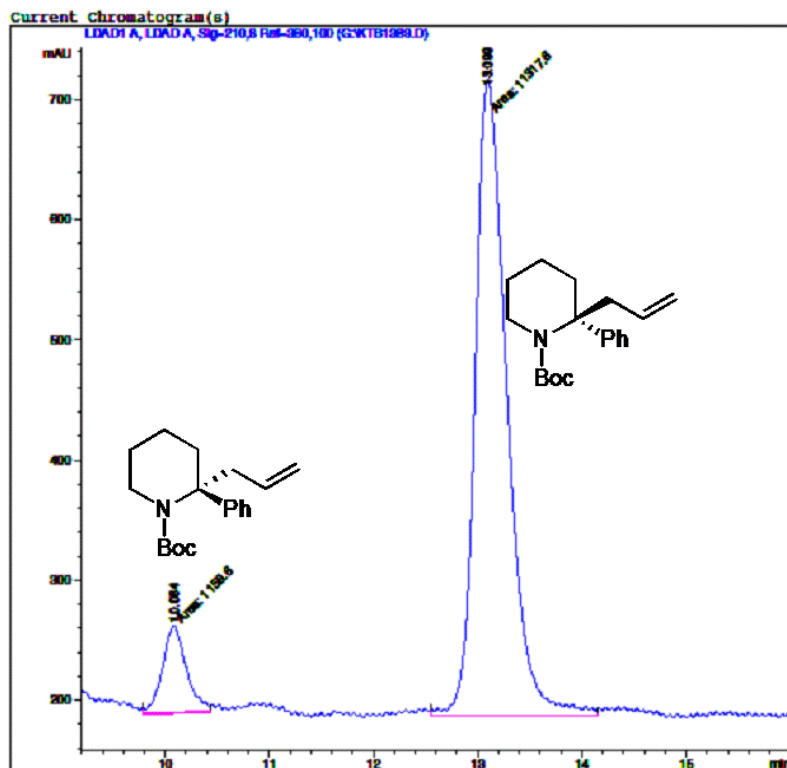
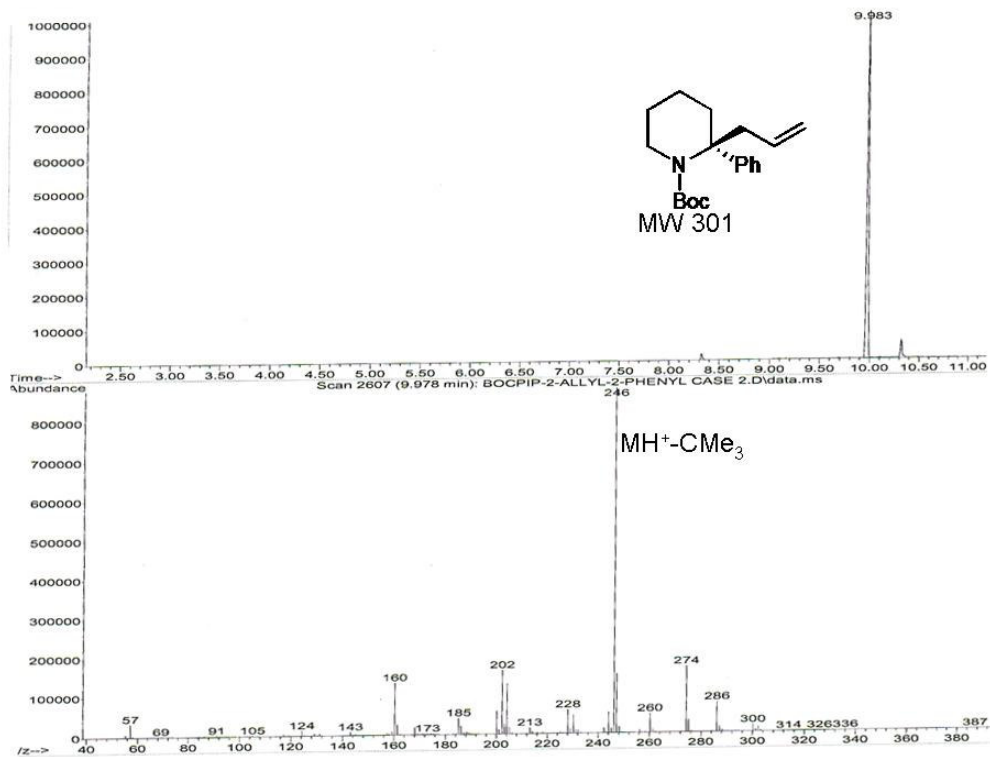


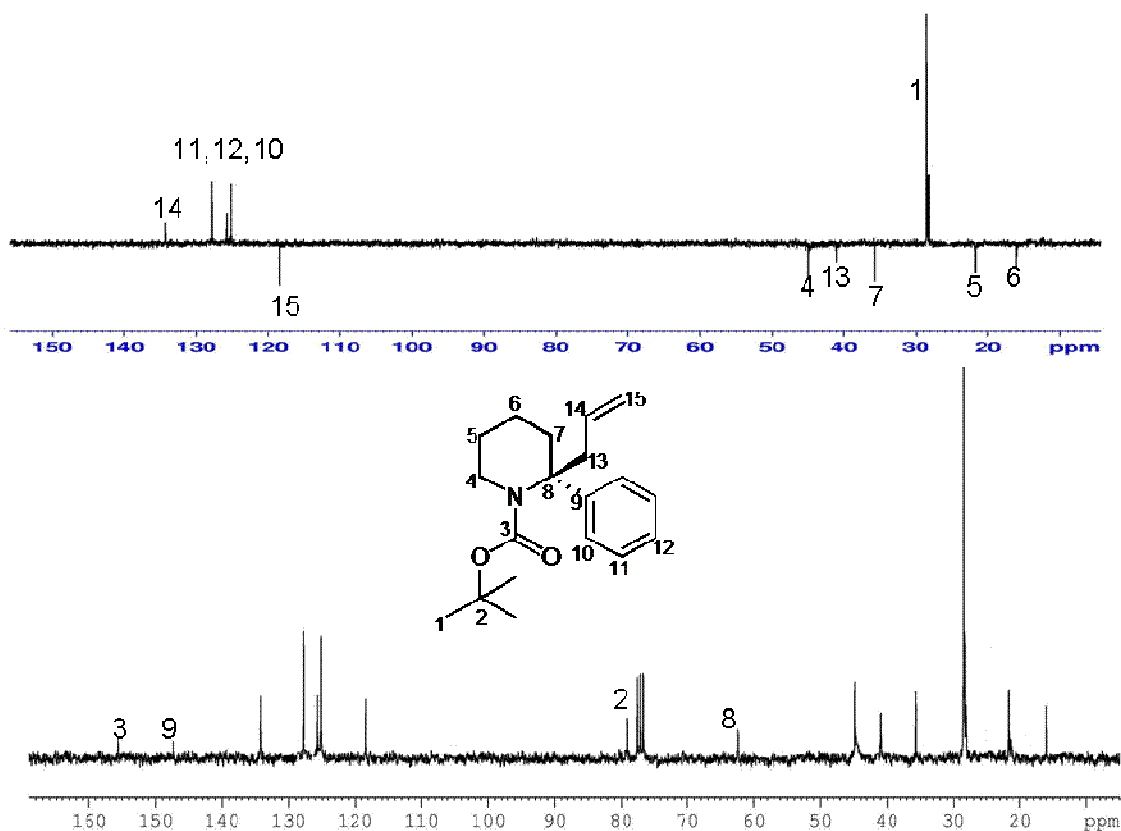


4.6. With allyl bromide

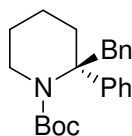


Using **General Procedure C**, *R*-**3** of 96:4 er (261 mg, 1.0 mmol), TMEDA (0.6 mL, 4.0 mmol, 4.0 equiv), Et₂O (10 mL), *s*-BuLi (1.0 mL, 1.0 mmol, 1.0 M, 1.0 equiv), ZnCl₂ (0.6 mL, 1.0 M solution in Et₂O, 0.6 equiv), CuCN·2LiCl [prepared from CuCN (107 mg, 1.2 mmol, 1.2 equiv) and LiCl (107 mg, 2.5 mmol, 2.5 equiv)], allyl bromide (0.13 mL, 1.5 mmol, 1.5 equiv) for 10 h prior to addition of 2 mL MeOH and warming to rt, gave the crude product as an oil. Purification by silica gel chromatography eluting with hexane-EtOAc (95:5) afforded 198 mg of *S*-**13** as an oil in 66% yield and 92:8 er. All other spectroscopic data as reported⁷ for *rac*-**13**. The enantiomer ratio was evaluated by CSP-SFC, under the following column conditions: **Column**: Pirkle Whelk-O-1, **Flow Rate** = 1.0 mL/min, **Polarity Modifier** = 3% EtOH. The minor enantiomer elutes after ~10.1 min and the major elutes after ~13.1 min.





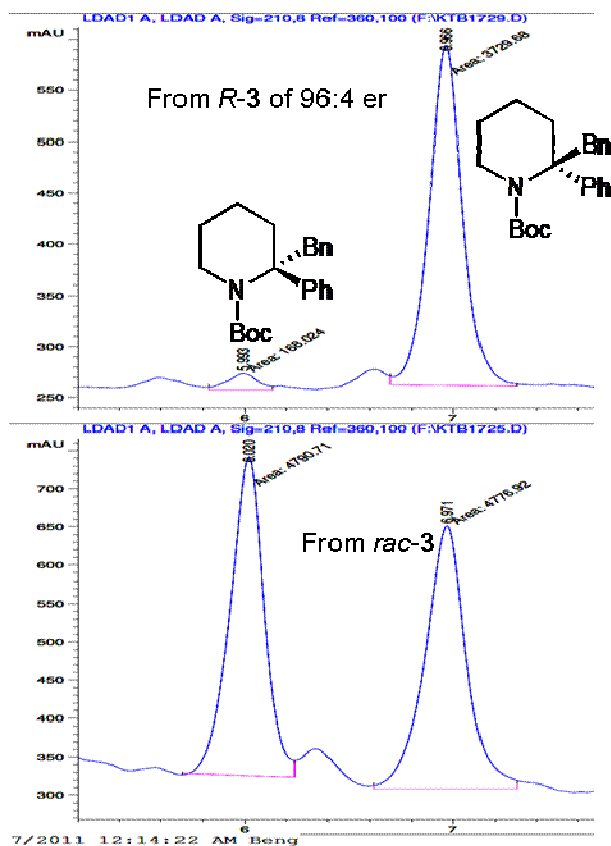
4.7. With benzyl bromide

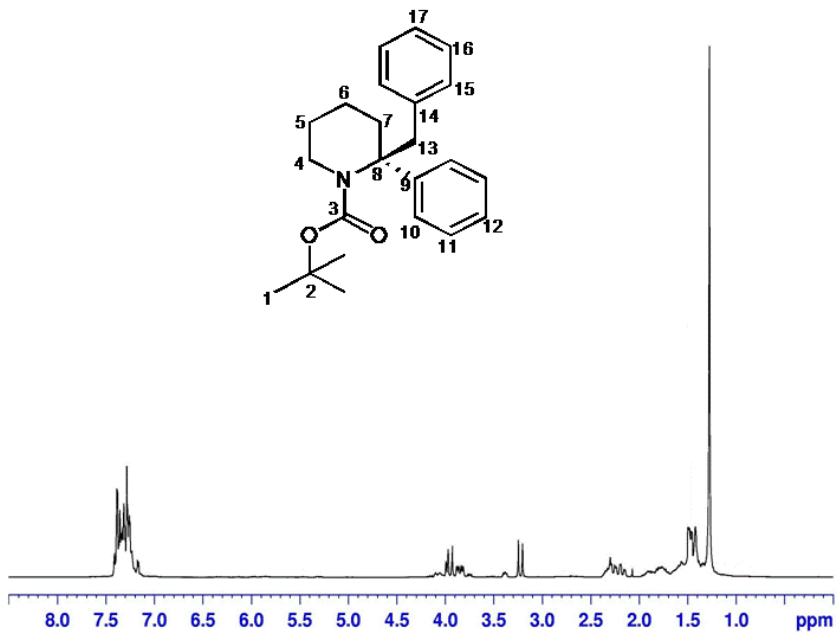
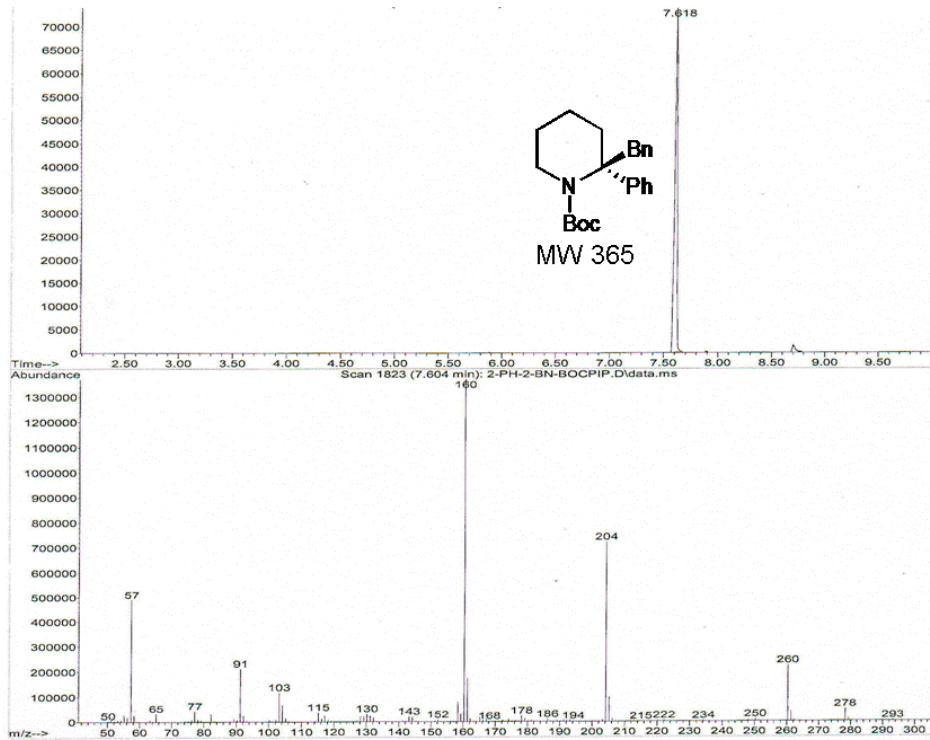


S-14

Using **General Procedure C**, *R-3* of 96:4 er (261 mg, 1.0 mmol), TMEDA (0.6 mL, 4.0 mmol, 4.0 equiv), Et₂O (10 mL), *s*-BuLi (1.0 mL, 1.0 mmol, 1.0 M, 1.0 equiv), ZnCl₂ (0.6 mL, 1.0 M solution in Et₂O, 0.6 equiv), CuCN·2LiCl [prepared from CuCN (107 mg, 1.2 mmol, 1.2 equiv) and LiCl (107 mg, 2.5 mmol, 2.5 equiv)], benzyl bromide (150 mg, 1.5 mmol, 1.5 equiv) for 10 h prior to addition of 2 mL MeOH and warming to rt, gave the crude product as an oil. Purification by silica gel chromatography eluting with hexane-EtOAc (95:5) afforded 259 mg of *S-14* as an oil in 71% yield and 94:6 er. ¹H NMR (300 MHz, CDCl₃) δ = 7.50–7.18 (10H, m), 4.21 – 3.48 (3H, m), 3.25 (1H, dd), 2.45–1.40 (6H, m), 1.35 (9H, s). ¹³C NMR (75.5 MHz, CDCl₃) δ = 155.5 (C=O), 138.6 (C), 137.8 (C), 128.5 (CH), 128.0 (CH), 127.8 (CH), 126.4 (CH), 125.8 (CH), 125.3 (CH), 79.7 (C), 63.3 (C), 43.8 (CH₂), 39.8 (CH₂), 40.0 (CH₂), 28.3 (3 x CH₃), 20.9 (CH₂), 14.8 (CH₂). The enantiomer ratio was evaluated by CSP-SFC, monitoring at

210 nm, by comparison a racemic sample, under the following column conditions: **Column:** Pirkle Whelk-O-1, **Flow Rate** = 1.0 mL/min, **Polarity Modifier** = 5.0% EtOH. The minor enantiomer elutes after ~6 min and the major elutes after ~7 min.



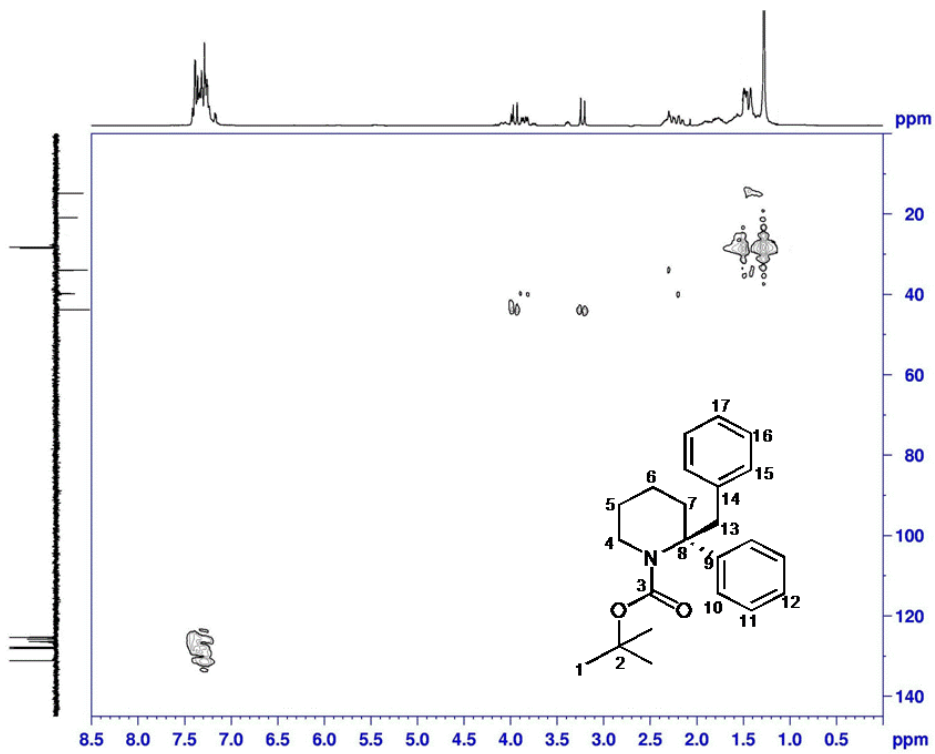
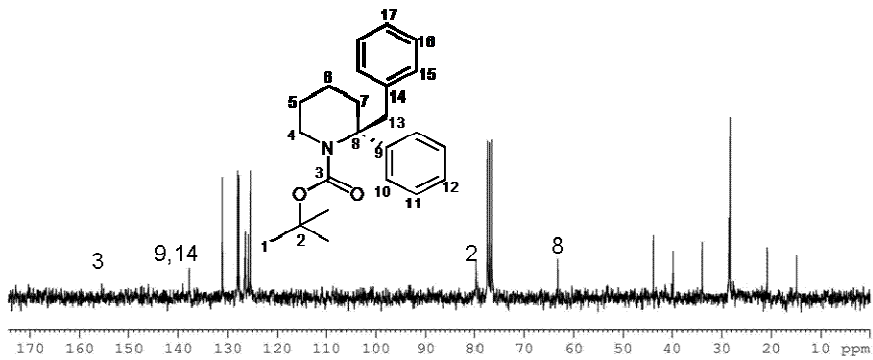
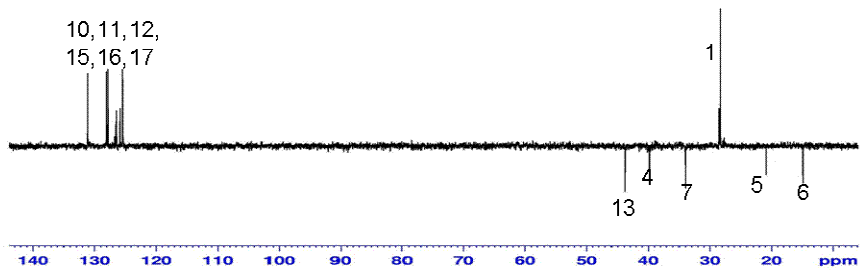


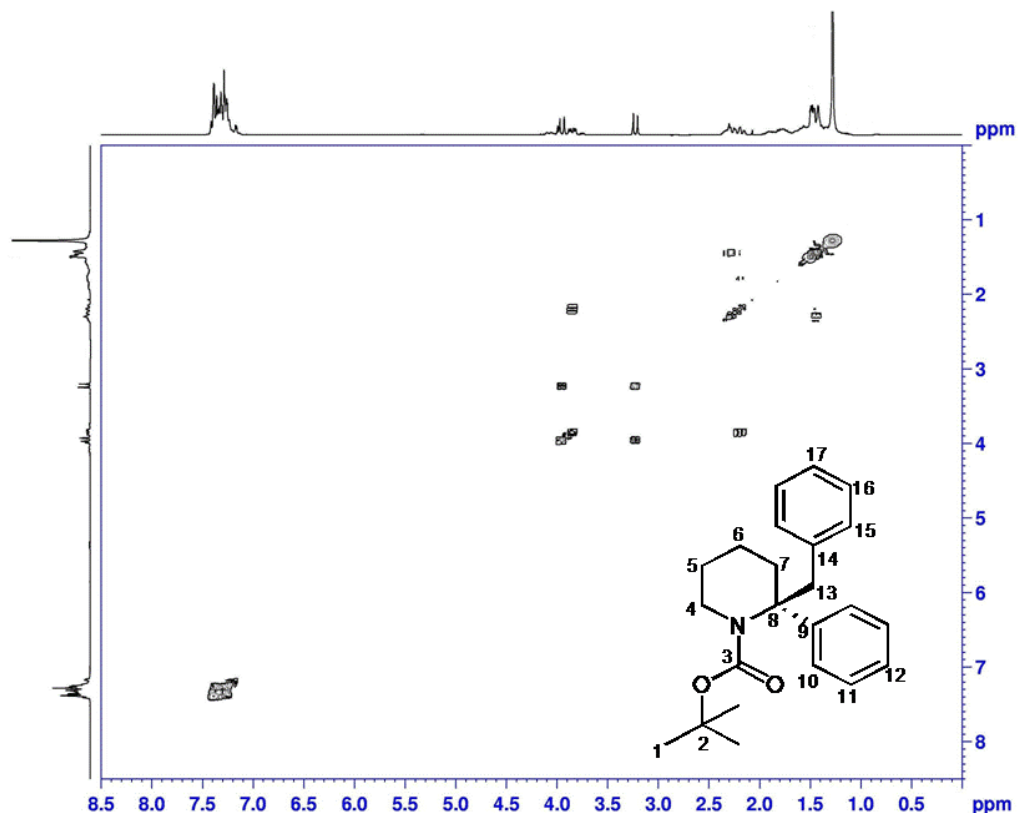
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 EXPNO 9
 PROCNO 1

F2 - Acquisition Parameters
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 Time 2.26
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 PULPROG zg
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 SOLVENT CDCl3
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 DS 0
 SWH 6172.839 Hz
 FIDRES 0.094190 Hz
 AQ 5.3084660 sec
 RG 50.8
 DW 81.000 usec
 DE 6.00 usec
 TE 295.6 K
 DI 1.0000000 sec
 MCREST 0.0000000 sec
 MCWRK 0.0150000 sec

***** CHANNEL f1 *****
 NUC1 1H
 P1 12.20 usec
 PL1 -1.00 dB
 SF01 300.1318534 MHz

F2 - Processing parameters
 SI 32768
 SF 300.1300000 MHz
 WDW EM
 SSB 0
 LB 0.30 Hz
 GB 0
 PC 1.40

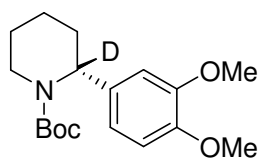




5. Lithiation-substitution of other (*R*)-*N*-Boc-2-arylpiperidines with several electrophiles

5.1. (*R*)-*N*-Boc-2-(3,4-dimethoxy)phenylpiperidine:

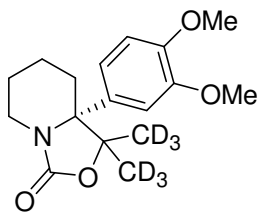
5.1.1. With MeOD



***R*-4-*d*₁**

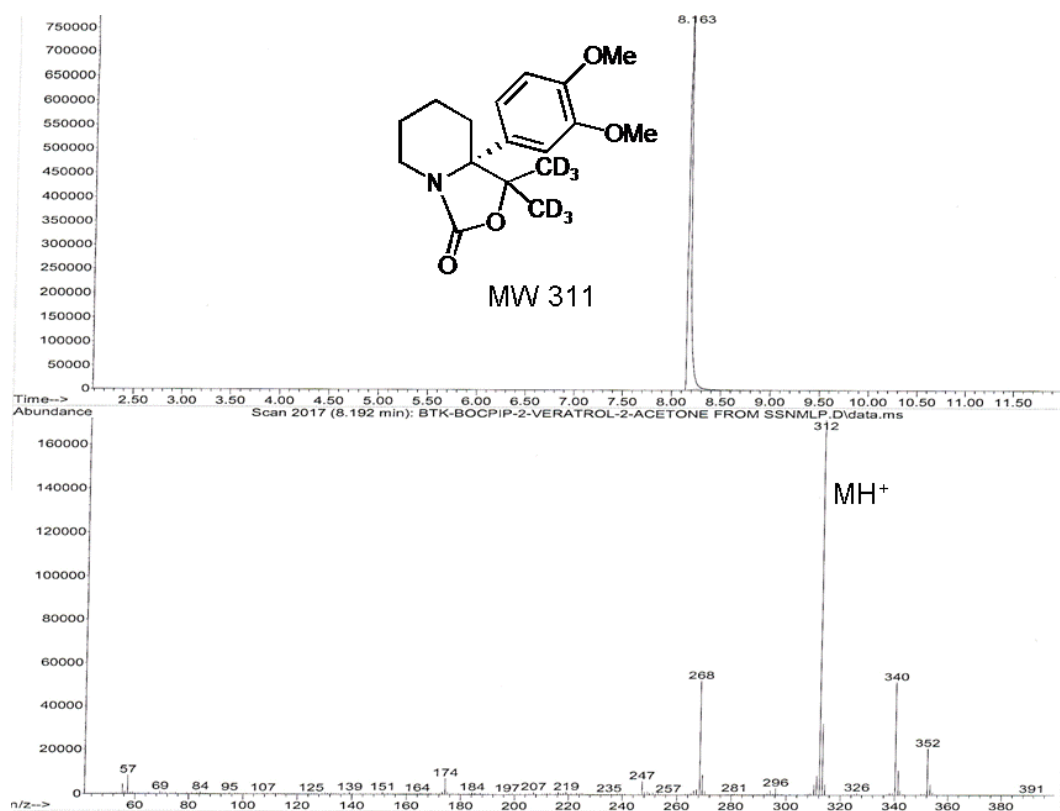
Using **General Procedure D**, *R*-4 of 97:3 er and 0.1 mL MeOD showed complete deuteration after 30 min. There is a noticeable shift of the protonated base peak from *m/z* 222 for **4** to *m/z* 223 for **4-*d*₁**.

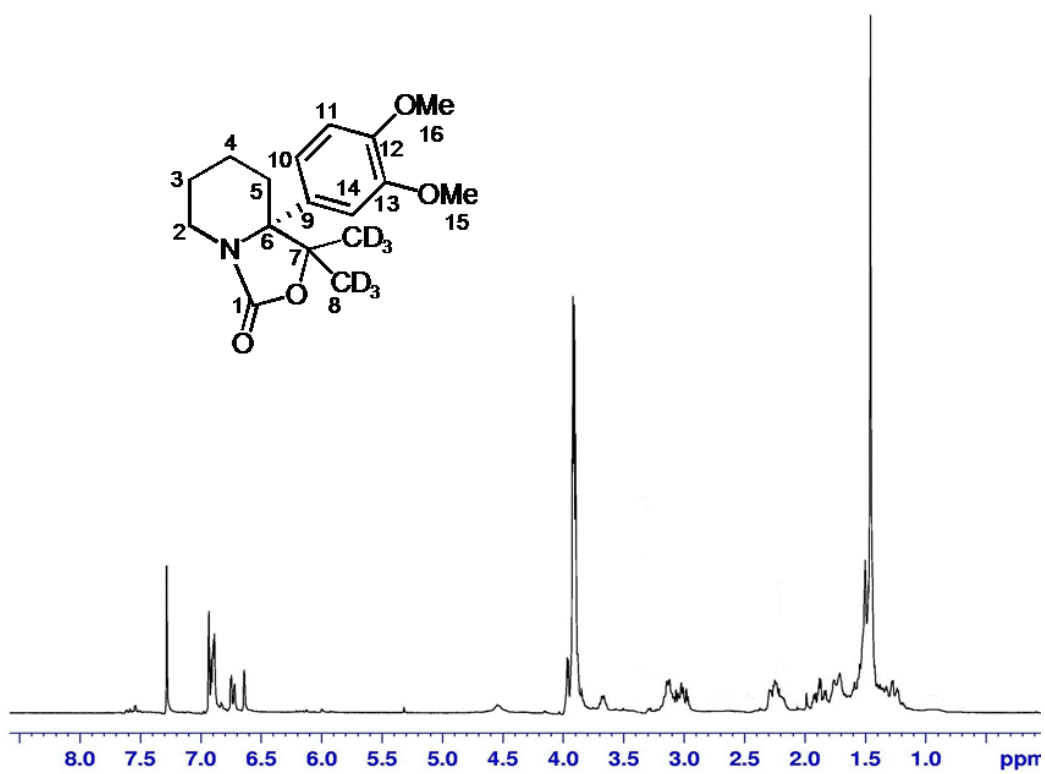
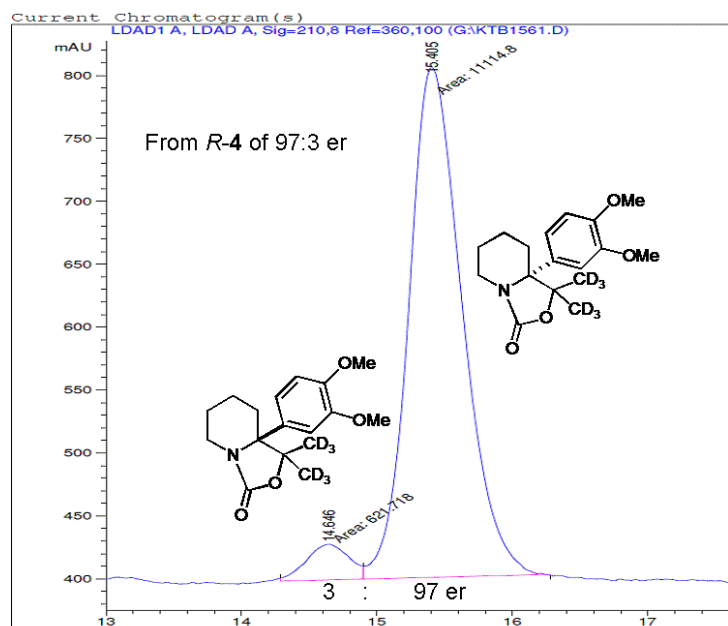
5.1.3. With acetone-*d*₆

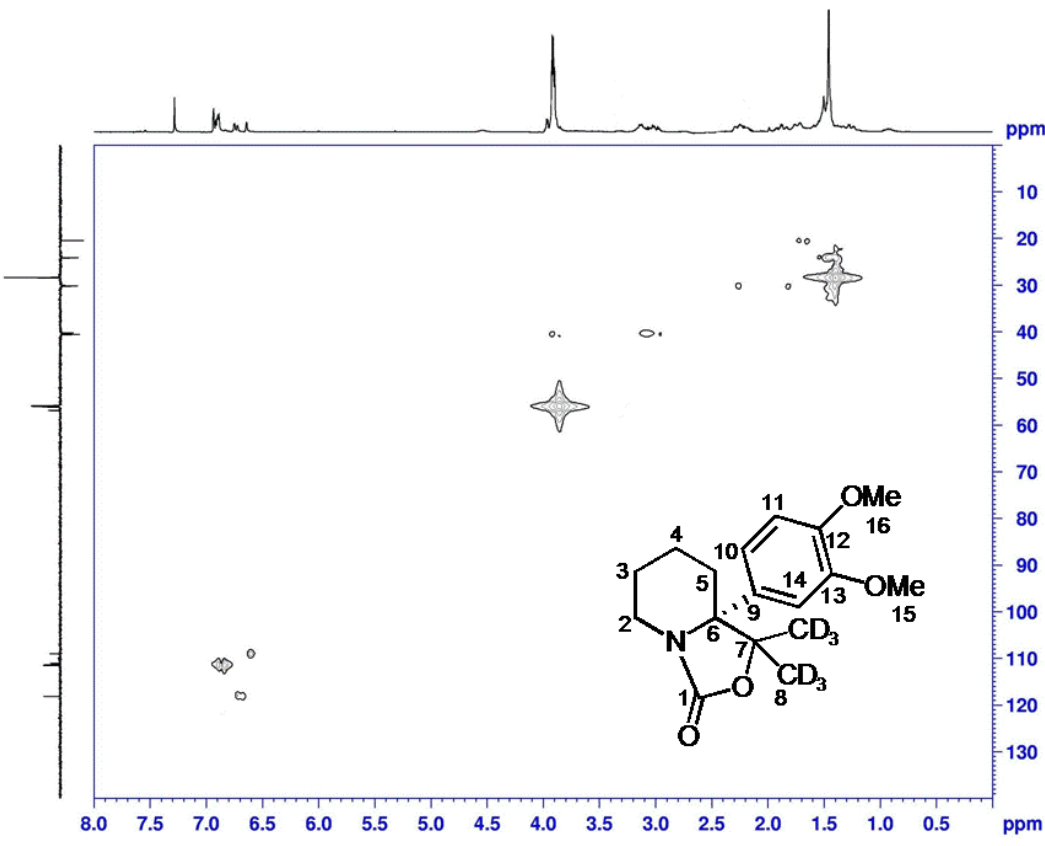
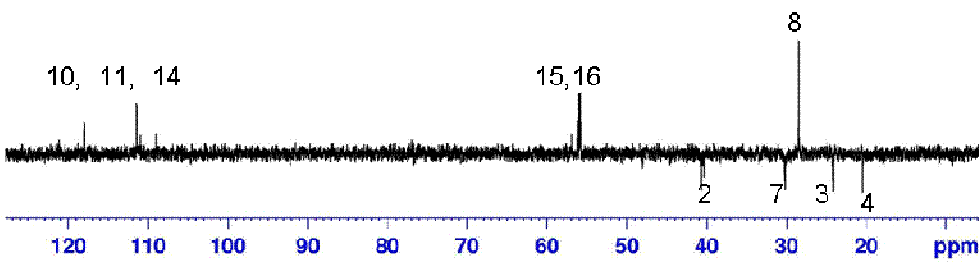
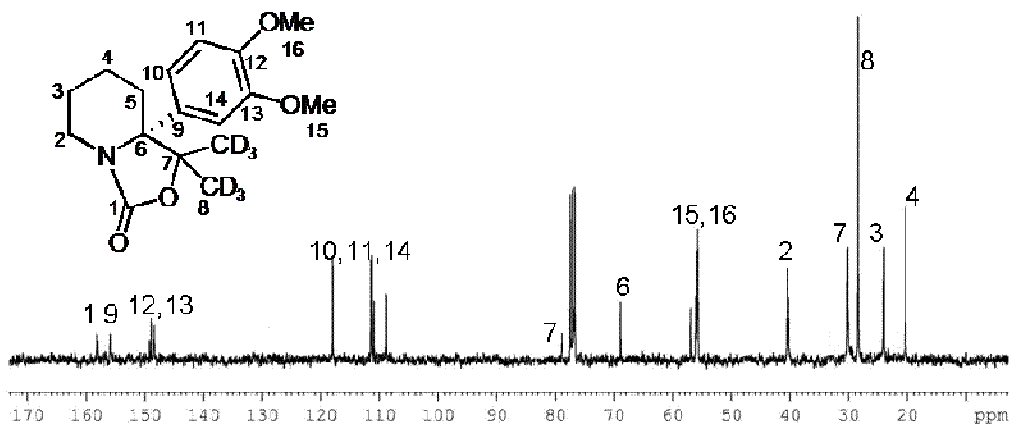


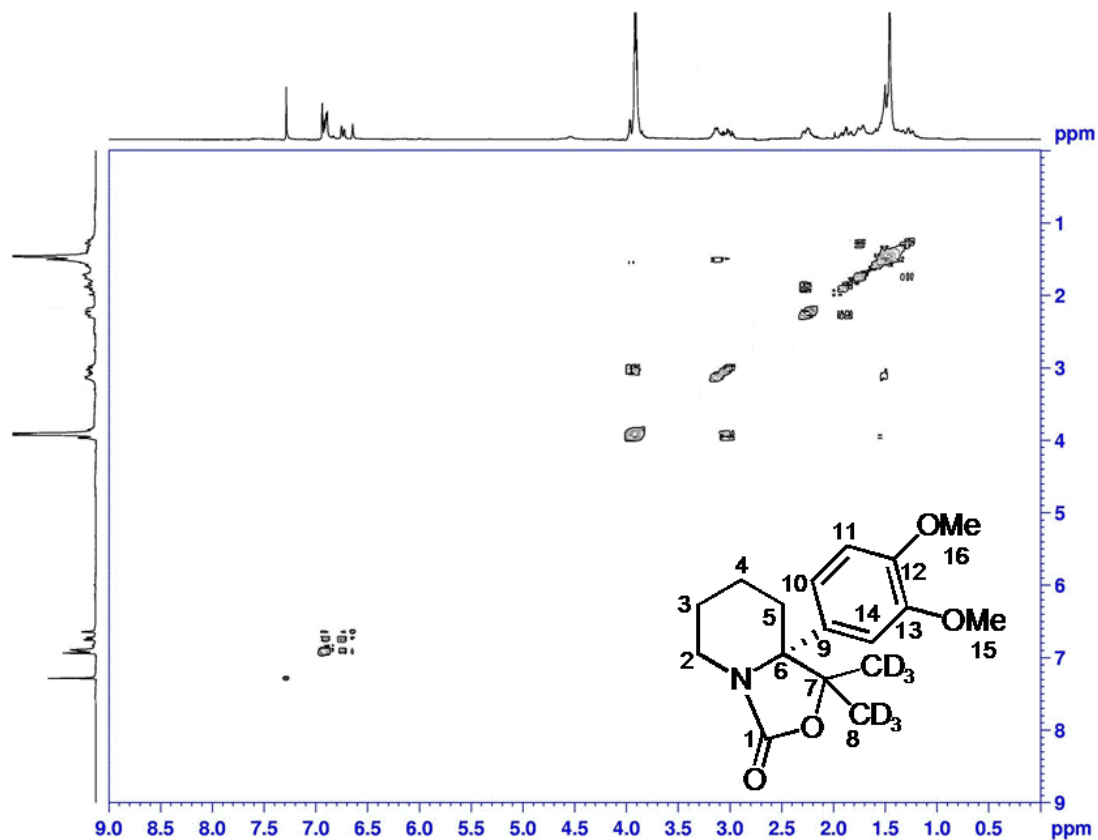
***R*-15**

Using **General Procedure B**, *R-4* of 97:3 er (321 mg, 1.0 mmol), TMEDA (0.6 mL, 4.0 mmol, 4.0 equiv), Et₂O (10 mL), *s*-BuLi (0.8 mL, 1.0 mmol, 1.2 M, 1.0 equiv), (CD₃)₂CO (96 mg, 1.5 mmol, 1.5 equiv) for 2 h prior to warming to rt and addition of 2 mL MeOH gave the crude product as an oil. Purification by silica gel chromatography eluting with hexane-EtOAc (30:70) afforded 289 mg of the oxazolidinone *R-15* as an amorphous solid in 93% yield and 97:3 er. ¹H NMR (300 MHz, CDCl₃) δ = 6.95–6.65 (3H, m), 4.10–3.68 (7H, m), 3.31–2.95 (1H, m), 2.25 (1H, m), 2.22–1.31 (5H and 6D, m) ¹³C NMR (75.5 MHz, CDCl₃) δ = 158.2 and 158.1 (C=O), 156.0 (C), 149.3, 149.1, and 148.4 (C), 118.0 (CH), 111.5 and 111.4 (CH), 109.0 (CH), 78.9 (C), 69.1 (C), 56.9, 56.1, 56.0, 55.9 (OMe), 40.6 and 40.3 (CH₂), 30.2, 30.0 (CH₂), 28.4 (2 x CD₃), 24.1 (CH₂), 20.4 (CH₂). The enantiomer ratio was evaluated by CSP-SFC, under the following column conditions: **Column:** Pirkle Whelk-O-1, **Flow Rate** = 2.0 mL/min, **Polarity Modifier** = 10% EtOH. The minor enantiomer elutes after ~14. min and the major elutes after ~15.4 min.



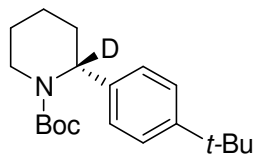






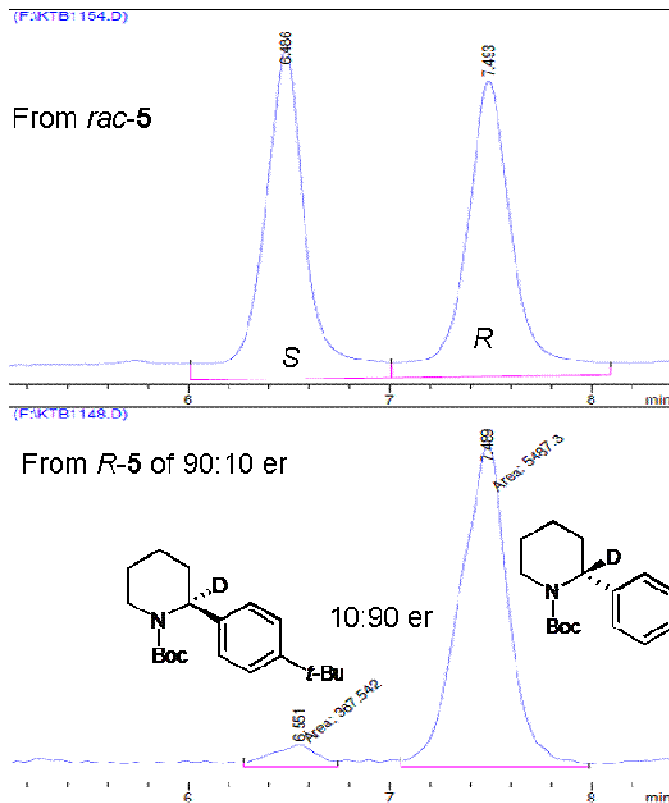
5.2. (*R*)-*N*-Boc-2-(4-*tert*-butyl)phenylpiperidine:

5.2.1. With MeOD



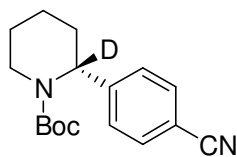
R-5- d_1

Using **General Procedure D**, *R*-5 of 90:10 er and 0.1 mL MeOD showed complete deuteration after 30 min.



5.3. (*R*)-*N*-Boc-2-(4-cyano)phenylpiperidine:

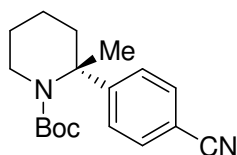
5.3.1. With MeOD



R-6-*d*₁

Using **General Procedure D**, *R*-6 of 91:9 er and 0.1 mL MeOD showed complete deuteration after 30 min and **6-*d*₁** was obtained with no loss of er. There is a noticeable shift of the protonated base peak from *m/z* 287 for **6** to *m/z* 288 for **6-*d*₁**.

5.3.2. With Me₂SO₄

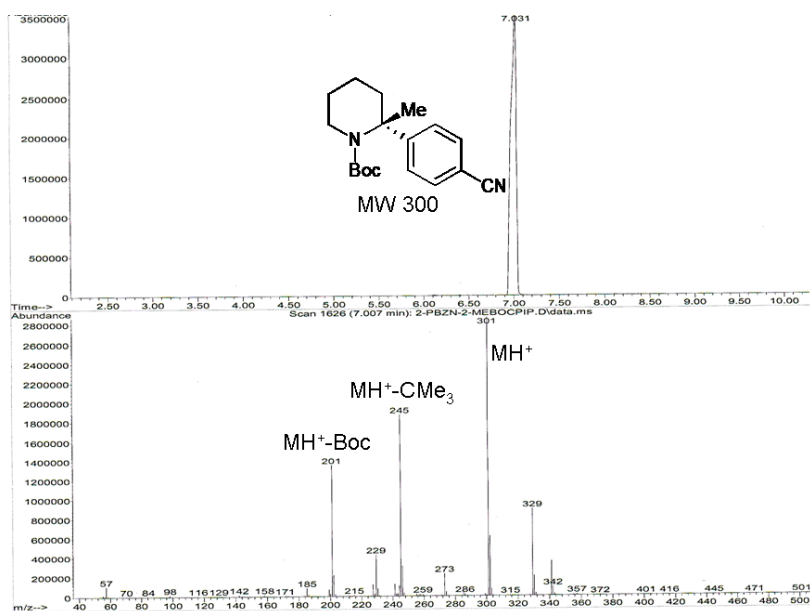


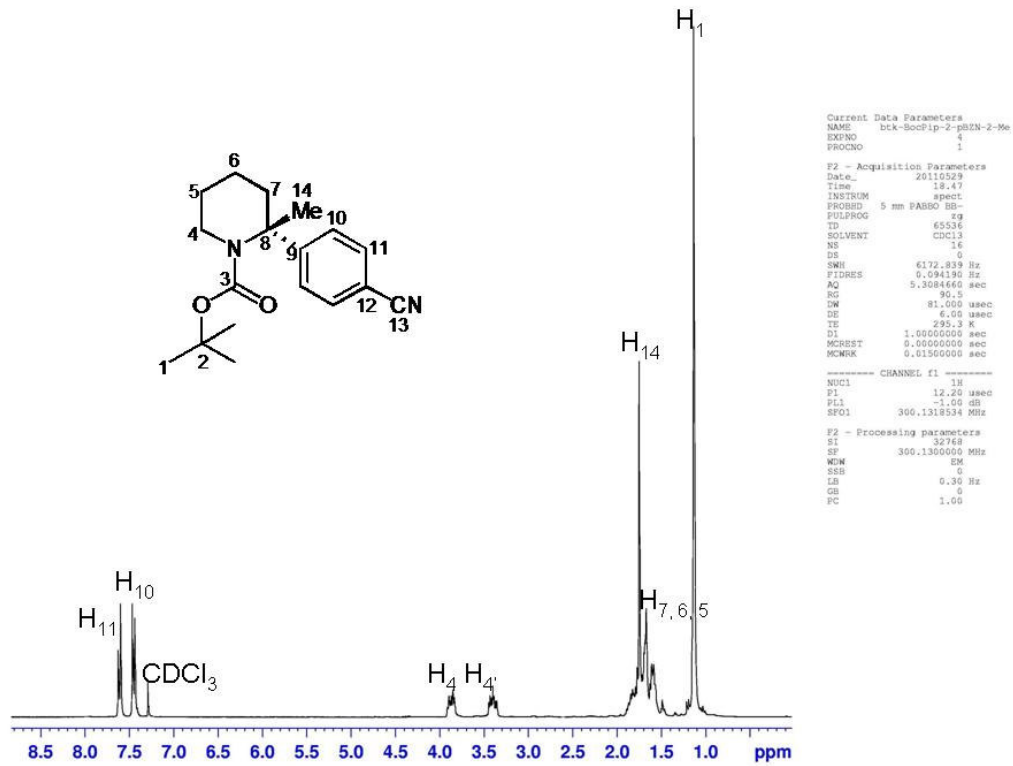
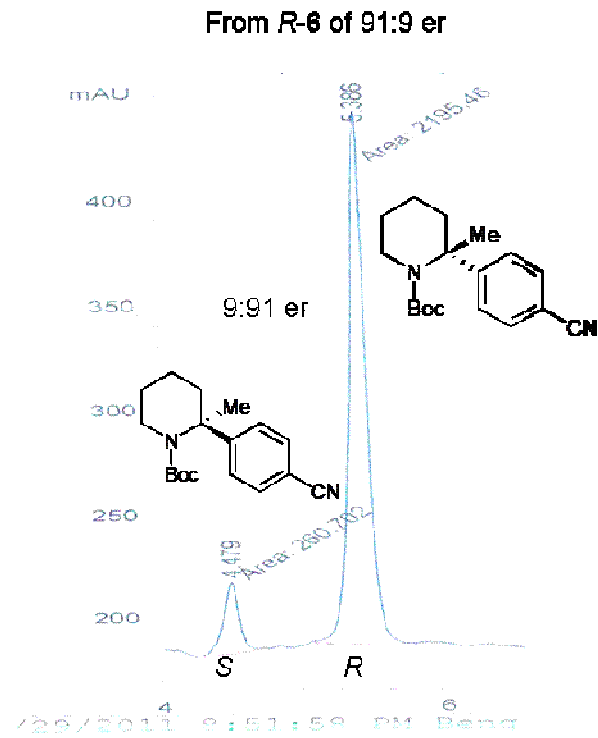
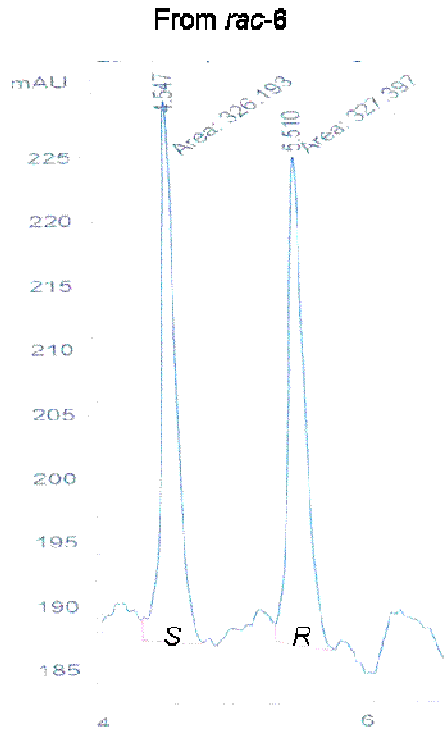
R-16

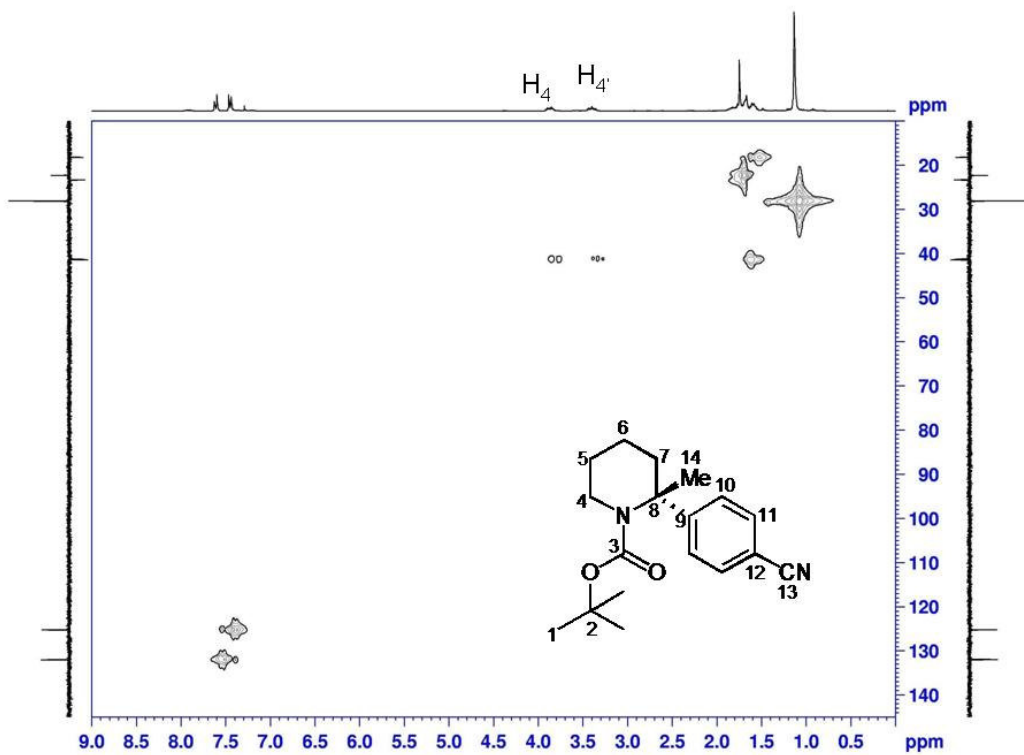
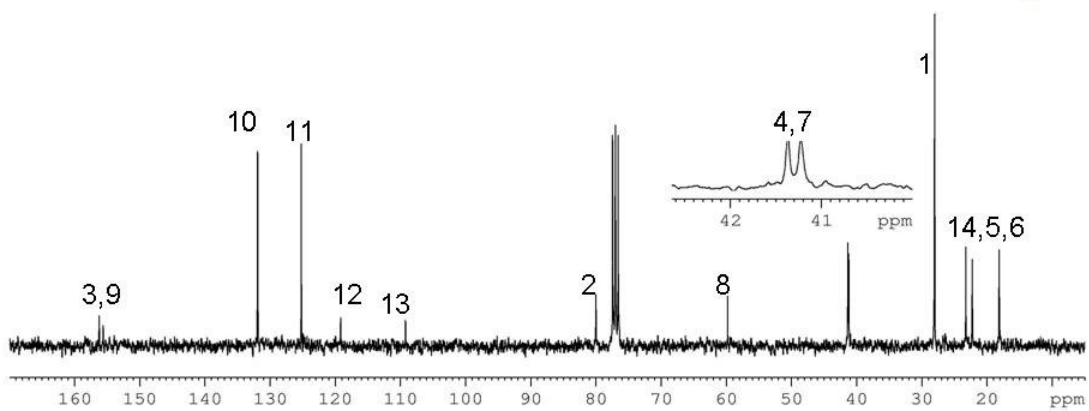
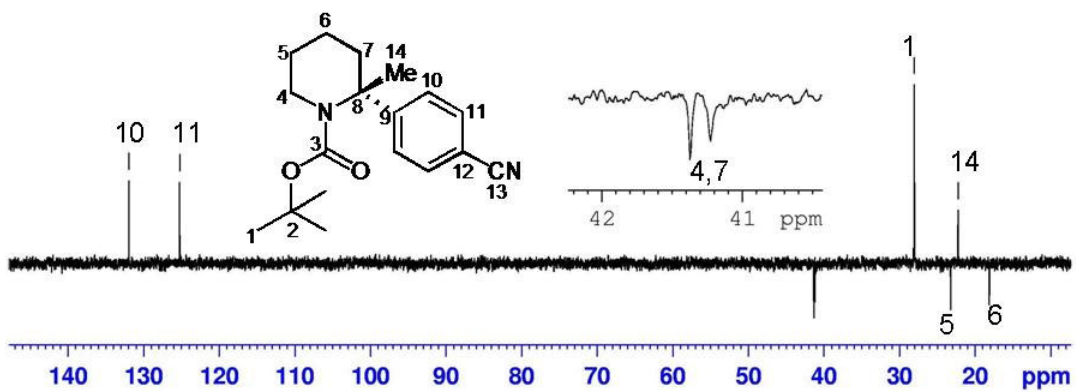
Using **General Procedure B**, *R*-6 of 90:10 er (286 mg, 1.0 mmol), TMEDA (0.6 mL, 4.0 mmol, 4.0 equiv), Et₂O (10 mL), *s*-BuLi (1.0 mL, 1.0 mmol, 1.0 M, 1.0 equiv), Me₂SO₄ (0.15 mL, 1.5

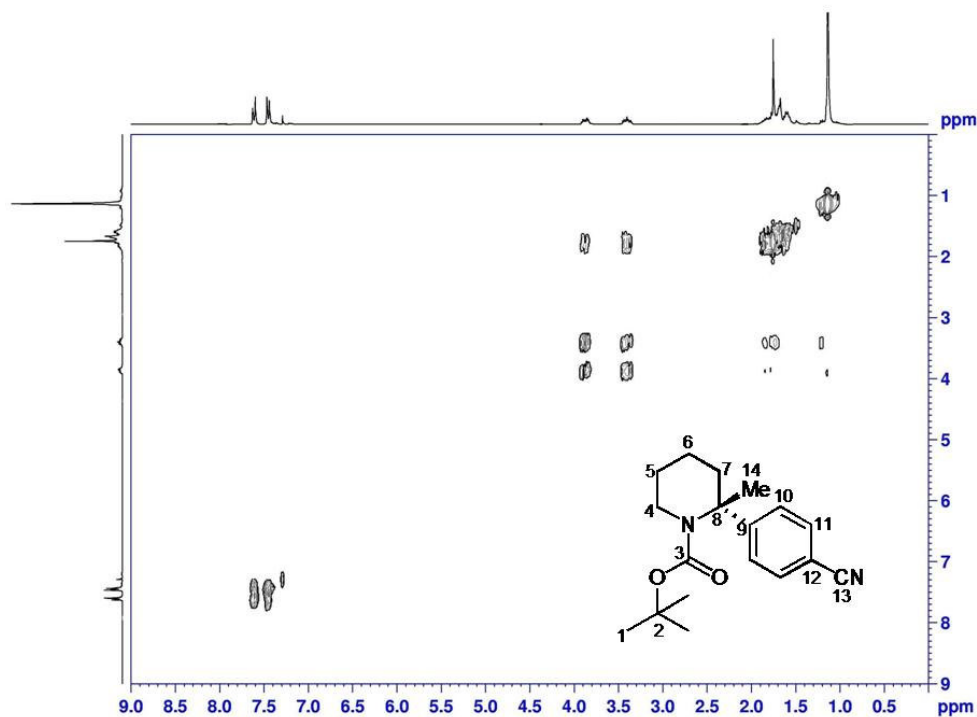
mmol, 1.5 equiv) for 18 h prior to addition of 2 mL MeOH, gave the crude product as an oil. Purification by silica gel chromatography eluting with hexane-EtOAc (90:10) afforded 213 mg of *R*-**16** as an oil in 71% yield and 90:10 er. ^1H NMR (300 MHz, CDCl_3) δ 7.63 (d, 2H), 7.45 (d, 2H), 3.88 (m, 1H), 3.41 (m, 1H), 1.92-1.51 (m, 9H) 1.12 (s, 9H), ^{13}C NMR (75.5 MHz, CDCl_3) δ 156.2 (C=O), 155.6 (C), 131.9 (CH), 125.2 (CH), 119.2 (C), 109.2 (C of nitrile), 80.0 (C), 59.8 (C), 41.4 (CH_2), 41.2 (CH_2), 28.1 (3 x CH_3), 23.3 (CH_2), 22.3 (CH_3), 18.1 (CH_2).

The enantiomer ratio was evaluated by CSP-SFC, monitoring at 210 nm, by comparison with an authentic racemic sample, under the following column conditions: **Column:** Pirkle Whelk-O-1, **Flow Rate** = 2.0 mL/min, **Polarity Modifier** = 3.0% EtOH. The minor enantiomer elutes after ~4.5 min and the major elutes after ~5.4 min.



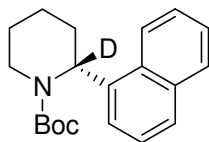






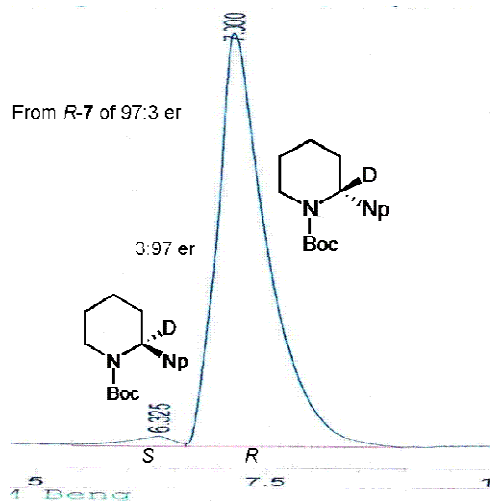
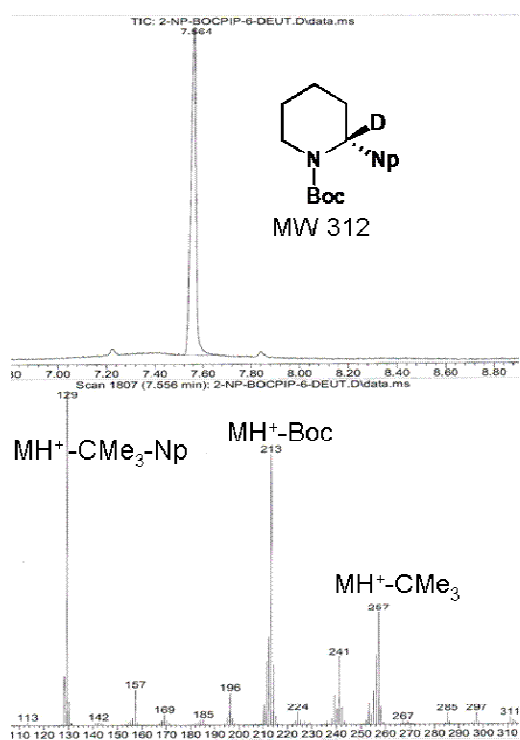
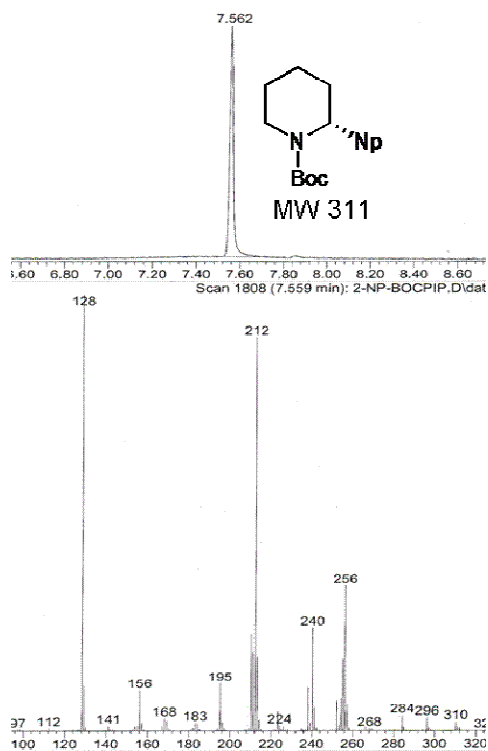
5.4. (*R*)-*N*-Boc-2-(1-naphthyl)piperidine:

5.4.1. With MeOD

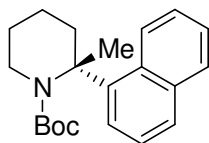


R-**7**·**d**₁

Using **General Procedure D**, *R*-**7** of 97:3 er and 0.1 mL MeOD showed complete deuteration after 30 min and *R*-**7**·**d**₁ was obtained with no loss of er. There is a noticeable shift of the protonated base peak from *m/z* 128 for **7** to *m/z* 129 for **7**·**d**₁.



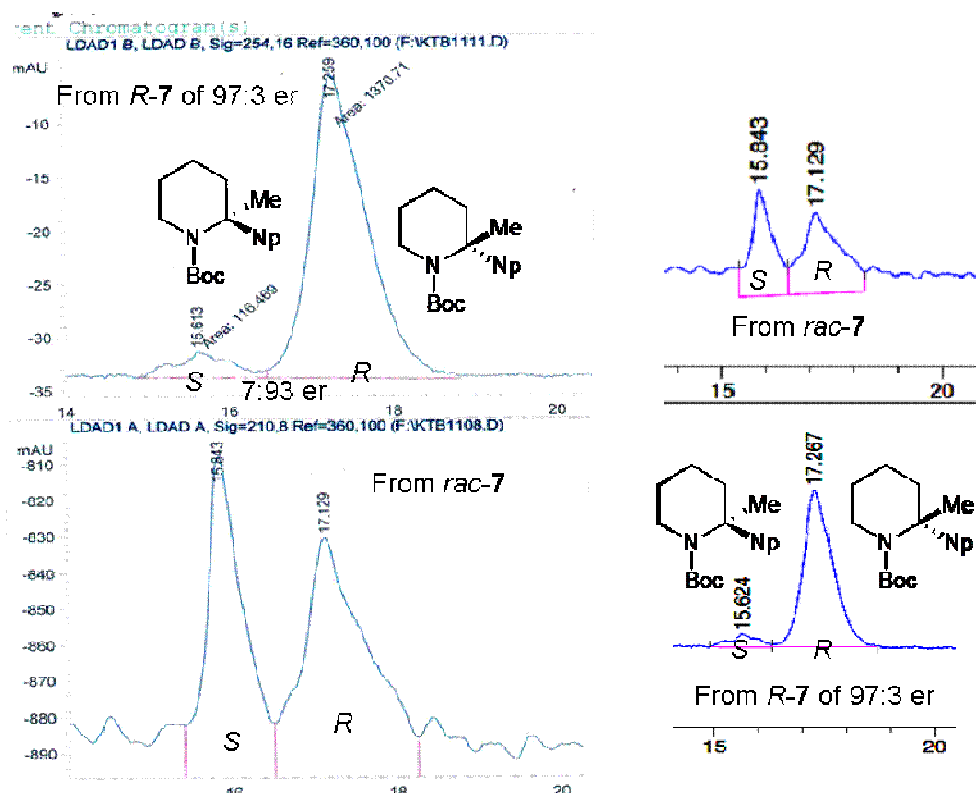
5.4.2. With Me₂SO₄

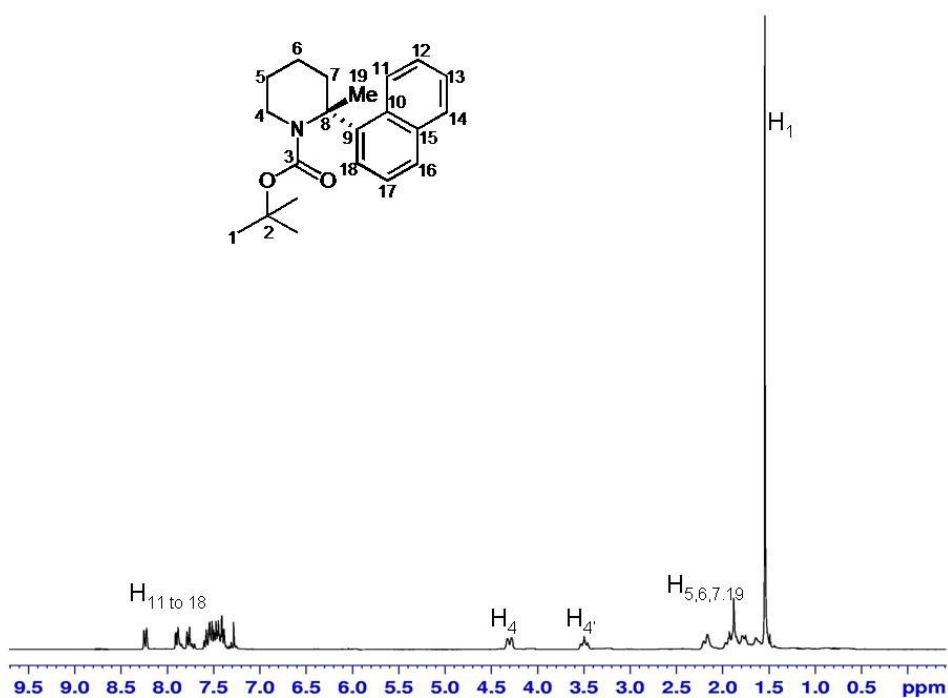
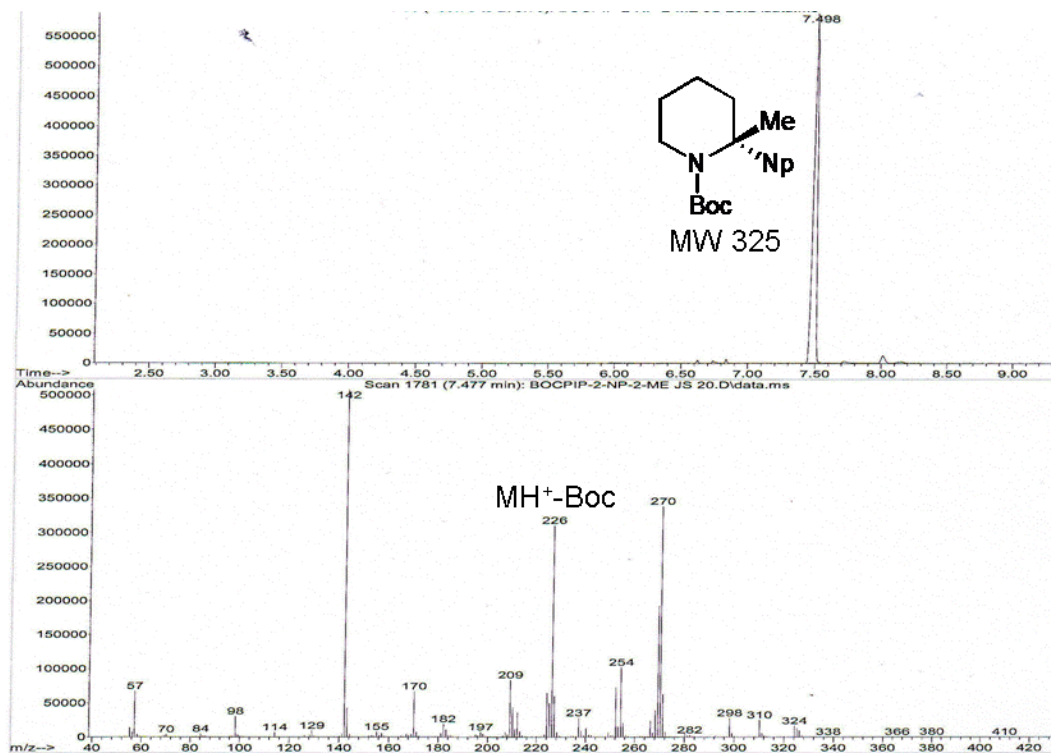


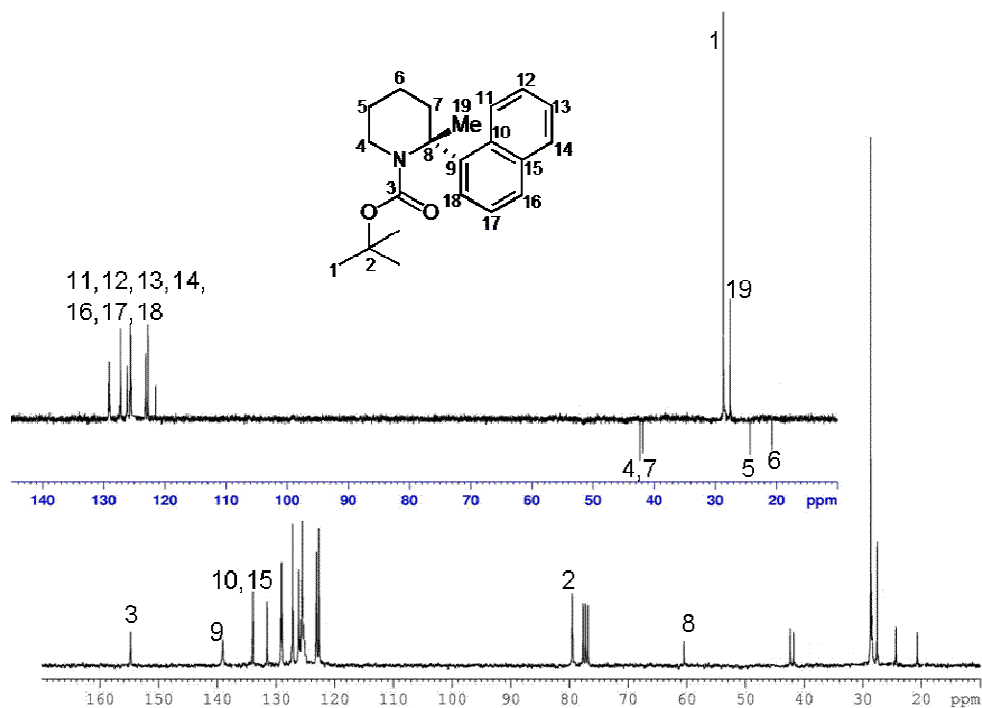
R-17

Using **General Procedure B**, R-7 of 97:3 er (311 mg, 1.0 mmol), TMEDA (0.6 mL, 4.0 mmol, 4.0 equiv), Et₂O (10 mL), *s*-BuLi (1.0 mL, 1.0 mmol, 1.0 M, 1.0 equiv), Me₂SO₄ (0.15 mL, 1.5 mmol, 1.5 equiv) for 18 h prior to addition of 2 mL MeOH, gave the crude product as an oil.

Purification by silica gel chromatography eluting with hexane-EtOAc (95:5) afforded 240 mg of *R*-**17** as an oil in 74% yield and 93:7 er. ^1H NMR (300 MHz, CDCl_3) δ = 8.34–7.37 (m, 6H), 4.35 (dd, 1H), 3.50 (m, 1H), 2.22 (m, 1H), 2.05–1.51 (m, 17H), ^{13}C NMR (75.5 MHz, CDCl_3) δ = 155.4 (C=O), 139.1 (C), 134.0 (C) 131.5 (C), 128.9 (CH), 127.3 (CH), 125.8 (CH), 125.4 (CH), 124.9 (CH), 123.5 (CH), 123.2 (CH) 79.5, 60.4 (C), 41.6 (CH_2), 41.2 (CH_2), 28.3 (3 x CH_3), 27.2 (CH_3), 25.1 (CH_2), 20.3 (CH_2). The enantiomer ratio was evaluated by CSP-SFC, monitoring at 210 nm, by comparison with an authentic racemic sample, under the following column conditions: **Column:** Pirkle Whelk-O-1, **Flow Rate** = 1.0 mL/min, **Polarity Modifier** = 3.0% EtOH. The minor enantiomer elutes after ~15.6 min and the major elutes after ~17.3 min.

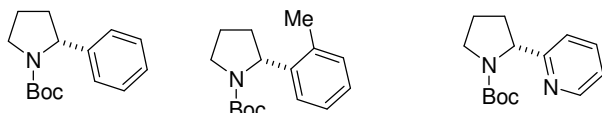
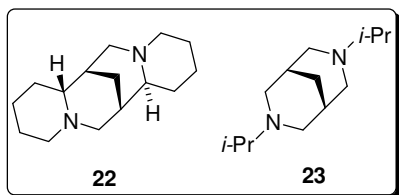
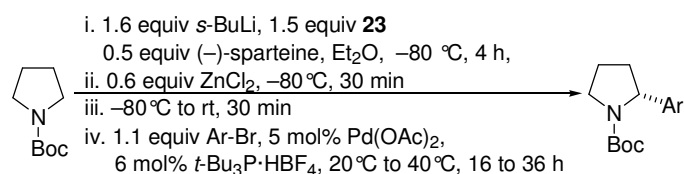






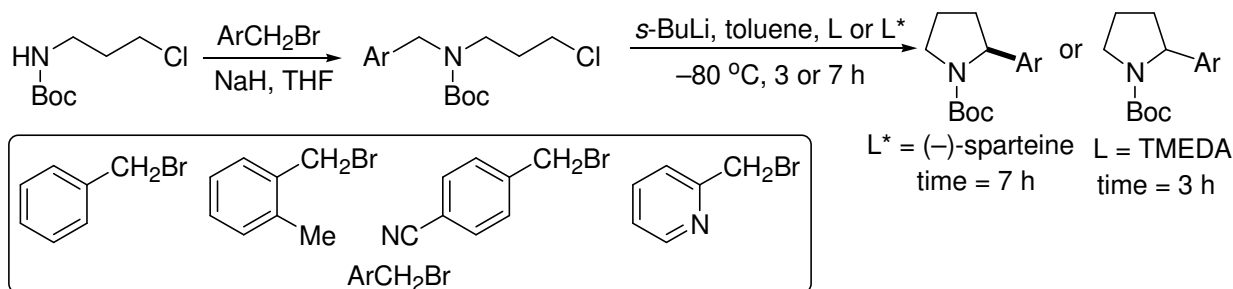
6. Synthesis of *N*-Boc-2-arylpyrrolidine

R-**18** (96:4 er) was synthesized using the Campos procedure⁹. Subsequent syntheses of (*R*)-*N*-Boc-2-arylpyrrolidines were accomplished using the two-ligand catalytic asymmetric deprotonation-transmetalation-Negishi coupling method reported by O'Brien and Campos.⁵



R-**18** (77%, 96:4 er) *R*-**19** (80%, 90:10 er) *R*-**20** (66%, 90:10 er)

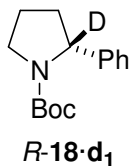
(*S*)-*N*-Boc-2-phenylpyrrolidine of 96:4 er was synthesized using Beak's lithiation-cyclization procedure⁴ with (-)-sparteine. When (-)-sparteine was replaced by TMEDA, the racemic 2-arylpyrrolidines, (for er evaluation purposes on CSP-SFC) were prepared in 10 mg scale.



Note: The racemic lithiation of *N*-Boc-pyrrolidine in the presence of TMEDA proceeds in very low yield under the Campos conditions.⁵ In some cases the racemic arylation was accomplished using the diamine-free route reported by O'Brien and coworkers.¹⁰

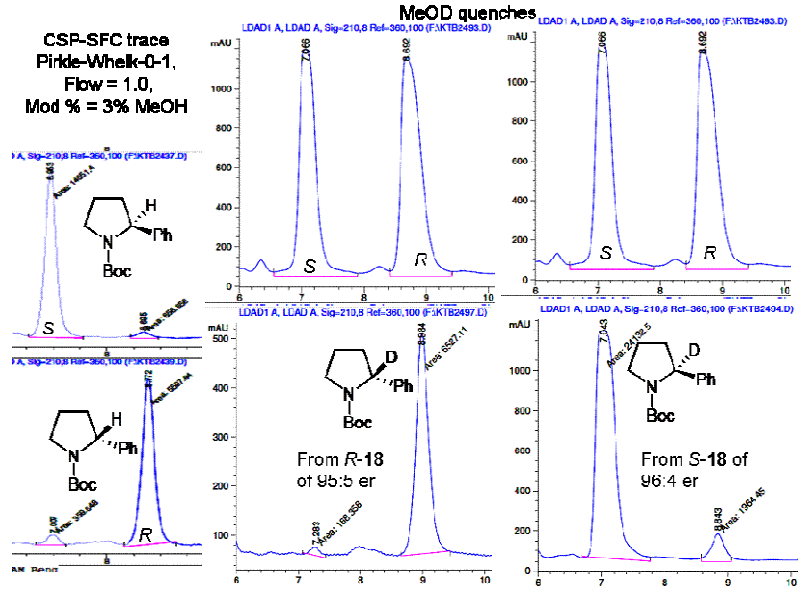
7. Lithiation-substitution of (*R*)-*N*-Boc-2-phenylpyrrolidine

7.1. Lithiation-substitution with MeOD

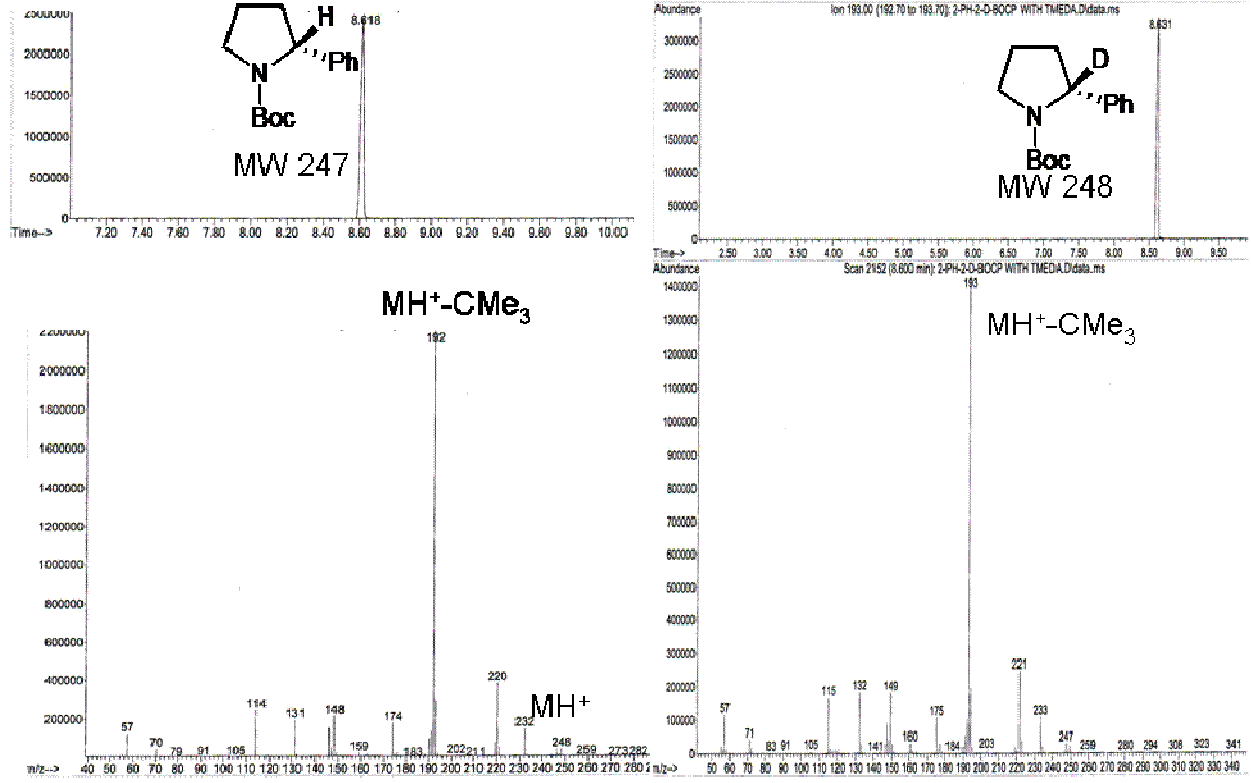


Using **General Procedure G**, *R*-**18** of 96:4 er and 0.1 mL MeOD showed complete deuteration after 3 h and *R*-**18**·d₁ was obtained with no loss of er. There is a noticeable shift of the protonated base peak from *m/z* 192 for **18** to *m/z* 193 for *R*-**18**·d₁.

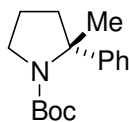
S-**18** of 96:4 er also gave the same results.



GC-MS traces from chemical ionization



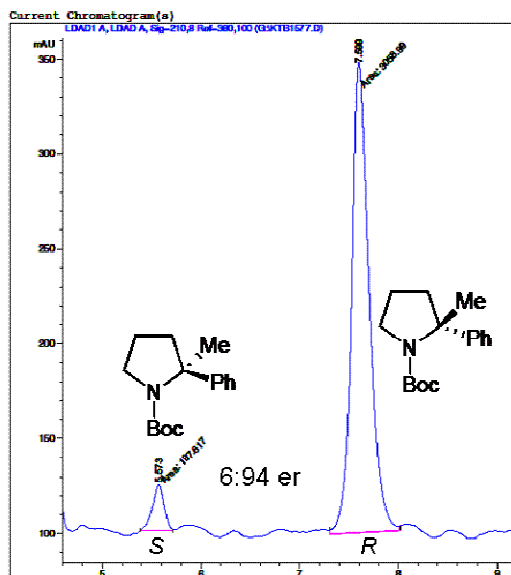
7.2. Lithiation-substitution with Me₂SO₄

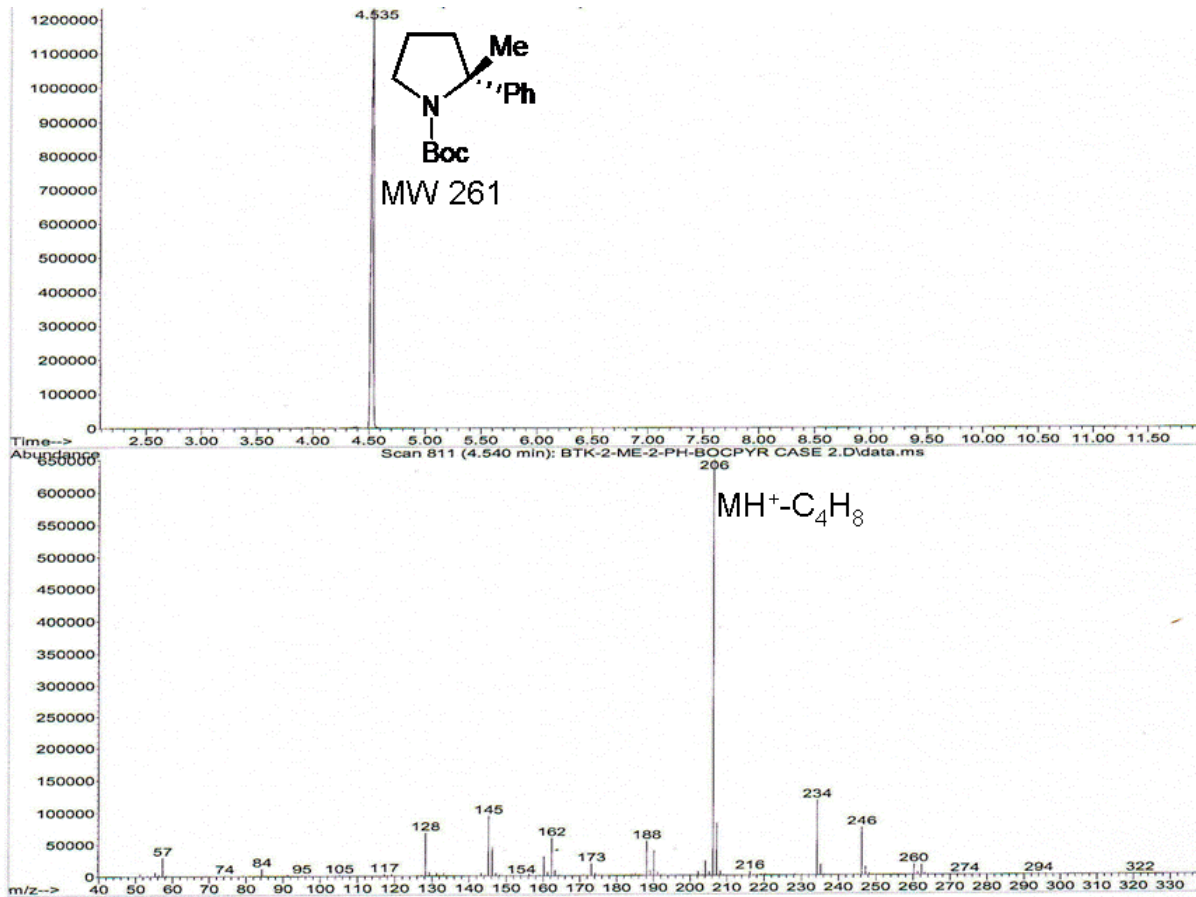


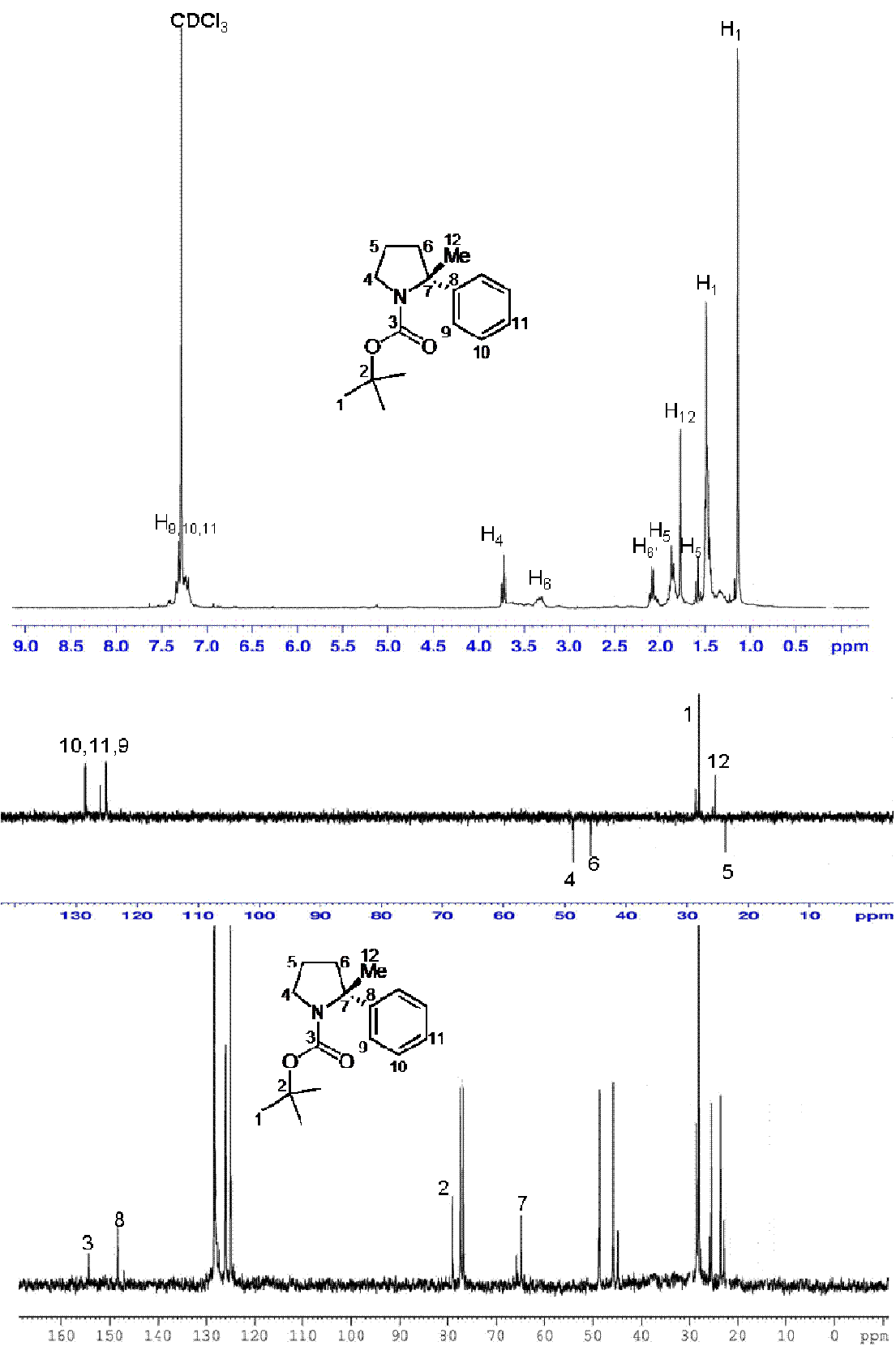
R-25

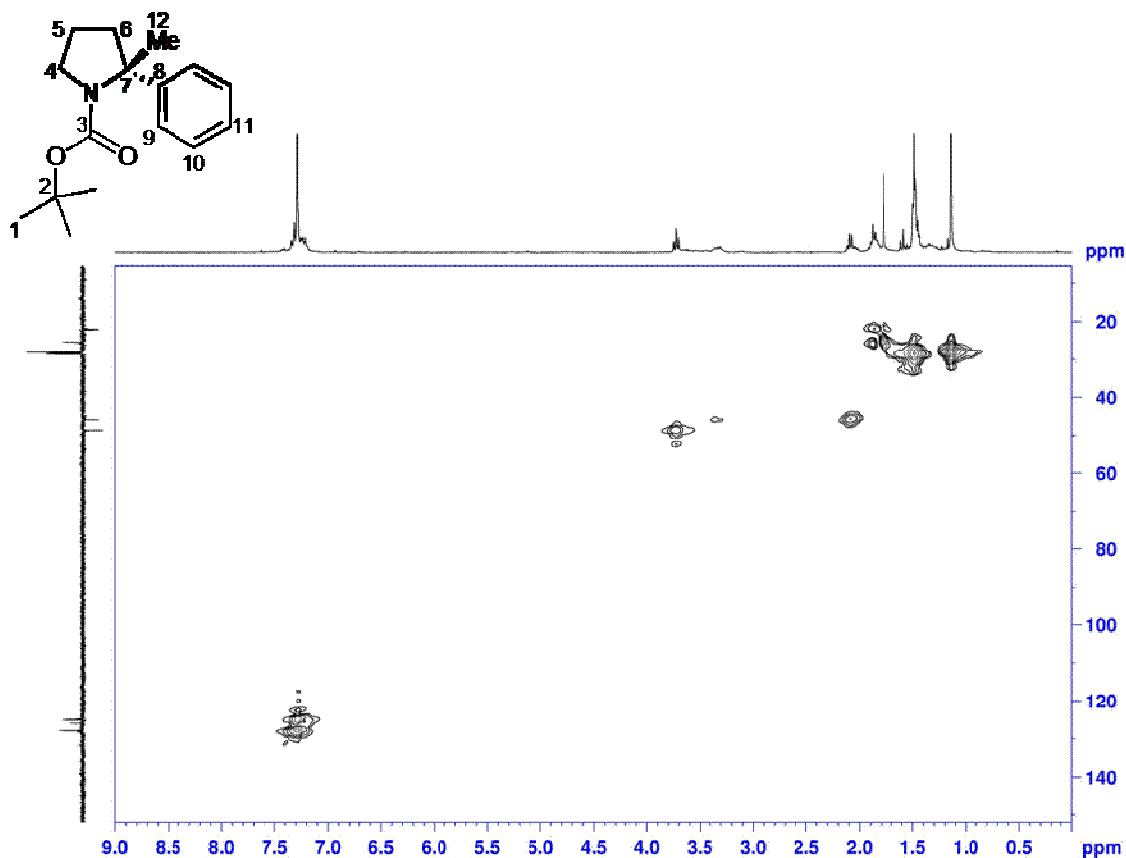
Using **General Procedure H**, **R-18** of 96:4 er (247 mg, 1.0 mmol), TMEDA (0.15 mL, 1.0 mmol, 1.0 equiv), Et₂O (10 mL), *n*-BuLi (0.5 mL, 1.0 mmol, 2.0 M, 1.0 equiv), Me₂SO₄ (0.15 mL, 1.5 mmol, 1.5 equiv) for 8 h at -60 °C prior to addition of 2 mL MeOH, gave the crude product as an oil. Purification by silica gel chromatography eluting with hexane-EtOAc (95:5) afforded 224 mg of **R-25** as an oil in 86% yield and 94:6 er. All other spectroscopic data as reported for *rac*-**25**.⁷ The enantiomer ratio was evaluated by CSP-SFC, monitoring at 210 nm, by comparison with an authentic racemic sample, under the following column conditions: **Column:** Pirkle Whelk-O-1, **Flow Rate** = 2.0 mL/min, **Polarity Modifier** = 2.0% EtOH. The minor enantiomer elutes after ~5.6 min and the major elutes after ~7.6 min.

CSP-SFC trace
Pirkle-Whelk-O-1, Flow = 2.0, Mod % = 2% MeOH
Me₂SO₄ quench after 3 h of lithiation at -60 °C in ether

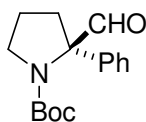








7.3. Lithiation-substitution with dimethyl formamide



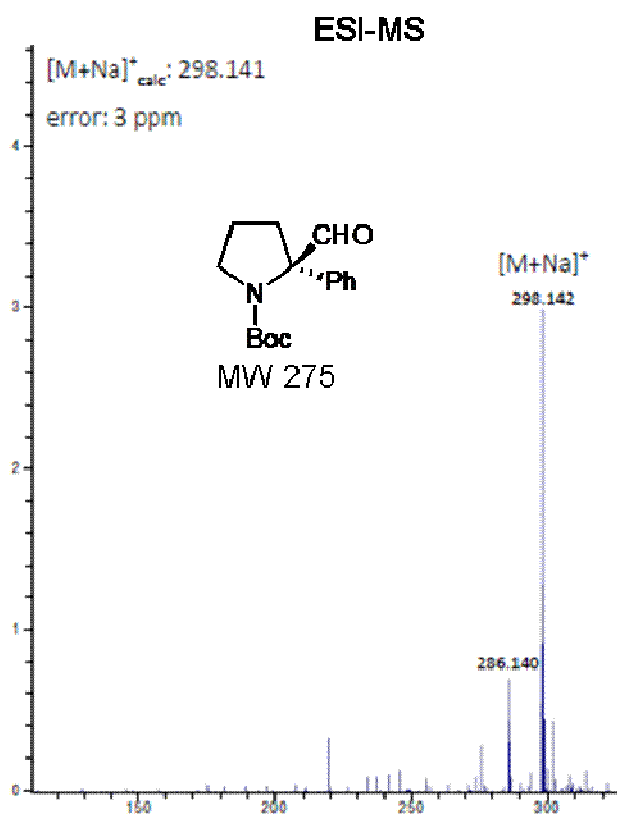
R-26

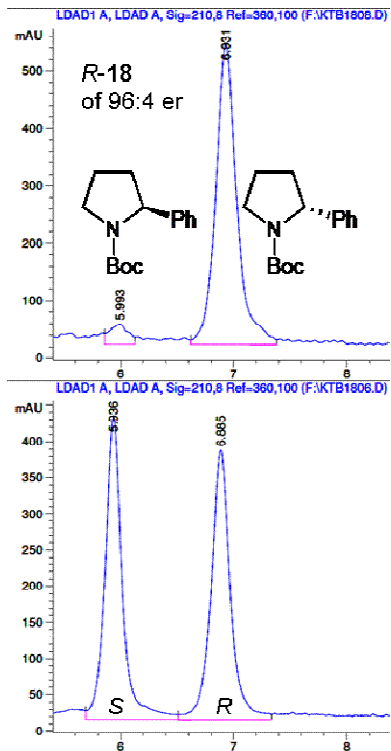
Using **General Procedure B**, **R-18** of 96:4 er (247 mg, 1.0 mmol), TMEDA (0.15 mL, 1.0 mmol, 1.0 equiv), Et₂O (10 mL), *s*-BuLi (1.0 mL, 1.0 mmol, 1.0 M, 1.0 equiv), dimethyl formamide (0.12 mL, 1.5 mmol, 1.5 equiv) for 8 h at $-80\text{ }^{\circ}\text{C}$ prior to addition of 2 mL MeOH, gave the crude product as an oil in 96:4 er. Purification by silica gel chromatography eluting with hexane-EtOAc (80:20) afforded 228 mg of **R-26** as an oil in 83% yield ([note 3](#)) and >99:1 er. ¹H NMR (300 MHz, CDCl₃), mixture of rotomers, δ 9.8–9.6 (1H, s, H of CHO), 7.55–7.10 (5H, m, Ph), 3.72 (2H, br, NCH), 2.44 (1H, br, CH), 2.02 (1H, br, CH), 1.92–1.15 (11H, m). ¹³C NMR (75.5 MHz, CDCl₃) δ = 198.2 and 197.5 (C=O of aldehyde), 153.7 (C=O), 138.8 (C), 128.3 (CH), 128.0 (CH), 127.3 (CH) and 126.3 (CH), 81.2 and 80.6 (C), 74.3 (C), 47.9 (CH₂), 39.3 and 38.3 (CH₂), 28.4 and 28.0 (3 x CH₃), 23.4 and 22.4 (CH₂). The enantiomer ratio was evaluated by CSP-SFC, monitoring at 210 nm, by comparison with an authentic racemic sample, under the

following column conditions: **Column:** Pirkle Whelk-O-1, **Flow Rate** = 1.0 mL/min, **Polarity Modifier** = 5.0% EtOH. The major enantiomer elutes after ~7.8 min and the minor elutes after ~9.6 min.

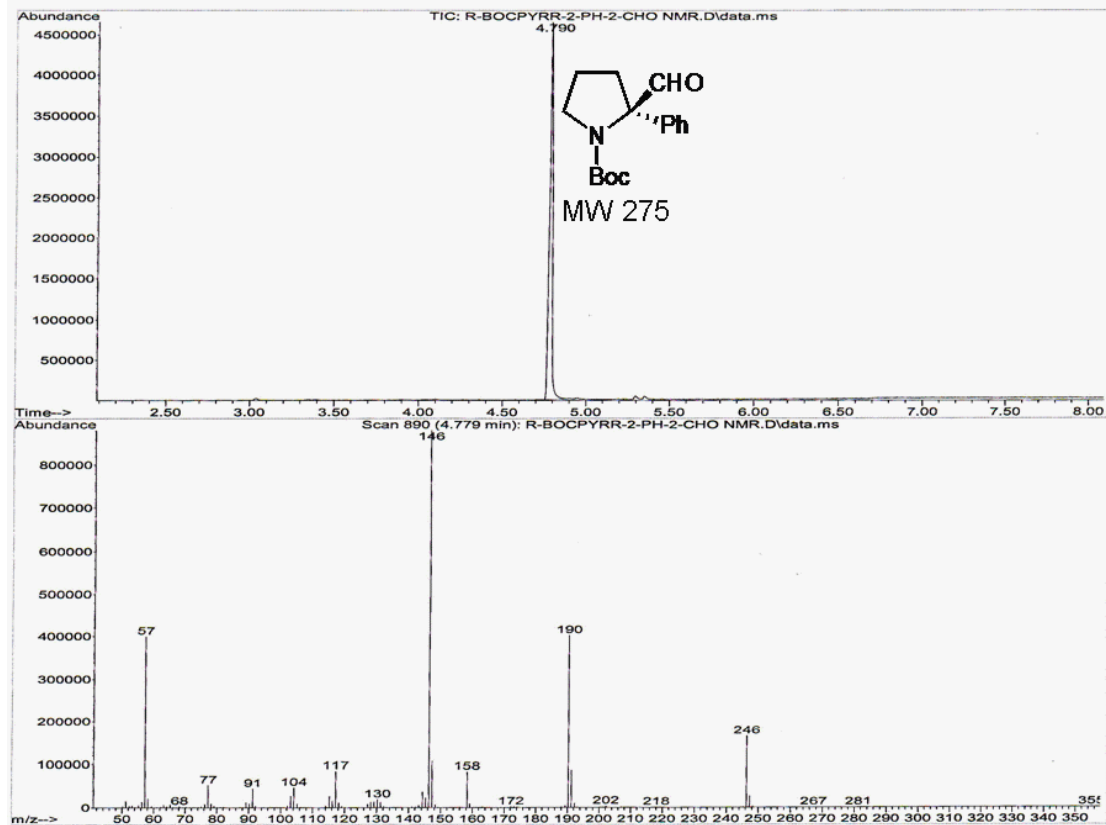
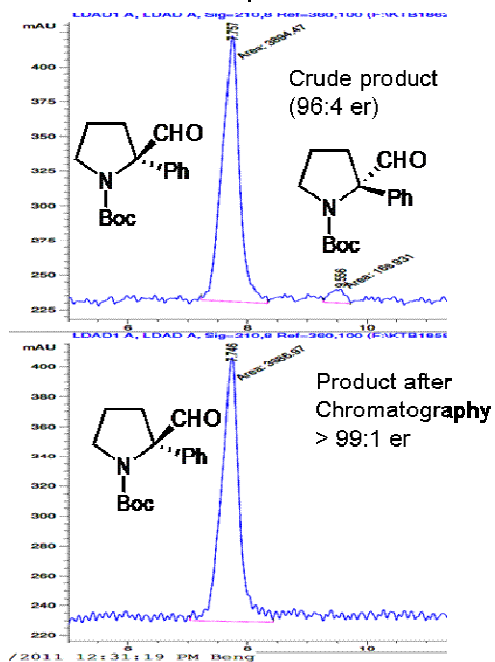
Note 3: The total yield includes some amount of the C-5 aldehyde obtained due to competitive lithiation at C-5 under the reaction conditions. Spectral data are based on a carefully re-chromatographed sample.

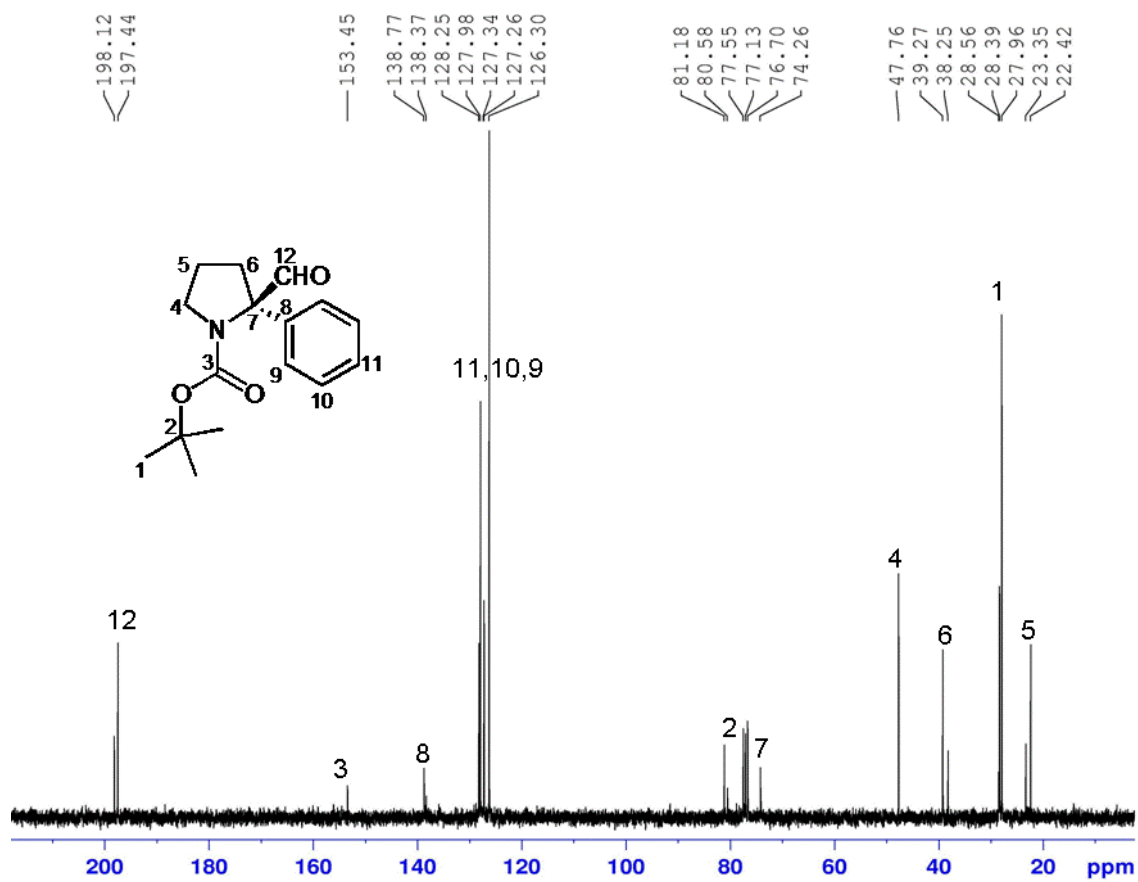
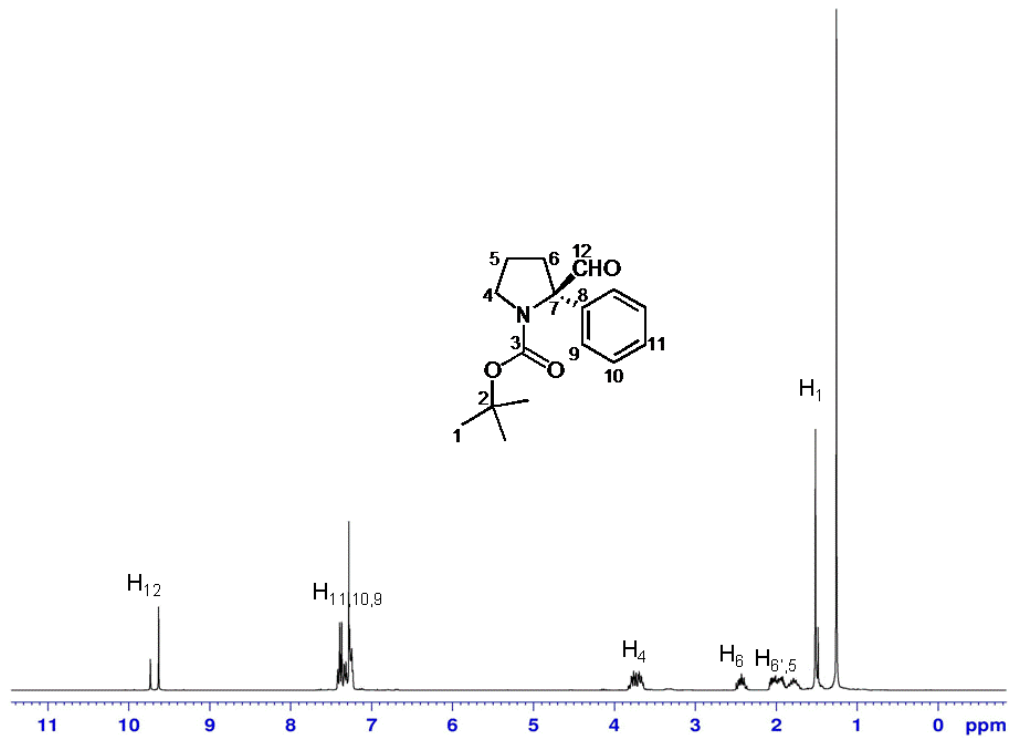
The experiment was repeated using General Procedure H but only the GC yield (88%) was obtained and the product wasn't purified further.

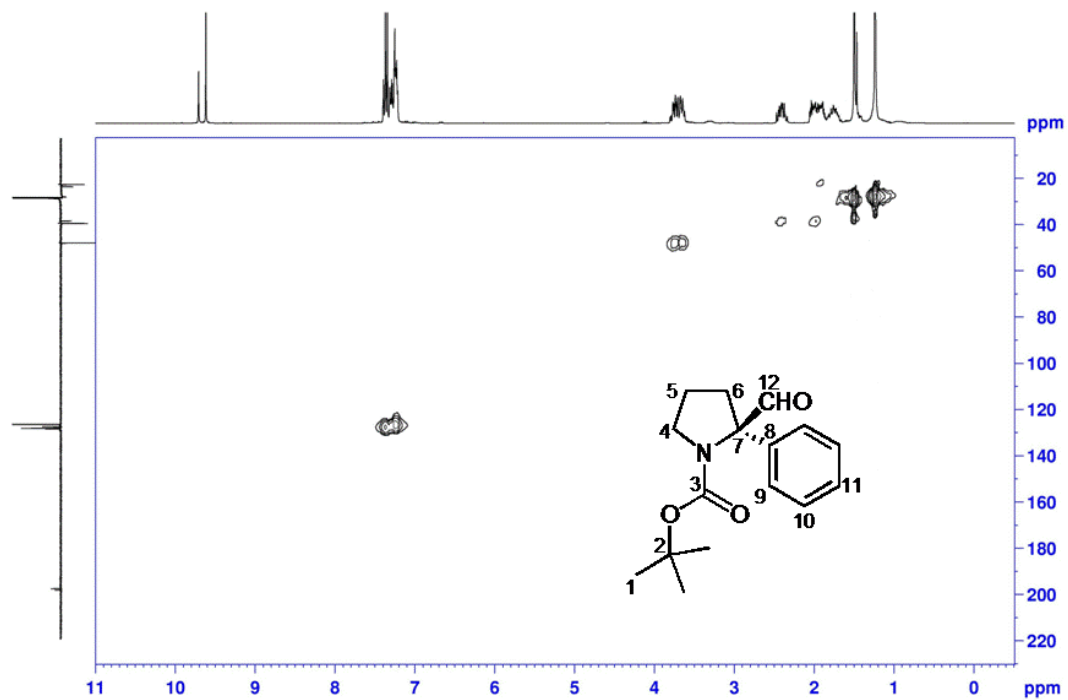
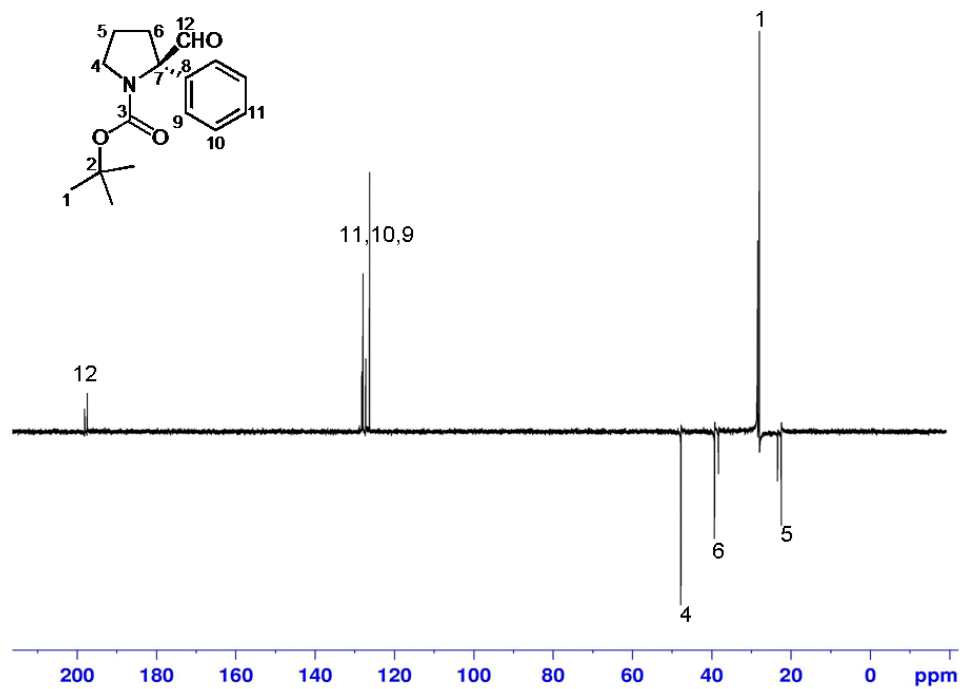


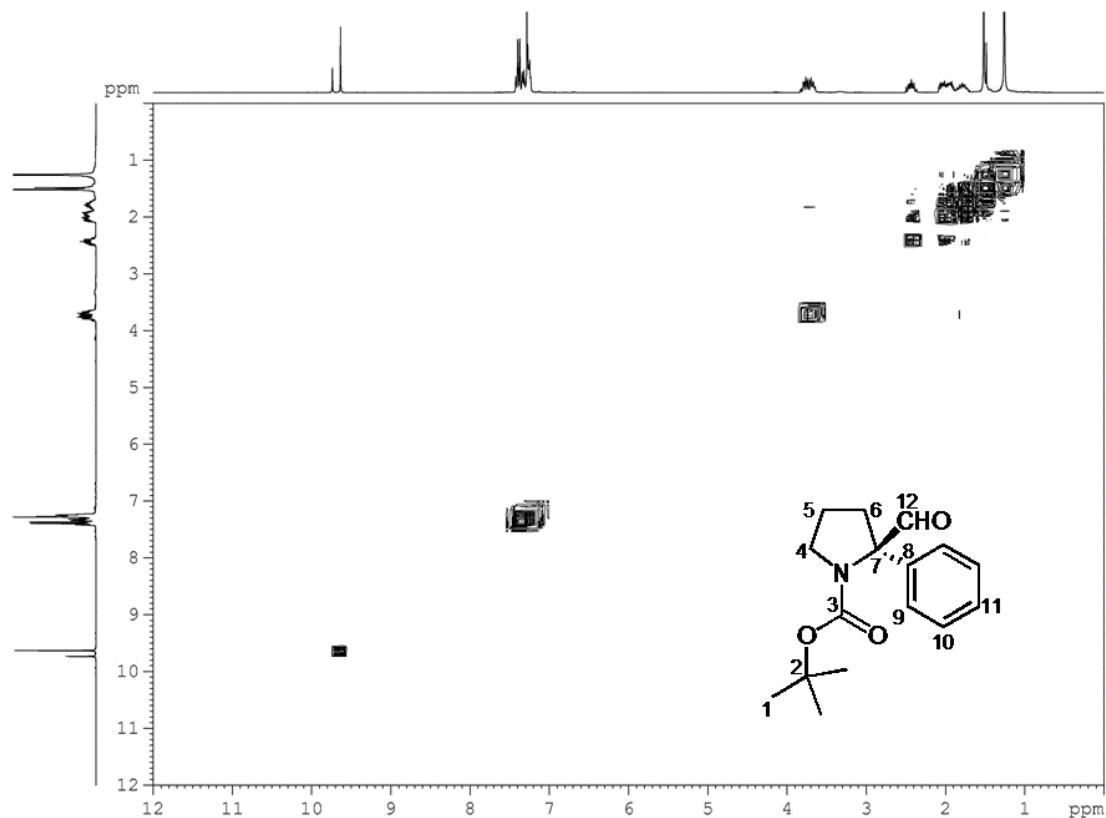


CSP-SFC trace
Pirkle-Whelk-0-1, Flow = 1.0, Mod % = 5% MeOH
DMF quench

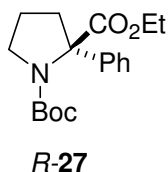








7.4. With EtOCOCl



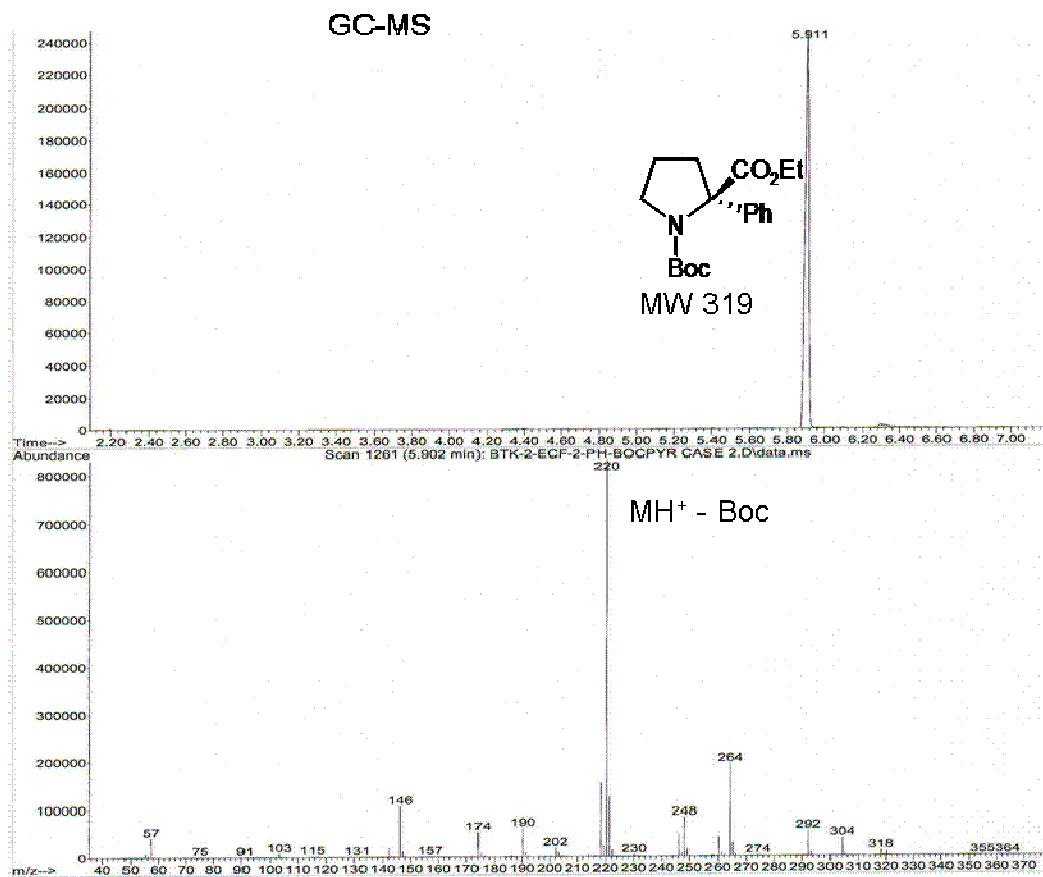
Using **General Procedure H**, **R-18** of 96:4 er (247 mg, 1.0 mmol), TMEDA (0.15 mL, 1.0 mmol, 1.0 equiv), Et₂O (10 mL), *s*-BuLi (1.0 mL, 1.0 mmol, 1.0 M, 1.0 equiv), EtOCOCl (0.13 mL, 1.5 mmol, 1.5 equiv) for 2 h (note 4) prior to addition of 2 mL MeOH and warming to rt, gave the crude product as an oil. Purification by silica gel chromatography eluting with hexane-EtOAc (75:25) afforded 283 mg of **R-27** as an oil in 70% yield (note 5) and 94:6 er. ¹H NMR (300 MHz, CDCl₃), mixture of rotomers, δ 7.48–7.15 (5H, m), 4.40–4.11 (2H, m), 3.57 (1H, m), 3.41 (1H, m), 2.65 (1H, m), 2.35 (1H, m), 1.97–1.15 (14H, m). ¹³C NMR (75.5 MHz, CDCl₃) δ = 172.2 (C=O of ester), 154.3 (C=O), 140.1 (C), 127.8 (CH), 125.1 (CH), 126.8 (CH), 79.5 (C), 72.5 (C), 61.6 (CH₂), 48.1 (CH₂), 44.5 (CH₂), 28.1 (3 x CH₃), 23.7 (CH₂), and 14.1 (CH₃). The enantiomer ratio was evaluated by CSP-SFC, monitoring at 210 nm, by comparison with an

authentic racemic sample, under the following column conditions: **Column:** Pirkle Welk-O-1, **Flow Rate** = 1.0 mL/min, **Polarity Modifier** = 2.0% MeOH. The minor enantiomer elutes after ~16.2 min and the major elutes after ~19.7 min.

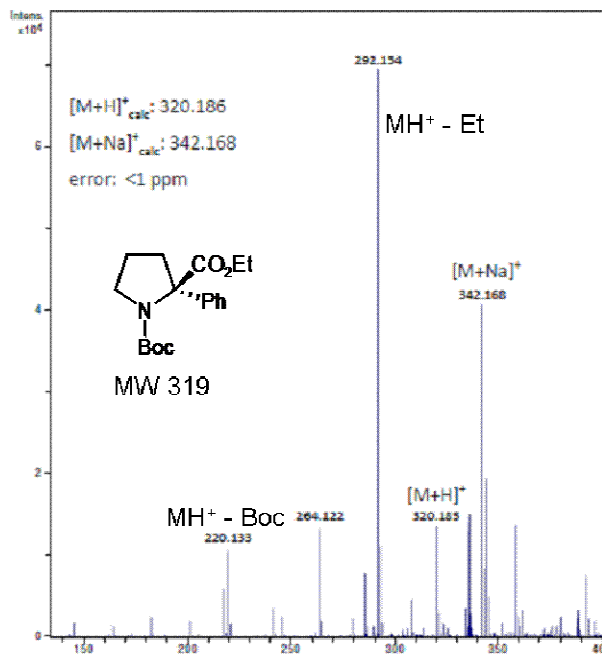
Note 4: The electrophilic quench was carried out for 2 h after lithiating for 3 h.

Note 5: The total yield includes some amount of the C-5 ester obtained due to competitive lithiation at C-5 under the reaction conditions. Spectral data are based on a carefully re-chromatographed sample.

The experiment was repeated using General Procedure H but only the GC yield (79%) was obtained and the product wasn't purified further.

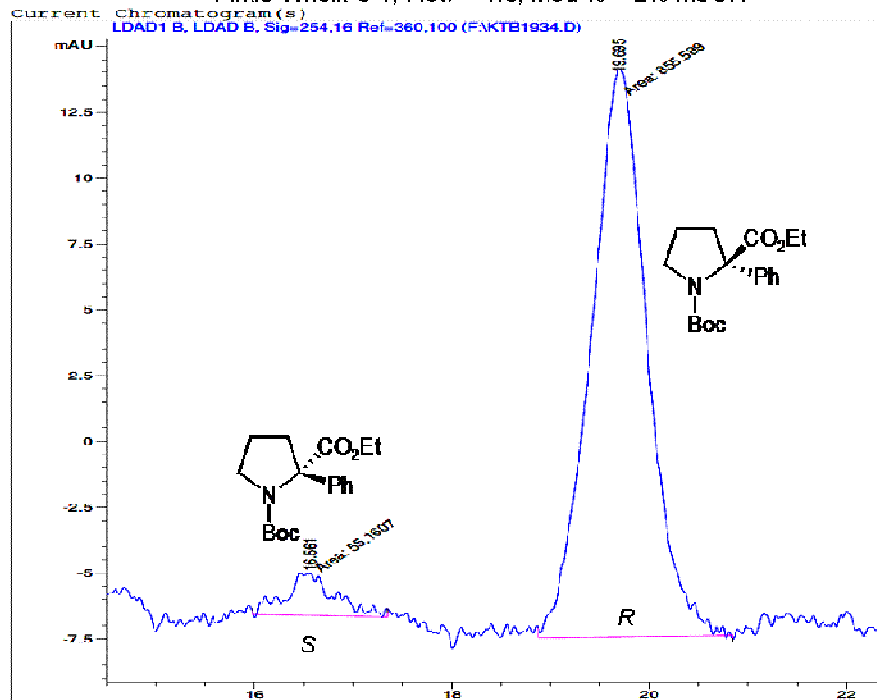


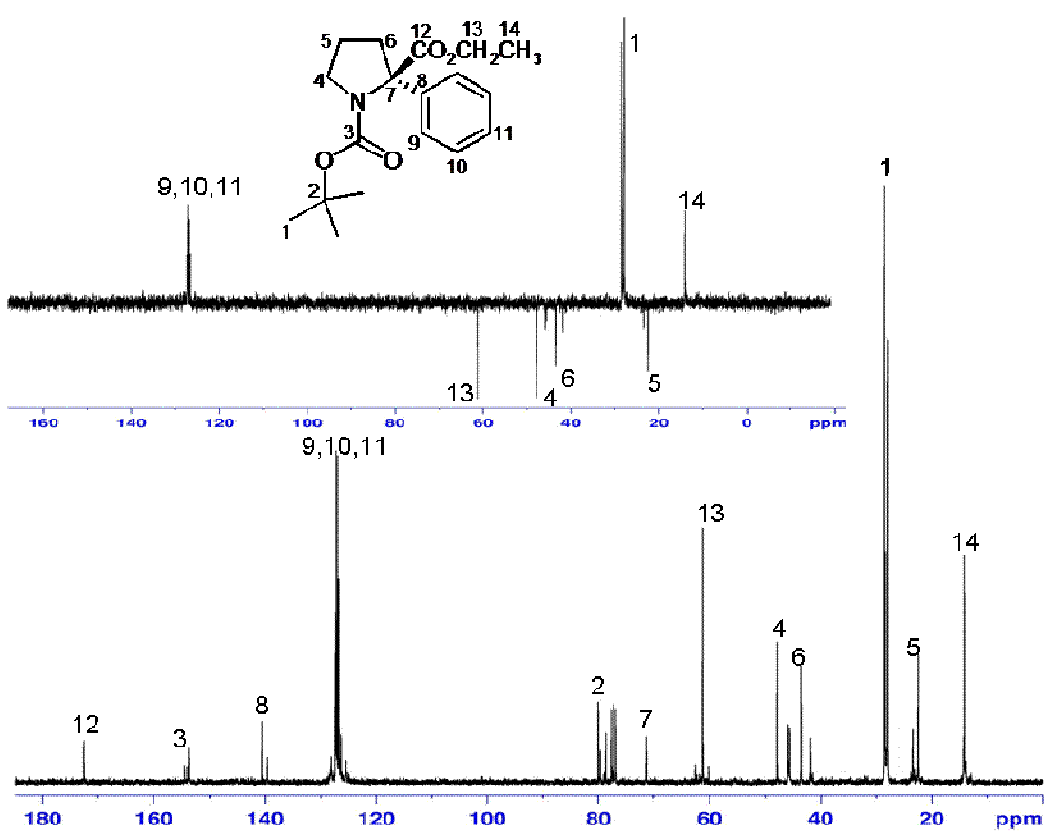
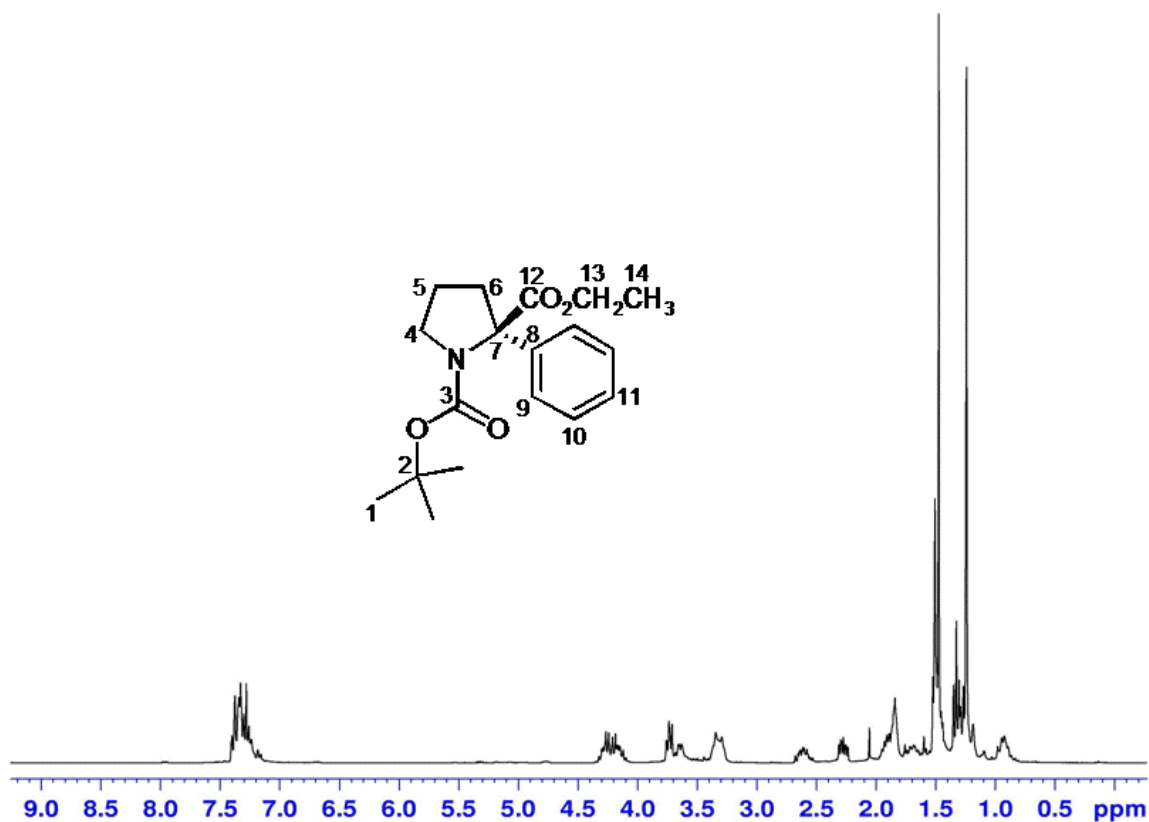
ESI-MS

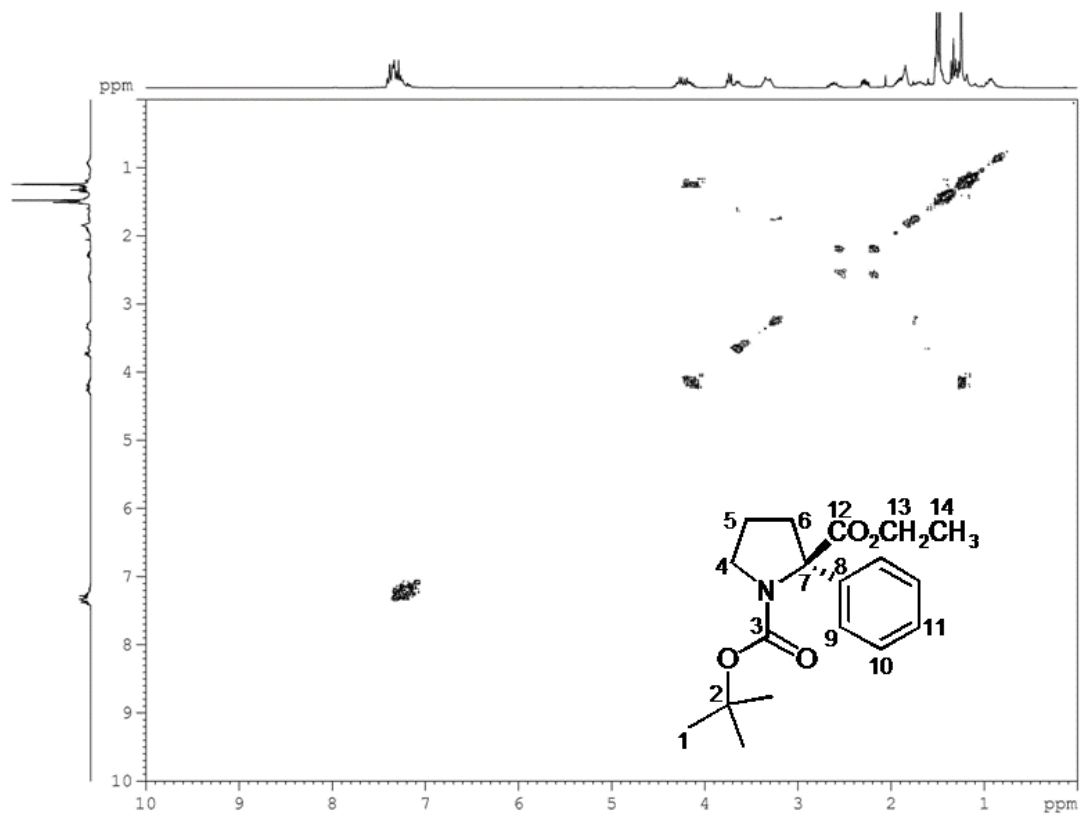
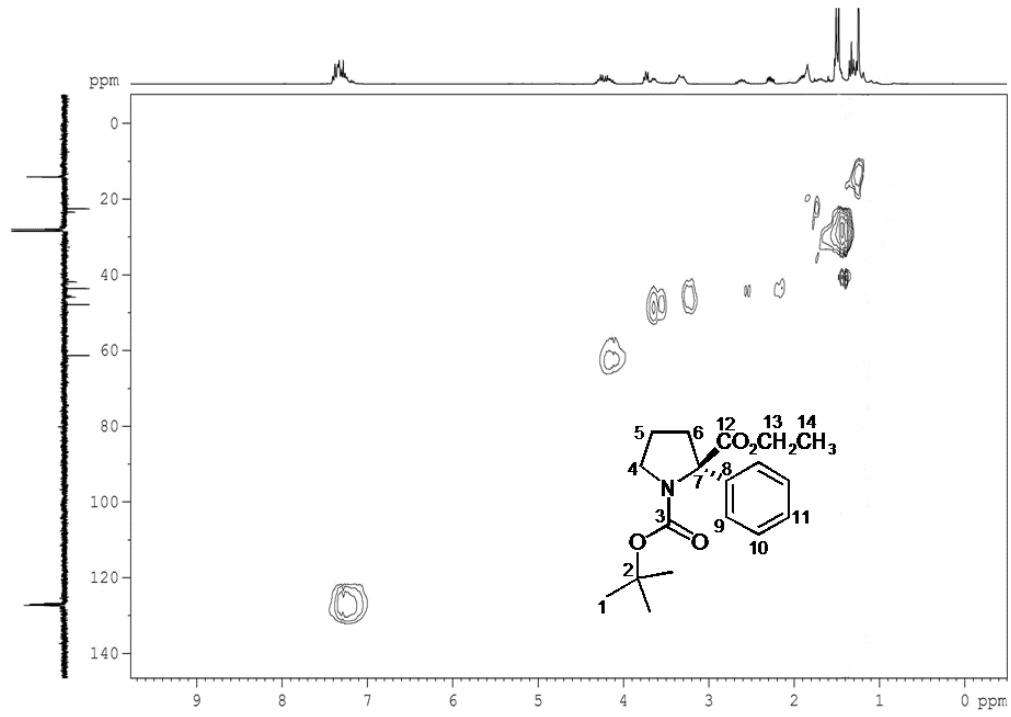


CSP-SFC trace

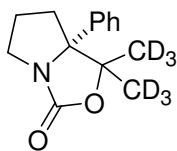
Pirkle-Whelk-0-1, Flow = 1.0, Mod % = 2% MeOH







7.5. Lithiation-substitution with acetone-d₆



R-28

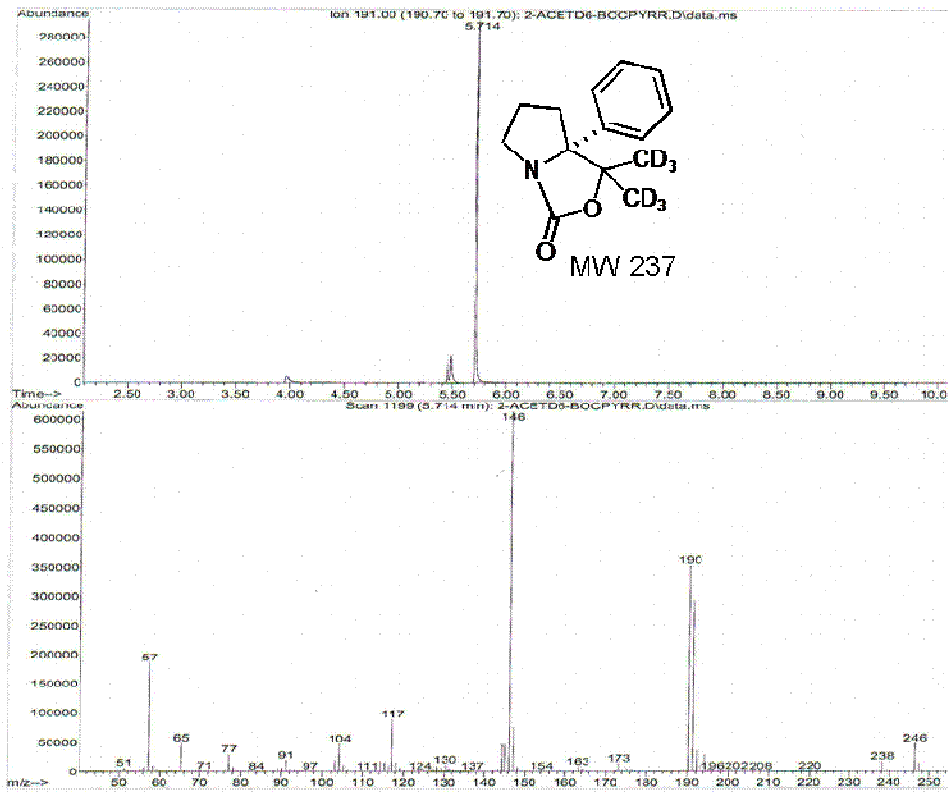
Using **General Procedure B**, **R-18** of 96:4 er (247 mg, 1.0 mmol), TMEDA (0.15 mL, 1.0 mmol, 1.0 equiv), Et₂O (10 mL), *s*-BuLi (1.0 mL, 1.0 mmol, 1.0 M, 1.0 equiv), (CD₃)₂CO (96 mg, 1.5 mmol, 1.5 equiv) for 2 h (**note 6**) prior to warming to rt and addition of 2 mL MeOH gave the crude product as an oil. Purification by silica gel chromatography eluting with hexane-EtOAc (60:40) afforded 201 mg of the oxazolidinone **R-28** as an amorphous solid in 85% yield (**note 7**) and 94:6 er. ¹H NMR (400 MHz, CDCl₃) δ = 7.55–7.15 (5H, m), 3.86 (1H, m), 3.15 (1H, m), 2.15 (1H, m), 2.10–1.15 (3H and 6D, m). ¹³C NMR (75.5 MHz, CDCl₃) δ = 161.9 (C=O), 138.1 (C), 128.6 (CH), 128.4 (CH), 127.9 (CH), 82.2 (C), 78.2 (C), 45.5 (CH₂), 33.4 (CH₂), 28.5 (2 x CD₃), 23.5 (CH₂). The enantiomer ratio was evaluated by CSP-SFC, under the following column conditions: **Column:** Pirkle Whelk-O-1, **Flow Rate** = 1.0 mL/min, **Polarity Modifier** = 2% EtOH. The minor enantiomer elutes after ~12.8 min and the major elutes after ~18.8 min.

Note 6: The electrophilic quench was carried out for 2 h after lithiating for 3 h.

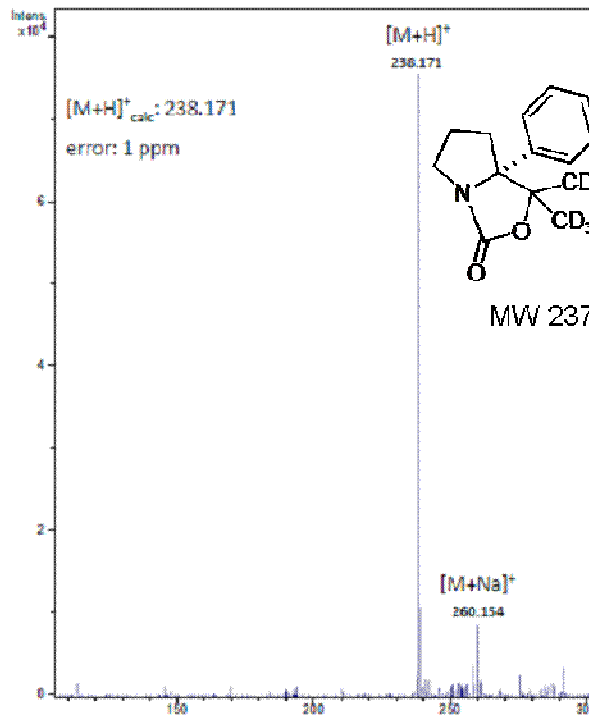
Note 7: The total yield includes some amount of the C-5 oxazolidinone obtained due to competitive lithiation at C-5 under the reaction conditions. Spectral data are based on a carefully recolumned sample.

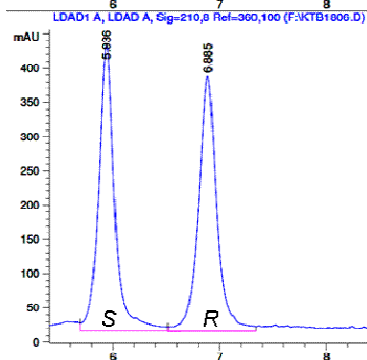
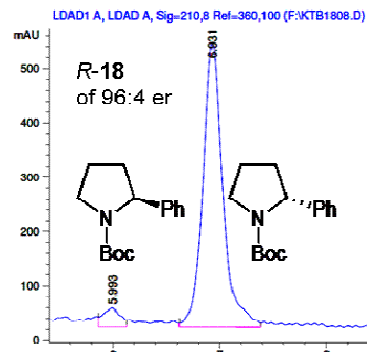
The experiment was repeated using General Procedure H but only the GC yield (92%) was obtained and the product wasn't purified further.

GC-MS trace from electron impact ionization

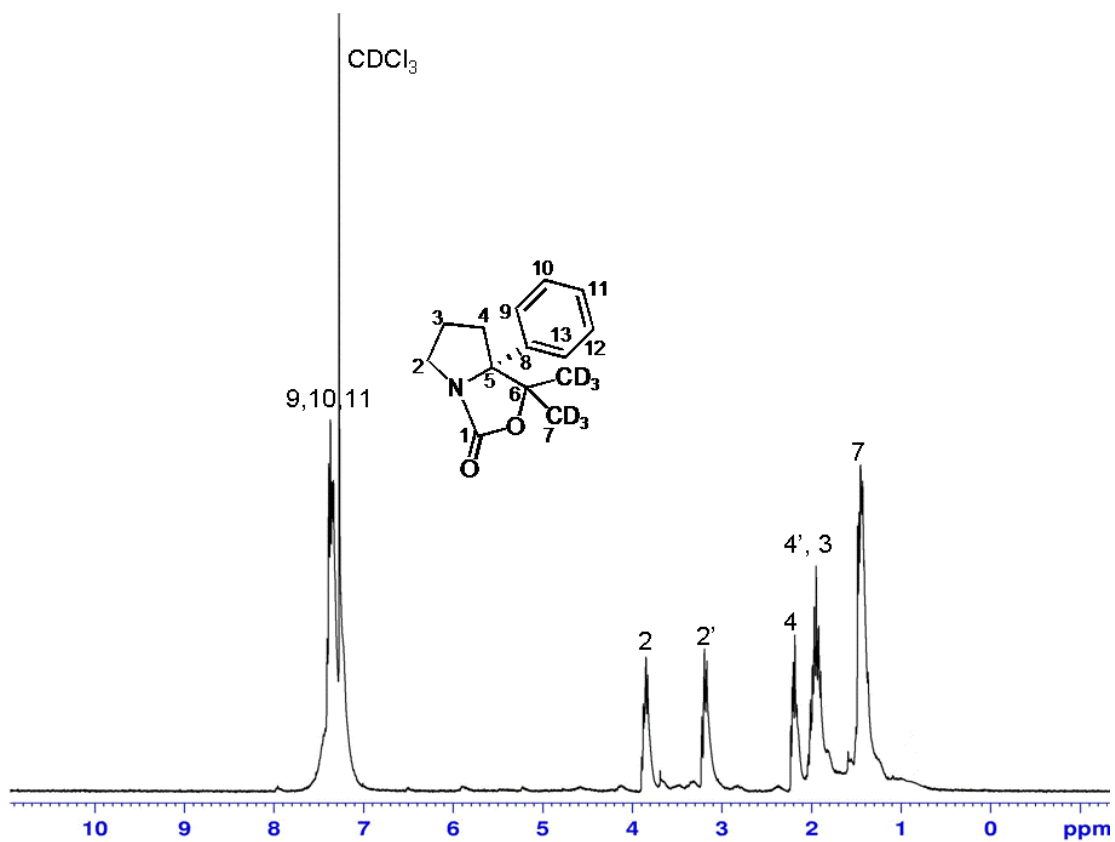
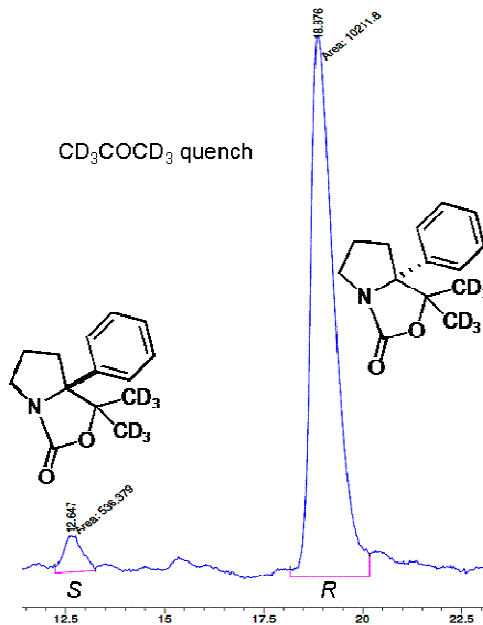


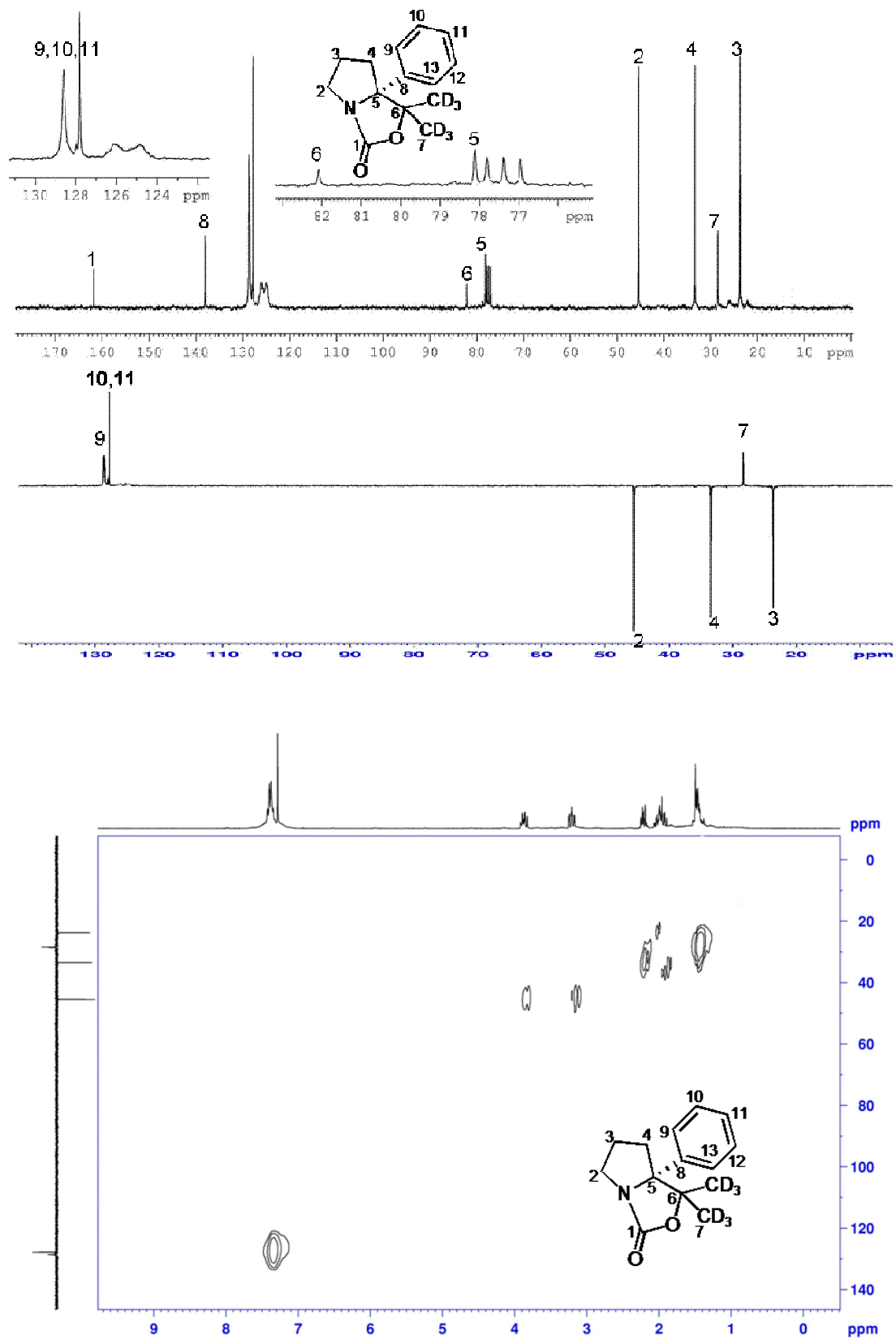
ESI-MS

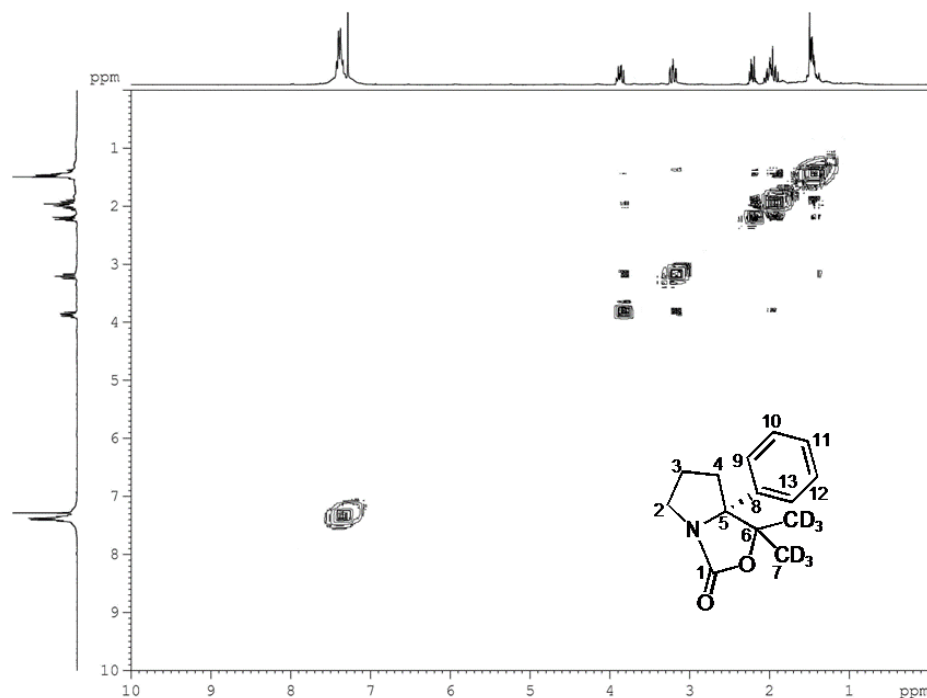




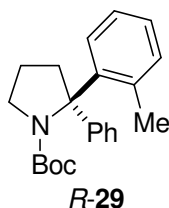
CSP-SFC trace
Pirkle-Whelk-O-1, Flow = 1.0, Mod % = 2% MeOH







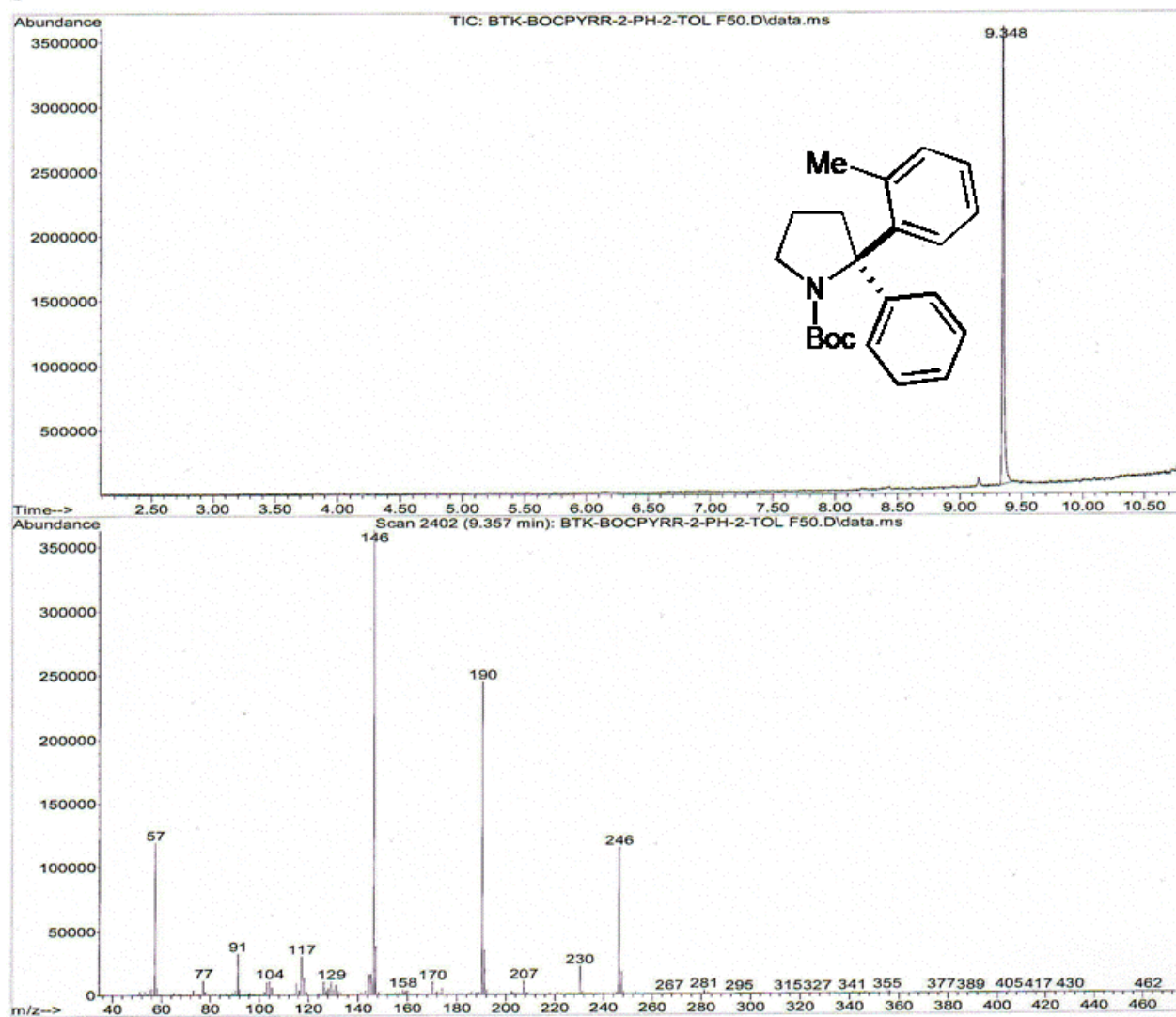
7.6. With 2-bromotoluene

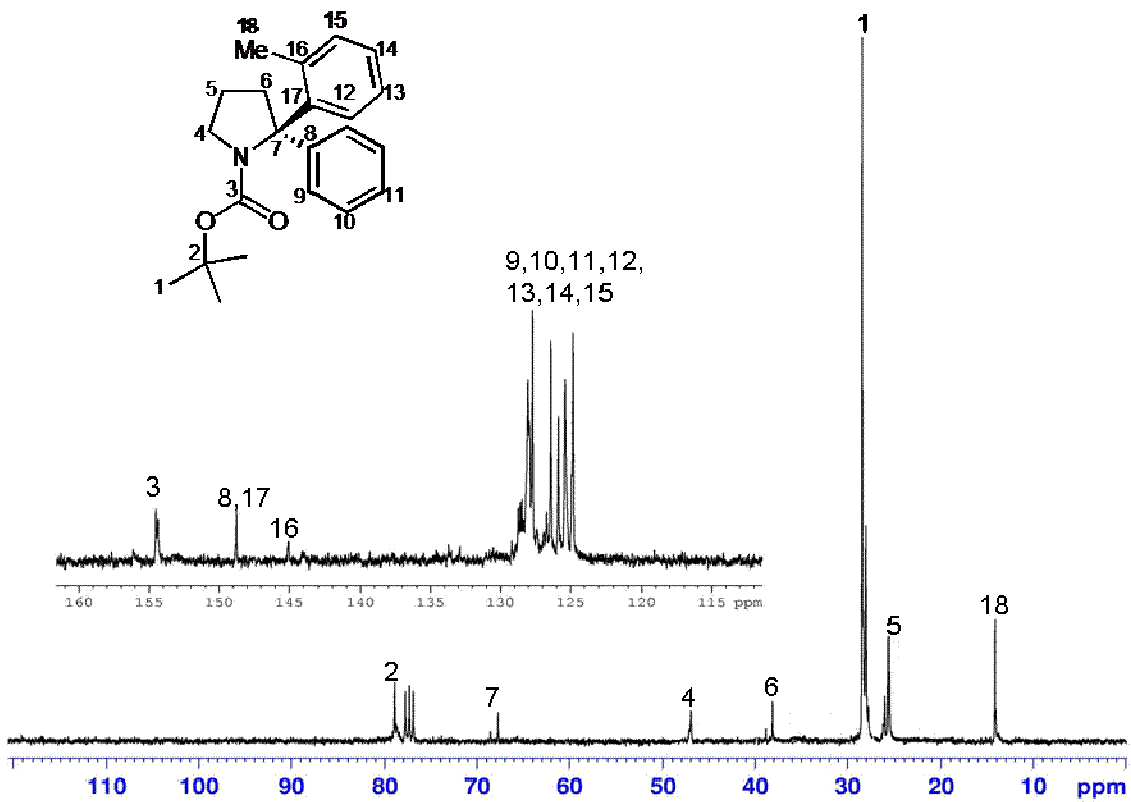
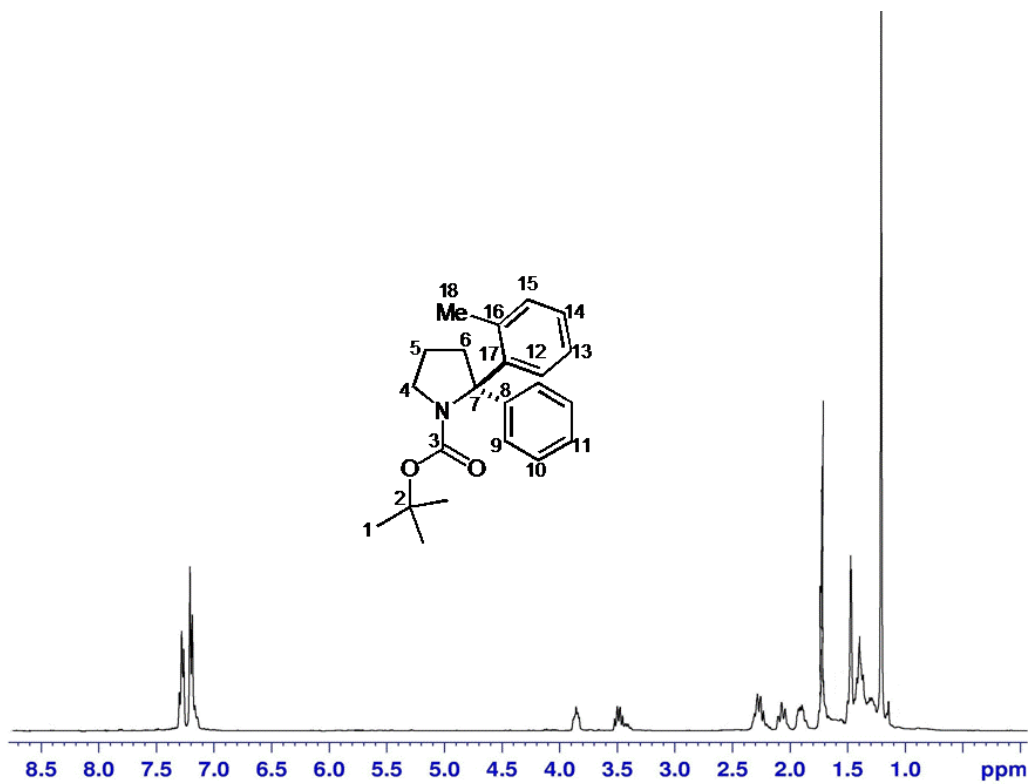


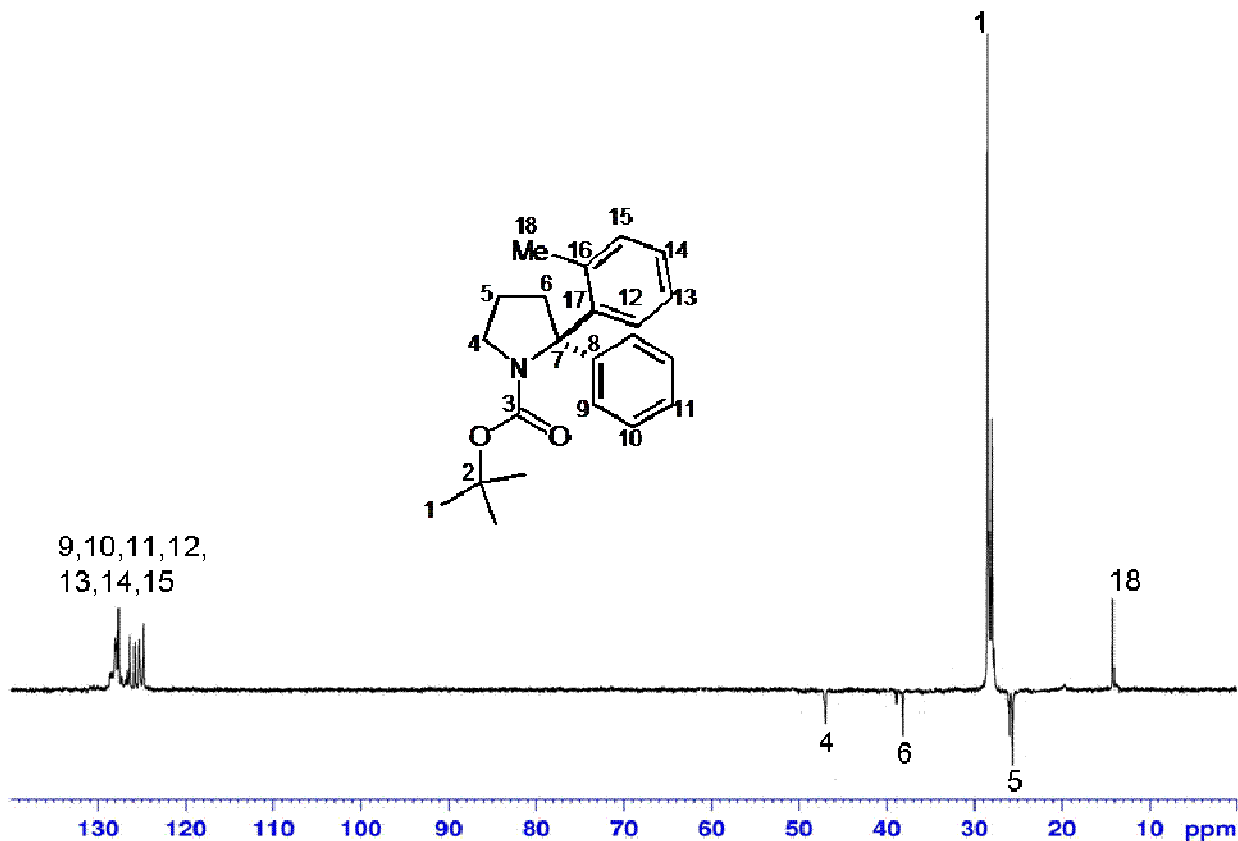
To an oven-dried, septum-capped round bottom flask equipped with a stir bar, was added *R-18* of 96:4 er (247 mg, 1.0 mmol, 1.0 equiv) in Et₂O (5 mL) under argon. The mixture was cooled to –60 °C and a solution of *s*-BuLi in hexanes (1.0 mL, 1.0 mmol, 1.0 M, 1.0 equiv) was added slowly. After 3 h at this temperature, a solution of ZnCl₂ (0.6 mL, 1.0 M solution in Et₂O, 0.6 equiv), was added slowly over a two minute period and the mixture was stirred for 30 minutes followed by warming to room temperature. After 30 minutes, Pd(OAc)₂ (10 mg, 4 mol%), *t*-Bu₃P·HBF₄ (23 mg, 8 mol%) and 2-bromotoluene (0.15 mL, 1.1 mmol, 1.1 equiv) were added sequentially. After stirring for 48 h at room temperature, NH₄OH (5 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 5 mL Et₂O. The filtrate was washed with 1 M HCl_(aq) (10 mL), then with water (2 x 5 mL), dried over Na₂SO₄ and evaporated under reduced pressure to obtain the crude product. Purification by silica gel chromatography eluting with hexane-EtOAc (90:10) afforded *R-29* as an oil in less than 10% yield and 92:8 er.

Note 8: When the lithiation of *R*-**18** was carried out using the conditions in **General Procedure H**, followed by arylation as described above, we obtained 34 mg of *R*-**29** in 8% yield and 92:8 er.

Note 9: When *rac*-**18** was lithiated in the absence of TMEDA at $-60\text{ }^{\circ}\text{C}$ for 3 h in Et_2O , then arylated as described above, we obtained 51 mg of *rac*-**29** in 12% yield.

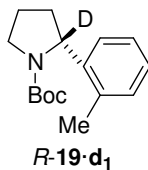






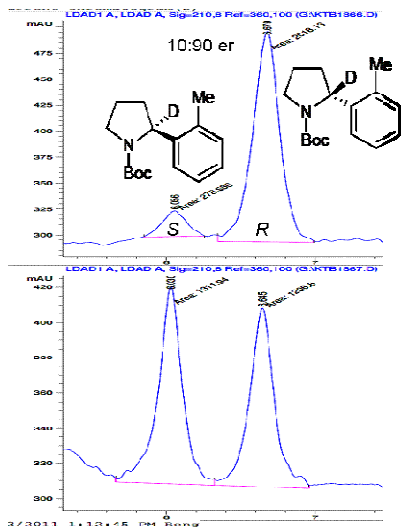
8. Lithiation-substitution of other *N*-Boc-2-arylpyrrolidines

8.1. Lithiation-substitution of (*R*)-*N*-Boc-2-(*o*-toluyl)pyrrolidine with MeOD

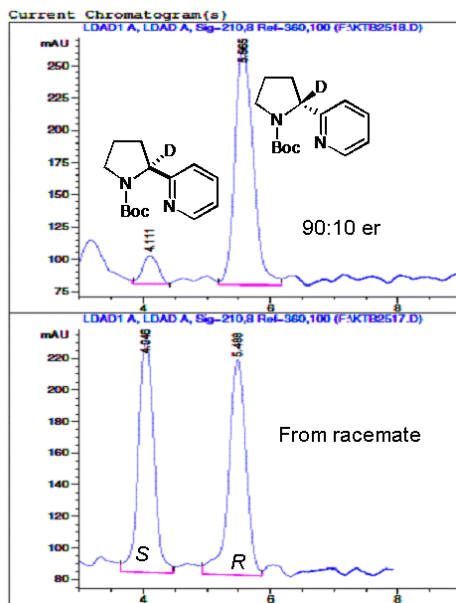


Using **General Procedure G**, *R*-**19** of 90:10 er and 0.1 mL MeOD showed complete deuteration after 3 h and *R*-**19**-*d*₁ was obtained with no loss of er. There is a noticeable shift of the protonated base peak from *m/z* 206 for **19** to *m/z* 207 for *R*-**19**-*d*₁.

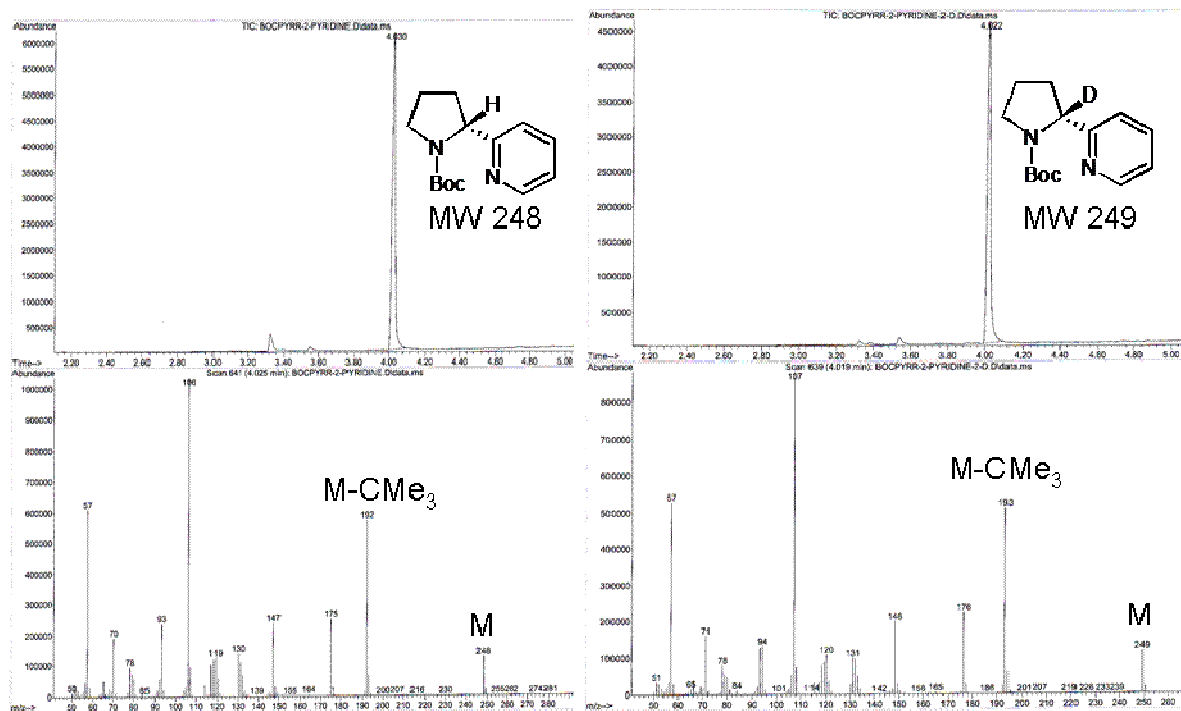
Pirkle-Whelk-0-1; Flow = 1.0, Modifier % = 5% MeOH



8.2. Lithiation-substitution of (R)-N-Boc-2-(2-pyridyl)pyrrolidine with MeOD



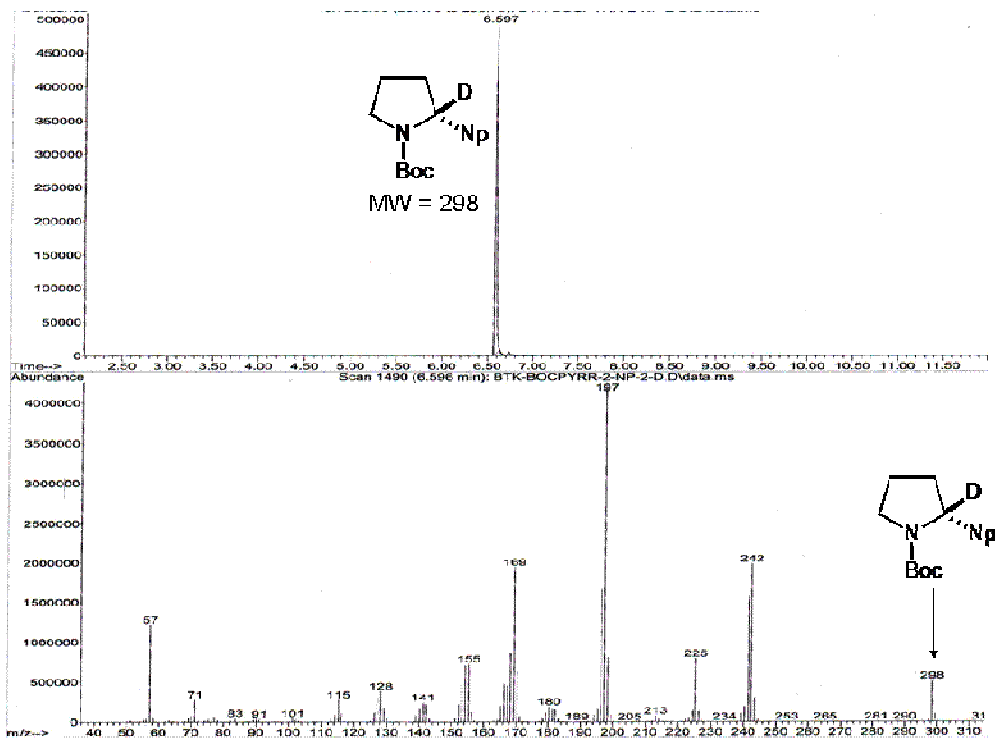
GC-MS traces from electron impact ionization



8.3. Lithiation-substitution of (*R*)-*N*-Boc-2-(1-naphthyl)pyrrolidine, **21**

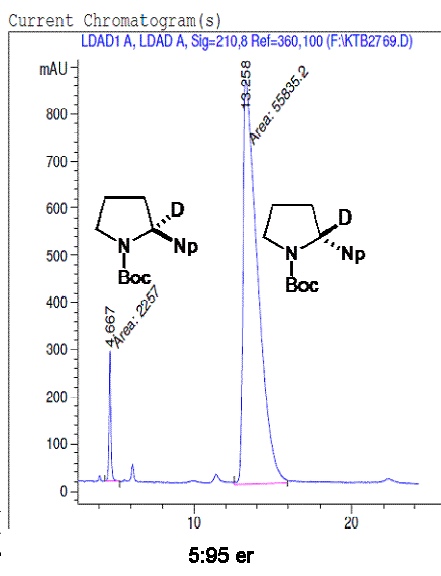
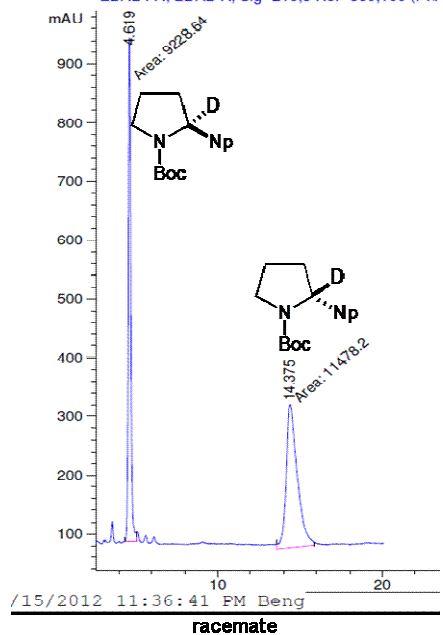
a) With MeOD

Using **General Procedure G**, *R*-**21** of 95:5 er and 0.1 mL MeOD showed complete deuteration after 3 h and *R*-**21**·**d**₁ was obtained with no loss of er. There is a noticeable shift of the protonated base peak from *m/z* 297 for **21** to *m/z* 298 for *R*-**21**·**d**₁.

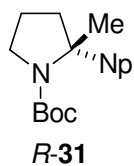


LDAD1 A, LDAD A, Sig=210,8 Ref=360,100 (F:\V

Flow = 2.0, Mod % = 5.0% MeOH



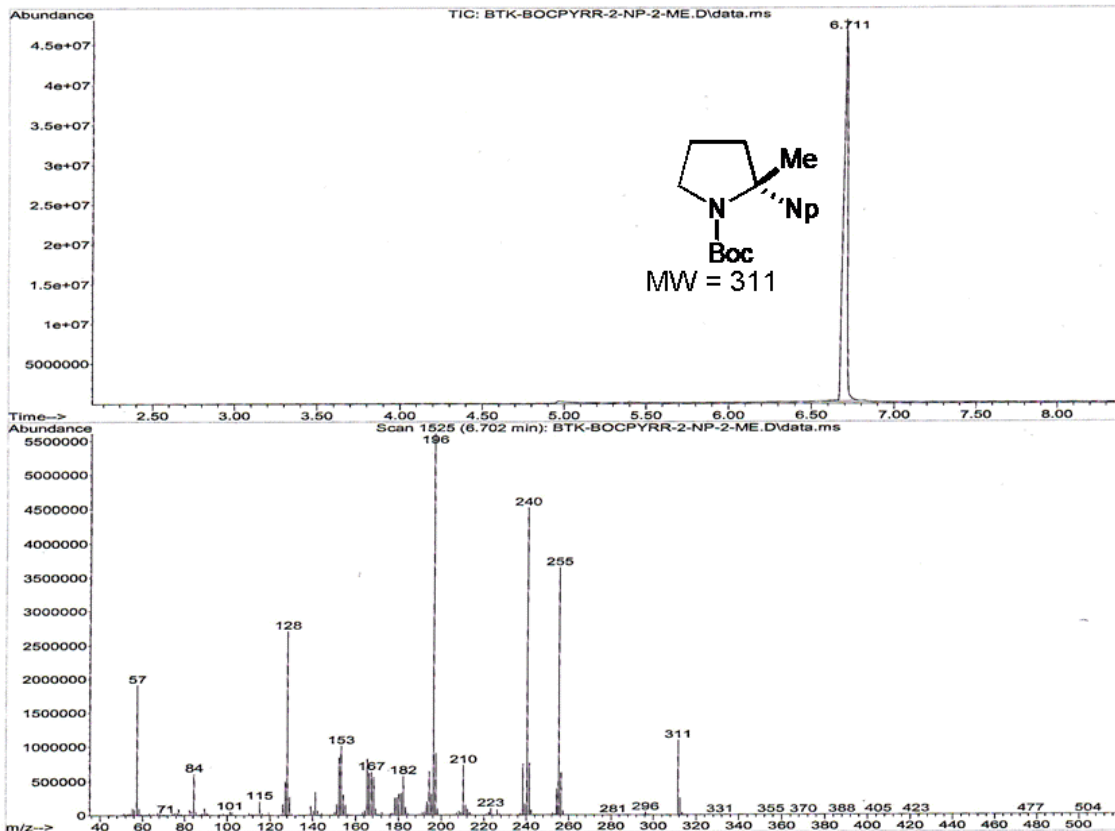
b) With Me₂SO₄



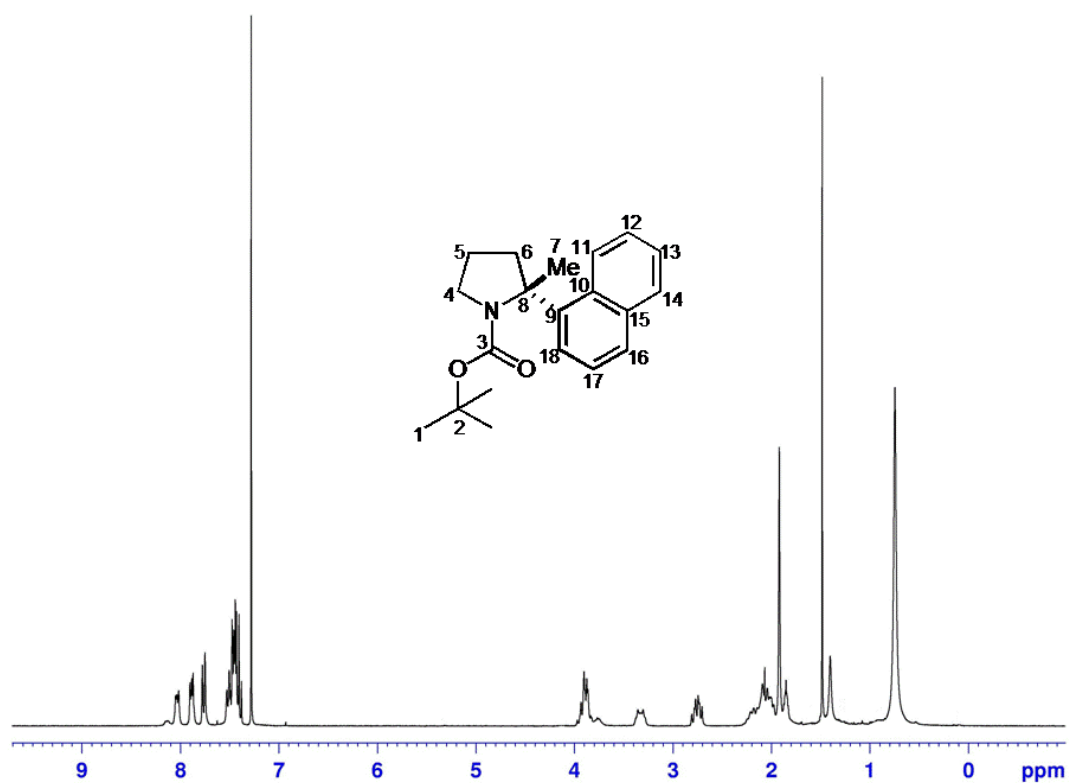
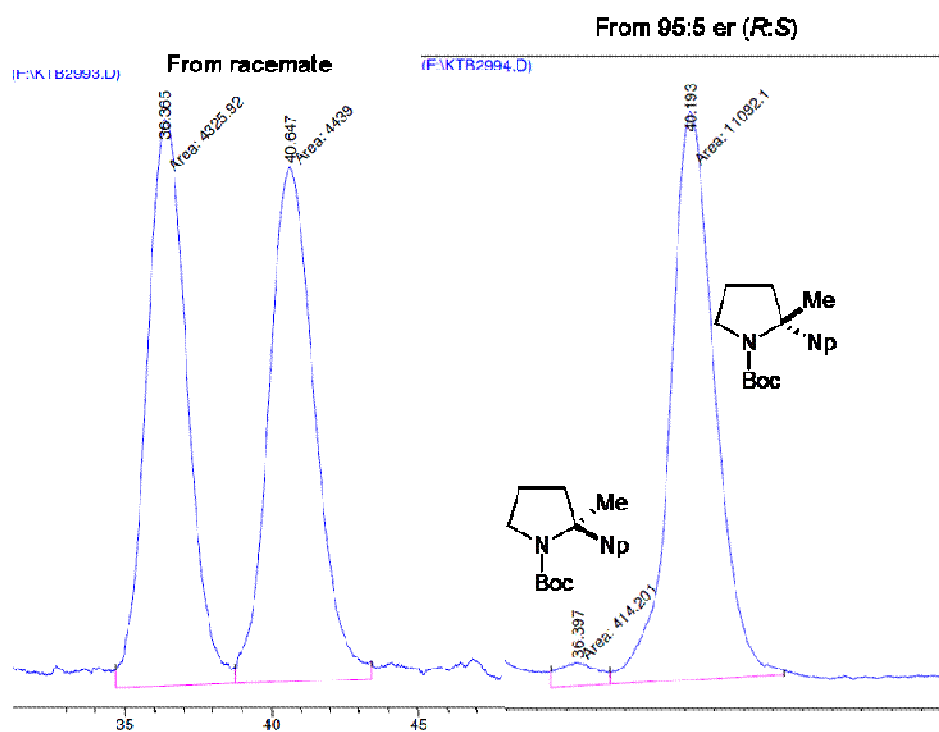
Using **General Procedure H**, *R*-**21** of 95:5 er (311 mg, 1.0 mmol), TMEDA (0.15 mL, 1.0 mmol, 1.0 equiv), Et₂O (10 mL), *n*-BuLi (0.5 mL, 1.0 mmol, 2.0 M, 1.0 equiv), Me₂SO₄ (0.15 mL, 1.5 mmol, 1.5 equiv) for 8 h at -80 °C prior to addition of 2 mL MeOH, gave the crude product as an oil. Purification by silica gel chromatography eluting with hexane-EtOAc (80:20) afforded 291 mg of *R*-**31** as an oil in 90% yield and 95:5 er. ¹H NMR (mixture of rotomers) (300 MHz, CDCl₃) δ = 8.23–7.37 (6H, m), 3.92 (1H, m), 3.56 (1H, m), 2.78 (1H, m), 2.29–1.82 (6H, m), 1.58 – 1.35 and 0.78 (9H, s) ¹³C NMR (75.5 MHz, CDCl₃) δ = 155.4 (C=O), 142.1 (C), 134.0 (C) 131.5 (C), 128.9 (CH), 127.3 (CH), 125.8 (CH), 125.4 (CH), 124.9 (CH), 123.5 (CH), 123.2 (CH) 79.5, 67.4 (C), 47.1 (CH₂), 41.5 (CH₂), 28.8 (CH₃), 28.3 (3 x CH₃), 22.3 (CH₂). The enantiomer ratio was evaluated by CSP-SFC, monitoring at 210 nm, by comparison with an authentic racemic sample, under the following column conditions: **Column:** Pirkle Whelk-O-1, **Flow Rate** = 0.5 mL/min, **Polarity Modifier** = 10.0% MeOH.

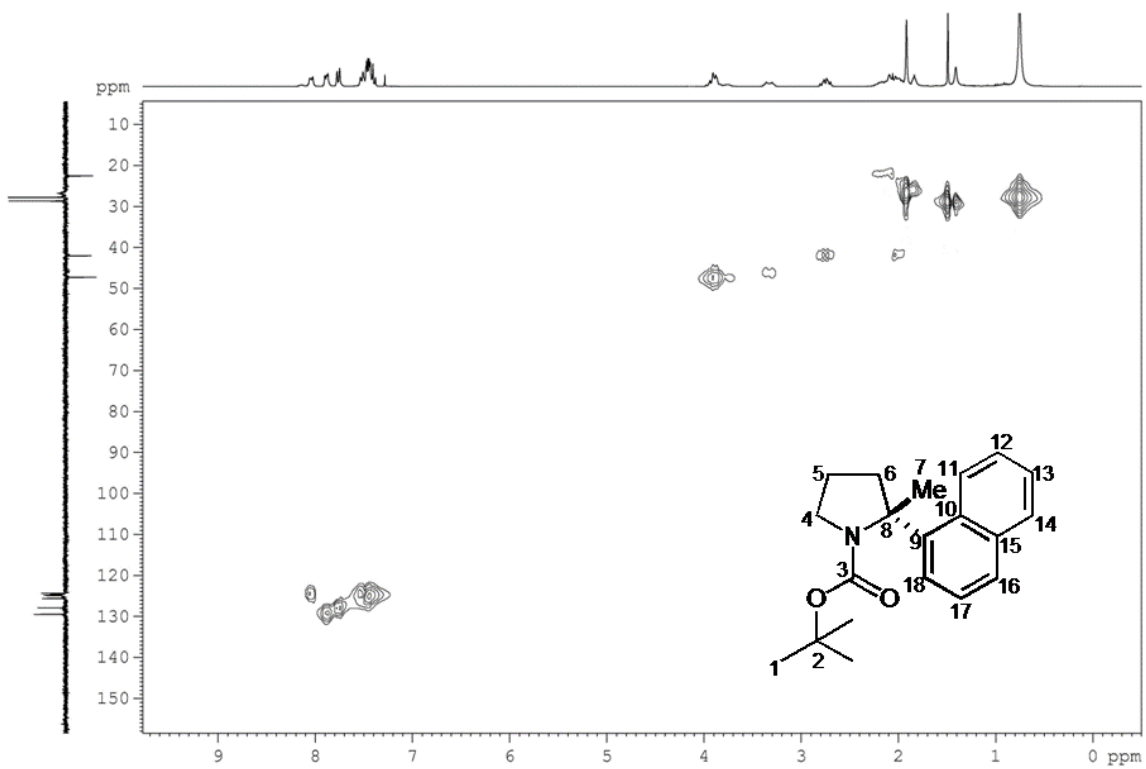
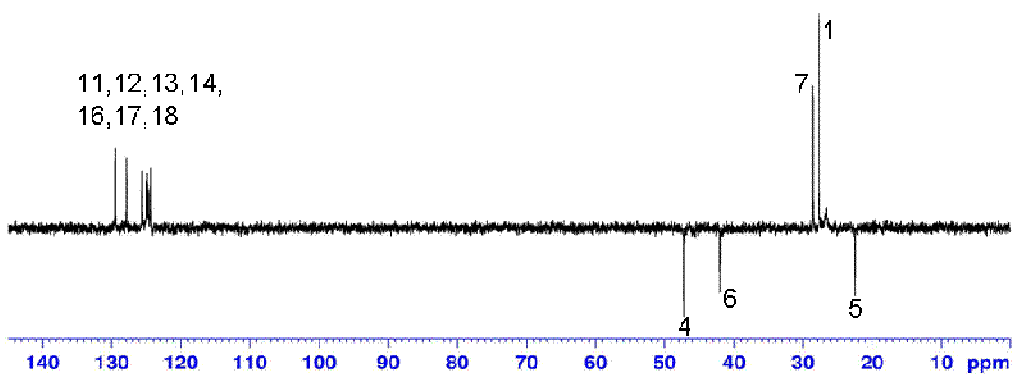
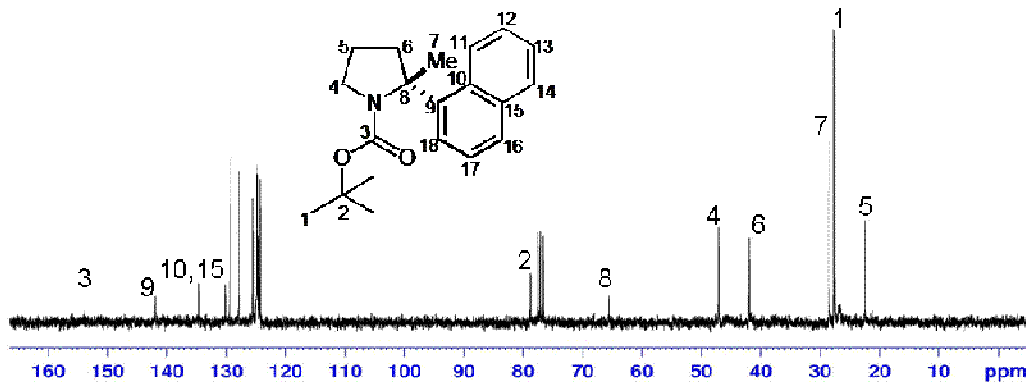
Operator : Beng
 Instrument : Instrument #1
 Acquired : 6 Feb 2012 21:04
 Sample Name: BocPyrr-2-Np-2-Me
 Misc Info : starting material

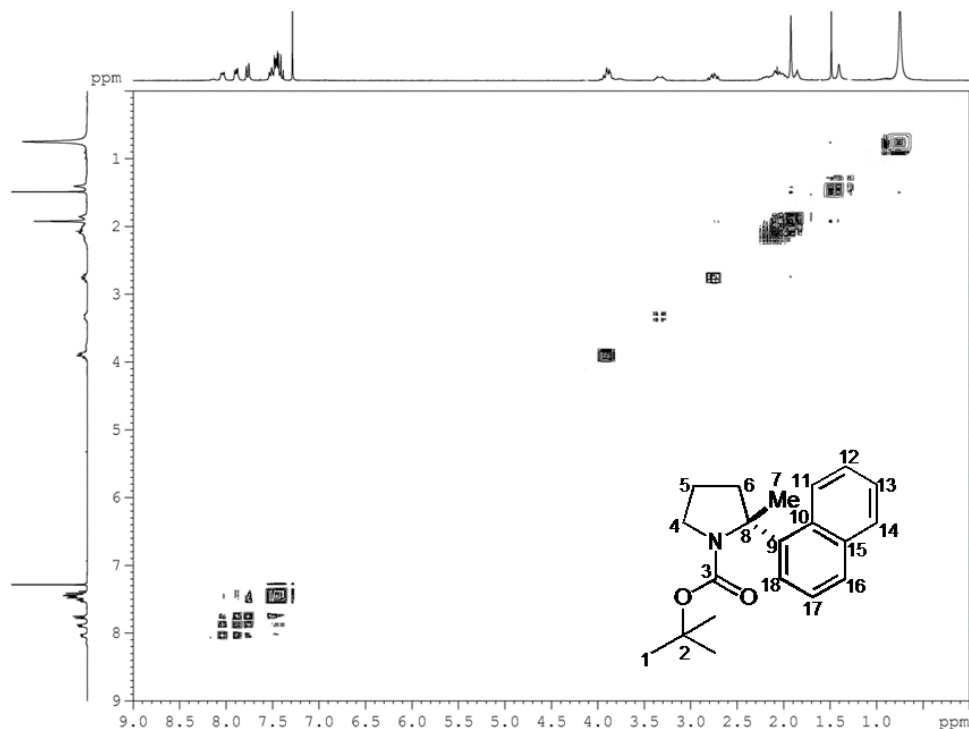
using AcqMethod ALH-EI-1.M



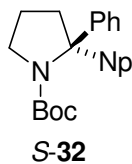
CSP-SFC trace; Column: Pirke Wheelk-0-1, flow rate= 0.5, modifier = 10% MeOH







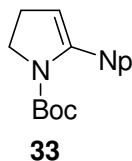
c) With bromobenzene:



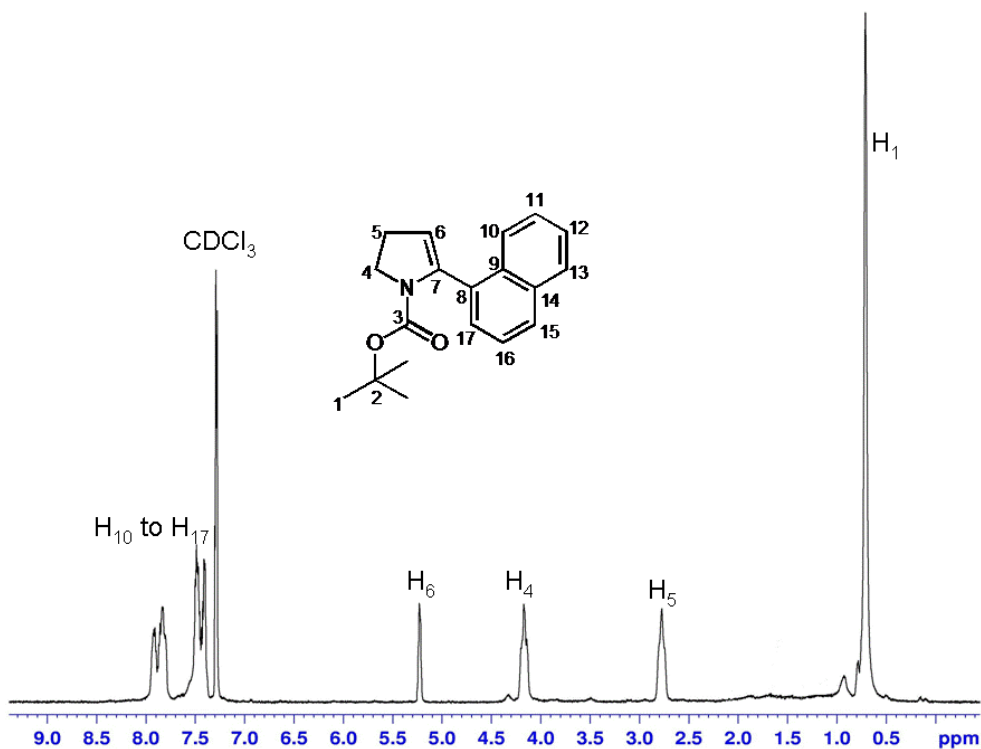
To an oven-dried, septum-capped round bottom flask equipped with a stir bar, was added *R*-**21** of 95:5 er (75 mg, 0.25 mmol, 1.0 equiv) in Et₂O (2 mL) under argon. The mixture was cooled to –60 °C and a solution of *n*-BuLi in hexanes (0.1 mL, 0.25 mmol, 2.5 M, 1.0 equiv) was added slowly. After 3 h at this temperature, a solution of ZnCl₂ (0.15 mL, 1.0 M solution in Et₂O, 0.6 equiv), was added slowly over a two minute period and the mixture was stirred for 30 minutes followed by warming to room temperature. After 30 minutes, Pd(OAc)₂ (2.5 mg, 4 mol%), *t*-Bu₃P·HBF₄ (6 mg, 8 mol%) and phenyl bromide (0.033 mL, 0.28 mmol, 1.1 equiv) were added sequentially. After stirring for 48 h at 40 °C, NH₄OH (2 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 5 mL Et₂O. The filtrate was washed with 1 M HCl_(aq) (10 mL), then with water (2 x 5 mL), dried over Na₂SO₄ and evaporated under reduced pressure to obtain the crude

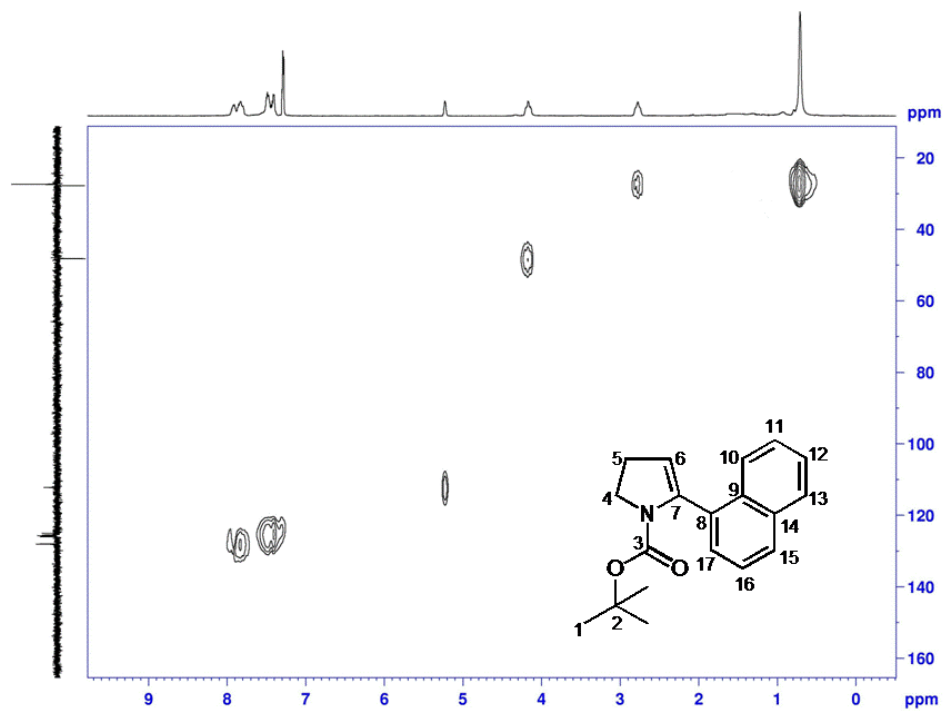
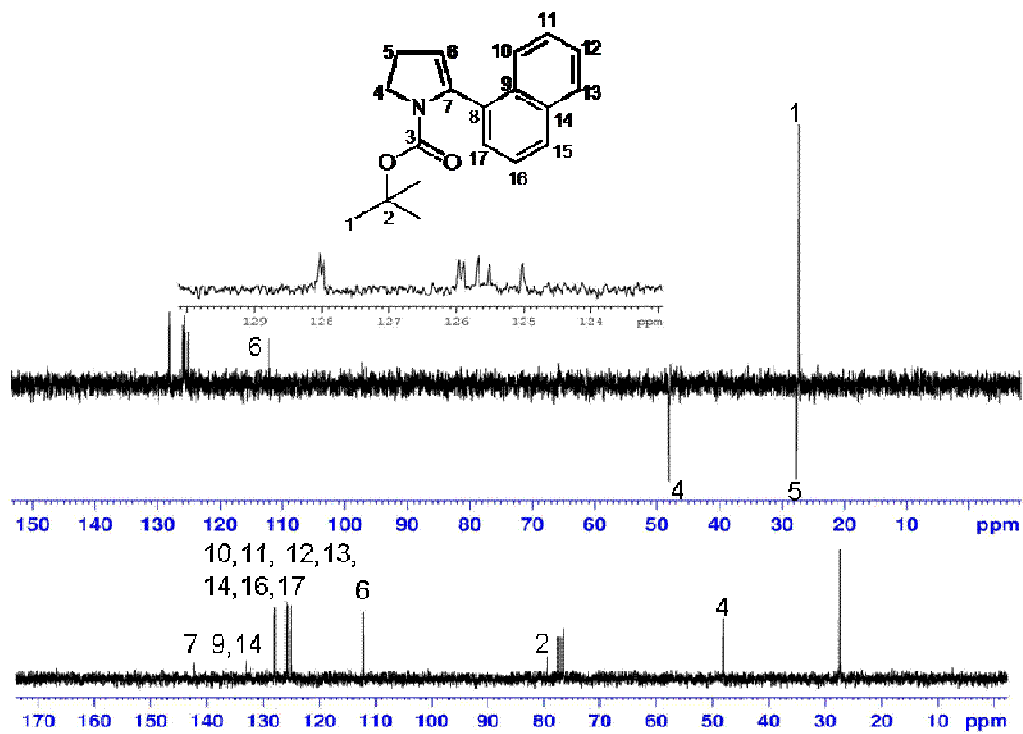
product. Analysis of the crude product by CG-MS showed complete conversion of **21** but less than 5% yield of **32** was present.

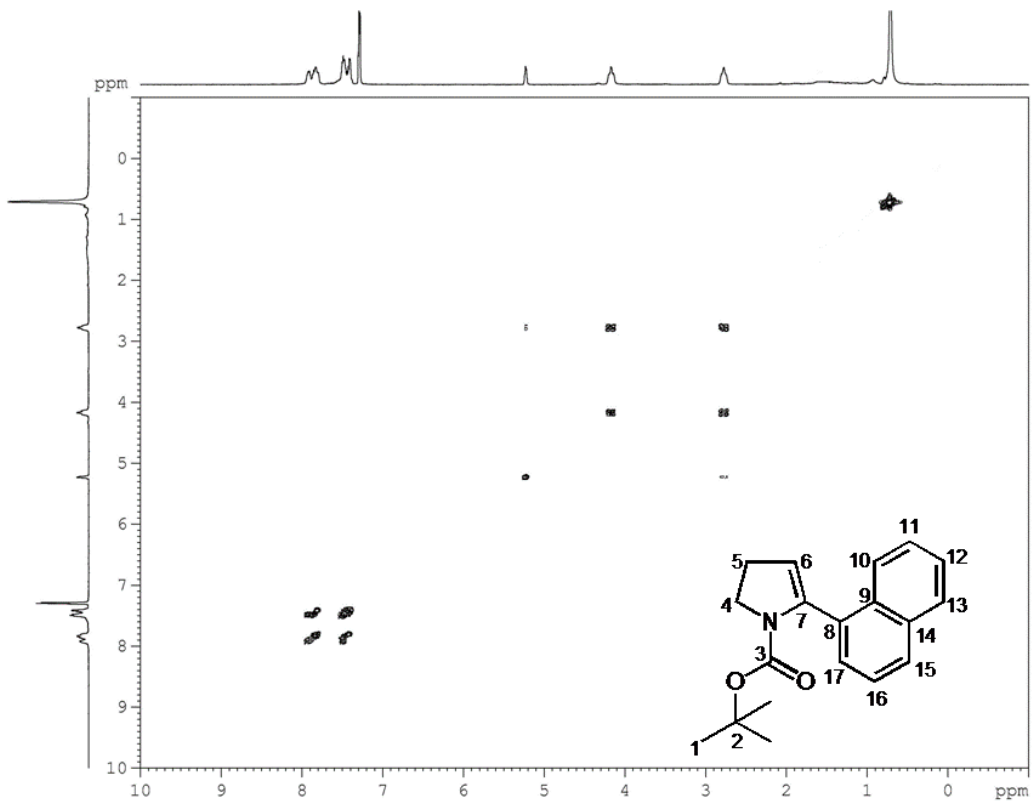
Enamine byproduct formed during Pd-catalyzed arylation of Boc-Pyrr-2-Np with phenyl bromide:



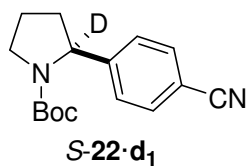
^1H NMR (mixture of rotomers) (300 MHz, CDCl_3) δ = 8.23–7.37 (6H, m), 5.23 (1H, t, br), 4.26 (2H, t, br), 2.81 (2H, t, br), 1.01 – 0.61 (9H, s, br) ^{13}C NMR (75.5 MHz, CDCl_3) δ = 155.4 (C=O), 142.1 (C), 141.8 (C), 134.0 (C) 131.5 (C), 128.9 (CH), 127.3 (CH), 125.8 (CH), 125.4 (CH), 124.9 (CH), 123.5 (CH), 123.2 (CH) 112.2 (CH), 79.8, 48.2 (CH_2), 28.8 (CH_2), 28.3 (3 x CH_3).



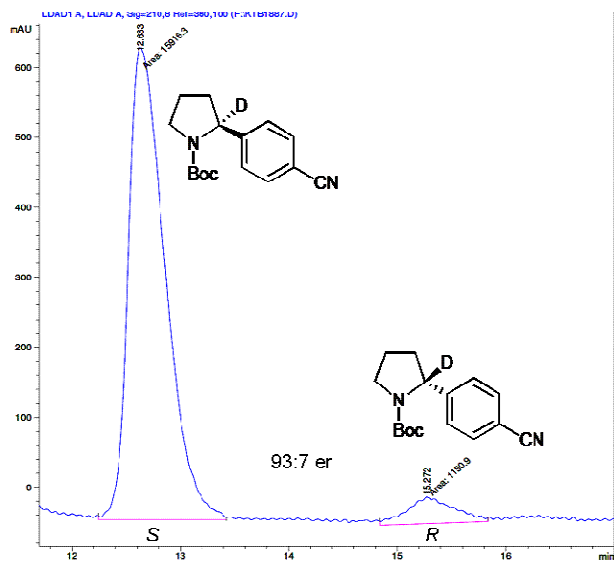




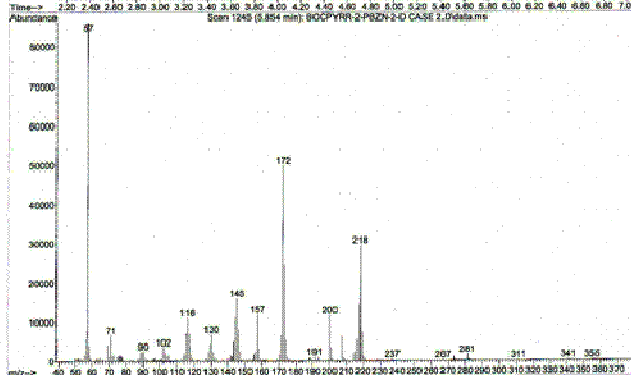
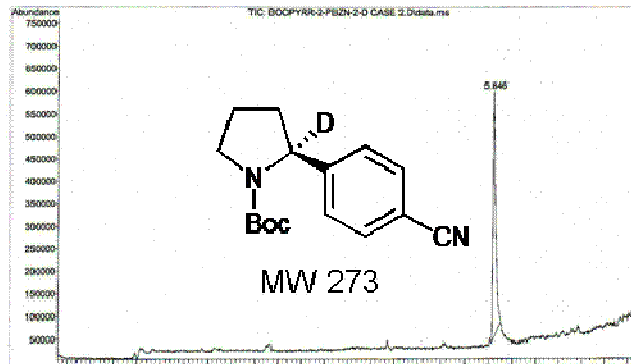
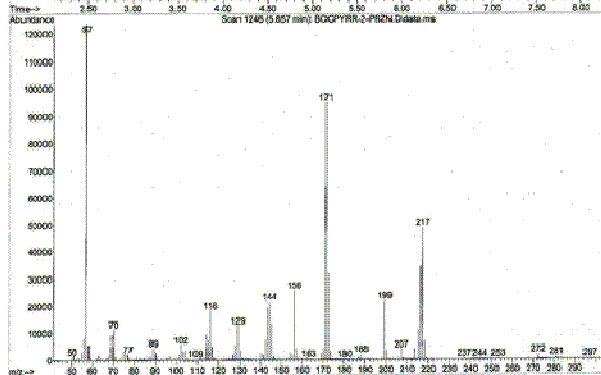
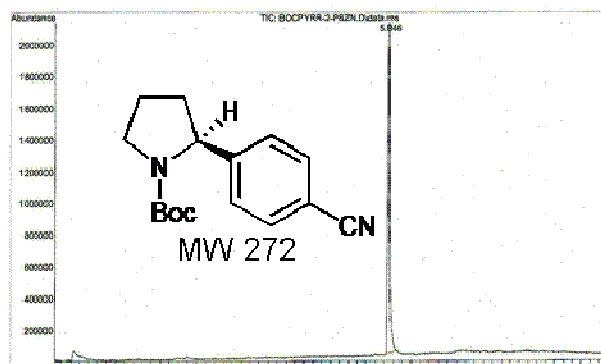
8.4. Lithiation-substitution of (*S*)-*N*-Boc-2-(4-cyanophenyl)pyrrolidine with MeOD



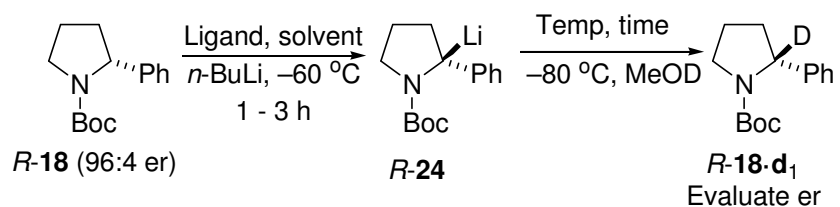
Pirde-Wheik-D-1; Flow = 1.0, Modifier % = 3% MeOH



GC-MS traces from electron impact ionization



9. Dynamics of Inversion of **24**



Typical kinetic run:

In oven-dried, septum-capped tubes equipped with a stir bar, **R-18** (0.06 M in ether, 0.5 mL) and 0.06 M TMEDA (0.00 or 1.00 equiv) were treated with *n*-BuLi (1.0 equiv) at $-60\text{ }^\circ\text{C}$ for 3 h under nitrogen. The total volume of each tube was maintained at 1.0 mL. The tubes were quickly transferred to a second bath thermostatted at the desired temperature (see tables below). At various time intervals over a four-hour period, a tube was transferred to a bath at $-80\text{ }^\circ\text{C}$ and rapidly quenched with MeOD. Each tube was analyzed by GC-MS to ensure 100% deuterium incorporation (indicative of complete lithiation). The enantiomer ratio (er) of **18** $\cdot\text{d}_1$ was determined by CSP-SFC monitoring at 210 nm under the following column conditions: **Column:** Pirkle Whelk-O-1, **Flow Rate** = 2.0 mL/min, **Polarity Modifier** = 2.0% EtOH. **S-18** $\cdot\text{d}_1$ elutes after ~ 4.2 min and **R-18** $\cdot\text{d}_1$ elutes after ~ 5.7 min. The rate constants were determined by non-linear fitting of the zero-order plots using reversible first-order kinetics. Using reversible first-order kinetics, the fraction of the *R*-enantiomer starting from **R-18** (96:4 er) as a function of time (*t*), is given by $(R)_t = 0.5 + (0.96 - 0.50)(e^{-k_{\text{rac}}t})$ where k_{rac} is the observed rate constant for the racemization. The enantiomerization rate constant, $k_{\text{ent}} = k_{\text{rac}}/2$.

Notes

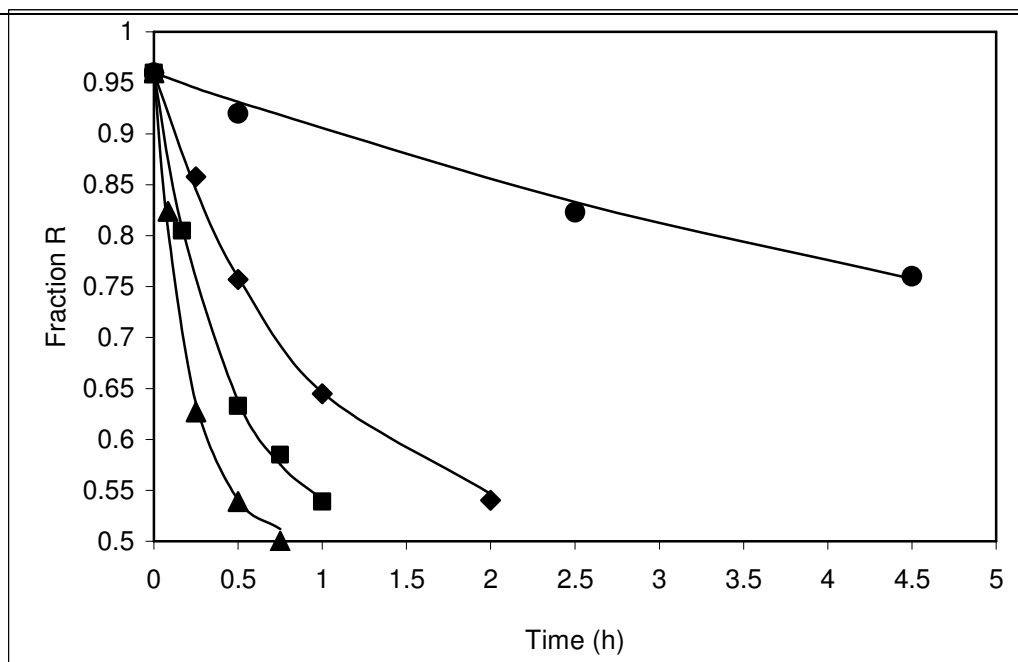
- In Et_2O , the lithiation of **R-18** (96:4 er) was carried out for 3 h both in the absence of any ligand and in the presence of TMEDA or **23**.
- In THF, the lithiation of **S-18** (96:4 er) was carried out for 1 h in the absence of any ligand.
- In 2-MeTHF, the lithiation of **R-18** (96:4 er) was carried out for 1 h in the absence of any ligand.

Table S1. Enantiomer ratios for racemization of **24** in the absence of any ligand in Et₂O

| a) at -20 °C | | c) at 0 °C | |
|--------------|------------|------------|------------|
| Time (h) | Fraction R | Time (h) | Fraction R |
| 0 | 0.960 | 0 | 0.960 |
| 0.5 | 0.915 | 0.1667 | 0.805 |
| 2.5 | 0.823 | 0.5 | 0.633 |
| 4.5 | 0.753 | 0.75 | 0.585 |
| | | 1 | 0.539 |

| b) at -7 °C | | d) at 8 °C | |
|-------------|------------|------------|------------|
| Time (h) | Fraction R | Time (h) | Fraction R |
| 0 | 0.960 | 0 | 0.960 |
| 0.25 | 0.858 | 0.083333 | 0.824 |
| 0.5 | 0.757 | 0.25 | 0.627 |
| 1 | 0.645 | 0.5 | 0.539 |
| 2 | 0.541 | 0.75 | 0.501 |

Figure S1. Evolution of er in the enantiomerization of *R*-**24** in the absence of any ligand in Et₂O.



KEY: 281 K; triangles, 273 K; squares, 266 K; diamonds, 253 K; circles

Enantiomerization in the absence of any ligand at 281 K in Et₂O

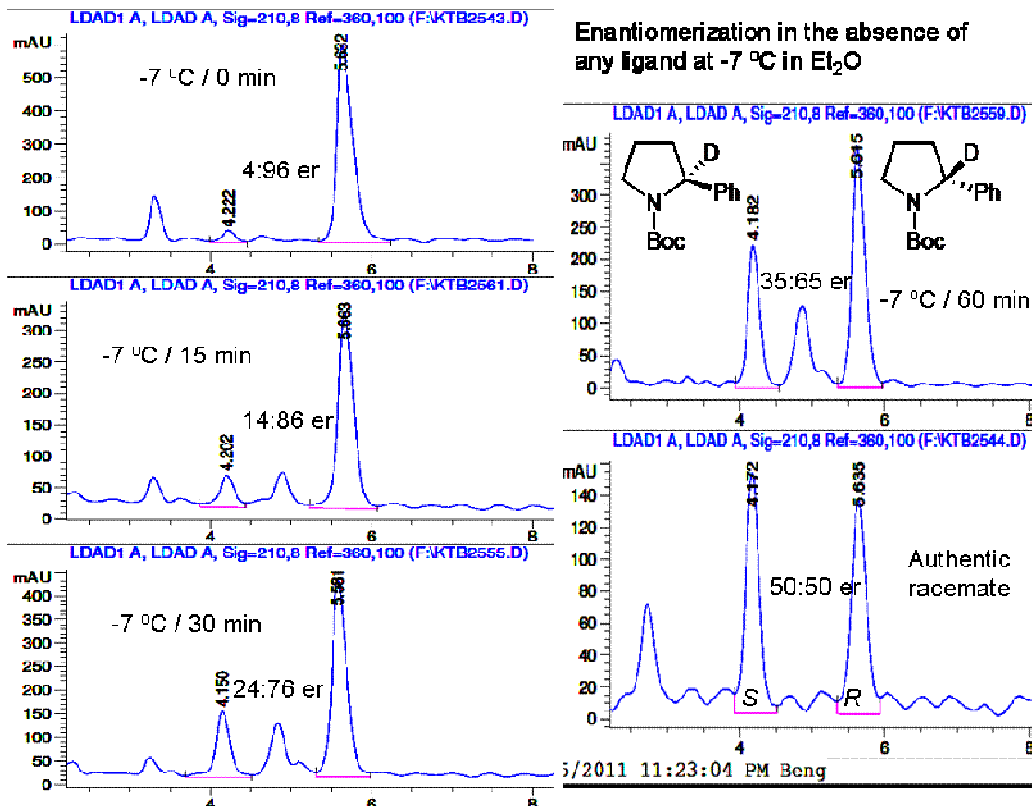
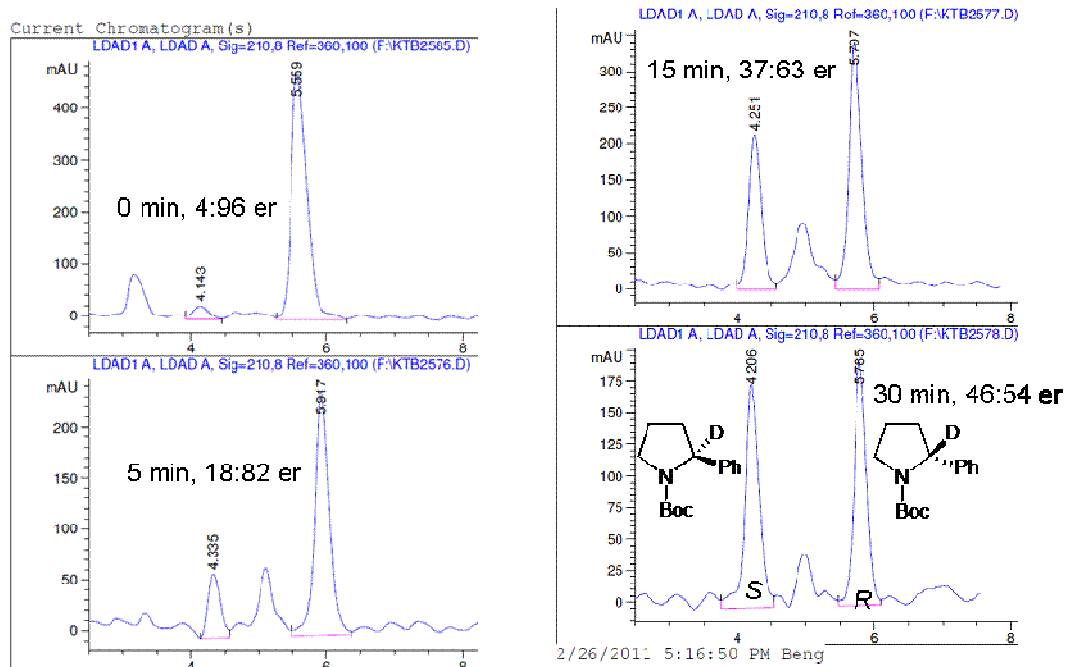
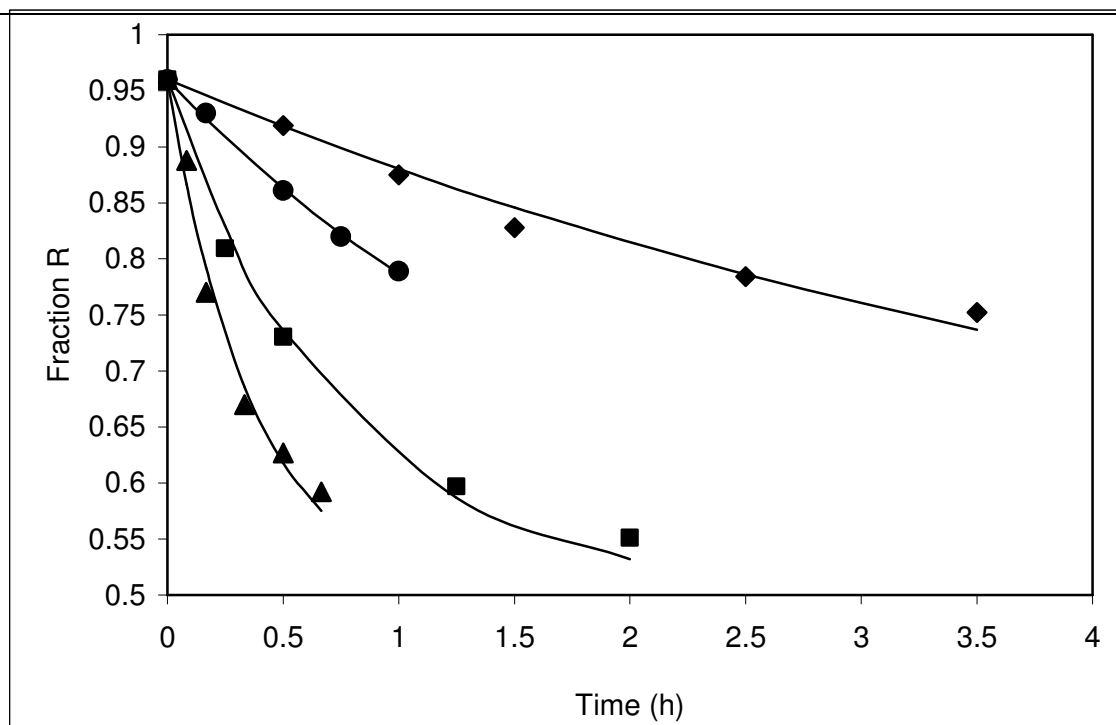


Table S2. Enantiomer ratios for enantiomerization of **24** in the presence of 1 equiv TMEDA in Et₂O

| a) at -7 °C | | c) at 8 °C | |
|-------------|------------|------------|------------|
| Time (h) | Fraction R | Time (h) | Fraction R |
| 0 | 0.960 | 0 | 0.960 |
| 0.5 | 0.919 | 0.25 | 0.8095 |
| 1 | 0.875 | 0.5 | 0.7305 |
| 1.5 | 0.828 | 1.25 | 0.597 |
| 2.5 | 0.784 | 2 | 0.551 |
| 3.5 | 0.752 | | |

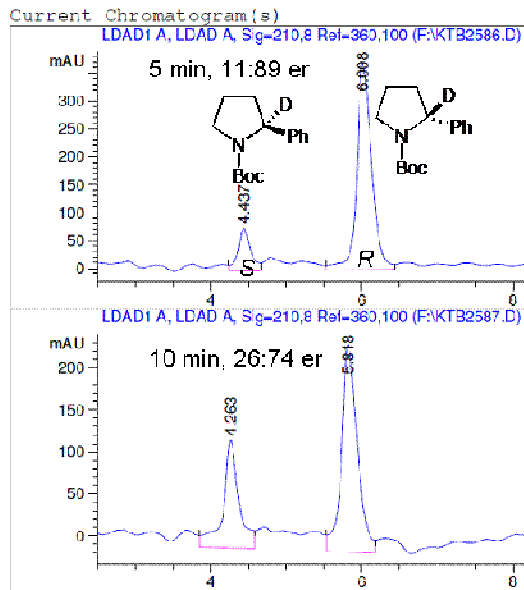
| b) at 0 °C | | d) at 18 °C | |
|------------|------------|-------------|------------|
| Time (h) | Fraction R | Time (min) | Fraction R |
| 0 | 0.96 | 0 | 0.96 |
| 0.1667 | 0.93 | 5 | 0.888 |
| 0.5 | 0.861 | 10 | 0.77 |
| 0.75 | 0.82 | 20 | 0.67 |
| 1 | 0.789 | 30 | 0.627 |
| | | 40 | 0.592 |

Figure S2. Evolution of er in the enantiomerization of *R*-**24** in the presence of 1 equiv TMEDA in Et₂O at various temperatures.



KEY: 291 K; triangles, 281 K; squares, 273 K; circles, 266 K; diamonds

**Enantiomerization in the presence
of 1 equiv TMEDA at 291 K in Et₂O**



**Enantiomerization in the presence
of 1 equiv TMEDA at 281 K in Et₂O**

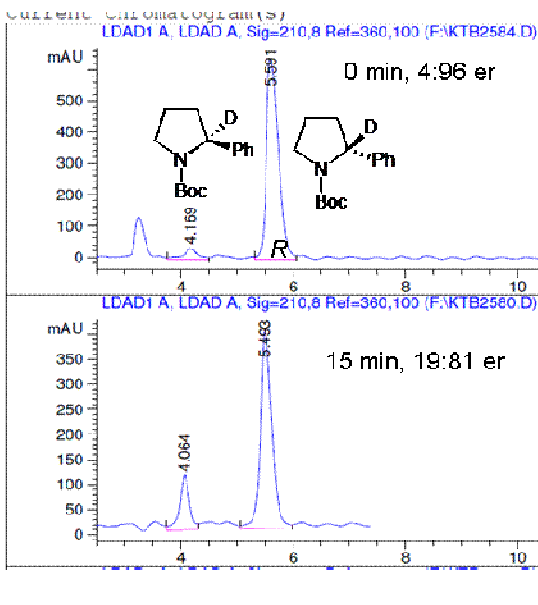


Table S3. Enantiomer ratios for enantiomerization of **24** in the presence of 1 equiv DIB, **23**, in Et₂O

a) at -2 °C

| Time (h) | Fraction <i>S</i> |
|----------|-------------------|
| 0 | 0.96 |
| 0.1667 | 0.945 |
| 0.5 | 0.922 |
| 1 | 0.893 |

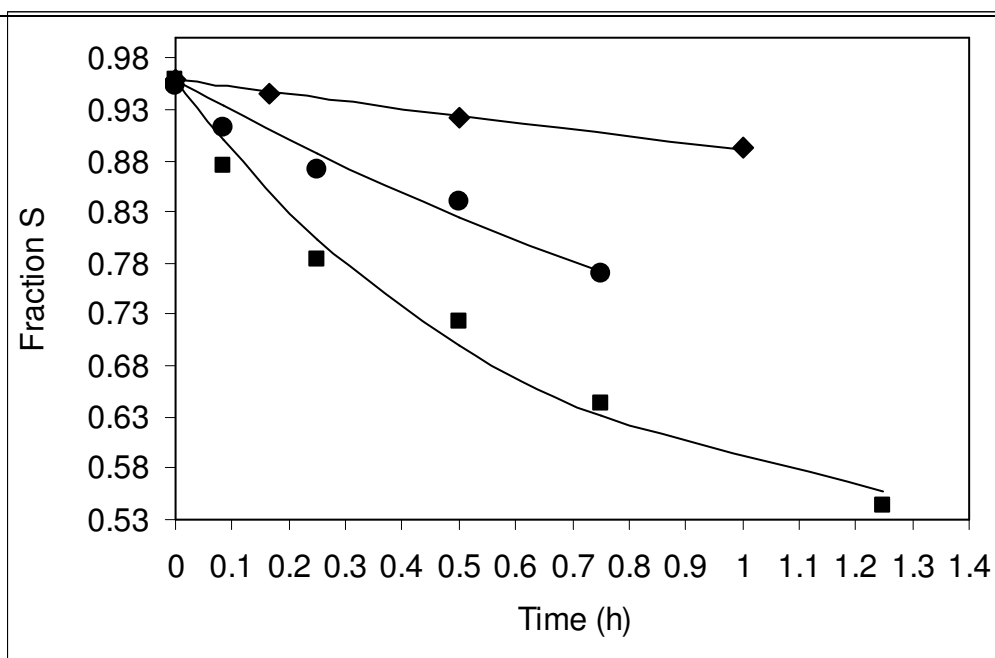
b) at 8 °C

| Time (h) | Fraction <i>S</i> |
|----------|-------------------|
| 0 | 0.953 |
| 0.08333 | 0.913 |
| 0.25 | 0.872 |
| 0.5 | 0.84 |
| 0.75 | 0.77 |

c) at 14 °C

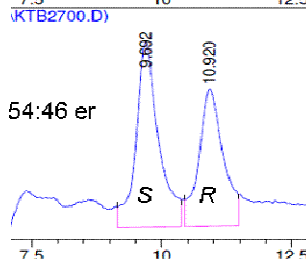
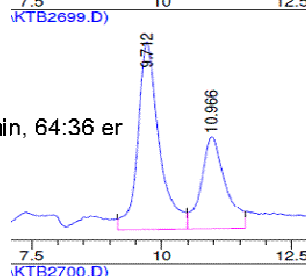
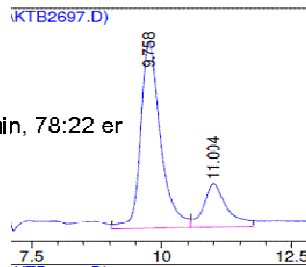
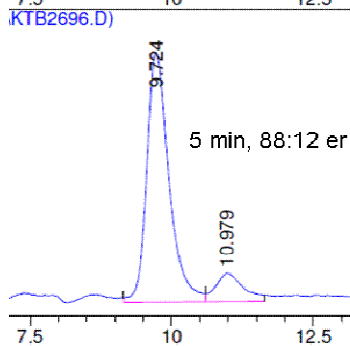
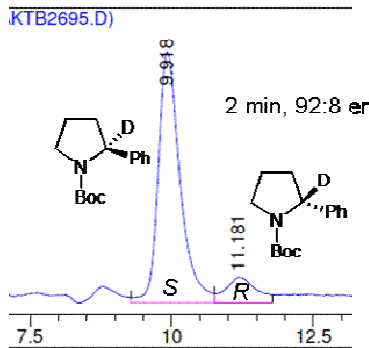
| Time (min) | Fraction <i>S</i> |
|------------|-------------------|
| 0 | 0.96 |
| 0.08333 | 0.875 |
| 0.25 | 0.784 |
| 0.5 | 0.724 |
| 0.75 | 0.643 |
| 1.25 | 0.543 |

Evolution of er in the enantiomerization of *R*-**24** in the presence of 1 equiv DIB in Et₂O at various temperatures.



KEY: 287 K; squares, 281 K; circles, 271 K; diamonds

Enantiomerization in the presence of 1 equiv DIB at 287 K in Et₂O
 CSP-SFC conditions: Flow rate = 0.5, Mod % = 10



Enantiomerization in the presence of 1 equiv DIB at 281 K in Et₂O
 CSP-SFC conditions: Flow rate = 0.5, Mod % = 10

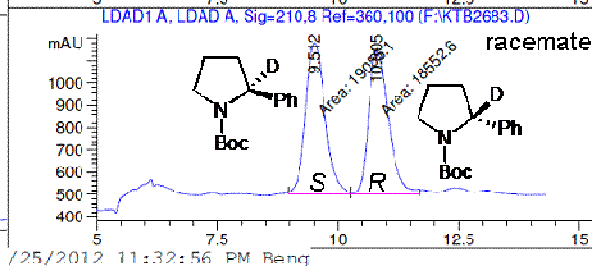
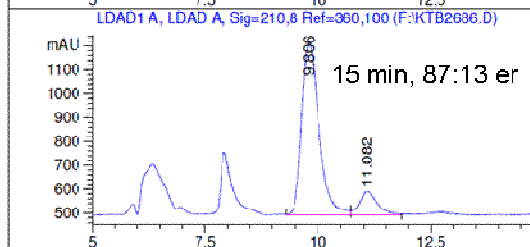
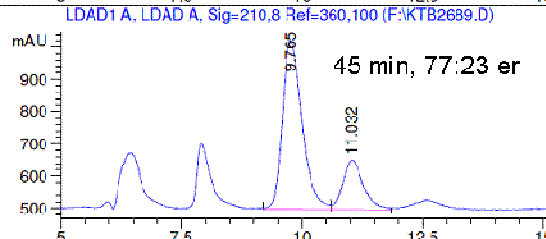
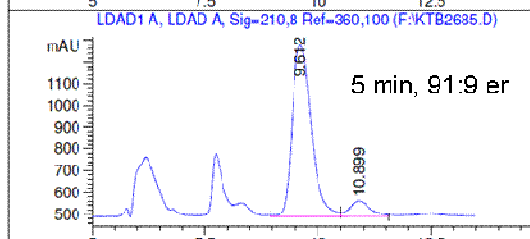
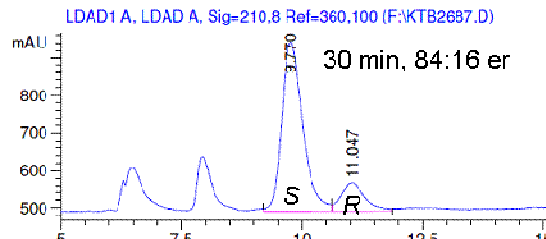
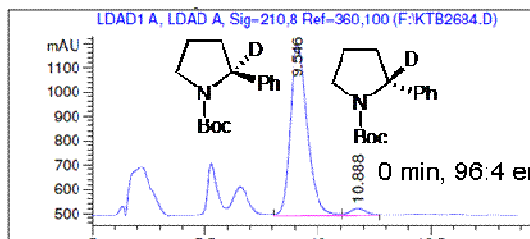


Table 4. Enantiomer ratios for enantiomerization of *S*-24 in the absence of any ligand in THF (lithiation with *n*-BuLi).

a) at $-57\text{ }^{\circ}\text{C}$

| Time (h) | Fraction <i>S</i> |
|----------|-------------------|
| 0.5 | 0.88 |
| 1 | 0.8 |
| 2 | 0.701 |
| 4 | 0.628 |
| 8 | 0.51 |

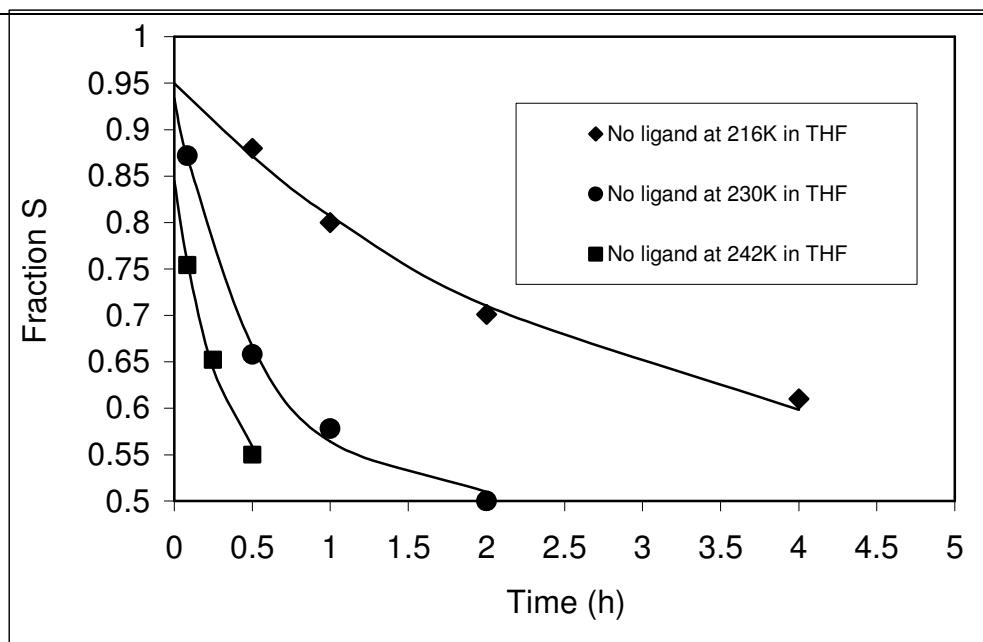
c) at $-31\text{ }^{\circ}\text{C}$

| Time (h) | Fraction <i>S</i> |
|----------|-------------------|
| 0.083333 | 0.754 |
| 0.25 | 0.652 |
| 0.5 | 0.603 |
| 1 | 0.519 |

b) at $-43\text{ }^{\circ}\text{C}$

| Time (h) | Fraction <i>S</i> |
|----------|-------------------|
| 0.08333 | 0.872 |
| 0.5 | 0.658 |
| 1 | 0.578 |
| 2 | 0.512 |

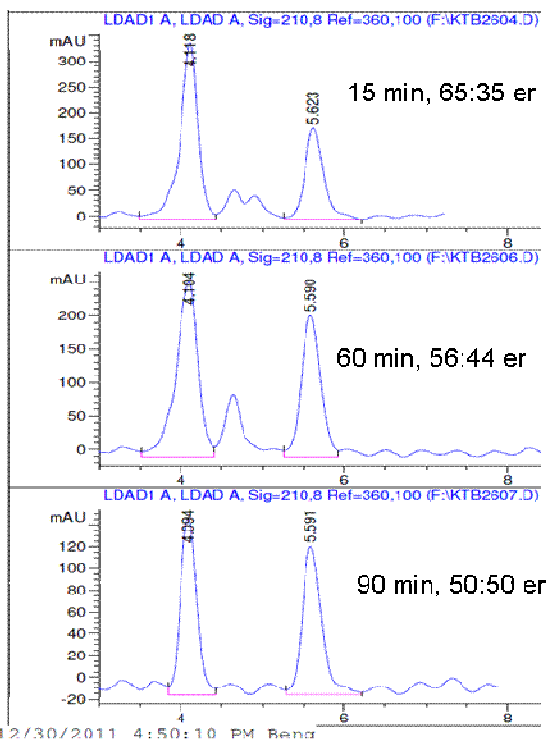
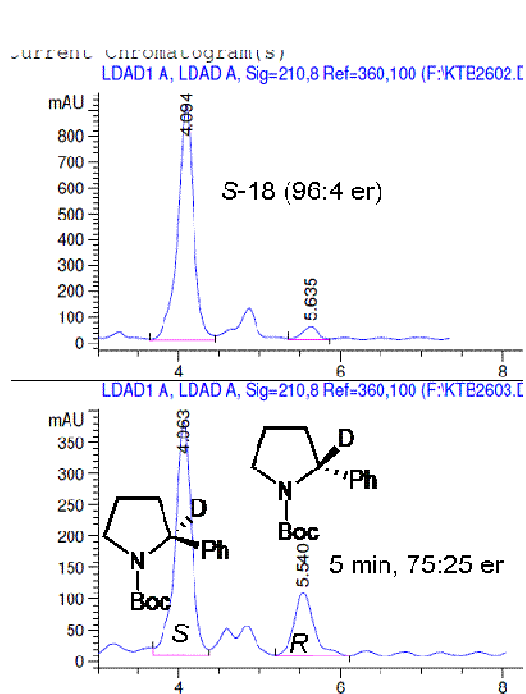
Evolution of er in the enantiomerization of *S*-24 in the absence of any ligand in THF at various temperatures.



The rate constants were obtained from a nonlinear fit of the equation $(S)_t = 0.5 + (S_{ini} - 0.50)(e^{-k_{rac}t})$

Since the initial values at $t=0$, S_{ini} , were not determined experimentally, S_{ini} and k_{rac} were both treated as variable parameters.

Enantiomerization in the absence of any ligand at -31 °C in THF



Enantiomerization in the absence of any ligand at -57 °C in THF

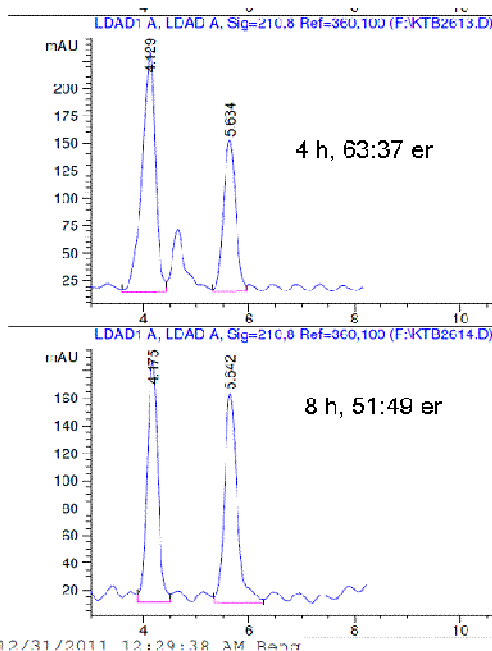
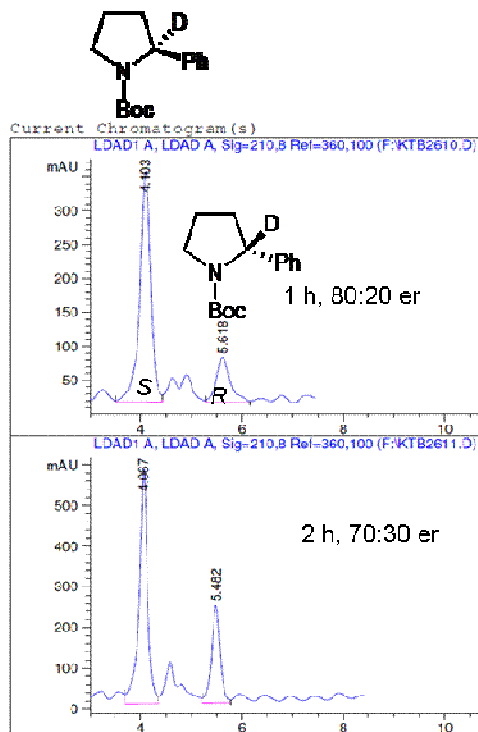


Table 5. Enantiomer ratios for enantiomerization of *R*-**24** in the absence of any ligand in 2-MeTHF at $-31\text{ }^{\circ}\text{C}$

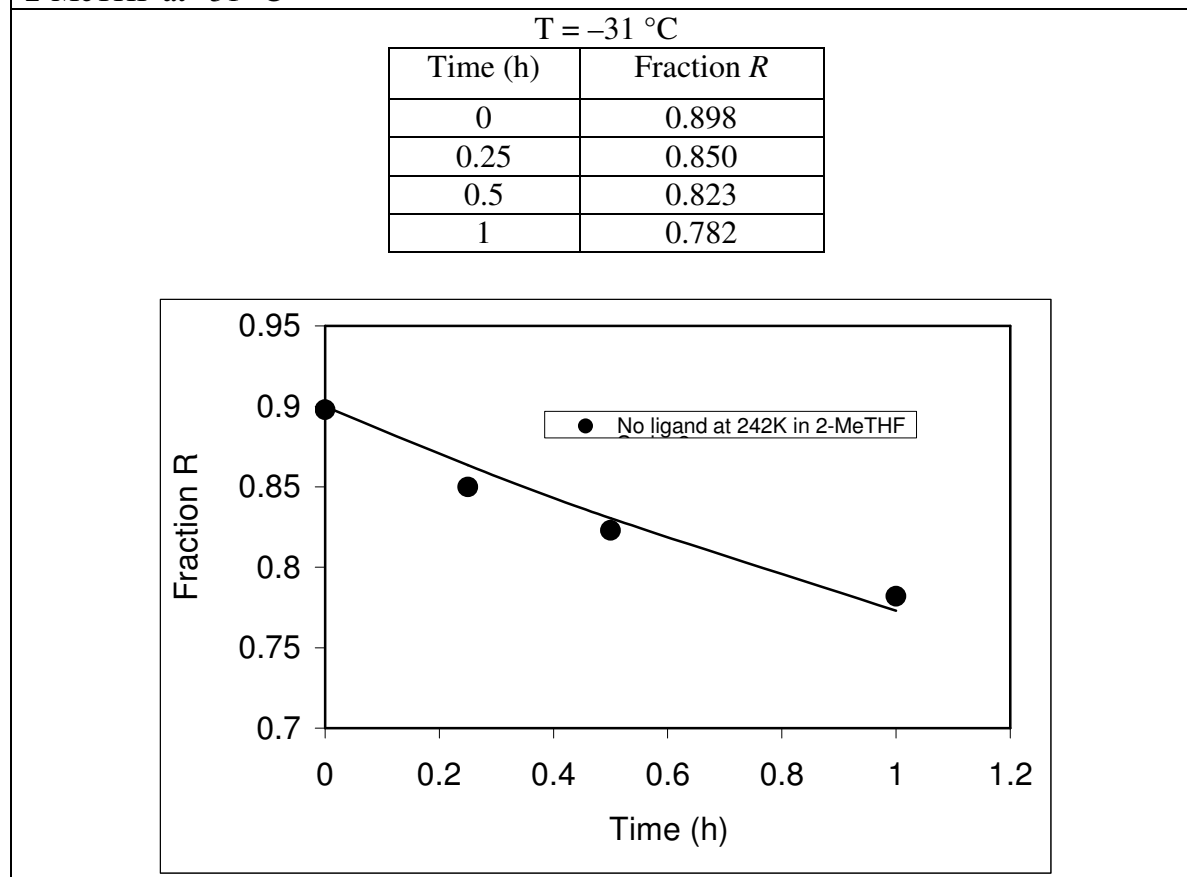


Table 6. Eyring plot parameters for enantiomerization of **24**

Eyring analysis of the rate constants at their respective temperatures was performed using the

equation
$$\ln\left(\frac{k_{ent}}{T}\right) = -\frac{\Delta H^{\ddagger}}{RT} + \ln\frac{k_B}{h} + \frac{\Delta S^{\ddagger}}{R}$$
 where k_{ent} = rate constant for the

enantiomerization (*S* to *R* or *vice versa*), T = absolute temperature, ΔH^{\ddagger} = enthalpy of activation,

R = molar gas constant, k_B = Boltzmann's constant, h = Planck's constant, ΔS^{\ddagger} = entropy of activation.

The analysis of the Eyring plots is based on the assumption that A (the Arrhenius pre-exponential factor), E_a (the activation energy), and ΔH^{\ddagger} are independent of temperature.¹¹ This

approximation is generally considered valid over a small temperature range, such as used in these experiments.

(a) No ligand in Et₂O

| Temp (K) | 1/T (K ⁻¹) | k_{rac} (x 10 ⁻⁴ s ⁻¹) ^a | ln(k_{rac} /T) | ln(k_{ent} /T) |
|----------|------------------------|--|-------------------|-------------------|
| 253 | 0.00395257 | 0.358 ± 0.06 | -15.770 | -16.463 |
| 266 | 0.0037594 | 3.184 ± 0.61 | -13.636 | -14.329 |
| 273 | 0.003663 | 6.703 ± 0.93 | -12.917 | -13.610 |
| 281 | 0.00355872 | 13.53 ± 1.04 | -12.244 | -12.937 |

(b) 1 equiv TMEDA in Et₂O

| Temp (K) | 1/T (K ⁻¹) | k_{rac} (x 10 ⁻⁴ s ⁻¹) ^a | ln(k_{rac} /T) | ln(k_{ent} /T) |
|----------|------------------------|--|-------------------|-------------------|
| 266 | 0.0037594 | 0.528 ± 0.07 | -15.433 | -16.126 |
| 273 | 0.003663 | 1.314 ± 0.03 | -14.547 | -15.240 |
| 281 | 0.00355872 | 3.705 ± 0.07 | -13.539 | -14.232 |
| 291 | 0.00343643 | 7.564 ± 1.04 | -12.860 | -13.553 |

(c) 1 equiv DIB in Et₂O

| Temp (K) | 1/T (K ⁻¹) | k_{rac} (x 10 ⁻⁴ s ⁻¹) ^a | ln(k_{rac} /T) | ln(k_{ent} /T) |
|----------|------------------------|--|-------------------|-------------------|
| 271 | 0.00369004 | 0.4598 ± 0.008 | -15.589 | -16.282 |
| 281 | 0.00355872 | 1.910 ± 0.02 | -14.201 | -14.894 |
| 287 | 0.00348432 | 4.429 ± 0.08 | -13.382 | -14.075 |

(d) No ligand in THF

| Temp (K) | 1/T (K ⁻¹) | k_{rac} (x 10 ⁻⁴ s ⁻¹) ^a | ln(k_{rac}/T) | ln(k_{ent}/T) |
|----------|------------------------|--|-------------------|-------------------|
| 216 | 0.00462963 | 1.06 ± 0.12 | -14.531 | -15.224 |
| 230 | 0.00434783 | 5.3 ± 0.19 | -12.980 | -13.674 |
| 242 | 0.00413223 | 9.8 ± 1.4 | -12.416 | -13.109 |

a. $k_{rac} = k_{RS} + k_{SR} = 2k_{ent}$

From an Eyring plot,

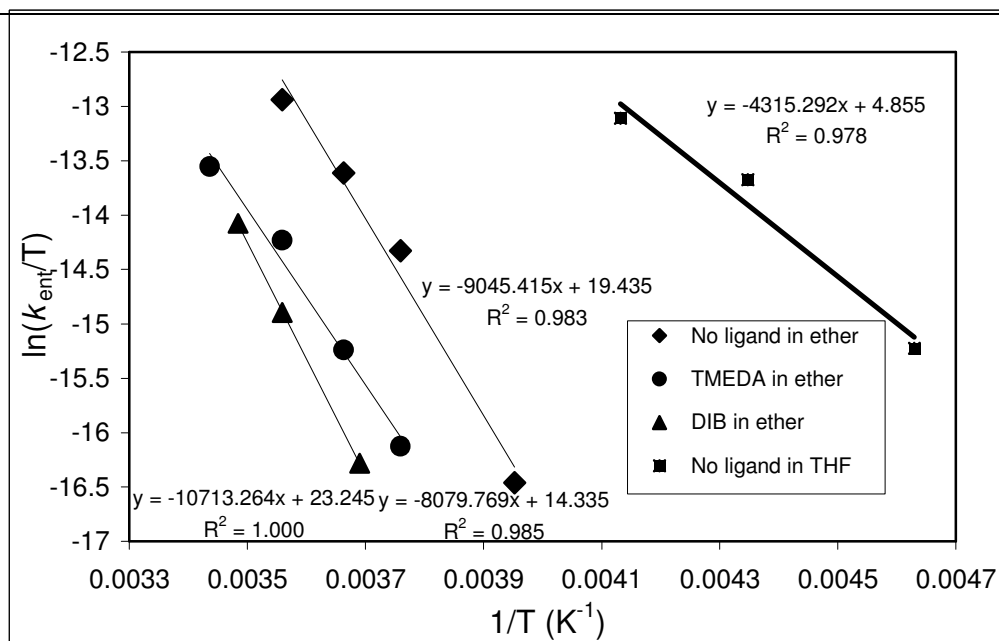
$$\Delta H^\ddagger = -\text{slope} \cdot R; \frac{Err(\Delta H)}{\Delta H} = \sqrt{\left(\frac{err(\text{slope})}{\text{slope}}\right)^2 + \left(\frac{err(R)}{R}\right)^2} = \sqrt{\left(\frac{err(\text{slope})}{\text{slope}}\right)^2} \text{ since } err(R) = 0$$

$$\text{Similarly, } \Delta S^\ddagger = \text{Intercept} \cdot R - R \ln(k_B/T); \frac{Err(\Delta S)}{\Delta S} = \sqrt{\left(\frac{err(\text{intercept})}{\text{intercept}}\right)^2 + \left(\frac{err(R)}{R}\right)^2} = \sqrt{\left(\frac{err(\text{intercept})}{\text{intercept}}\right)^2}$$

$$\Delta G^\ddagger = \Delta H^\ddagger - T\Delta S^\ddagger \text{ such that } \frac{Err(T\Delta S)}{T\Delta S} = \sqrt{\left(\frac{err(T)}{T}\right)^2 + \left(\frac{err(\Delta S)}{\Delta S}\right)^2}$$

$$Err(\Delta G) = \sqrt{(err(dH))^2 + (err(TdS))^2}$$

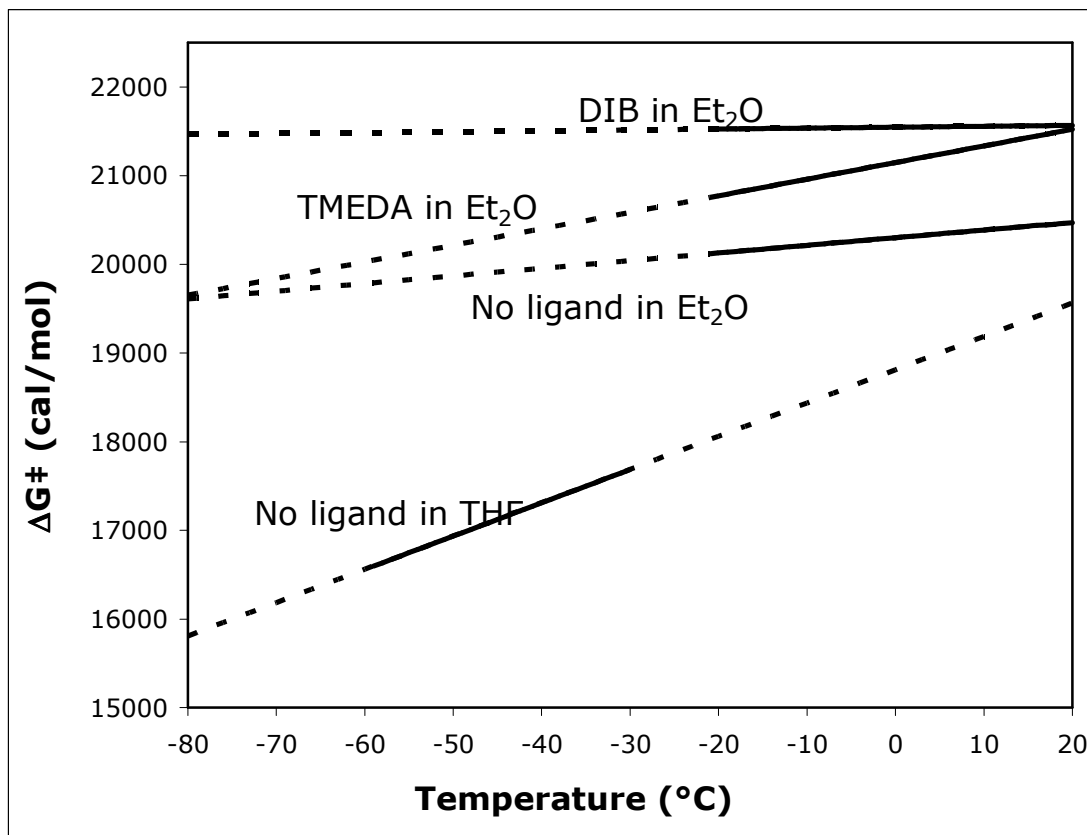
Eyring plots for enantiomerization of **24**.



Relationship between free energy of activation and temperature for enantiomerization of **24**.

$$\Delta G^\ddagger = \Delta H^\ddagger - T\Delta S^\ddagger$$

| Entry | Description | ΔH^\ddagger (kcal/mol) | ΔS^\ddagger (cal/mol·K) |
|-------|--|--------------------------------|---------------------------------|
| 1 | No ligand in Et ₂ O | 18.0 ± 1.7 | -8.6 ± 0.3 |
| 2 | 1 equiv TMEDA in Et ₂ O | 16.0 ± 1.3 | -18.7 ± 1.6 |
| 3 | 1 equiv 23 in Et ₂ O | 21.3 ± 0.2 | -1.0 ± 0.4 |
| 4 | No ligand in THF | 8.6 ± 1.6 | -37.5 ± 2.5 |



10. Dynamics of Inversion of **8**

Typical kinetic run:

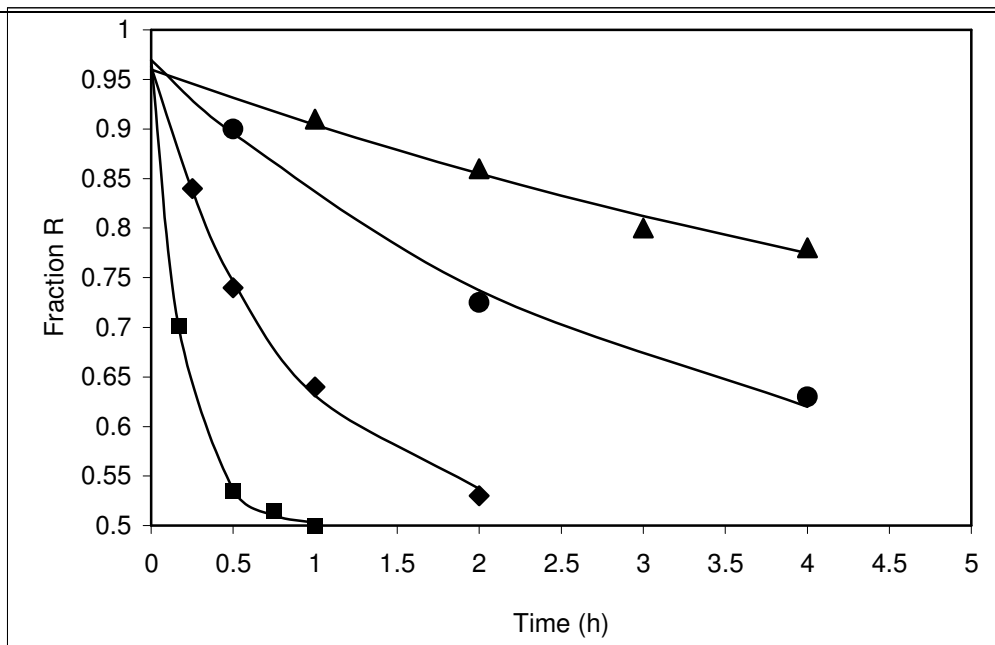
In oven-dried, septum-capped tubes equipped with a stir bar, **R-3** (0.06 M in ether, 0.5 mL) and 0.06 M TMEDA (0.00 or 1.00 equiv) were treated with *n*-BuLi (1.0 equiv) at $-80\text{ }^{\circ}\text{C}$ for 1 h under nitrogen. The total volume of each tube was maintained at 1.0 mL. The tubes were quickly transferred to a second bath thermostated at the appropriate temperature (see tables below). At various time intervals over a four-hour period, a tube was transferred to the bath at $-80\text{ }^{\circ}\text{C}$ and rapidly quenched with MeOD. Each tube was analyzed by GC-MS to ensure 100% deuterium incorporation (indicative of complete lithiation). The enantiomer ratio (er) of **3-d₁** was determined by CSP-SFC monitoring at 210 nm under the following column conditions: **Column:** Pirkle Whelk-O-1, **Flow Rate** = 0.5 mL/min, **Polarity Modifier** = 10.0% IPA. **S-3-d₁** elutes after ~17.2 min and **R-3-d₁** elutes after ~21 min. In some cases, the enantiomer ratio (er) of **3-d₁** was determined by CSP-HPLC monitoring at 254 nm. The rate constants were determined by non-linear fitting of the zero-order plots using reversible first-order kinetics. The rate constants were obtained from a nonlinear fit of the equation $(R)_t = 0.5 + (R_{ini} - 0.5)(e^{-k_{rac}t})$

Since the initial values at $t=0$, R_{ini} , were not determined experimentally, R_{ini} , and k_{rac} were both treated as variable parameters in the fitted equation; k_{rac} is the observed rate constant for the racemization. The enantiomerization rate constant, $k_{ent} = k_{rac}/2$.

Table 1. Enantiomer ratios for enantiomerization of **8** in the absence of any ligand in Et₂O

| | | | |
|-------------|------------|-------------|------------|
| a) at 225 K | | c) at 239 K | |
| Time (h) | Fraction R | Time (h) | Fraction R |
| | | | |
| 1 | 0.91 | 0.25 | 0.84 |
| 2 | 0.86 | 0.5 | 0.74 |
| 3 | 0.80 | 1 | 0.64 |
| 4 | 0.78 | 2 | 0.53 |
| b) at 232 K | | d) at 248 K | |
| Time (h) | Fraction R | Time (h) | Fraction R |
| | | | |
| 0.5 | 0.9 | 0.1667 | 0.701 |
| 2 | 0.725 | 0.5 | 0.535 |
| 4 | 0.63 | 0.75 | 0.515 |
| | | 1 | 0.5 |

Evolution of er in the enantiomerization of **8** in the absence of any ligand in Et₂O.



KEY: 225 K; triangles, 232 K; circles, 239 K; diamonds, 248 K; squares

Kinetics of racemization

CSP-HPLC traces for enantiomerization with no ligand in Et₂O at -36 °C

AGILENT HPLC 5/26/2012

 Injection Date : 5/26/2012 5:24:47 PM
 Sample Name : BocPip-2-Ph-2-Li Location
 Acq. Operator : Beng
 Acq. Method : C:\HPCHEM\1\METHODS\THOMAS-1.M
 Last changed : 5/26/2012 4:53:46 PM by Beng
 (modified after loading)
 Analysis Method : C:\HPCHEM\1\METHODS\THOMAS-1.M
 Last changed : 5/26/2012 7:03:08 PM by Beng
 (modified after loading)

Pirkle Wheel-0-1
 Flow rate = 2.0
 Hex:IPA (98:2)

zorbax-sil. Using 2,6 piv online

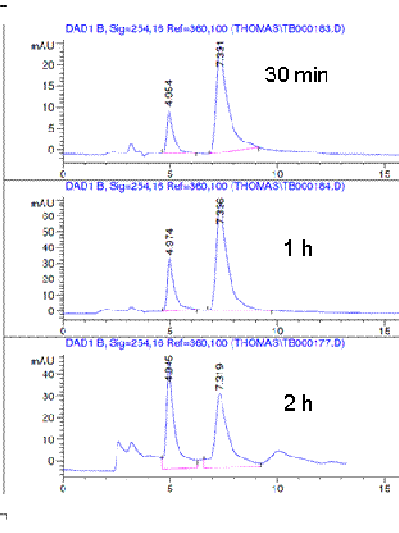
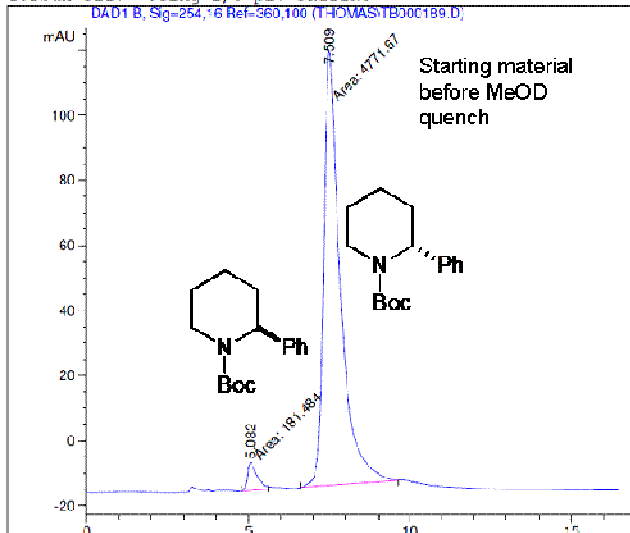
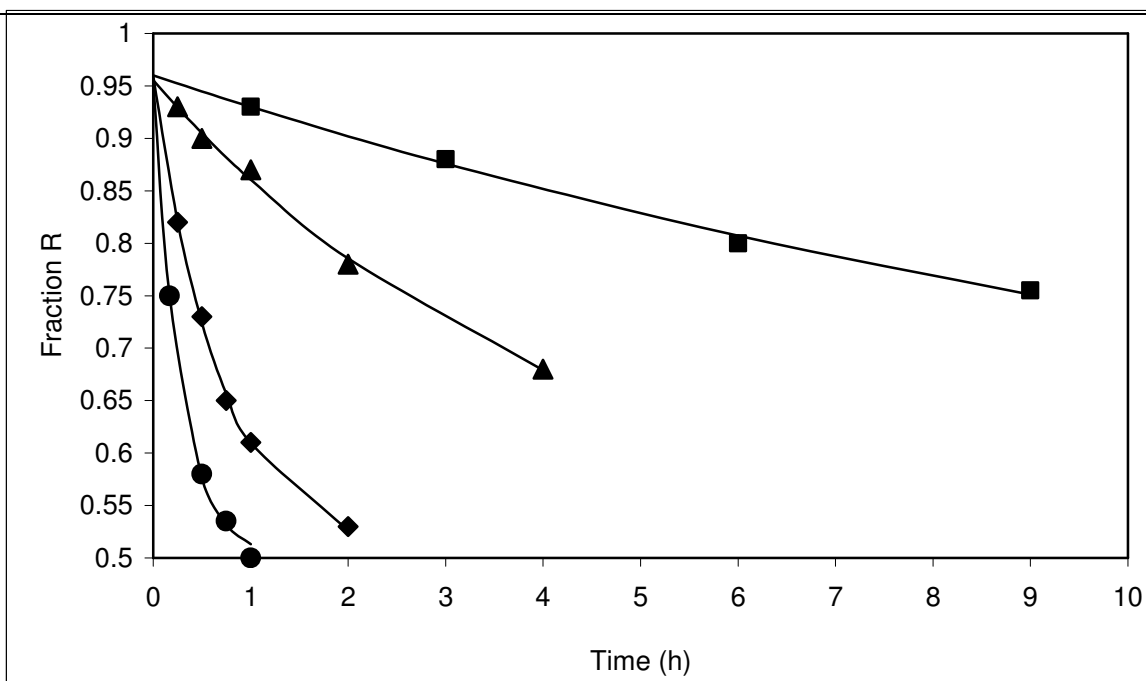


Table 2. Enantiomer ratios for enantiomerization of **8** in the presence of 1 equiv TMEDA in Et₂O

| a) at 225 K | | c) at 243 K | |
|-------------|-------------------|-------------|-------------------|
| Time (h) | Fraction <i>R</i> | Time (h) | Fraction <i>R</i> |
| | | | |
| 1 | 0.93 | 0.25 | 0.82 |
| 3 | 0.88 | 0.5 | 0.73 |
| 6 | 0.8 | 0.75 | 0.65 |
| 9 | 0.755 | 1 | 0.61 |
| | | 2 | 0.53 |

| b) at 233 K | | d) at 253 K | |
|-------------|-------------------|-------------|-------------------|
| Time (h) | Fraction <i>R</i> | Time (h) | Fraction <i>R</i> |
| | | | |
| 0.25 | 0.93 | 0.1667 | 0.75 |
| 0.5 | 0.9 | 0.5 | 0.58 |
| 1 | 0.87 | 0.75 | 0.535 |
| 2 | 0.78 | 1 | 0.50 |
| 4 | 0.68 | | |

Evolution of er in the enantiomerization of **8** in the presence of 1 equiv TMEDA in Et₂O at various temperatures.



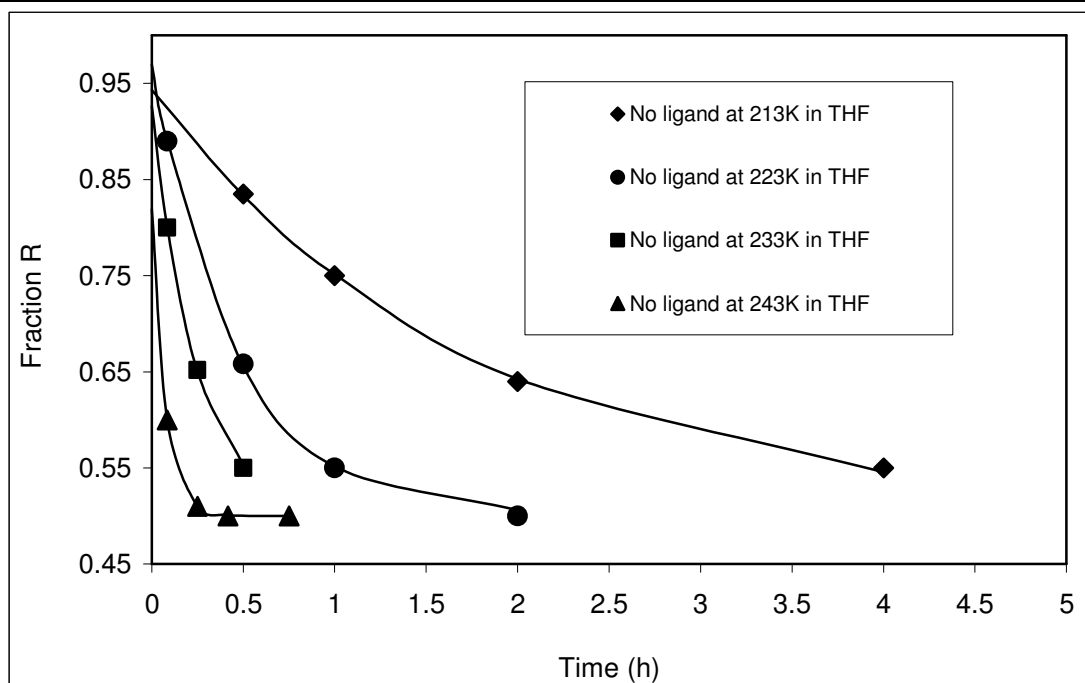
KEY: 225 K; circles, 233 K; diamonds, 243 K; triangles, 248 K; squares

Table 4. Enantiomer ratios for enantiomerization of **8** in the absence of any ligand in THF

| a) at 213 K | | c) at 233 K | |
|-------------|-------------------|-------------|-------------------|
| Time (h) | Fraction <i>R</i> | Time (h) | Fraction <i>R</i> |
| | | | |
| 0.5 | 0.835 | 0.083333 | 0.8 |
| 1 | 0.75 | 0.25 | 0.652 |
| 2 | 0.64 | 0.5 | 0.55 |
| 4 | 0.55 | | |

| b) at 223 K | | d) at 243 K | |
|-------------|-------------------|-------------|-------------------|
| Time (h) | Fraction <i>R</i> | Time (h) | Fraction <i>R</i> |
| | | | |
| 0.083333 | 0.89 | 0.083333 | 0.6 |
| 0.5 | 0.658 | 0.25 | 0.51 |
| 1 | 0.55 | 0.41667 | 0.5 |
| 2 | 0.5 | 0.75 | 0.5 |

Evolution of *er* in the enantiomerization of **8** in the absence of any ligand in THF at various temperatures.



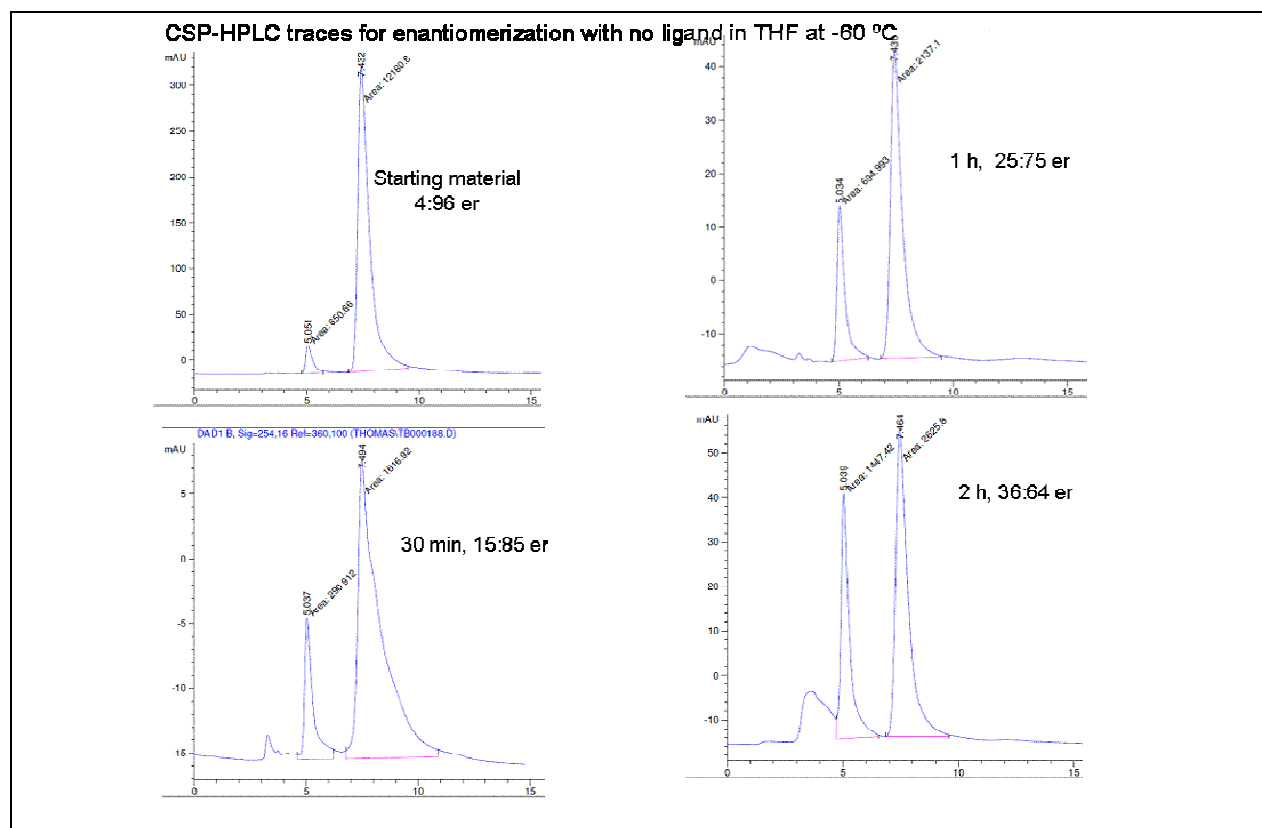


Table 6. Eyring plot parameters for enantiomerization of **8**

a) No ligand in Et₂O

| Temp, K | 1/T | k_{rac} | k_{ent} | $\ln(k_{ent}/T)$ |
|---------|------------|-------------|-------------|------------------|
| 225 | 0.00444444 | 3.58413E-05 | 1.79206E-05 | -16.3456584 |
| 232 | 0.00431034 | 9.48636E-05 | 4.74318E-05 | -15.4029551 |
| 239 | 0.0041841 | 0.000350222 | 0.000175111 | -14.1265529 |
| 248 | 0.00403226 | 0.00141522 | 0.00070761 | -12.7670461 |

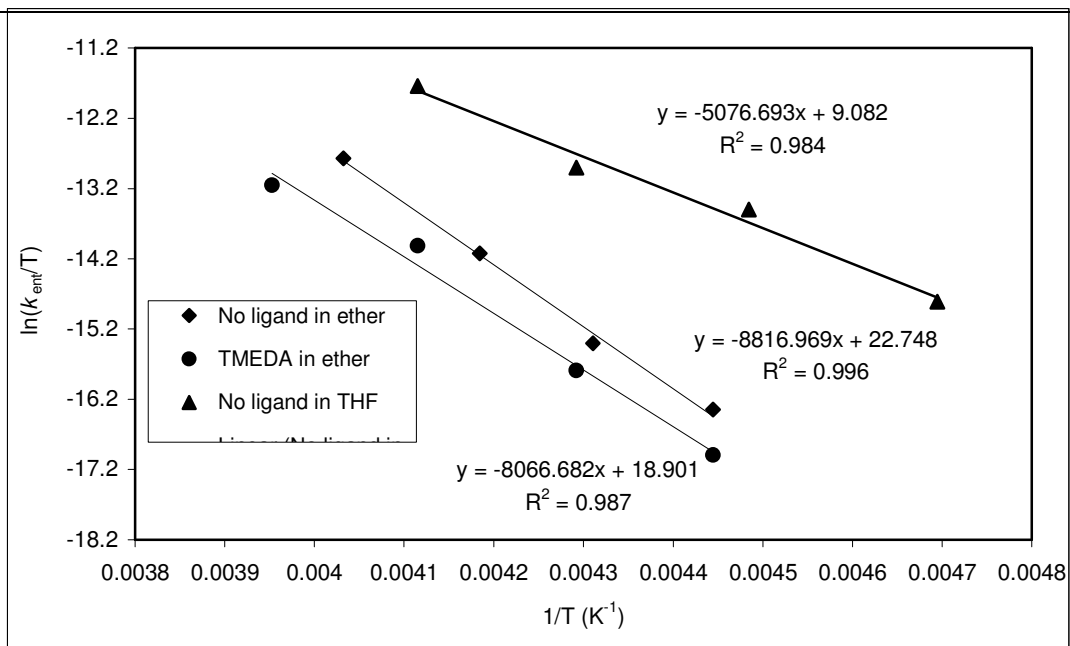
b) 1 equiv TMEDA in Et₂O

| Temp, K | 1/T | k_{rac} | k_{ent} | $\ln(k_{ent}/T)$ |
|---------|------------|-------------|-------------|------------------|
| 225 | 0.00444444 | 1.87E-05 | 9.35035E-06 | -16.9961975 |
| 233 | 0.00429185 | 6.48182E-05 | 3.24091E-05 | -15.7881093 |
| 243 | 0.00411523 | 0.000398194 | 0.000199097 | -14.0147796 |
| 253 | 0.00395257 | 0.000985167 | 0.000492583 | -13.1492365 |

c) No ligand in THF

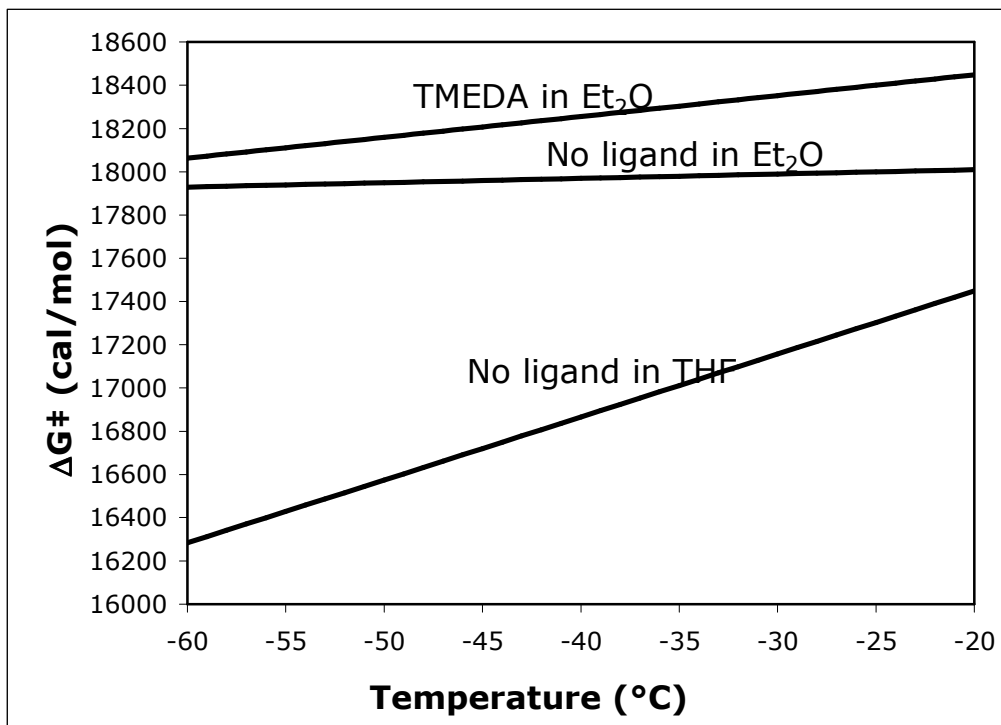
| Temp, K | 1/T | k_{rac} | k_{ent} | $\ln(k_{ent}/T)$ |
|---------|------------|-------------|-------------|------------------|
| 213 | 0.00469484 | 0.000157504 | 7.8752E-05 | -14.8104985 |
| 223 | 0.0044843 | 0.000612632 | 0.000306316 | -13.4980645 |
| 233 | 0.00429185 | 0.001162146 | 0.000581073 | -12.9016728 |
| 243 | 0.00411523 | 0.003868864 | 0.001934432 | -11.741003 |

Eyring plots for enantiomerization of **8**.



Relationship between free energy of activation and temperature for enantiomerization of **8**.

| Entry | Description | $\Delta G^\ddagger = \Delta H^\ddagger - T\Delta S^\ddagger$ | |
|-------|------------------------------------|--|---------------------------------|
| | | ΔH^\ddagger (kcal/mol) | ΔS^\ddagger (cal/mol·K) |
| 1 | No ligand in Et ₂ O | 17.5 ± 0.8 | -2.0 ± 0.06 |
| 2 | 1 equiv TMEDA in Et ₂ O | 16.0 ± 1.3 | -9.6 ± 0.5 |
| 3 | No ligand in THF | 10.1 ± 0.9 | -29.1 ± 4.2 |



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