Supporting Information for:

Highly Enantioselective Catalytic Dynamic Resolution of *N*-Boc-2-lithiopiperidine: Synthesis of (*R*)-(+)-*N*-Boc-pipecolic acid, (*S*)-(–)-Coniine, (*S*)-(+)-Pelletierine, (+)-β-Conhydrine, (*S*)-(–)-Ropivacaine, and Formal Synthesis of (–)-Lasubine II and (+)-Cermizine C

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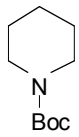
Contents:

1. Structures



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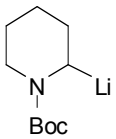

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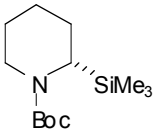

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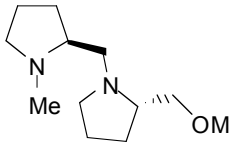

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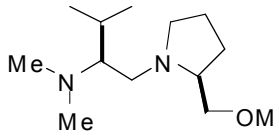

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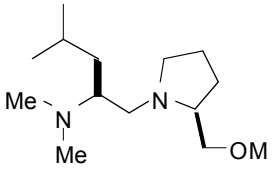

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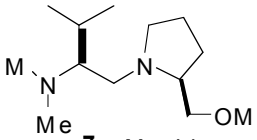

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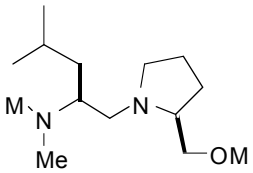

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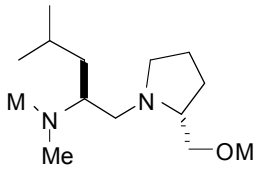

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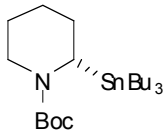

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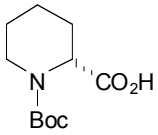

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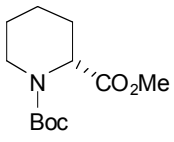

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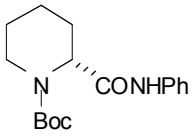

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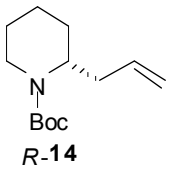

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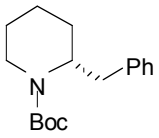

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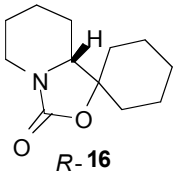

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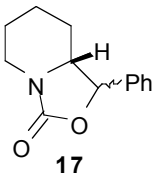

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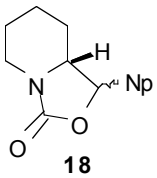

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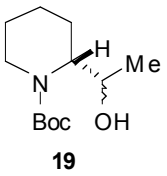

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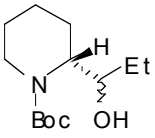

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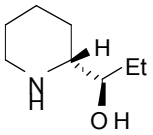

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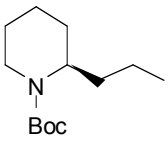

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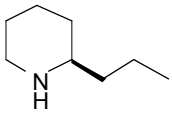

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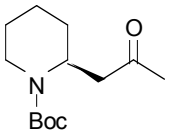

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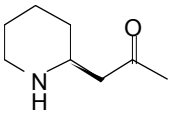

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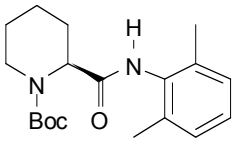

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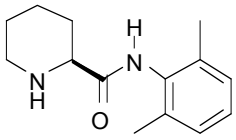

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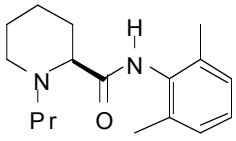


S-(-)-ropivacaine

2. General/Typical Procedures

All experiments involving organolithium reagents were carried out under an inert atmosphere of argon or nitrogen and using freshly distilled solvents. Diethyl ether (Et_2O) was distilled from sodium benzophenone ketyl. The ligands **4** to **9** were purified by Kugelrohr distillation. Commercial *N,N,N',N'*-tetramethylethylene diamine (TMEDA), tributyltin chloride, trimethylsilyl chloride, phenyl isocyanate, 2,6-dimethylphenyl isocyanate, benzaldehyde, 1-naphthaldehyde, acetaldehyde, propionaldehyde, cyclohexanone, methyl chloroformate, allyl chloride, allyl bromide, benzyl bromide, 1-bromopropane, were further purified prior to use. The concentrations of commercial *s*-BuLi (solution in cyclohexane) and *n*-BuLi (solution in hexanes) were determined prior to use by No-D NMR spectroscopy. Column chromatography was performed on silica gel (230-400 mesh). For all enantiomer ratio (er) analyses, authentic racemic compounds were used to establish the method of separation of the enantiomers. The temperature was controlled by a thermostatted cooling coil and all reported temperatures were internal to a reaction vessel.

A. Procedures for the synthesis of chiral ligands

i) *N*-Boc-*(S)*-Leucine

To a solution of (*S*)-leucine (10 g, 76.2 mmol) in 2 M $NaOH_{(aq)}$ (200 mL), di-*tert*-butyl dicarbonate (22.4 g, 91.5 mmol, 1.2 equiv) was added slowly. The mixture was stirred for 18 h at room temperature prior to addition of CH_2Cl_2 (50 mL). The layers were separated and the aqueous layer was acidified with citric acid (20 g) and extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were dried over $MgSO_4$, filtered and evaporated to give 17.1 g of the *N*-Boc-(*S*)-leucine in 97% yield as an oil.

ii) *(S)*-Proline methyl ester hydrochloride

To a solution of (*S*)-proline (5.8 g, 50.0 mmol) in anhydrous MeOH (35 mL) at 0 °C, was added $SOCl_2$ (4.0 mL, 55 mmol, 1.1 equiv) dropwise over a five minute period. The mixture was stirred for 2 h and then concentrated under high vacuum to give 8.28 g of the desired product in 100% yield.

iii). *N*-Boc-Leu-Pro-OMe:

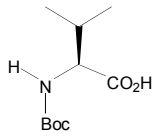
To a stirred solution of *N*-Boc-(*S*)-leucine (5.8 g, 25 mmol, 1.0 equiv) in $CHCl_3$ (100 mL) was added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide, EDCI (4.9 g, 25 mmol, 1.0 equiv) and 1-

hydroxybenzotriazole, HOBt (3.8 g, 25 mmol, 1.0 equiv). The suspension was stirred for 10 min and (*S*)-proline methyl ester hydrochloride (4.14 g, 25 mmol, 1.0 equiv) in Et_3N (10 mL) / $CHCl_3$ (50 mL) was added. After 10 h at room temperature, the solvents were evaporated. Ethylacetate (150 mL) was added and the mixture was stirred for 30 min. The solution was filtered and the filtrate was washed with 10% citric acid (3 x 100 mL) and then with 10% $NaHCO_3$ (3 x 50 mL). The organic layer was dried over Na_2SO_4 and evaporated to give 7.52 g of the pure dipeptide ester as a pale yellow oil in 88% yield.

iv). Reduction of *N*-Boc-dipeptide esters:

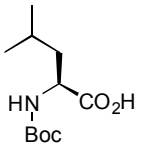
To a stirred suspension of $LiAlH_4$ (6.0 g, 158 mmol, 7.7 equiv) in THF (50 mL), cooled to 0 °C, was added dropwise a solution of the dipeptide ester (7.0 g, 20 mmol, 1.0 equiv) in THF (100 mL). The mixture was stirred for 10 min at room temperature, then heated under reflux for 16 h. The mixture was cooled to 0 °C and Et_2O (100 mL) was added. The mixture was carefully quenched by slow addition of NaOH, 2M (200 mL) upon stirring until all the salts appeared white. The solvent was decanted, and the remaining white solid was washed with Et_2O. The Et_2O extracts were concentrated to 100 mL and extracted with 2 M $HCl_{(aq)}$ (3 x 20 mL). The aqueous layer was then basified with 50% KOH (aq) to pH 14 and extracted with Et_2O (3 x 50 mL). The combined organic layers were dried over Na_2SO_4 and evaporated to give the crude product. Purification by Kugelrohr distillation gave 3.51 g of alcohol (conjugate acid of **8**) as a colorless oil in 82% yield.

3.1.1. (*S*)-*N*-Boc-Valine



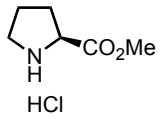
Using **Typical Procedure A(i)**, (*S*)-Valine (10 g, 85.4 mmol) in 2 M NaOH (200 mL), di-*tert*-butyl dicarbonate (22.4 g, 102.5 mmol, 1.2 equiv) gave 17.8 g of the *N*-Boc-protected amino acid in 96% yield as an oil, data as reported.[2]

3.1.2. (*S*)-*N*-Boc-Leucine



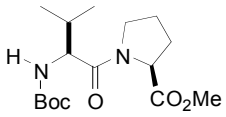
Using **Typical Procedure A(i)**, (*S*)-Leucine, (10 g, 76.2 mmol) in 2 M NaOH (200 mL), di-*tert*-butyl dicarbonate (20 g, 91.5 mmol, 1.2 equiv) gave 17.1 g of the *N*-Boc-protected amino acid in 97% yield as an oil, data as reported.[2]

3.1.3. (*S*)-Proline methyl ester hydrochloride



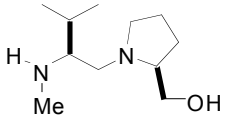
Using **Typical Procedure A(ii)**, (*S*)-Proline (5.8 g, 50.0 mmol), MeOH (35 mL) and $SOCl_2$ (4.0 mL, 55 mmol, 1.1 equiv) gave 8.28 g of the desired product in 100% yield, data as reported.[2]

3.1.4. (*S*,*S*)-*N*-Boc-Val-Pro-OMe



Using **Typical Procedure A(iii)**, *N*-Boc-(*S*)-valine (5.43 g, 25 mmol, 1.0 equiv), $CHCl_3$ (100 mL), EDCI (4.9 g, 25 mmol, 1.0 equiv), HOBt (3.8 g, 25 mmol, 1.0 equiv), (*S*)-proline methyl ester hydrochloride (4.14 g, 25 mmol, 1.0 equiv) in Et_3N (10 mL) / $CHCl_3$ (50 mL) gave 7.54 g of the pure dipeptide ester as a pale yellow oil in 92% yield, data as reported [2] ^{13}C NMR (75.5 MHz, $CDCl_3$) (mixture of rotamers) δ = 172.6 (C=O of ester), 170.1 and 169.1 (C=O of amide), 156.5 (C=O of carbamate), 80.2 and 79.8 (C), 59.3 and 58.5 (CH), 56.8 and 56.2 (CH), 52.6 (CH_3), 46.7(CH_2), 31.7 (CH), 28.5 (CH_2), 28.1 and 28.0, 27.8 (3 x CH_3), 25.0 and 24.9 (CH_2), 19.4 and 19.0 (CH_3), 18.4 and 18.2 (CH_3)

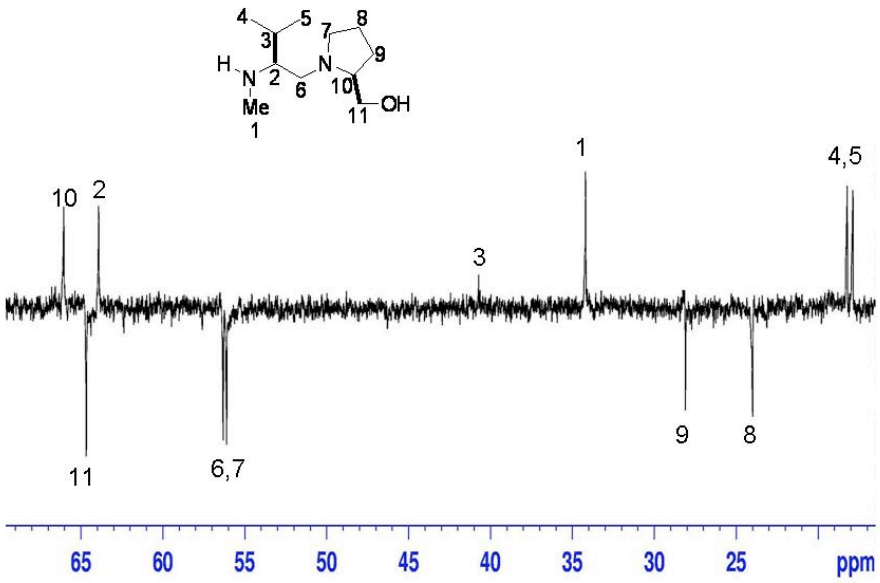
3.1.5. ((*S*)-1-((*S*)-3-methyl-2-(methylamino)butyl)pyrrolidin-2-yl) methanol, conjugate acid of ligand 7

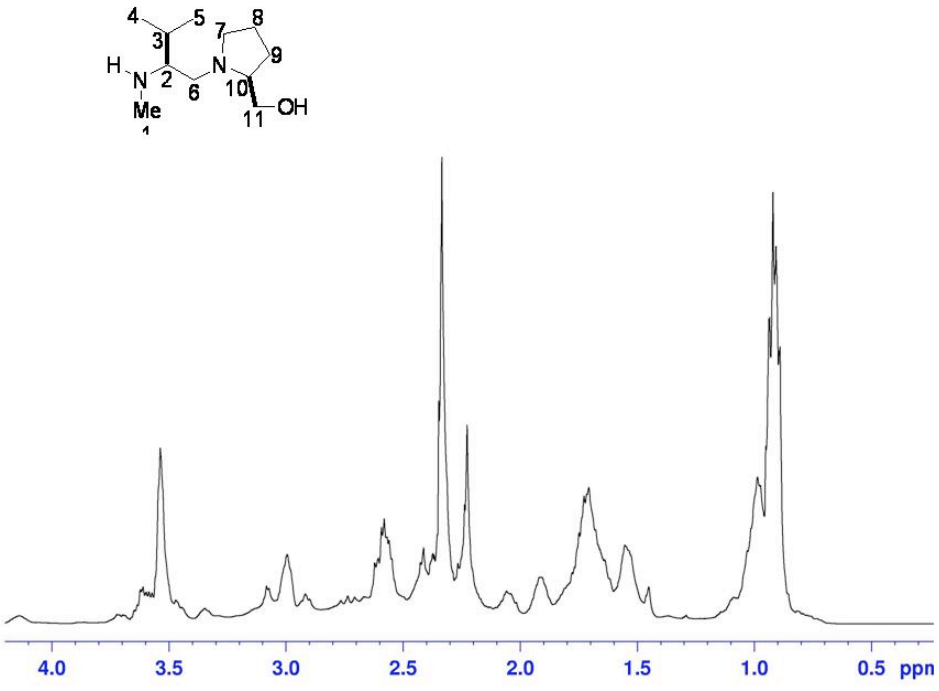


Using **Typical Procedure A(iv)**, $LiAlH_4$ (6.0 g, 158 mmol, 7.7 equiv) in THF (50 mL), the dipeptide, (*S*,*S*)-*N*-Boc-Val-Pro-OMe (6.84 g, 20 mmol, 1.0 equiv) in THF (100 mL) gave 3.44 g of the desired alcohol of **7** as a colorless oil in 86% yield. ^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 66.4 (CH), 64.4 (CH_2), 63.6 (CH), 56.7 (CH_2), 56.1 (CH_2), 40.5 (CH), 34.1 (CH_3), 28.3 (CH_2), 24.0 (CH_2), 18.5 (CH_3) and 17.9 (CH_3).

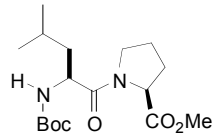
Spectral data of **7a**

DEPT-135





3.1.6. (*S*,*S*)-*N*-Boc-leucylproline methyl ester

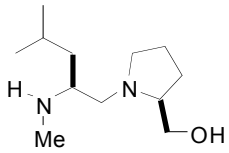


39

Using **Typical Procedure A(iii)**, *N*-Boc-(*S*)-leucine (5.8 g, 25 mmol, 1.0 equiv), $CHCl_3$ (100 mL), EDCI (4.9 g, 25 mmol, 1.0 equiv), HOBt (3.8 g, 25 mmol, 1.0 equiv), (*S*)-proline methyl ester hydrochloride (4.14 g, 25 mmol, 1.0 equiv) in Et_3N (10 mL) / $CHCl_3$ (50 mL) gave 7.52 g of the pure dipeptide ester as a pale yellow oil in 88% yield, data as reported [2] $[\alpha]^{22}_D$ -2.8 (*c* = 0.25, MeOH); ^{13}C NMR (75.5 MHz, $CDCl_3$) (mixture of rotamers) δ = 172.6 (C=O of ester), 170.1 and 169.1 (C=O of amide), 155.8 (C=O of carbamate), 80.2 and 79.8 (C), 58.5 (CH), 52.4 (CH_3), 50.6 (CH), 46.7 (CH_2), 41.3 (CH_2), 29.2 and 29.1 (CH_2), 28.5, 28.4 and 28.3 (3 x CH_3), 25.0 and 24.9 (CH_2), 23.7 (CH), 23.2 (CH_3), 23.1 (CH_3).

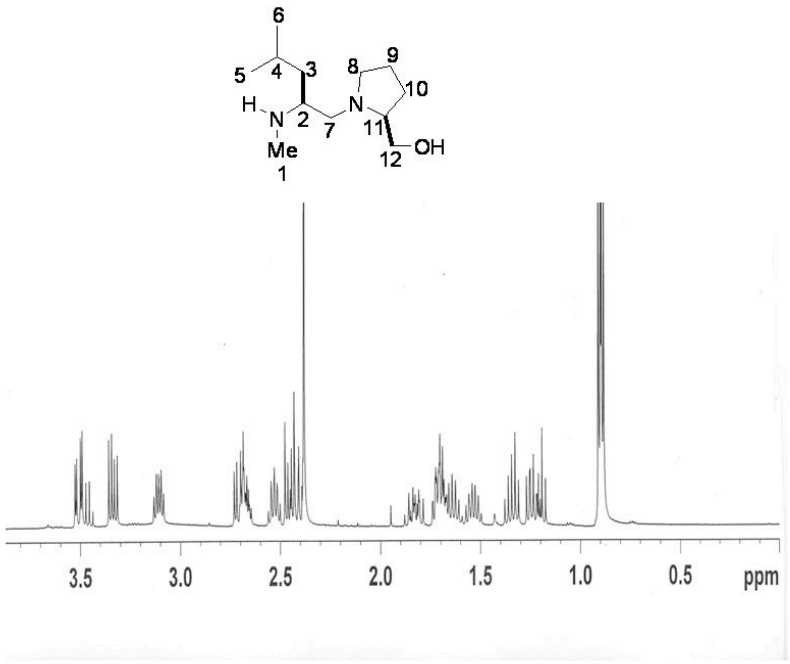
Note: It is necessary to maintain a 1:1 molar stoichiometry of Boc-leucine to proline methylester; otherwise column chromatography on silica is required for purification, eluting with Hexane/EtOAc; (80:20)

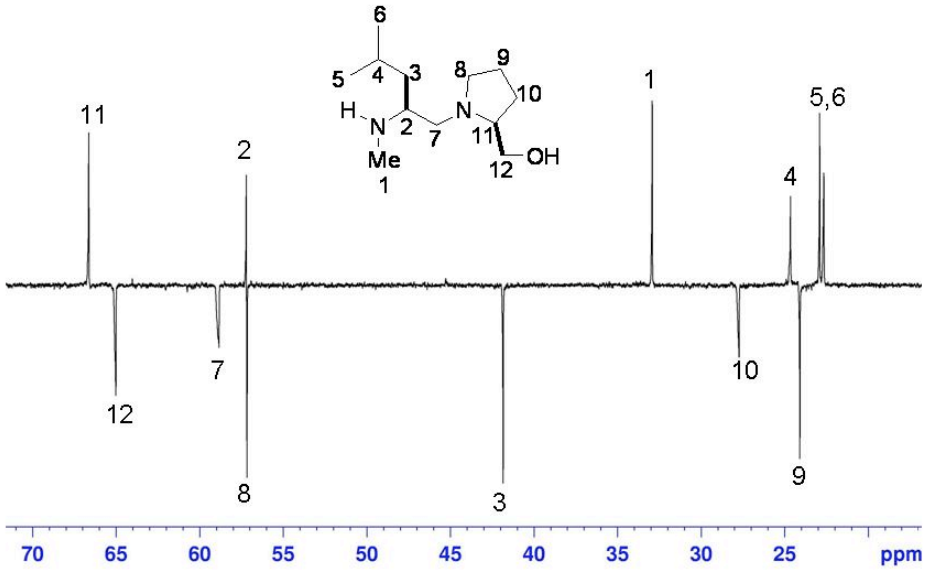
3.1.7. [(*S*)-1-((*S*)-2-Methylamino-4-methylpentyl)pyrrolidin-2-yl]methanol, conjugate acid of ligand 8



Using **Typical Procedure A(iv)**, $LiAlH_4$ (6.0 g, 158 mmol, 7.7 equiv) in THF (50 mL), dipeptide ester (7.0 g, 20 mmol, 1.0 equiv) in THF (100 mL) gave 3.51 g of the desired alcohol of **8** as a colorless oil in 82% yield. $[\alpha]^{22}_D$ +18.15 (c = 2.0, MeOH); FT-IR ν_{max} (film)/cm^{-1} 3330, 2960, 2860, 2820, 1455, 1260, 1080, 1010; ^1H NMR (400 MHz, $CDCl_3$) δ = 3.41 (1H, dd, C*H*OH), 3.24 (1H, dd, C*H*OH), 3.21–3.16 (1H, quin, CHN), 2.72–2.41 (4H, m, 4 x CHN), 2.4 (3H, s, NCH_3), 2.38 (1H, q, CHN), 1.83–1.25 (7H, m, 5 x CH, NH, OH), 0.97–0.80 (8H, m, 2 x CH, 2 x CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 66.8 (CH), 65.2 (CH_2), 59.1 (CH_2), 57.3 (CH), 57.2 (CH_2), 42.0 (CH_2), 33.1 (CH_3), 27.9 (CH_2), 24.8 (CH), 24.2 (CH_2), 23.0 (CH_3) and 22.8 (CH_3).

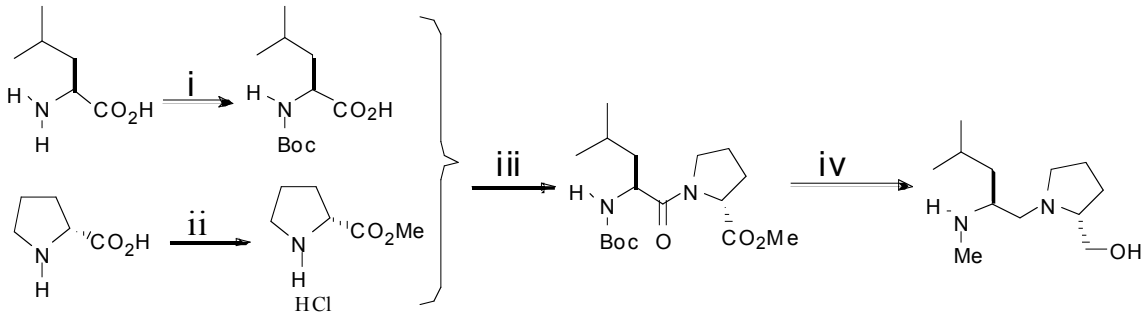
NMR Spectra of **8a**





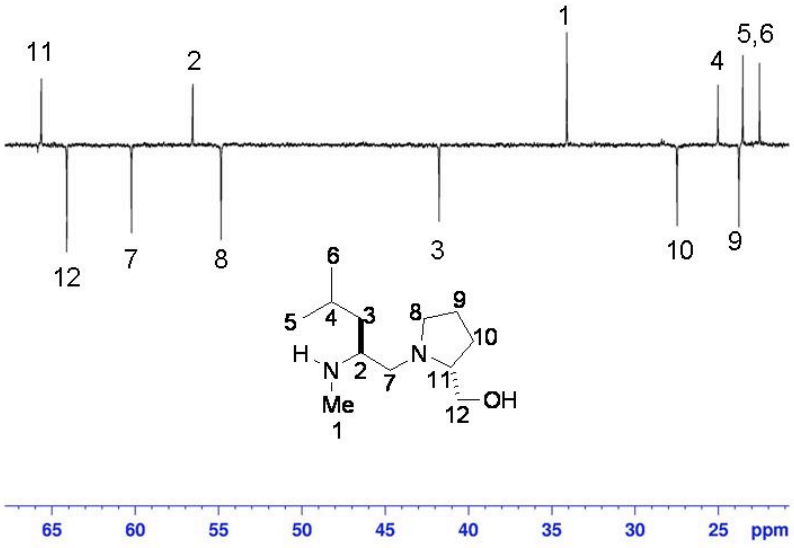
3.1.8. ((*R*)-1-((*S*)-4-methyl-2-(methylamino)pentyl)pyrrolidin-2-yl) methanol, conjugate acid of ligand 9:

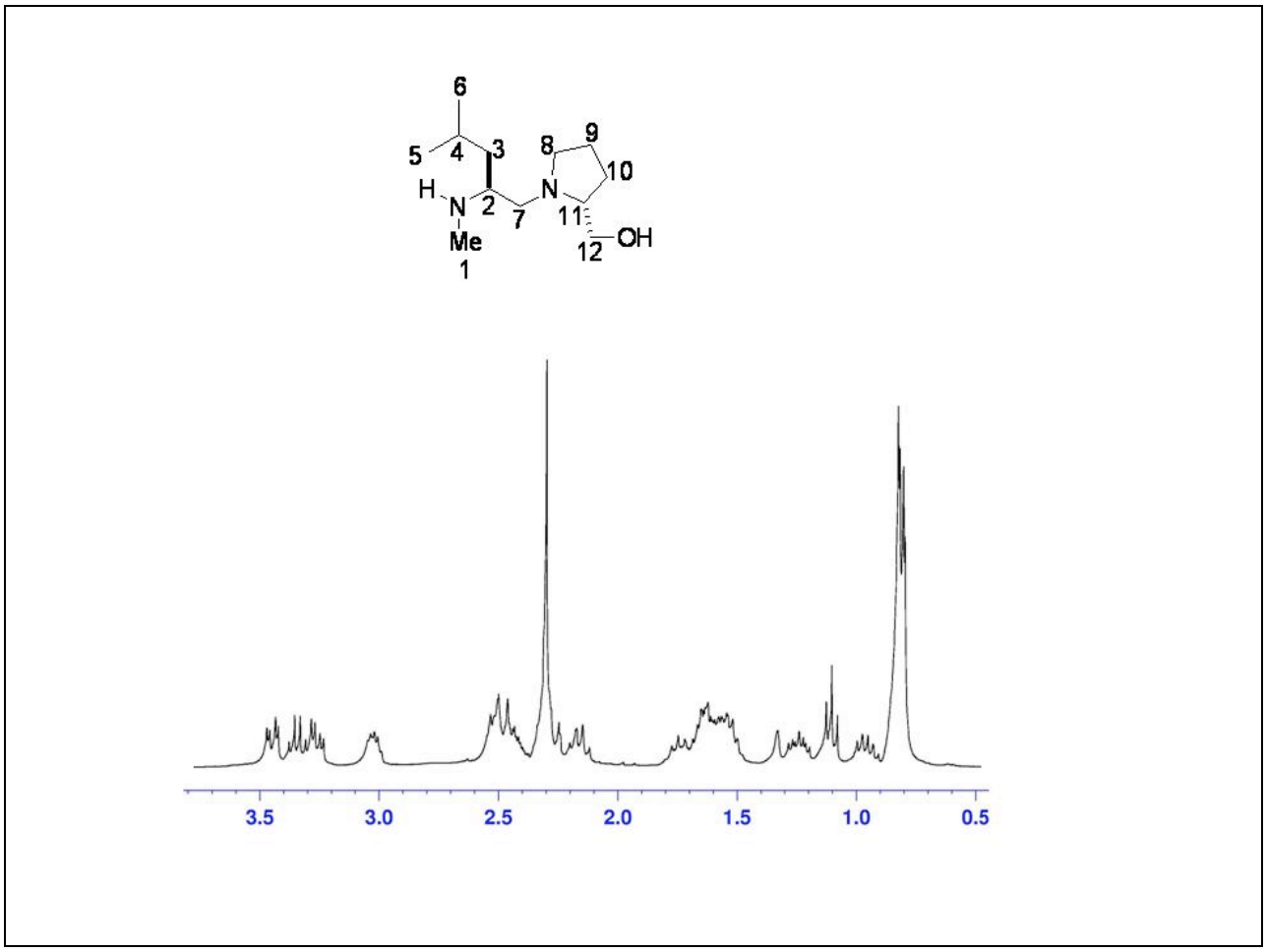
The dilithiated diamino alcohol **9a**, precursor of **9** was synthesized in the same way as **8a,** starting from (*S)*-leucine and (*R)*-proline.



Scheme 1. Preparation of **9a.** i) NaOH (2 M), Boc_2O (1.2 equiv in CH_2Cl_2), rt, 18 h; 98%, ii) $SOCl_2$ (1.1 equiv), MeOH, 0 ºC, 2 h, 100%, iii) EDCI, HOBt, Et_3N, $CHCl_3$), rt, 10 h; 92%, $[\alpha]^{22}_D$ 18 (*c* = 0.20, MeOH) iv) $LiAlH_4$, THF, 0 ºC then heat, 16 h; 85%, $[\alpha]^{22}_D$ 66.25 (*c* = 2.0, MeOH).

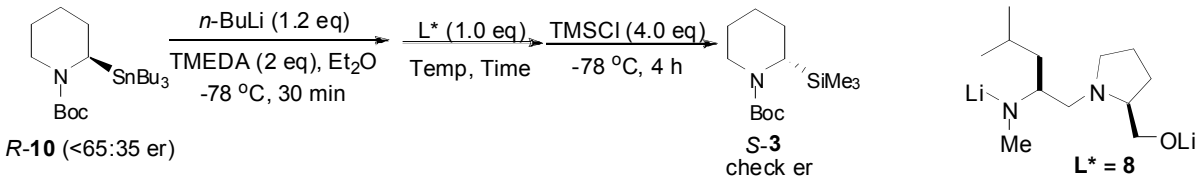
Spectral data of **9a**




6
5
4
3
8
9
10
H
N
2
7
N
11
Me
1
12
OH
3.5
3.0
2.5
2.0
1.5
1.0
0.5

4. Activation parameters for DTR of *N*-Boc-2-lithiopiperidine 2 in the presence of TMEDA and 8

The progress of the resolution was followed by generating the organolithium **2** using tin–lithium exchange in Et_2O at –78 °C with *n*-BuLi and TMEDA, followed by addition of **8** (1.0 equiv) and warming to the desired temperature for different time periods, then cooling to –78 °C and electrophilic quench with excess Me_3SiCl as previously described.[3]



Scheme 4. Resolution of *R*-**2** (<65:35 er) in the presence of 1.0 equiv **8** and 2.0 equiv TMEDA

Typical kinetic run:

In oven-dried, septum-capped vials equipped with a stir bar, *R*-**10** (60:40 er, 0.06 M in Et_2O) and TMEDA (2.0 equiv) were treated with *n*-BuLi (1.2 equiv) at –78 °C for 30 min under argon to effect tin-lithium exchange. The alcohol **8a**, (precursor of **8**; 1.0 equiv, 0.06 M in Et_2O) was treated with freshly titrated *sec*-BuLi (2.0 equiv). After complete transmetalation as noted by the disappearance of **10**, the preformed alkoxide **8** was then added and the flask was quickly transferred to a second thermostatted bath at –20 °C. At various time intervals a vial was cooled to –78 °C and rapidly quenched with excess Me_3SiCl. After 4 h, MeOH was added and the mixture was extracted into Et_2O. The silanes were subsequently analyzed by CSP-GC or CSP-SFC. The rate constants were determined by non-linear fits to the zero-order plots.

Table 1. Evolution of er in the DTR of **2·8** with TMEDA (2.0 equiv)

A). T = 253 K

k_{obs} = 1.88 ± 0.08 x 10^{-3} s^{-1}

Time (min)	er (*S*:*R*)
0	37:63
5	60:40
15	87:13
30	96:4
60	96:4

The DTR of **2** in the presence of **8** converges to 96:4, using TMSCl. The equilibrium constant is 96:4 (*S*:*R*).

B). T = 245 K

k_{obs} = 9.32 ± 0.48 x 10^{-4} s^{-1}

Time (min)	er (*S*:*R*)
0	45:55
15	73:27
30	88:12
60	93:7
90	96:4
120	96:4

C) T = 233 K

k_{obs} = 2.09 ± 0.03 x 10^{-4} s^{-1}

Time (min)	er (*S*:*R*)
0	44:56
30	60:40
60	71:29
150	89:11

D). T = 223 K

k_{obs} = 6.94 ± 0.32 x 10^{-5} s^{-1}

Time (min)	er (*S*:*R*)
0	45:55
60	56:44
120	63:37
210	74:26
300	84:16

E). T = 213 K

k_{obs} = 3.65 ± 0.05 x 10^{-5} s^{-1}

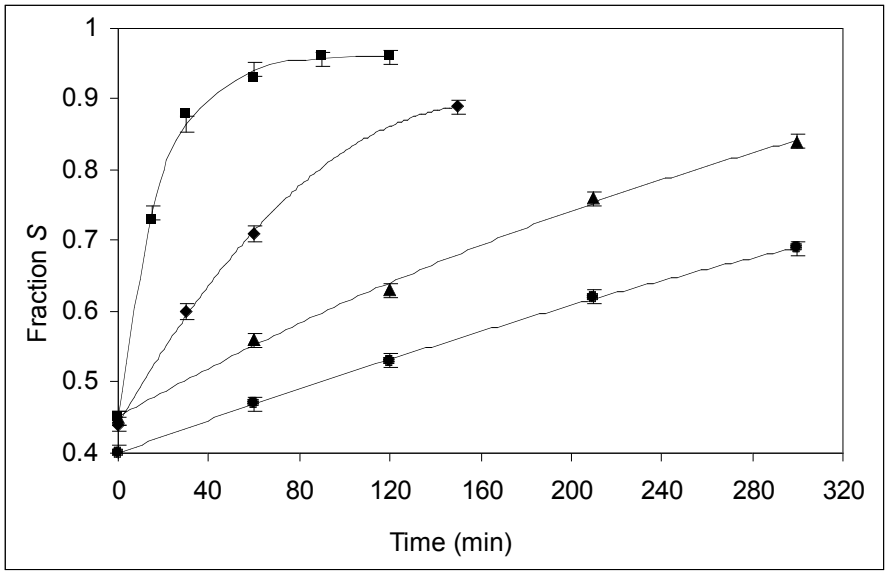
Time (min)	er (*S*:*R*)
0	41:59
60	45:55
120	51:49
210	58:42
300	71:29

F) Rate constants

Temp (K)	k_{obs} (x 10^{-5} s^{-1})
253	188 ± 8
245	93.2 ± 4.8
233	20.9 ± 0.3
223	6.94 ± 0.32
213	3.65 ± 0.05

Figure 1. DTR of **2** (0.06 M) in the presence of **8** (1.0 equiv.) and TMEDA (2.0 equiv) in Et_2O.

a) Zero order plots: KEY: 245 K; squares, 233 K; diamonds, 223 K, triangles, 213 K, circles



b) Fitted equation: $(S)_t = (S)_{eq} + ((S)_0 - (S)_{eq})\exp(-k_{obs}t)$

where k_{obs} = observed rate constant, $(S)_0$ = initial fraction of the *S*-enantiomer and $(S)_{eq}$ = fraction of the *S*-enantiomer at equilibrium. At T = 253 K, $(S)_o = 0.37$ such that

$(S)_t = 0.96 + (0.37 - 0.96)\exp(-k_{obs}t)$

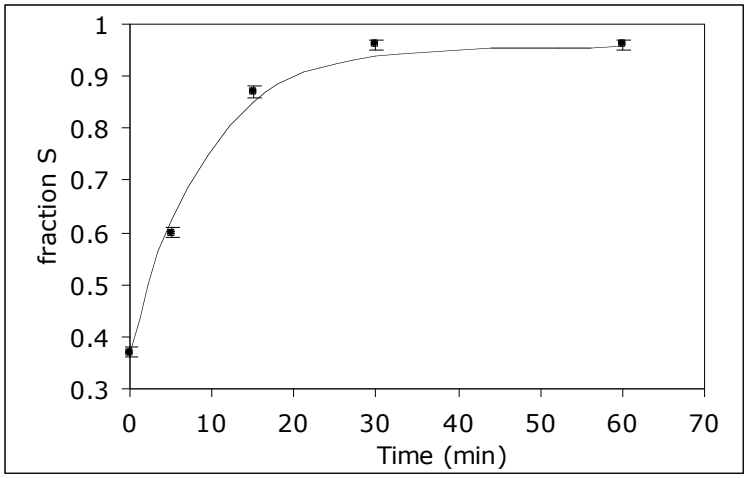


Table 2. Eyring plot parameters for DTR of **2** in the presence of 1.0 equiv **8** and 2.0 equiv TMEDA

Temp (K)	1/T (K^{-1})	k_{obs} (x 10^{-4} s^{-1})[a]	-ln(k_{obs}/T)	-ln(k_{RS}/T)	-ln(k_{SR}/T)
253	0.003952	18.84 ± 0.08	-12.5008	-12.5416	-15.7197
245	0.00408	9.32 ± 0.48	-12.4794	-12.5202	-15.6983
233	0.004292	2.09 ± 0.03	-13.9230	-13.9642	-17.1423
223	0.004484	0.72 ± 0.03	-14.9829	-15.0237	-18.2018
213	0.004695	0.36 ± 0.05	-15.5799	-15.6207	-18.7987

a. $k_{obs} = k_{RS} + k_{SR}$; $K_{eq} = \frac{k_{RS}}{k_{SR}} = \frac{[S]_{eq}}{[R]_{eq}} = \frac{96}{4} = 24$ $k_{RS} = \frac{k_{obs}K_{eq}}{1+K_{eq}}$ and $k_{SR} = \left(1 - \frac{K_{eq}}{1+K_{eq}}\right)k_{obs}$

From the Eyring equation, the activation parameters can be calculated using regression analysis as previously described.[3]

$$\ln\left(\frac{k}{T}\right) = -\frac{\Delta H^{\ddagger}}{RT} + \ln\frac{k_B}{h} + \frac{\Delta S^{\ddagger}}{R}$$

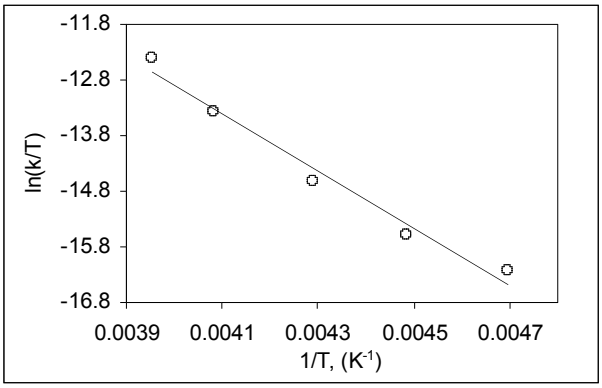
For DTR of **2·8**, the equation of the line is

y = -5304.15x + 9.02

$\Delta H^{\ddagger}$ = –slope·R, $\Delta S^{\ddagger}$ = Intercept·R – Rln(k_B/T), $\Delta G^{\ddagger} = \Delta H^{\ddagger} - T\Delta S^{\ddagger}$

Figure 2. (a) Eyring plot for DTR of **2** in the presence of **8** and 2.0 equiv TMEDA (b) The relationship between $\Delta G^{\ddagger}$ and temperature for inversion of **2**

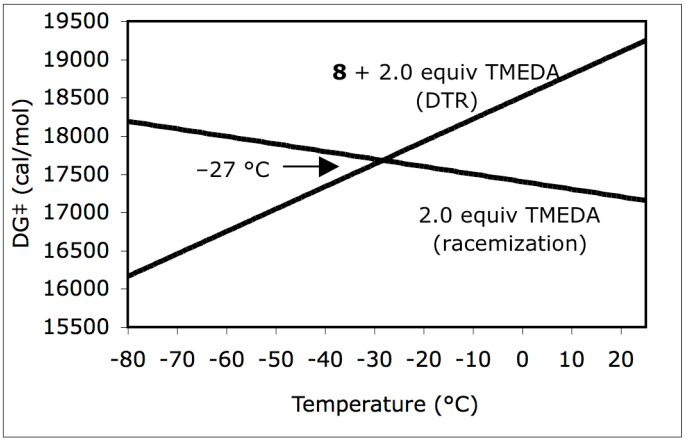
a) $\ln\left(\frac{k_{obs}}{T}\right) = -\frac{\Delta H^{\ddagger}}{RT} + \ln\frac{k_B}{h} + \frac{\Delta S^{\ddagger}}{R}$



Thermodyamic parameters for DTR of **2·8**

RLi·L	$\Delta H^{\ddagger}$ (kcal/mol)	$\Delta S^{\ddagger}$ ($R \rightarrow S$) (cal/mol·K)
2·8·TMEDA	10.5 ± 0.9	-29.3 ± 3.7

b) $\Delta G^{\ddagger} = \Delta H^{\ddagger} - T\Delta S^{\ddagger}$



B. General Procedure for Catalytic Dynamic Resolution (CDR) of 2-lithio-*N*-Boc-piperidine by Deprotonation

In an oven-dried, septum-capped 25 mL round bottom flask equipped with a stir bar, *N*-Boc-piperidine (1.0 equiv) and freshly distilled TMEDA (4.0 equiv) were dissolved in freshly distilled Et_2O under argon. The solution was cooled to –78 °C and *s*-BuLi (1.2 equiv) was added slowly by means of a syringe over a ten minute period. The mixture was stirred for 3 h to effect deprotonation, affording *rac*-**2**·TMEDA. The extent of deprotonation was monitored by quenching an aliquot of the reaction mixture with methanol-d_1 (CH_3OD) and checking for deuterium incorporation by GC-MS. The dilithiated diamino alcohol **8a** (10 mol%) in Et_2O was treated with freshly titrated *s*-BuLi (20 mol%). After complete deprotonation of *N*-Boc-piperidine as noted by MS, the preformed alkoxide **8** was then added and the flask was quickly transferred to a second thermostatted bath at –45 °C, and allowed to stir for 3 h. The mixture was cooled to –78 °C and rapidly quenched with excess electrophile (>1.5 equiv). After 2 – 4 h, 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 Et_2O. The combined organic layers were dried over $MgSO_4$ and evaporated to obtain the crude product. Purification by silica gel column chromatography was accompanied by er (and dr when applicable) determination.

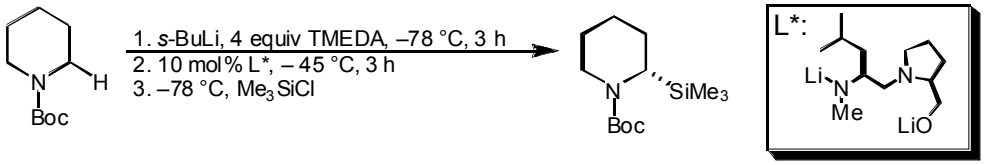
C. General Procedure for Catalytic Dynamic Resolution (CDR) of 2-lithio-*N*-Boc-piperidine by Deprotonation followed by Negishi coupling

In an oven-dried, septum-capped 25 mL round bottom flask equipped with a stir bar, *N*-Boc-piperidine (1.0 equiv) and freshly distilled TMEDA (4.0 equiv) were dissolved in freshly distilled Et_2O under argon. The solution was cooled to –78 °C and *s*-BuLi (1.2 equiv) was added slowly by means of a syringe over a ten minute period. The mixture was stirred for 3 h to effect deprotonation, affording *rac*-**2**·TMEDA. The extent of deprotonation was monitored by quenching an aliquot of the reaction mixture with methanol-d_1 (CH_3OD) and checking for deuterium incorporation by GC-MS. The dilithiated diamino alcohol **8a** (10 mol%) in Et_2O was treated with freshly titrated *s*-BuLi (20 mol%). After complete deprotonation of *N*-Boc-piperidine as noted by MS, the preformed alkoxide **8** was then added and the flask was quickly transferred to a second thermostatted bath at –45 °C, and allowed to stir for 3 h. The mixture was

cooled to –78 °C and a solution of $ZnCl_2$ (1.3 equiv) in THF 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, the electrophile (allyl or benzyl halide) (3.0 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 NH_4Cl was added and the aqueous layer was extracted with Et_2O. The combined organic layers were dried over Na_2SO_4 and evaporated to give the crude product. Purification by silica gel column chromatography was accompanied by er determination.

4. Catalytic Dynamic Resolution (CDR) of *N*-Boc-2-lithiopiperidine 2 in the presence of 10 and TMEDA; Variation of the nature of the Electrophile.

4.1. Electrophilic quench with trimethylsilyl chloride



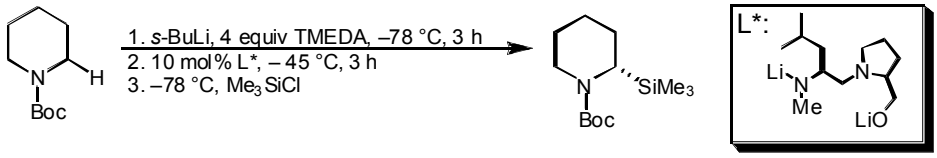
Scheme 5. Synthesis of *S*-**3.** i) *s*-BuLi (1.2 equiv), Et_2O, TMEDA (4.0 equiv), –78 °C, 3 h, ii) L* (ligand **8**, 10 mol%), –45 °C, 3 h, iii) Me_3SiCl (3.0 equiv), –78 °C, 4 h, then MeOH, rt, 74%.

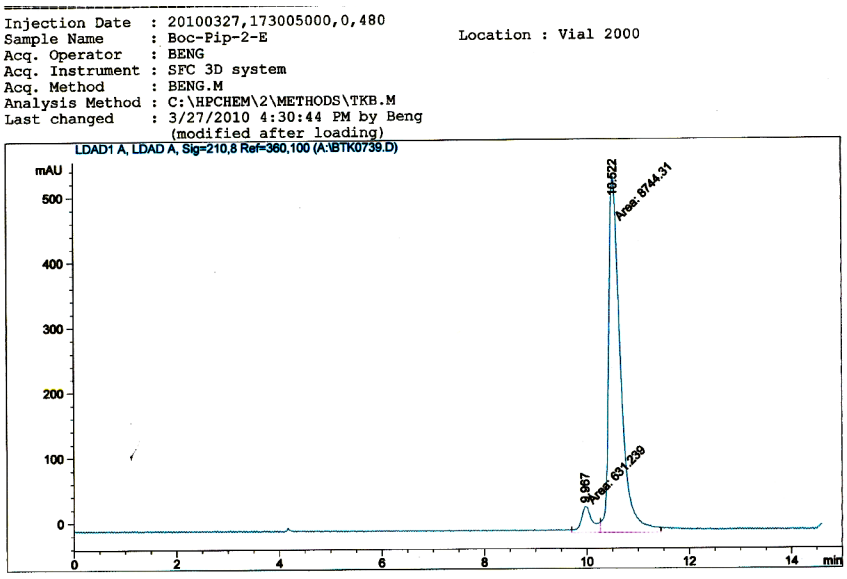
Using **General Procedure B**, *N*-Boc-piperidine (185 mg, 1.0 mmol), TMEDA (0.6 mL, 4 mmol, 4.0 equiv) in 10 mL Et_2O, chiral ligand **8a** (21.4 mg, 10 mol%) in 1.0 mL Et_2O, Me_3SiCl (0.36 g, 3.0 mmol, 3.0 equiv) for 4 h, gave the crude product as a pale yellow oil. Purification by silica gel chromatography eluting with hexane- EtOAc (98:2) afforded 188 mg of *S*-**3** as a colorless oil in 74% yield (96:4 er), data as reported.[4]. $[\alpha]_D^{22}$ +38 (c = 2, $CHCl_3$), lit.[2,4] for *S*-**3** of 95:5 er, +36.4, *c* = 1.95, $CHCl_3$). Evaluation of the enantiomer ratio was performed 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. Pressure = 15 psi, Initial temperature = 70 °C, Final temperature = 90 °C, Hold time = 2 min, Rate = 5 °C/min. *S*-**3** elutes after 60.2 min and *R*-**3** elutes after 61.6 min.

Alternatively, the enantiomers were resolved by CSP-SFC under the following conditions: **Column:** Regis Technologies Pirkle Whelk-O-1, **Chiral Stationary Phase**: 4-(3,5-dinitrobenzamido) tetrahydrophenanthrene, covalently bound to silica, **Flow Rate** = 1.0 mL/min,

Polarity Modifier = 1.0% EtOH; Outlet Pressure **= 150 psi**, **Oven Temperature** = 35 ºC, Hold time = 3.0 min. *(R)*-**3** elutes after 9.97 min and *(S)*-**3** elutes after 10.5 min.

CSP-GC trace for CDR of **2** and electrophilic quench with trimethylsilyl chloride

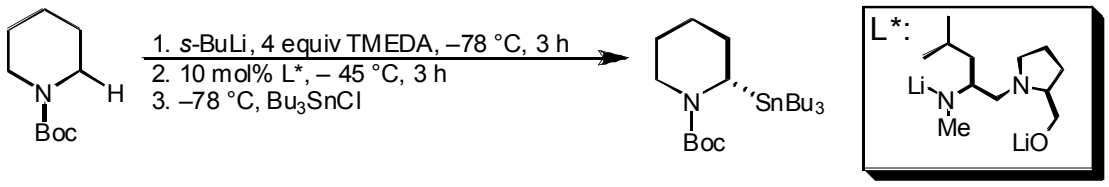




S-**3** (96:4 er)

Note: *R*-**3** (98:2 er) was prepared in 70% yield, in the same way as *S*-**3** using **9** as the chiral ligand, L*.

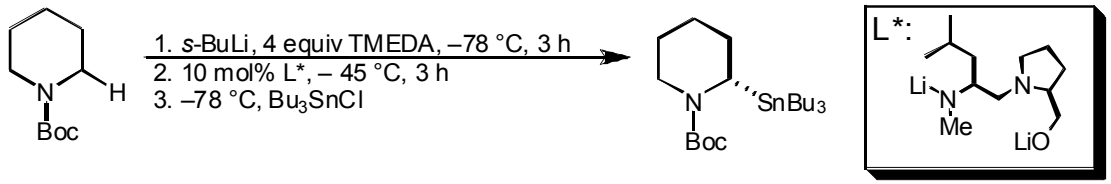
4.2. Electrophilic quench with tributyltin chloride

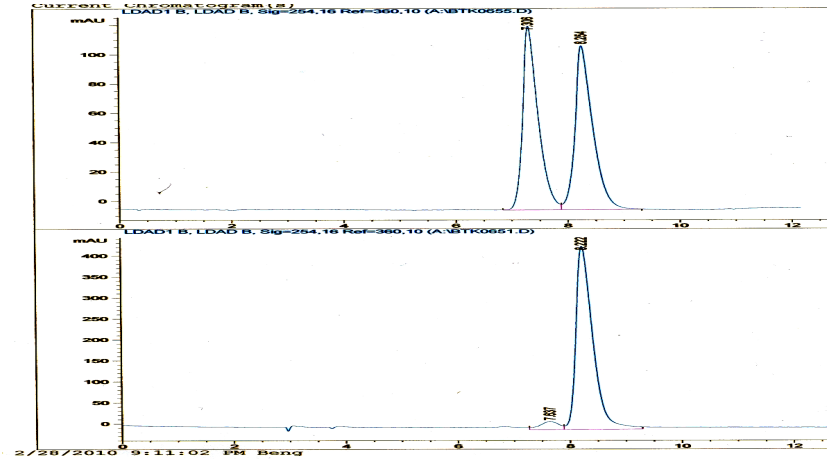


Scheme7. Synthesis of *S*-**10.** 1) *s*-BuLi (1.2 equiv), Et_2O, TMEDA (4.0 equiv), –78 °C, 3 h, 2) L* (ligand **8**, 10 mol%), –45 °C, 3 h, 3) Bu_3SnCl (3.0 equiv), –78 °C, 4 h, then MeOH, rt, 66%.

Using **General Procedure B**, *N*-Boc-piperidine (0.43 g, 2.35 mmol), TMEDA (1.4 mL, 9.24 mmol, 4.0 equiv) in 10 mL Et_2O, chiral ligand **8a** (50.5 mg, 0.24 mmol, 10 mol%.) in 1.0 mL Et_2O, Bu_3SnCl (0.75 mL, 2.8 mmol, 1.2 equiv) for 4 h, gave the crude product as a pale yellow oil. Purification by silica gel chromatography eluting with hexane-EtOAc (99:1) afforded 730 mg of *S*-**10** as a colorless oil in 66% yield and 96:4 er, data as reported.[5] $[\alpha]_D^{22}$ +41 (c = 2, $CHCl_3$), lit. for *S*-**10** (80:20 er, +28, *c* = 1.0, $CHCl_3$) and for *R*-**10** (>99:1 er, $[\alpha]_D^{22}$ –42.2 (*c* = 1.8, $CHCl_3$). The enantiomers were resolved by CSP-SFC under the following conditions: **Column:** Regis Technologies Whelk-O-1, **Chiral Stationary Phase**: 4-(3,5-dinitrobenzamido) tetrahydrophenanthrene, covalently bound to silica, **Flow Rate** = 1.0 mL/min, **Polarity Modifier =** 1.2% Methanol; Outlet Pressure **= 150 psi**, **Oven Temperature** = 35 ºC, *(R)*-**10** elutes after 7.5 minutes and *(S)*-**10** elutes after 8.3 minutes.

CSP-SFC traces for CDR of **2** and electrophilic quench with tributyltin chloride



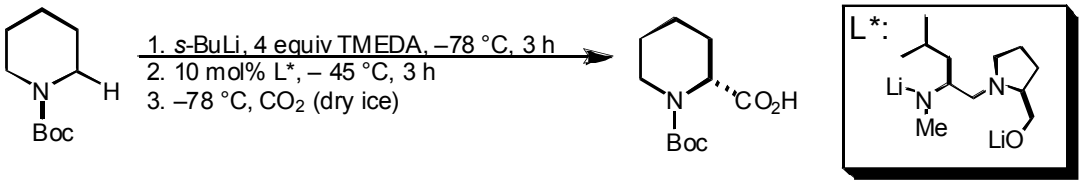


Top; authentic *rac*-**10**, bottom; *S*-**10** (96:4 er)

4.3. (*R*)-*N*-Boc-2-(tributylstannyl)piperidine *R*-10

R-**10** (97:3 er) was prepared in 62% yield, in the same way as *S*-**10** using **9** as the chiral ligand, L*. $[\alpha]_D^{22}$ –38.5 (c = 2, $CHCl_3$), lit. for *R*-**10** (>99:1 er, $[\alpha]_D^{22}$ –42.2 (*c* = 1.8, $CHCl_3$).

4.4. Electrophilic quench with carbon dioxide: Synthesis of *N*-Boc-(*R*)-(+)-pipecolic acid (*R*-11)

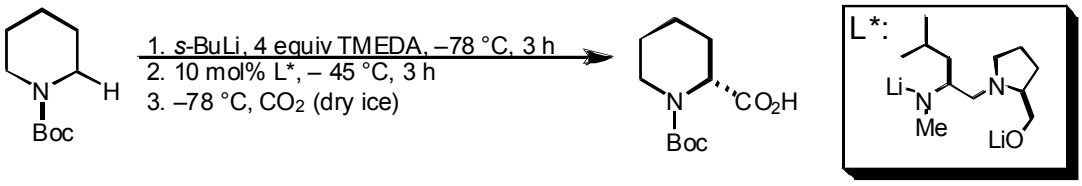


Scheme8. Synthesis of *R*-**11.** 1) *s*-BuLi (1.2 equiv), Et_2O, TMEDA (4.0 equiv), –78 °C, 3 h, 2) L* (ligand **8**, 10 mol%), –45 °C, 3 h, 3) CO_2 (3.0 equiv), –78 °C, 2 h, then MeOH, rt, 78%.

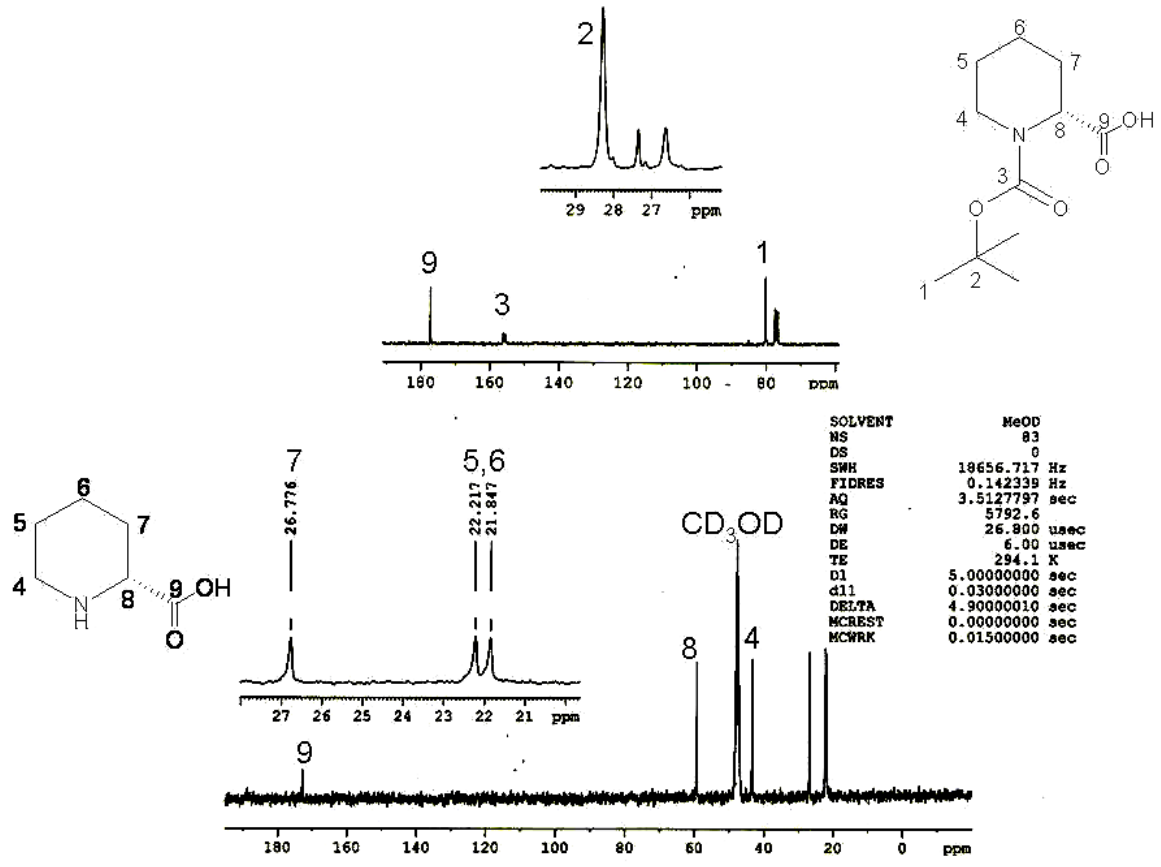
Using **General Procedure B**, *N*-Boc-piperidine (185 mg, 1.0 mmol), TMEDA (0.6 mL, 4 mmol, 4.0 equiv) in 10 mL Et_2O, chiral ligand **8** (21.4 mg, 10 mol%) in 1.0 mL Et_2O were stirred for 3 h at –45 ºC. The solution was cooled to –78 °C and quenched by bubbling dry ice (88 mg, 2 mmol, 2.0 equiv) into the reaction mixture via cannula. for 2 h prior to addition of MeOH (2 mL) and warming to room temperature. Purification by silica gel chromatography eluting with hexane-EtOAc (40:60) afforded 179 mg of *R*-**11** as a colorless oil in 78% yield and 98:2 er, data as reported.[6] $[\alpha]_D^{22}$ +42.0 (*c = 1*, MeOH), {lit[6] for (*S*)-**11** of >99:1 er $[\alpha]_D^{22}$ –45.777 (*c* = 1.0 MeOH). ^{1}H NMR (300 MHz, $CDCl_3$, rotamers) δ = 11.6 (1H, br s, CO_2H), 4.90 and 4.71 (1H, s, NCH), 4.00 and 3.91 (1H, d, NCH), 2.96 and 2.88 (1H, t, NCH), 2.21 (1H, t, CH), 1.75-1.55 (5H, m, 2 x CH_2 and CH), 1.45 and 1.43 (9H, s, *t*-Bu); ^{13}C NMR (75.5 MHz, $CDCl_3$, rotamers) δ = 177.7 (C=O), 80.3 (C), 54.7 & 53.6 (CH), 42.1 & 41.0 (CH_2), 28.3 (CH_3), 26.6 (CH_2), 24.7, 24.5 (CH_2), 20.8 (CH_2); The er was determined by converting *R*-**11** to its corresponding methyl ester, *R*-**12**.

Note: *S*-**11** (97:3 er) was prepared in 81% yield, in the same way as *R*-**11** using **9** as the chiral ligand, L*.

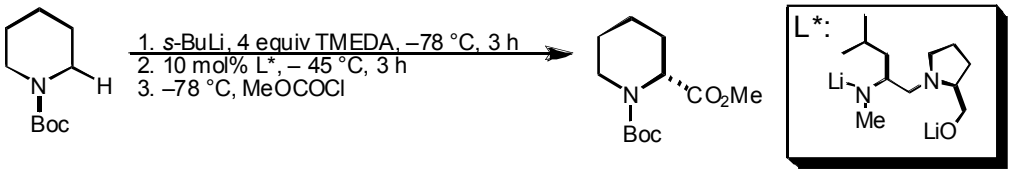
Spectroscopic data for CDR of **2** and electrophilic quench with CO_2



a. ^{13}C NMR Spectrum



4.5. Electrophilic quench with methylchloro formate: Synthesis of *(R)-N*-Boc-piperidine-2-carboxylic acid methyl ester *R*-12



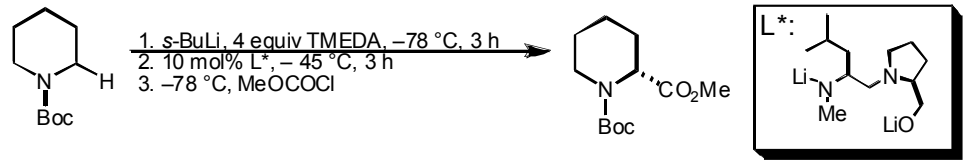
Scheme 9. Synthesis of *R*-**12.** 1) *s*-BuLi (1.2 equiv), Et_2O, TMEDA (4.0 equiv), –78 °C, 3 h, 2) L* (ligand **8**, 10 mol%), –45 °C, 3 h, 3) MeOCOCl (3.0 equiv), –78 °C, 2 h, then MeOH, warm to rt, 88%, >99:1 er.

Using **General Procedure B**, *N*-Boc-piperidine (370 mg, 2.0 mmol), TMEDA (1.2 mL, 8.0 mmol, 4.0 equiv) in 10 mL Et_2O, chiral ligand **8a** (43.0 mg, 0.2 mmol, 10 mol%) in 10 mL Et_2O, freshly distilled methyl chloroformate (0.57 g, 0.45 mL, 6 mmol, 3.0 equiv) for 2 h, gave the crude product as an oil. Purification by silica gel chromatography eluting with hexane-EtOAc (95:5) afforded 428 mg of *R*-**12** as a colorless oil in 88% yield, 98:2 er. $[\alpha]_D^{22}$ +45.2 (c = 2, $CHCl_3$), lit[7a] for *S*-**12** of 85% ee); $[\alpha]_D^{20}$ –48.1 (*c* = 1.11, $CHCl_3$) and of 88:12 er; $[\alpha]_D^{20}$ –31.7 (*c* = 1.0, $CHCl_3$).[7b.] ^{1}H NMR (300 MHz, $CDCl_3$) δ = 4.4 (1H, s, NCH), 3.4 (3H, s, OCH_3), 2.84–2.72 (1H, m, NCH), 2.32 (1H, d, *J* 14 Hz, CH), 1.96–1.83 (1H, m, CH), 1.66–1.51 (4H, m, 2 x CH_2), 1.35 (9H, s, *t*-Bu);^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 170.5 (C=O), δ = 156.2 (C=O), 80.7 (C), 55.7 (CH_3), 54.7 (CH), 42.2 (CH_2), 28.2 (CH_3), 25.1 (CH_2), 24.6 (CH_2) and 20.1 (CH_2). The enantiomers were resolved by CSP-SFC under the following conditions: **Column:** Regis Technologies Whelk-O 1, **Chiral Stationary Phase**: 4-(3,5-dinitrobenzamido) tetrahydrophenanthrene, covalently bound to silica, **Flow Rate** = 1.0 mL/min, **Polarity Modifier =** 1.2% MeOH, Outlet Pressure **= 150 psi**, **Oven Temperature** = 35 ºC. *R*-**12** elutes after *S*-**12** after *ca* 16 minutes.

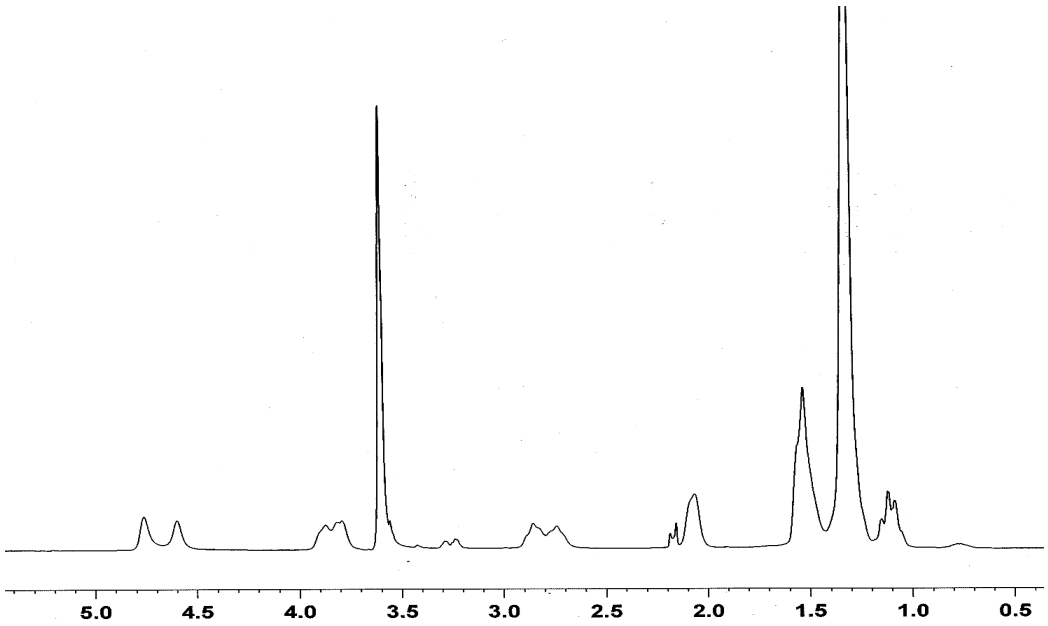
Alternatively, the enantiomers were resolved by CSP GC {β-cyclodextrin-permethylated 120 fused silica capillary column [30 m × 0.25 mm i.d., 20% permethylated β-cyclodextrin in SPB-35 poly(35% diphenyl/65% dimethyl)siloxane, Pressure = 15 psi, Initial temperature = 100 ºC, Final temperature = 150 ºC, Hold time = 5 min, Rate = 0.5 ºC/min. *S*-**12** elutes before *R*-**12** after *ca* 55 minutes.

Note: *S*-**12** (>99:1 er) was prepared in 85% yield, in the same way as *R*-**12** using **9** as the chiral ligand, L*.

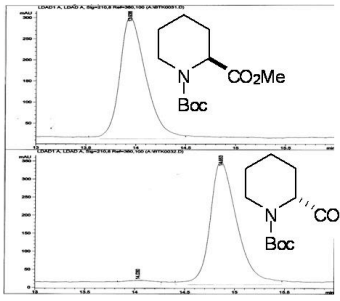
Spectroscopic data for CDR of **2** and electrophilic quench with methyl chloroformate



^{1}H NMR



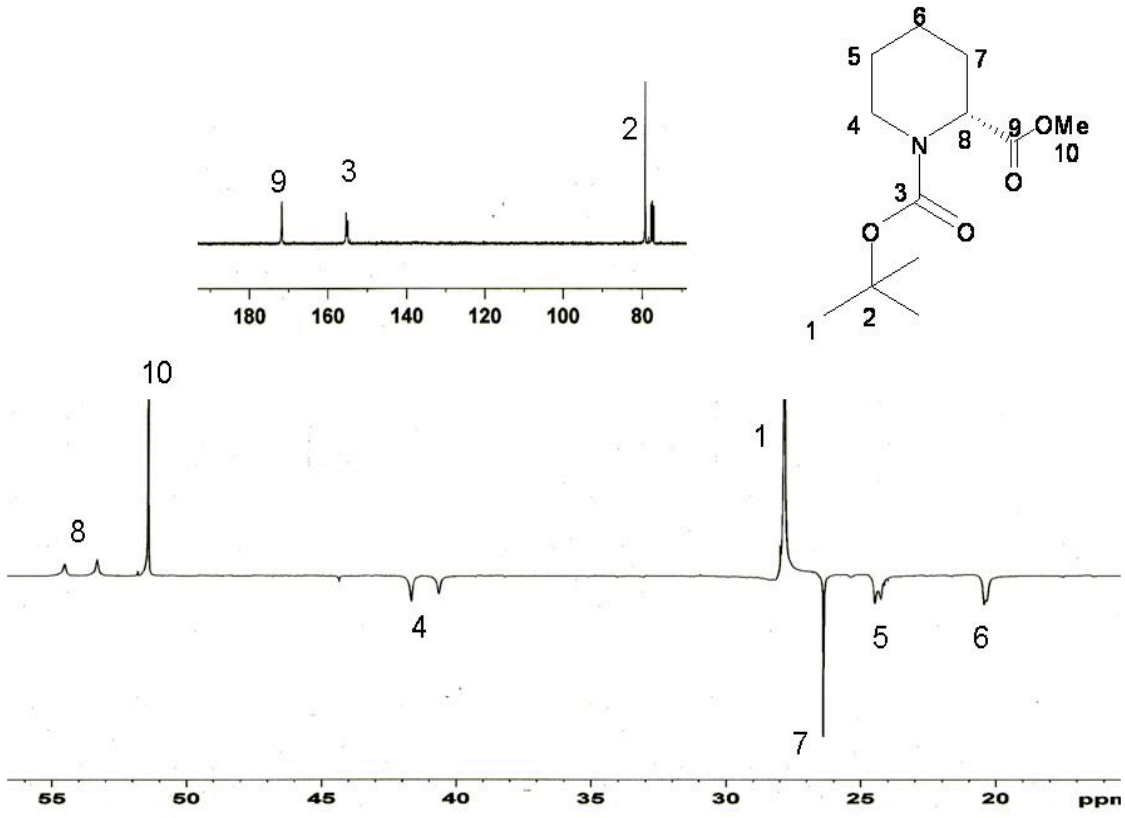
CSP-SFC traces



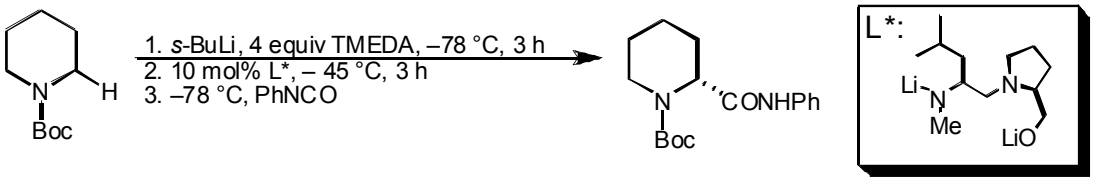
from CDR using ligand **9**

from CDR using ligand **8**

^{13}C NMR



4.6. Electrophilic quench with phenyl isocyanate: Synthesis of *(R)-N*-Boc-piperidine-2-carboxylic acid phenyl amide *R*-13



Scheme 10. Synthesis of *R*-**13.** 1) *s*-BuLi (1.2 equiv), Et_2O, TMEDA (4.0 equiv), –78 °C, 3 h, 2) L* (ligand **8**, 10 mol%), –45 °C, 3 h, 3) PhNCO (3.0 equiv), –78 °C, 2 h, then MeOH, rt, 68%, >99:1 er.

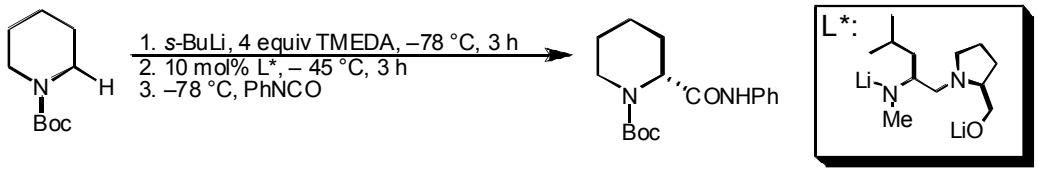
Using **General Procedure B**, *N*-Boc-piperidine (370 mg, 2.0 mmol), TMEDA (1.2 mL, 8.0 mmol, 4.0 equiv) in 10 mL Et_2O, chiral ligand **8a** (43.0 mg, 0.2 mmol, 10 mol%) in 1.0 mL Et_2O, phenyl isocyanate (0.66 mL, 6.0 mmol, 3.0 equiv.) for 2 h prior to addition of 2 mL

MeOH, gave the crude product as a yellowish solid. Purification by silica gel chromatography eluting with hexane-EtOAc (90:10) afforded 414 mg of *R*-**13** as a white crystalline solid in 68% yield and 98:2 er. $[\alpha]_D^{22}$ +41 (c = 2, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ = 8.2 (1H, s, CONH), 7.44–6.91 (5H, m, Ph), 4.6 (1H, s, NCH), 4.13–4.02 (1H, br, NCH), 2.84–2.72 (1H, m, NCH), 2.32 (1H, d, *J* 14 Hz, CH), 1.96–1.83 (1H, m, CH), 1.66–1.51 (4H, m, 2 x CH_2), 1.35 (9H, s, *t*-Bu); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 170.5 (C=O), δ = 156.2 (C=O), 137.7 (C), 128.8 (CH), 123.9 (CH), 119.5 (CH), 80.7 (C), 54.7 (CH), 42.2 (CH_2), 28.2 (CH_3), 25.1 (CH_2), 24.6 (CH_2) and 20.1 (CH_2).

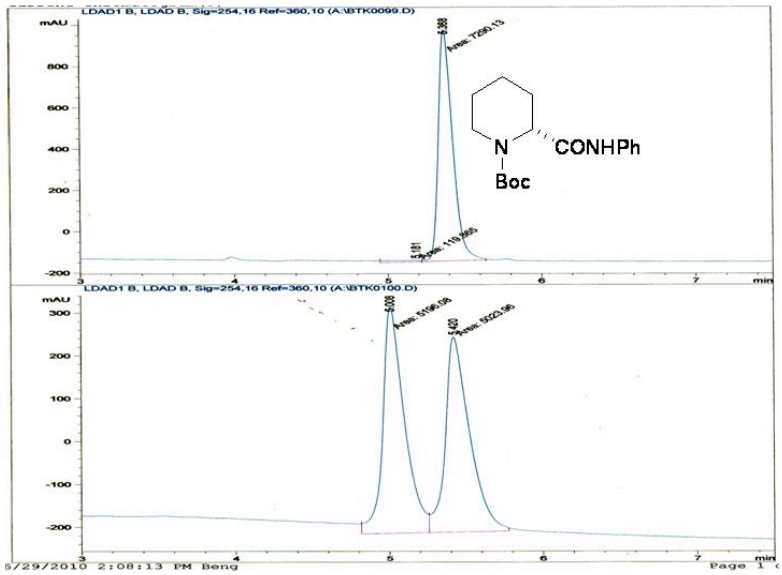
The enantiomer ratio was evaluated by CSP-SFC monitoring at 210 or 254 nm by comparison with an authentic racemic sample, under the following column conditions:

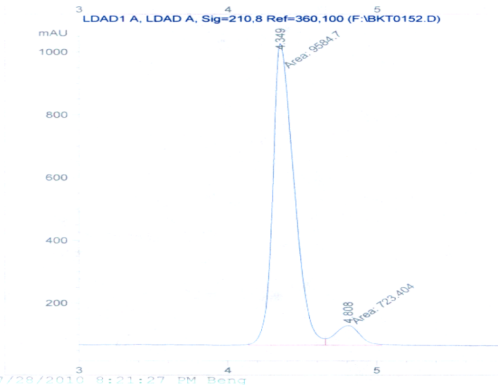
Column: Regis Technologies Pirkle Whelk-O-1, **Chiral Stationary Phase**: 4-(3,5-dinitrobenzamido) tetrahydrophenanthrene, covalently bound to silica. **Flow Rate** = 3.0 mL/min, **Polarity Modifier =** 3.2% EtOH, **Outlet Pressure =** 150 psi, **Oven Temperature** = 35 ºC, *S*-**13** elutes after 5.1 minutes and *R*-**13** elutes after 5.5 minutes. Alternatively, the er was determined using a different column as follows: **Column:** Daicel Chiralcel OD-H, **Chiral Stationary Phase**: 4-Cellulose tris-(3,5-dimethylphenylcarbamate) coated on 5μm silica-gel. **Flow Rate** = 3.5 mL/min, **Polarity Modifier =** 5.0% EtOH, *S*-**13** elutes after 2.2 minutes and *R*-**13** elutes after 3.5 minutes.

Spectral data for CDR of **2** and electrophilic quench with phenyl isocyanate



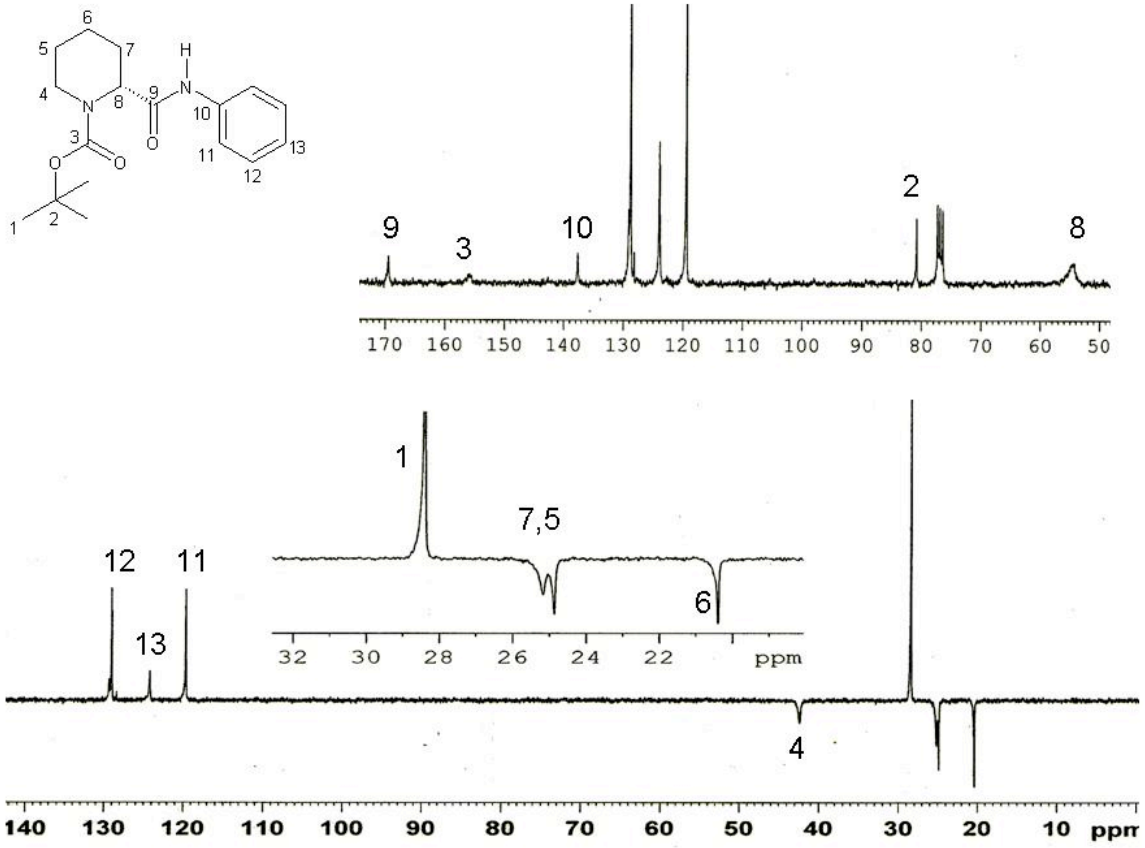
CSP-SFC traces



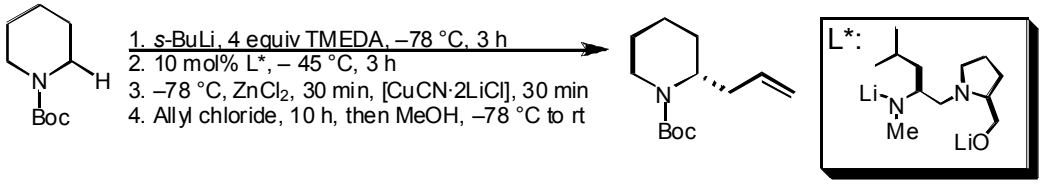


Key: top; *R*-**13** (>99:1 er) from CDR using ligand **8**, middle; authentic *rac*-**13**, bottom; *S*-**13** (95:5 er) from CDR using ligand **9**, prepared in 72% yield.

^{13}C NMR Spectrum



4.7. Electrophilic quench with allyl chloride: Synthesis of *(R)-tert*-Butyl-2-allylpiperidine-1-carboxylate *R*-14



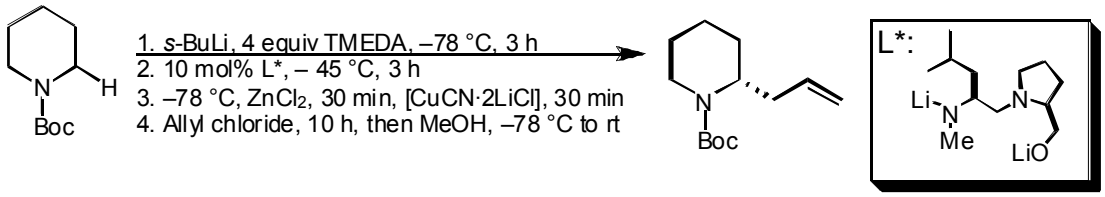
Scheme 11. Synthesis of *R*-**14.** 1) *s*-BuLi (1.2 equiv), Et_2O, TMEDA (4.0 equiv), –78 °C, 3 h, 2) **8**, (10 mol%), –45 °C, 3 h, 3) –78 °C, $ZnCl_2$ (1.3 equiv in THF), 30 min, CuCN·2LiCl (in THF), 30 min, 4) allyl chloride (3.0 equiv), 10 h, then MeOH, warm to rt, 63%, 95:5 er.

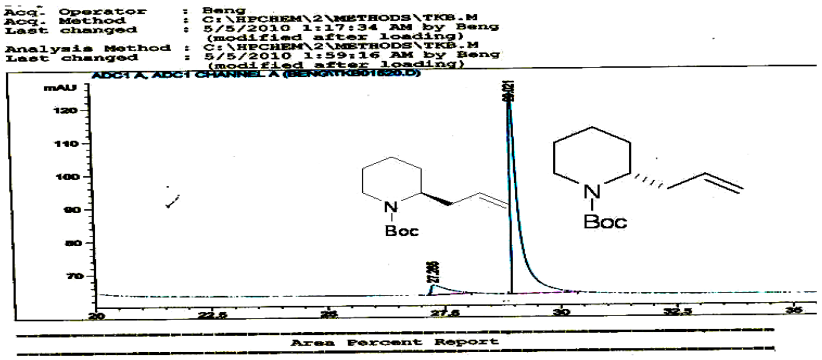
Using **General Procedure C**, *N*-Boc-piperidine (185 mg, 1.0 mmol, 0.25 M), TMEDA (586 mg, 4.0 mmol, 0.62 mL, 4.0 equiv), Et_2O (4 mL), *s*-BuLi (1.2 mL, 1.0 M, 1.2 mmol, 1.2 equiv), **8**a (21.4 mg, 0.1 mmol, 10 mol%, in 0.40 mL Et_2O pretreated with freshly titrated *s*-BuLi), $ZnCl_2$

(0.18 mg, 1.3 mmol, 1.3 equiv) in THF (2 mL), CuCN·2LiCl [prepared from CuCN (107 mg, 1.2 mmol, 1.2 equiv) and LiCl (107 mg, 2.5 mmol, 2.5 equiv)] in THF (3 mL), allyl chloride (0.35 mL, 3.0 mmol, 3.0 equiv.), MeOH (2 mL), NH_4Cl (5 mL), gave the crude product. Purification by silica gel chromatography eluting with hexane-EtOAc (98:2) afforded 152 mg of *R*-**14** as a colorless oil in 63% yield and 95:5 er, data as reported.[8] $[\alpha]_D^{22}$ +45 (c = 1, $CHCl_3$), lit[3a]. for *R*-**14** of 79:21 er, $[\alpha]_D^{22}$ +40, (*c* = 0.85, $CHCl_3$).[1] lit[8]. for *S*-**14** (>99:1 er, $[\alpha]_D^{25}$ –49.2 (*c* = 0.9, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.72 (1H, ddt, C*H*=CH_2), 5.10□4.87 (2H, m, CH=CH_2), 4.25 (1H, br t, NCH), 3.94 (1H, br d, NCH), 2.85□2.63 (1H, m, CH), 2.45□2.10 (2H, m, CH_2), 1.65□1.46 (6H, m, 3 x CH_2), 1.42 (9H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 155.1 (C=O), 135.6 (CH), 116.5 (CH_2), 79.0 (C), 50.0 (CH), 38.8 (CH_2), 34.4 (CH_2), 28.4 (3 x CH_3), 27.6 (CH_2), 25.4 (CH_2), 18.8 (CH_2). The enantiomers were resolved by CSP-SFC under the following conditions: **Column:** Regis Technologies Whelk-O-1, **Chiral Stationary Phase**: 4-(3,5-dinitrobenzamido) tetrahydrophenanthrene, covalently bound to silica, **Flow Rate** = 1.0 mL/min, **Polarity Modifier =** 1.2 % MeOH, Outlet Pressure **= 150 psi**, **Oven Temperature** = 35 ºC. *S*-**14** elutes before *R*-**14** after *ca* 12 minutes.

Alternatively, the enantiomers were resolved by CSP-GC {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, Pressure = 100 kPa, Initial temperature = 100 ºC, Final temperature = 150 ºC, Hold time = 2 min, Rate = 1.0 ºC/min. *S*-**14** elutes before *R*-**14** after *ca* 30 minutes.

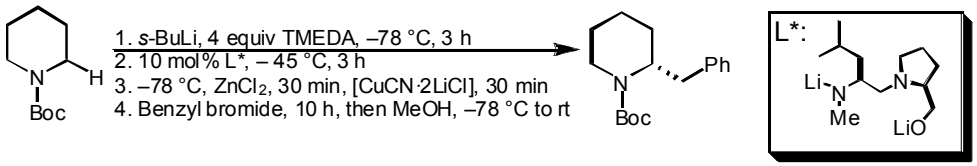
CSP-GC trace for CDR of **2** followed by Negishi coupling and electrophilic quench with allyl chloride





Note: When the equilibrated ratio of **2**·**8** was cooled to –78 °C and quenched directly with allyl chloride, *R*-**14** was obtained in low yield (29%) and low er (57:43).

4.8. Electrophilic quench with benzyl bromide: Synthesis of (*R*)-*N*-Boc-2-benzylpiperidine *R*-15



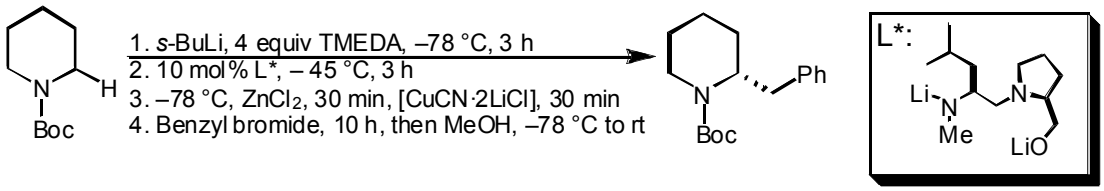
Scheme 12. Synthesis of *R*-**15.** 1) *s*-BuLi (1.2 equiv), Et_2O, TMEDA (4.0 equiv), –78 °C, 3 h, 2) **8**, (10 mol%), –45 °C, 3 h, 3) –78 °C, $ZnCl_2$ (1.3 equiv in THF), 30 min, CuCN·2LiCl (in THF), 30 min, 4) benzyl bromide (3.0 equiv), 10 h, then MeOH, warm to rt, 65%, 98:2 er.

Using **General Procedure C**, *N*-Boc-piperidine (185 mg, 1.0 mmol, 0.25 M), TMEDA (586 mg, 4.0 mmol, 0.62 mL, 4.0 equiv) in Et_2O (4 mL), *s*-BuLi (1.2 equiv), **8** (21.4 mg, 0.1 mmol, 10 mol%, 0.25 M in 0.40 mL Et_2O), $ZnCl_2$ (0.18 mg, 1.3 mmol, 1.3 equiv) in THF (2 mL), CuCN·2LiCl [prepared from CuCN (107 mg, 1.2 mmol, 1.2 equiv) and LiCl (107 mg, 2.5 mmol, 2.4 equiv)] in THF (3 mL), benzyl bromide (300 mg, 3.0 mmol, 3.0 equiv) for 18 h, MeOH (2 mL), NH_4Cl (5 mL) gave the crude product. Purification by silica gel chromatography eluting with hexane-EtOAc (98:2) afforded 178 mg of *R*-**15** as a colorless oil in 65% yield and >99:1 er, data as reported.[10] ^{13}C NMR (75.6 MHz, $CDCl_3$) δ = 154.8 (C=O),139.3 (C), 129.2 (2 x CH), 128.3 (2 x CH), 126.1 (CH), 79.9 (C), 52.4 (CH), 38.9 (CH_2), 36.1 (CH_2), 28.3 (CH_3), 27.3 (CH_2) and 25.6 (CH_2), 19.0 (CH_2). The enantiomers were resolved by CSP GC {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, Pressure = 100 kPa, Initial temperature = 100 ºC, Final temperature = 150 ºC, Hold time = 2 min, Rate = 1.0 ºC/min. *S*-**15** elutes after 82 min and *R*-**15** elutes after 84 min. Alternatively, the enantiomers were resolved by CSP-SFC under the following conditions: **Column:** Regis Technologies Whelk-O-1, **Chiral Stationary Phase**: 4-(3,5-dinitrobenzamido) tetrahydrophenanthrene, covalently bound to silica, **Flow Rate** = 1.0 mL/min, **Polarity Modifier =** 1.2% MeOH, Outlet Pressure **= 150 psi**, **Oven Temperature** = 35 ºC. *S*-**15** elutes before *R*-**15** after *ca* 11 minutes.

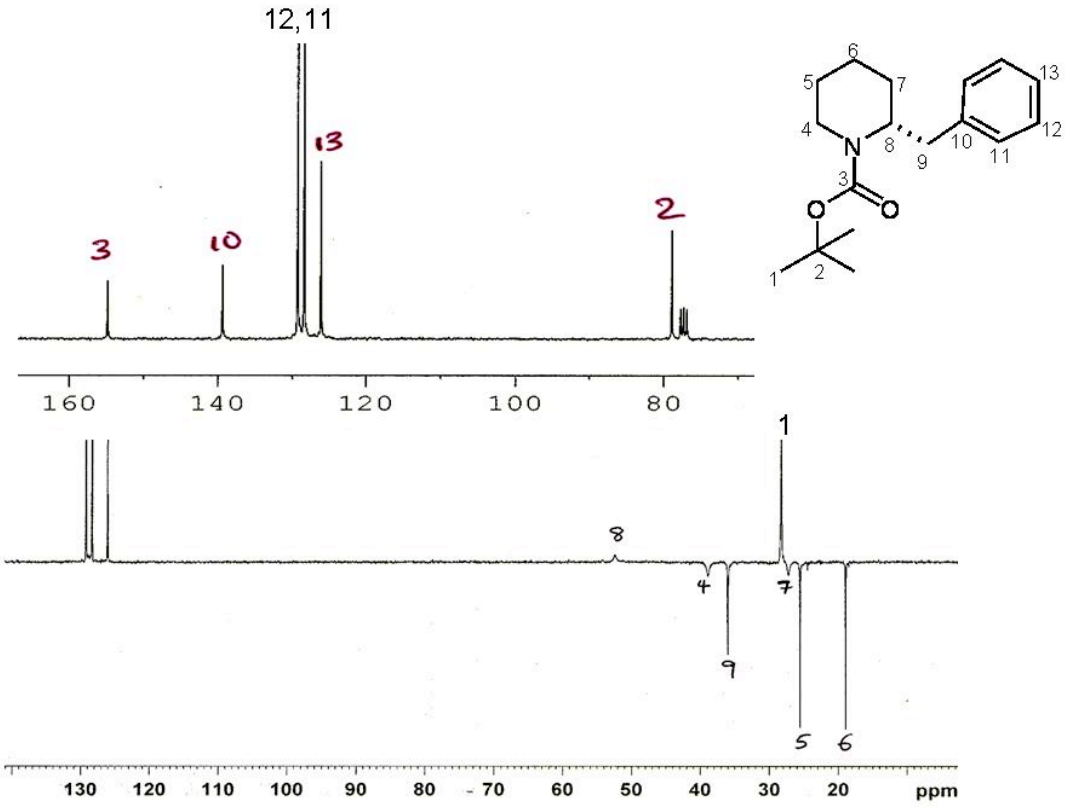
Note 1: When the equilibrated ratio of **2·8** was cooled to –78 °C and quenched directly with benzyl bromide, *R*-**15** was obtained in low er (58:42).

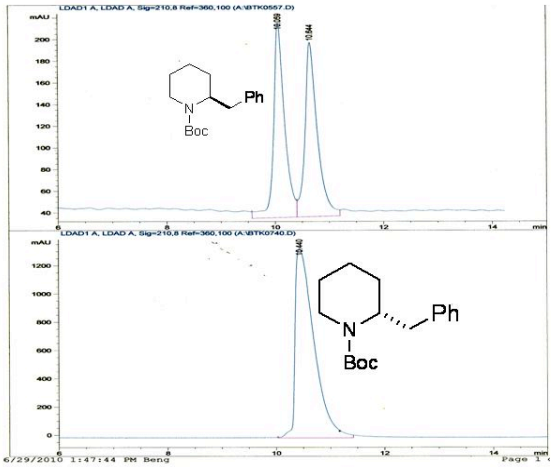
Note 2: Hydrolysis of the *N*-Boc-group affords enantiopure 2-benzylpiperidine, whose racemic form is used as a stimulant drug and is known to boost norepinephine levels to around the same extent as *D*-amphetamine. It is mostly used as a synthetic intermediate for the synthesis of other drugs.

^{13}C NMR and SFC traces for CDR of **2** followed by Negishi coupling and electrophilic quench with benzyl bromide

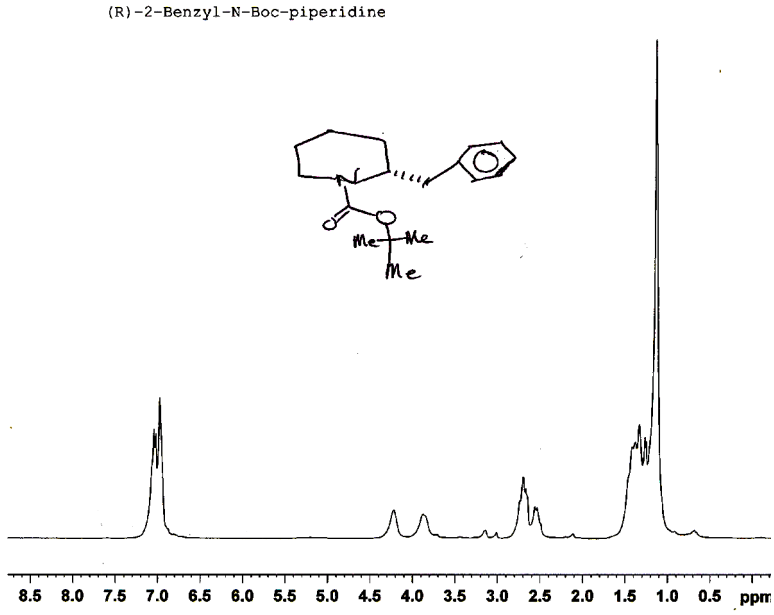


a. ^{13}C NMR spectrum



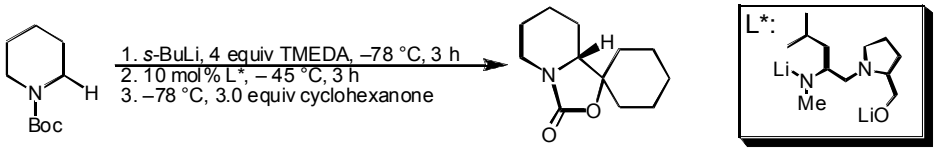


b. CSP-SFC traces: Top; authentic *rac*-**15**, middle; *R*-**15** (>99:1 er).



c) ^{1}H NMR spectrum

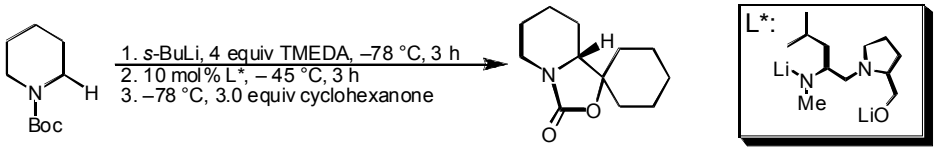
4.12. Electrophilic quench with cyclohexanone: Synthesis of the oxazolidinone *R*-16

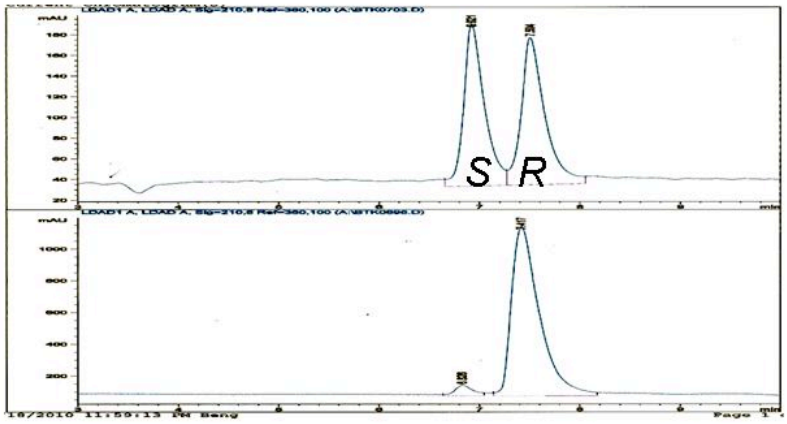


Scheme 13. Synthesis of *R*-**16.** 1) *s*-BuLi (1.2 equiv), Et_2O, TMEDA (4.0 equiv), –78 °C, 3 h, 2) L* (ligand **8** 10 mol%), –45 °C, 3 h,, 3) cyclohexanone (3.0 equiv), –78 °C, 2 h, then rt, MeOH, 60%, 94:6 er.

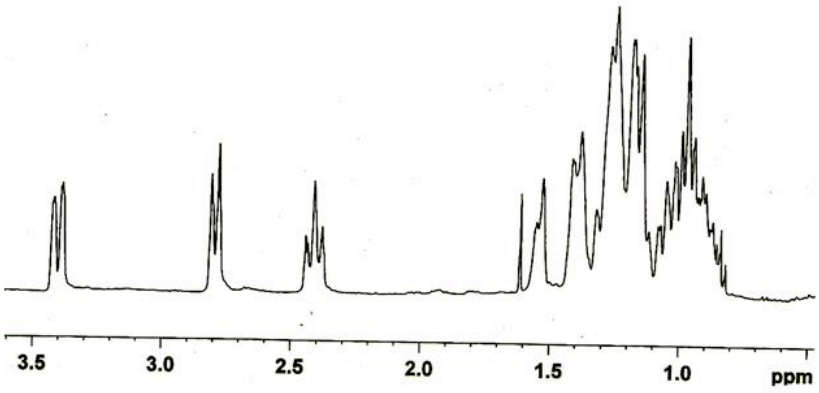
Using **General Procedure B**, *N*-Boc-piperidine (185 mg, 1.0 mmol), TMEDA (0.6 mL, 4.0 mmol, 4.0 equiv) in 10 mL Et_2O, chiral ligand **8** (21.4 mg, 0.1 mmol, 10 mol%) in 1.0 mL Et_2O, cyclohexanone (294 mg, 3.0 mmol, 3.0 equiv) for 2 h, warming to room temperature and addition of MeOH (2 mL), gave the crude product as a yellowish, viscous oil. Purification by silica gel chromatography eluting with hexane-EtOAc (80:20) afforded 125.4 mg of a white solid in 60% yield and 94:6 er; mp 95 – 97 ºC, $[\alpha]_D^{22}$ –38 (c = 1, $CHCl_3$). The spectroscopic data was in accordance with the literature.[1] ^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 156.6 (C=O), 81.4 (C), 63.8 (CH), 41.7 (CH_2), 36.7 (CH_2), 31.1 (CH_2), 25.5 (CH_2), 25.2 (CH_2) and 24.2 (CH_2), 23.1 (CH_2), 22.1 (CH_2) and 21.9 (CH_2). The er was determined using the following conditions:
Column: Daicel Chiralcel OD-H, **Chiral Stationary Phase**: 4-Cellulose tris-(3,5-dimethylphenylcarbamate) coated on 5μm silica-gel. **Flow Rate** = 3.0 mL/min, **Polarity Modifier =** 3.0% EtOH, *R*-**16** elutes after 6.85 minutes and *S*-**16** elutes after 7.45 minutes.

Spectroscopic data for CDR of **2**·and electrophilic quench with cyclohexanone.

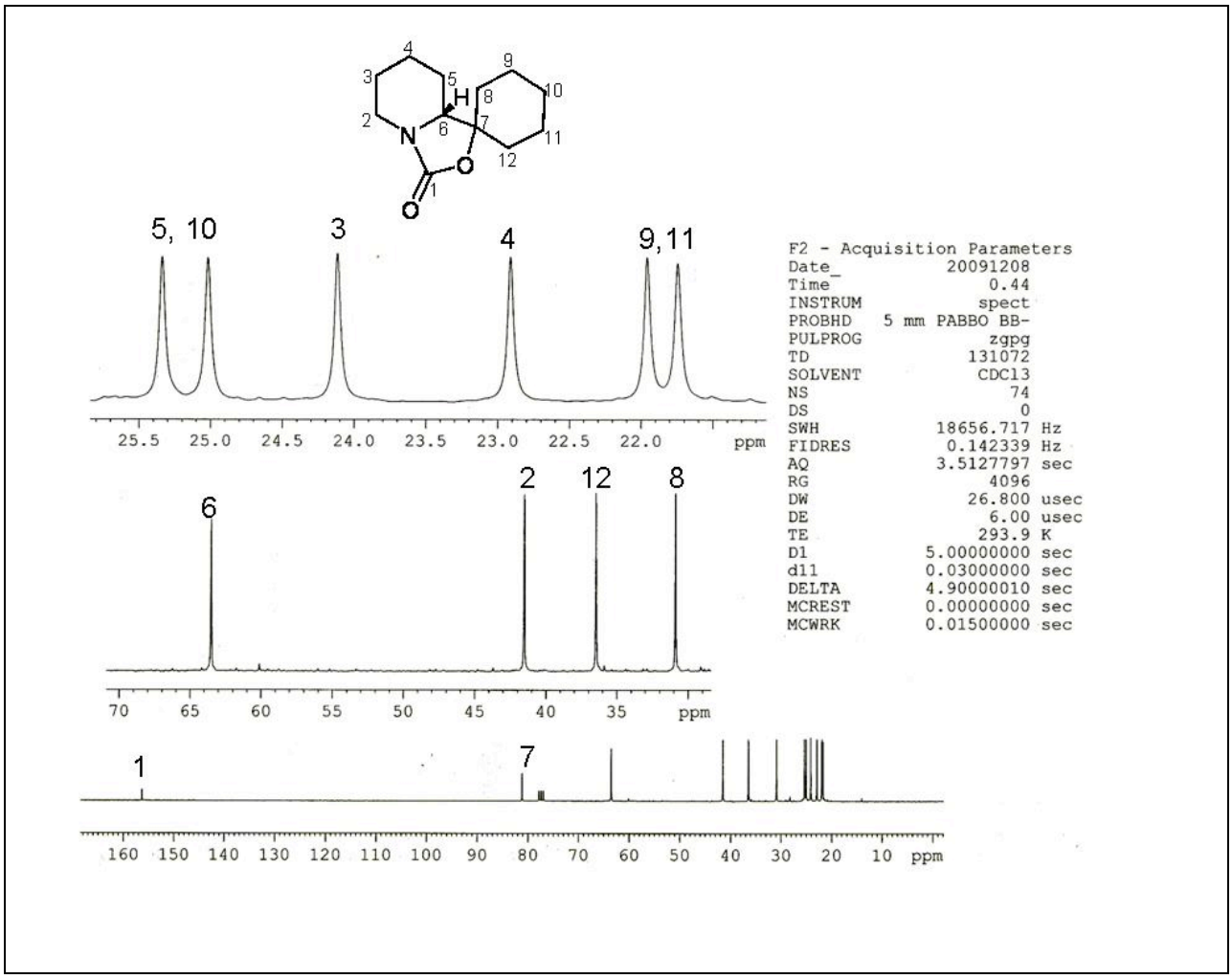




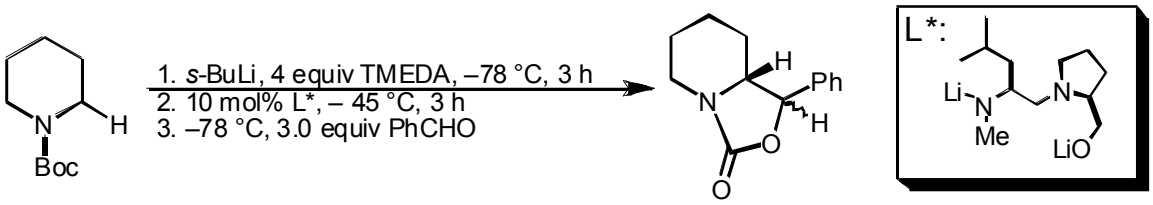
CSP-SFC



^{1}H NMR


5, 10
3
4
9,11
25.5 25.0 24.5 24.0 23.5 23.0 22.5 22.0 ppm
6
2
12
8
70 65 60 55 50 45 40 35 ppm
1
7
160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm
F2 - Acquisition Parameters
Date_ 20091208
Time 0.44
INSTRUM spect
PROBHD 5 mm PABBO BB-
PULPROG zgpg
TD 131072
SOLVENT CDCl3
NS 74
DS 0
SWH 18656.717 Hz
FIDRES 0.142339 Hz
AQ 3.5127797 sec
RG 4096
DW 26.800 usec
DE 6.00 usec
TE 293.9 K
D1 5.00000000 sec
d11 0.03000000 sec
DELTA 4.90000010 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec

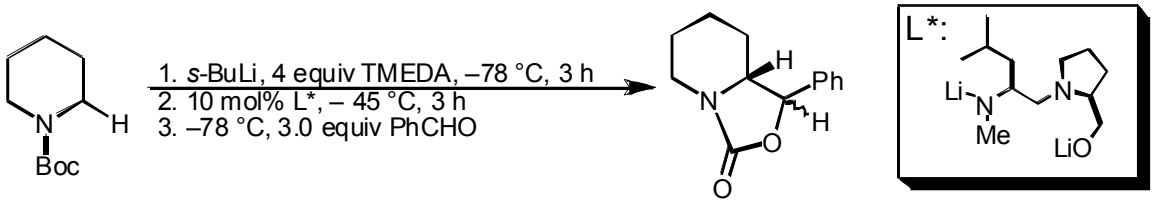
4.13. Electrophilic Quench with Benzaldehyde: Synthesis of the oxazolidinone 17

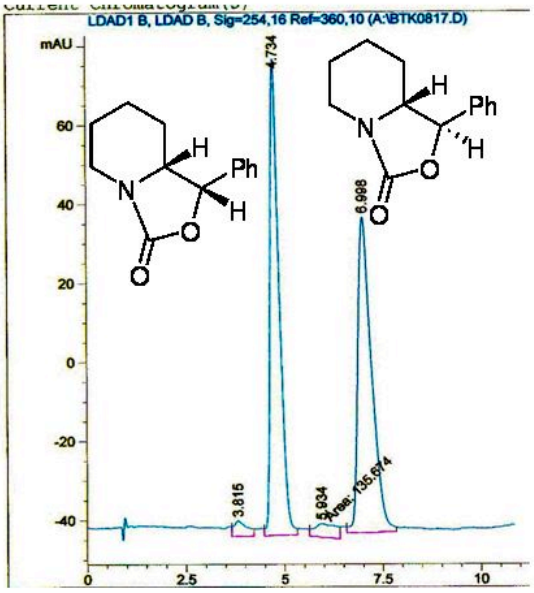


Scheme 14. Synthesis of **17.** 1) *s*-BuLi (1.2 equiv), Et_2O, TMEDA (4.0 equiv), –78 °C, 3 h, 2) L* (ligand **8,** 10 mol%.), –45 °C, 3 h, 3) benzaldehyde (3.0 equiv), –78 °C, 2 h, then warm to rt, MeOH, 74%, 1:1 to 2:1 dr, >99:1 er for (*R*,*S*)-**17**, 98:2 er for (*R*,*R*)-**17.**

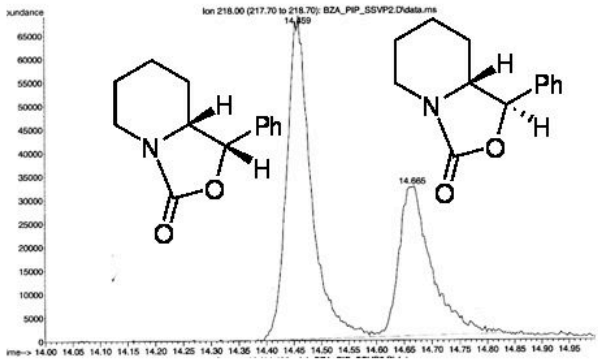
Using **General Procedure B**, *N*-Boc-piperidine (370 mg, 2.0 mmol), TMEDA (1.2 mL, 8.0 mmol, 4.0 equiv) in 10 mL Et_2O, chiral ligand **8** (43 mg, 0.2 mmol, 10 mol%) in 10 mL Et_2O, freshly distilled benzaldehyde (640 mg, 6 mmol, 3.0 equiv) for 2 h, warming to room temperature and addition of MeOH gave the crude product as a pale yellow oil. Purification by silica gel chromatography eluting with hexane-EtOAc (60:40) afforded 321 mg of **17,** as a mixture of diastereomers (dr ~62:38) in 74% yield. CSP-GC and CSP-SFC analyses gave four separate peaks (one for each enantiomer of the diastereomers) and revealed great enantioselectivity (major diastereomerer >99:1, minor diastereomer er 98:2). The spectroscopic data was in accordance with the literature.[12] $[\alpha]_D^{22}$ –7.7 (c = 1, $CHCl_3$), lit[4c]. for **17** of 80:20 dr; $[\alpha]_D^{22}$ –2.9 (*c* = 1.1, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.50-7.23 (5H, m, Ph), 5.61 (0.2H, d, CH), 5.01 (0.8 H, d, CH), 3.93 (1H, dd, NCH), 3.81-3.61 (0.5H, m, NCH), 3.52-3.23 (1.5H, m, NCH), 1.78-1.60 (2H, m, CH_2), 1.57-1.24 (4H, m, 2 × CH_2); ^{13}C NMR (75.5 MHz, $CDCl_3$, diastereomers) δ = 156.5 (C=O), 138.8 (C), 129.4 & 128.8 (CH), 128.4 and 126.8 (CH), 125.8 and 125.6 (CH), 81.8 and 77.6 (CH), 62.4 and 58.9 (CH), 42.1 & 41.4 (CH_2), 30.1 and 26.8 (CH_2), 24.6 and 24.2 (CH_2), 22.9 and 22.6 (CH_2). The er was determined by CSP-SFC as follows: **Column:** Daicel Chiralcel OD-H, **Chiral Stationary Phase**: 4-Cellulose tris-(3,5-dimethylphenylcarbamate) coated on 5μm silica-gel. **Flow Rate** = 3.0 mL/min, **Polarity Modifier =** 3.0% EtOH.

CSP-SFC trace for CDR of **2** and electrophilic quench with benzaldehyde (MeOH added after warming to room temperature)

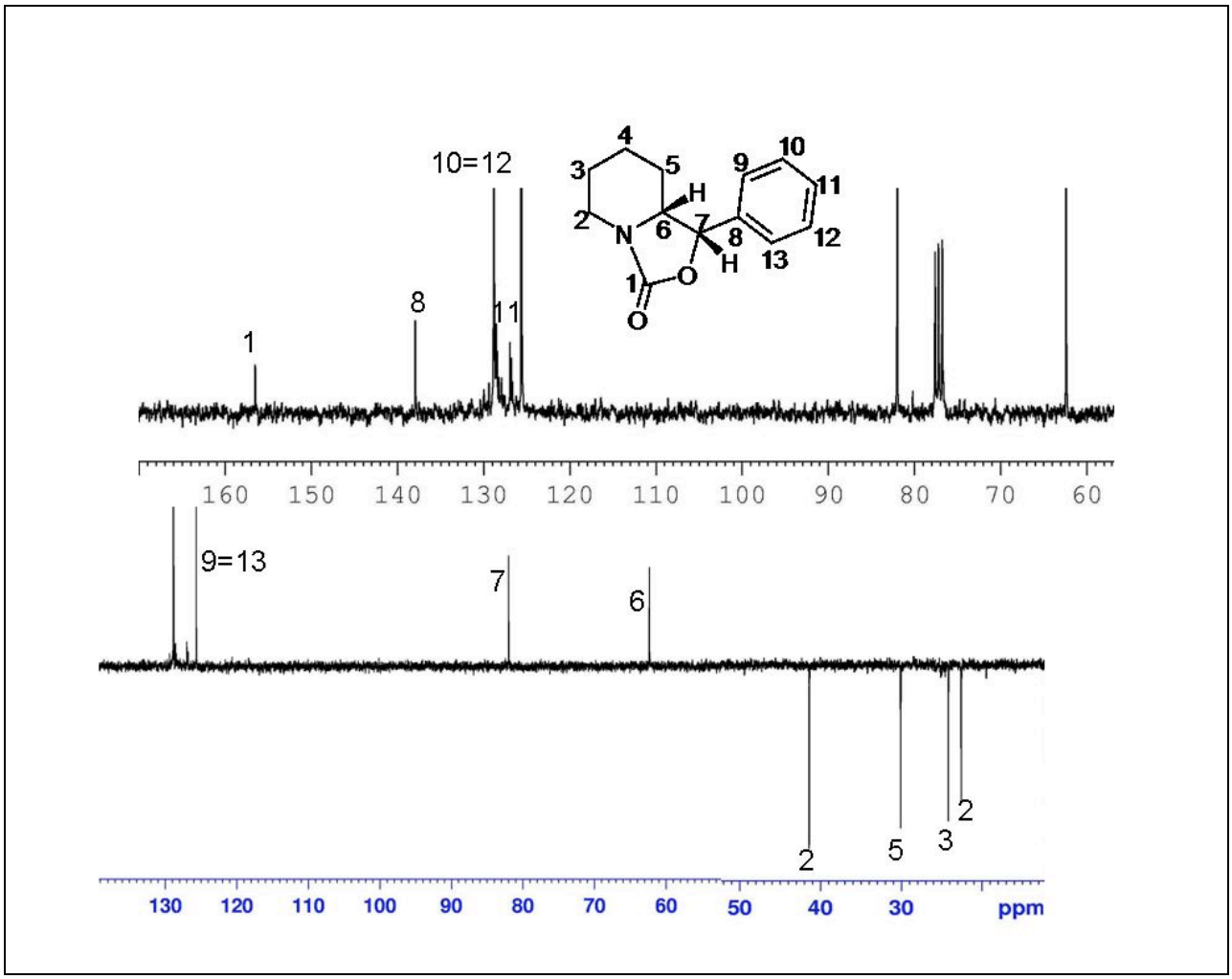




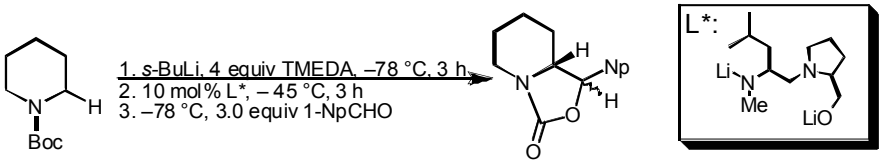
CSP-SFC traces
Major: 99:1 er
Minor: 98:2 er



GC-MS trace
62:38 dr


10=12
8
11
1
9=13
7
6
2
5
3
2
160 150 140 130 120 110 100 90 80 70 60
130 120 110 100 90 80 70 60 50 40 30 ppm

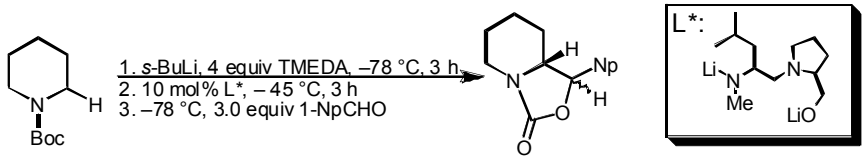
4.14. Electrophilic quench with 1-naphthaldehyde: Synthesis of the oxazolidinone 18



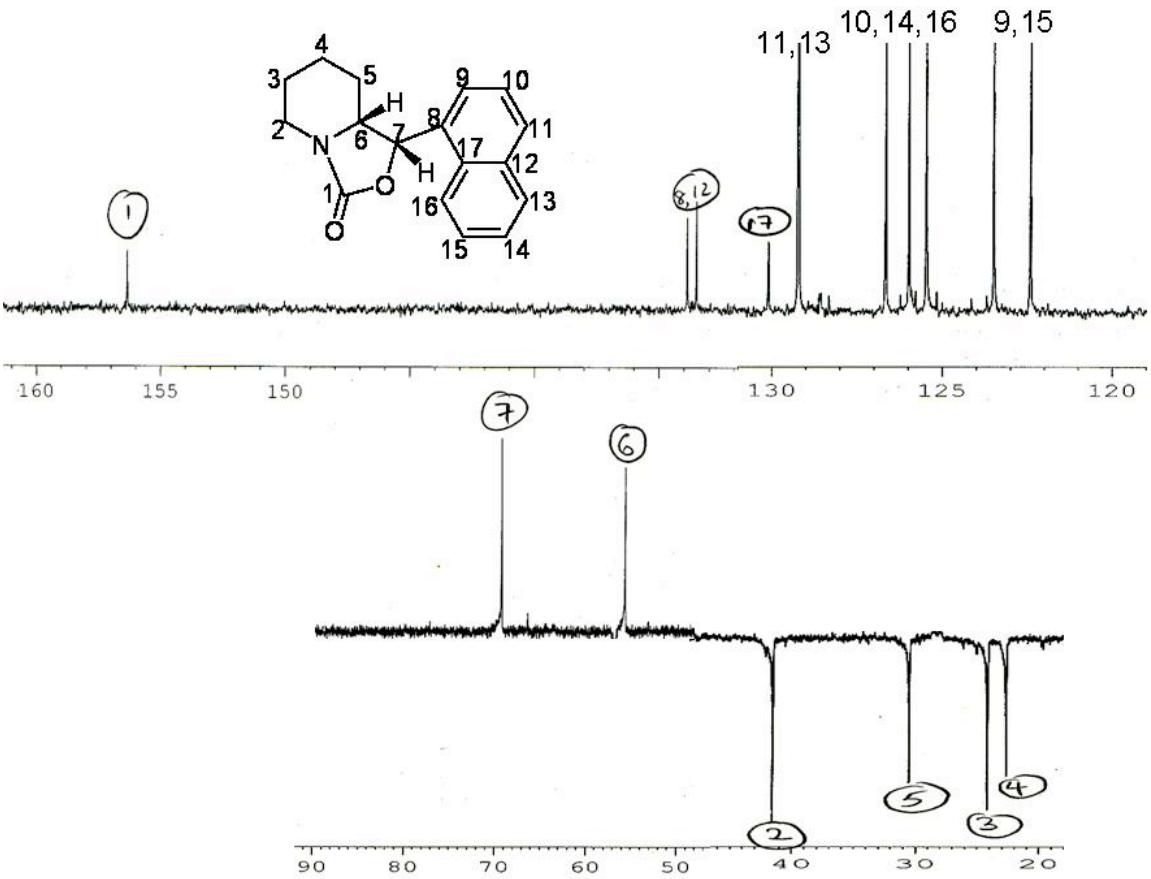
Scheme 15. Synthesis of **18.** 1) *s*-BuLi (1.2 equiv), Et_2O, TMEDA (4.0 equiv), –78 °C, 3 h, 2) L* (ligand **8**, 10 mol%), –45 °C, 3 h, 3) 1-naphthaldehyde (3.0 equiv), –78 °C, 2 h, then warm to rt, add MeOH, 66%, 82:18 dr (*R*,*S*:*R*,*R*), 94:6 er (*R*,*S*), 93:7 er (*R*,*R*).

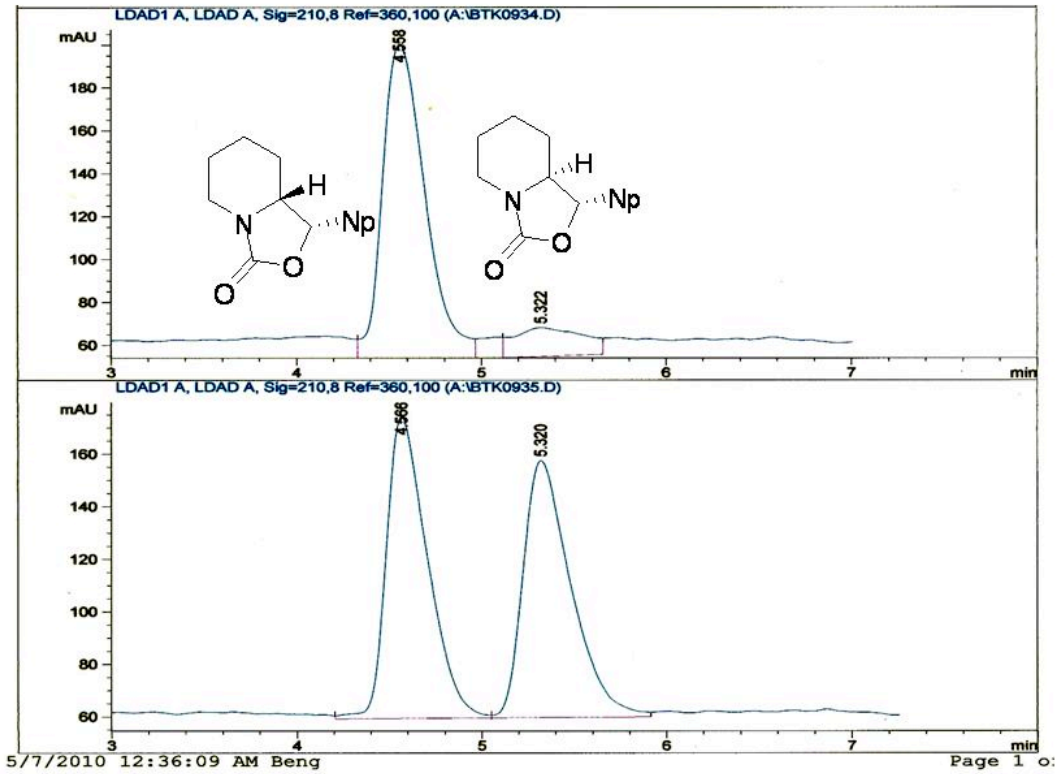
Using **General Procedure B**, *N*-Boc-piperidine (370 mg, 2.0 mmol), TMEDA (1.2 mL, 8.0 mmol, 4.0 equiv) in 10 mL Et_2O, chiral ligand **8** (43.0 mg, 0.2 mmol, 10 mol%) in 1.0 mL Et_2O, 1-naphthaldehyde (936 mg, 0.8 mL, 6 mmol, 3.0 equiv) for 2 h, warming to room temperature and addition of MeOH (2.0 mL) gave the crude product as a pale yellow oil. Purification by silica gel chromatography eluting with hexane-EtOAc (70:30) afforded 300 mg of **18** as a mixture of diastereomers (82:18) in 66% yield**.** CSP-GC and CSP-SFC analyses gave four separate peaks (one for each enantiomer of the diastereomers); 94:6 er for the major diastereomer, 93:7 er for the minor diastereomer).

Spectroscopic data for CDR of **2** and electrophilic quench with 1-naphthaldehyde (MeOH added after warming to rt)



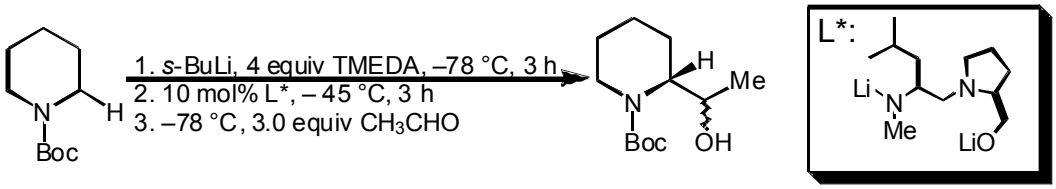
a. ^{13}C NMR spectrum





b. CSP-SFC trace: Bottom; authentic racemate, top: major diastereomer of **18**

4.15. Electrophilic quench with acetaldehyde: Synthesis of alcohol 19



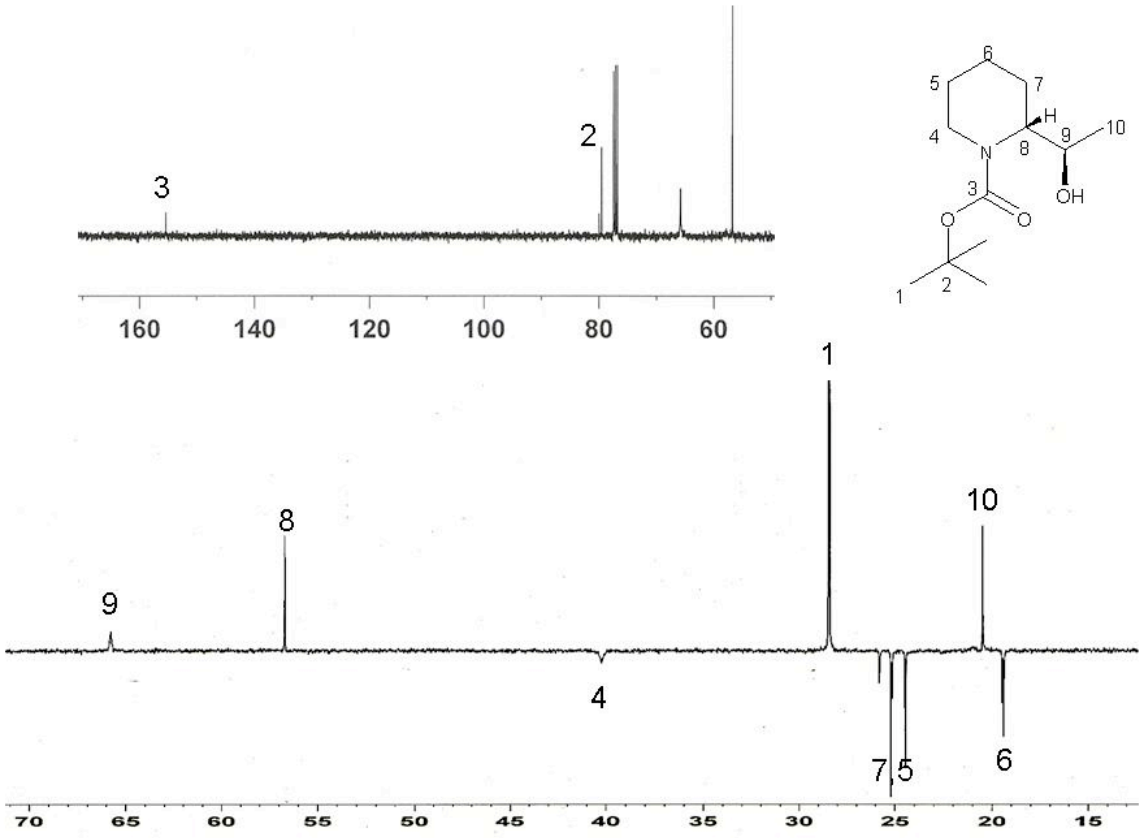
Scheme 16. Synthesis of **19.** 1) *s*-BuLi (1.2 equiv), Et_2O, TMEDA (4.0 equiv), –78 °C, 3 h, 2) L* (ligand **8**, 10 mol%), –45 °C, 3 h, 3) –78 °C, CH_3CHO (3.0 equiv), 2 h, then MeOH, warm to rt, 78%, 85:15 dr (*R*,*S*:*R*,*R*), >99:1 er for both (*R*,*S*) and (*R*,*R*) diastereomers.

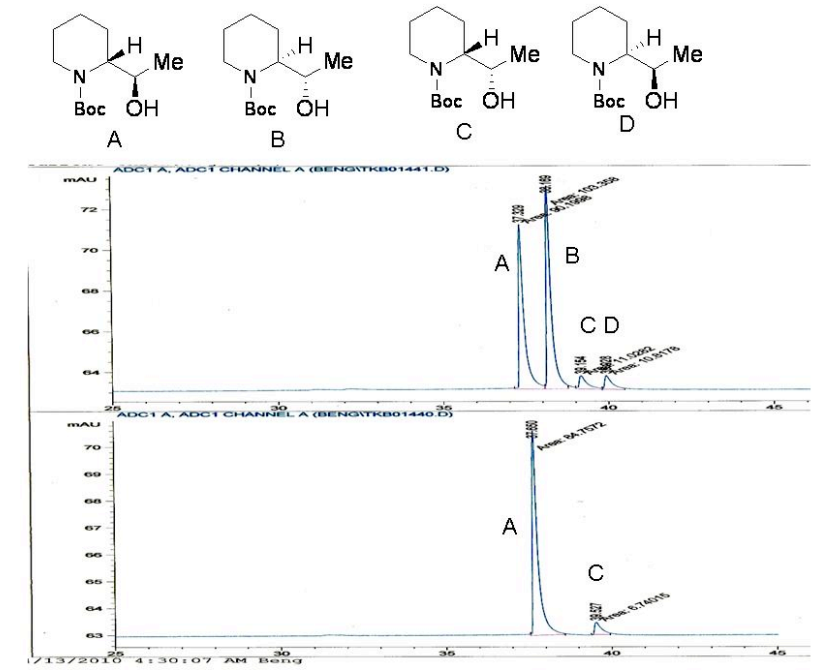
Using **General Procedure B**, *N*-Boc-piperidine (370 mg, 2.0 mmol), TMEDA (1.2 mL, 8.0 mmol, 4.0 equiv) in 10 mL Et_2O, chiral ligand **8** (43.0 mg, 0.2 mmol, 10 mol%) in 1.0 mL Et_2O, acetaldehyde (264 mg, 0.33 mL, 6 mmol, 3.0 equiv) for 2 h, 2 mL MeOH gave the crude product as a pale yellow oil. Purification by silica gel chromatography eluting with hexane-EtOAc (60:40) afforded 357 mg of the desired product as a colorless oil in 76% yield**,** as a mixture of diastereomers (85:15). CSP-GC and CSP-SFC analyses gave four separate peaks (one for each enantiomer of the diastereomers) with high enantioselectivity (>99:1 for both). ^{1}H NMR (300 MHz, $CDCl_3$) δ =3.94-3.86 (2H, m, 2 × NCH), 3.76-3.70 (1H, m, NCH), 2.70 (1H, d, CH), 2.49-2.29 (1H, m, CH), 2.0 (1H, br d, CH), 1.67-1.51 (4H, m, 2 × CH_2), 1.52-1.41 (11H, m, CH_2 and *t*-Bu), 1.1–1.35 (3H, d, CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ = 156.2 (C=O), 80.7 (C), 65.7 (CH), 56.2 (CH), 40.5 (CH_2), 28.2 (CH_3), 25.4 (CH_2), 24.6 (CH_2), 20.5 (CH_3) and 19.4 (CH_2). The enantiomers were resolved by CSP GC {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, Pressure = 100 kPa, Initial temperature = 150 ºC, Final temperature = 200 ºC, Hold time = 2 min, Rate = 1.0 ºC/min. The major diastereomer elutes before the minor diastereomer. For the major diastereomer, the *R*-enantiomer elutes after 37.5 minutes and *S*-enantiomer elutes after 38.4 minutes. For the minor diastereomer, the *R*-enantiomer elutes after 39.2 minutes and *S*-enantiomer elutes after 40 minutes. Alternatively, the enantiomers were resolved by CSP-SFC under the following conditions: **Column:** Daicel Chiralcel OD-H, **Flow Rate**: 1.0 mL/min, **Polarity Modifier %**: 1.0% EtOH, Outlet Pressure **= 150 psi**, **Oven Temperature** = 35 ºC. For the minor diastereomer, the *S*-

enantiomer elutes after 11.3 minutes and *R*-enantiomer elutes after 12.4 minutes. For the major diastereomer, the *S*-enantiomer elutes after 30 minutes and *R*-enantiomer elutes after 34 minutes.

Spectral data for CDR of **2** and electrophilic quench with acetaldehyde

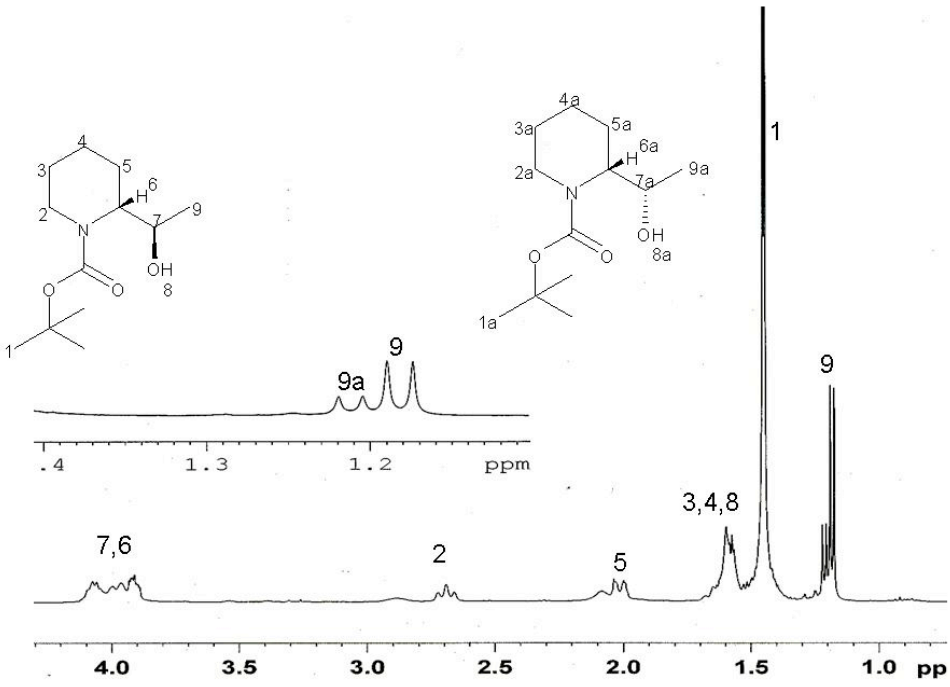
a) ^{13}C NMR



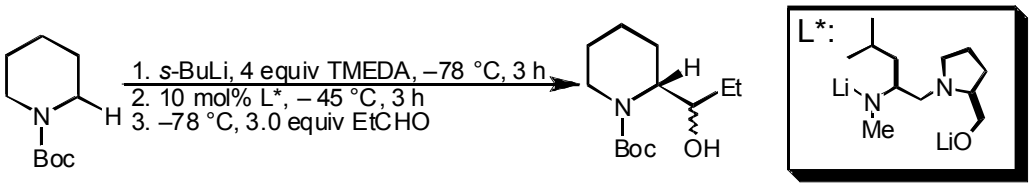


b). CSP-GC traces for *rac*-**19** (top) and *enr*-**19** (bottom) from CDR using ligand **8**

Note: Both CSP-GC traces are from the respective crude products, from which the dr was determined.



4.16. Electrophilic quench with propionaldehyde: Synthesis of *N*-Boc-(+)-β-conhydrine

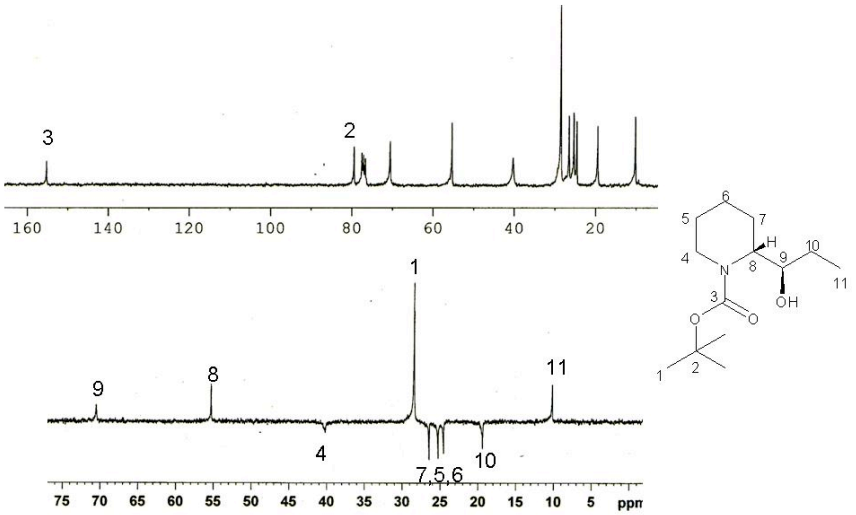


Scheme 17. Synthesis of *N*-Boc-(+)-β-conhydrine 1) *s*-BuLi (1.2 equiv), Et_2O, TMEDA (4.0 equiv), –78 °C, 3 h, 2) L* (ligand **8**, 10 mol%), –45 °C, 3 h, 3) –78 °C, CH_3CH_2CHO (3.0 equiv), 2 h, then MeOH, warm to rt, 84%, 70:30 to 80:20 dr (*R*,*S*:*R*,*R*), 96:4 for both diastereomers.

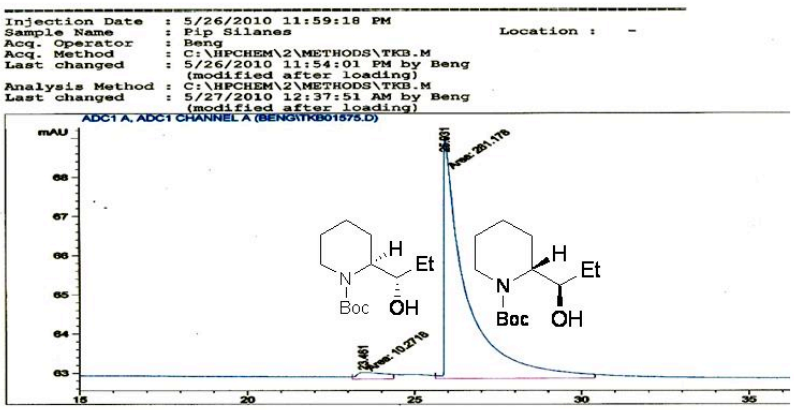
Using **General Procedure B**, *N*-Boc-piperidine (370 mg, 2.0 mmol), TMEDA (1.2 mL, 8.0 mmol, 4.0 equiv) in 10 mL Et_2O, chiral ligand **8** (43.0 mg, 0.2 mmol, 10 mol%) in 1.0 mL Et_2O, propionaldehyde (348 mg, 6 mmol, 3.0 equiv) for 2 h, 2 mL MeOH gave the crude product as a pale yellow oil. Purification by silica gel chromatography eluting with hexane-EtOAc (60:40) afforded 408 mg of *N*-Boc-conhydrine as a mixture of diastereomers (70:30) in 84% yield**.** CSP-GC and CSP-SFC analyses gave four separate peaks (one for each enantiomer of the diastereomers) and revealed high enantioselectivity (96:4 for both). The major diastereomer, *N*-Boc-(+)-β-conhydrine was isolated in 61% yield $[\alpha]_D^{22}$ +24.3 (*c = 1*, $CHCl_3$), {lit[4b] for *N*-Boc-(+)-β-conhydrine of 84:16 er $[\alpha]_D^{22}$ +17.8 (*c = 1.1*, $CHCl_3$) ^{1}H NMR (300 MHz, $CDCl_3$) δ =3.94-3.86 (2H, m, 2 × NCH), 3.76-3.70 (1H, m, NCH), 2.70 (1H, d, CH), 2.49-2.29 (1H, m, CH), 2.03 (1H, br d, CH), 1.67-1.51 (4H, m, 2 × CH_2), 1.49-1.32 (11H, m, CH_2 and *t*-Bu), 0.97 (3H, t, CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 155.2 (C=O), 79.4 (C), 70.5 (CH), 55.3 (CH), 40.3 (CH_2), 28.4 (CH_3), 26.4 (CH_2), 25.3 (CH_2), 24.6 (CH_2), 19.4 (CH_2) and 10.2 (CH_3). The enantiomers were resolved by CSP GC {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, Pressure = 100 kPa, Initial temperature = 150 ºC, Final temperature = 200 ºC, Hold time = 2 min, Rate = 1.0 ºC/min. For the major diastereomer, the *S*-enantiomer elutes after 23.5 minutes and *S*-enantiomer elutes after 25.9 minutes.

Alternatively, the enantiomers were resolved by CSP-SFC under the following conditions: **Column:** Daicel Chiralcel OD-H, **Flow Rate**: 1.0 mL/min, **Polarity Modifier %**: 1.0% EtOH, Outlet Pressure **= 150 psi**, **Oven Temperature** = 35 ºC.

Spectroscopic data for CDR of **2**·and electrophilic quench with propionaldehyde



CSP-GC trace for *N*-Boc-(+)-β-conhydrine



Area Percent Report

Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000
Use Multiplier & Dilution Factor with ISTDs

Signal 1: ADC1 A, ADC1 CHANNEL A

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
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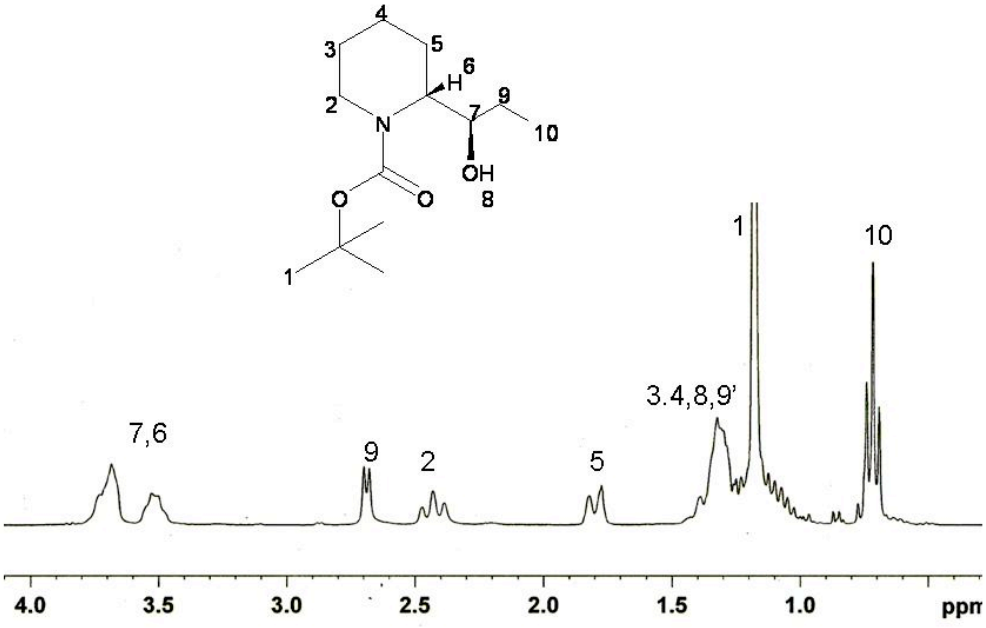
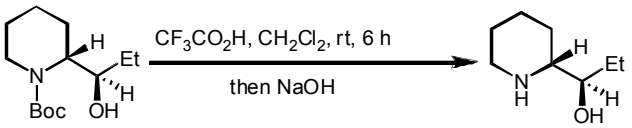
2	25.931	FM	0.7661	281.17807	6.11677	96.47561

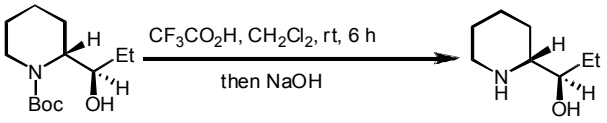


4.16b. Hydrolysis of *N*-Boc-(+)-β-conhydrine: Synthesis of (+)-β-conhydrine

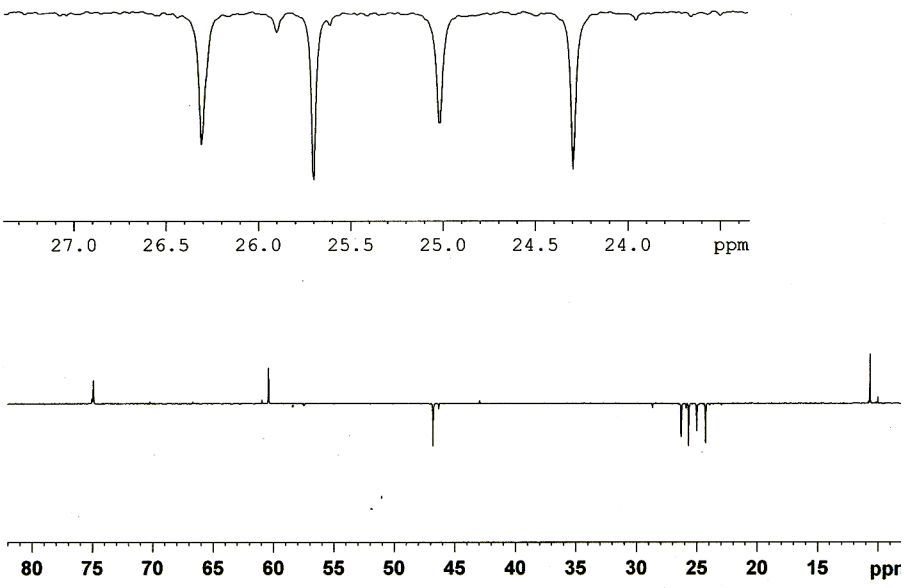


To *N*-Boc-(+)-β-conhydrine (146 mg, 0.6 mmol, 1.0 equiv) dissolved in freshly distilled CH_2Cl_2 (0.5 mL), was added CF_3CO_2H (1.0 mL) under argon at room temperature. The mixture was stirred for 6 h and water (1 mL) was added slowly. The mixture was basified to pH 10 by dropwise addition of 40% $NaOH_{(aq)}$. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 4 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give 85.8 mg of (+)-β-conhydrine in 100% yield. $[\alpha]_D^{22}$ +7.4 (*c* = 0.9, EtOH); lit[15] $[\alpha]_D^{22}$ +8.3 (*c* = 0.9, EtOH). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.44-3.34 (1H, m, CHOH), 3.08 (1H, d, CHN), 2.66 (1H, td, NCH), 2.53 (1H, dt, NCH), 1.90-1.74 (1H, m, CH), 1.65-1.52 (2H, m, CH_2), 1.51-1.19 (5H, m, CH and 2 × CH_2), 0.96 (3H, t, CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 74.8 (CH), 60.3 (CH), 46.5 (CH_2), 26.3 (CH_2), 25.7 (CH_2), 25.1 (CH_2), 24.3 (CH_2) and 10.7 (CH_3).

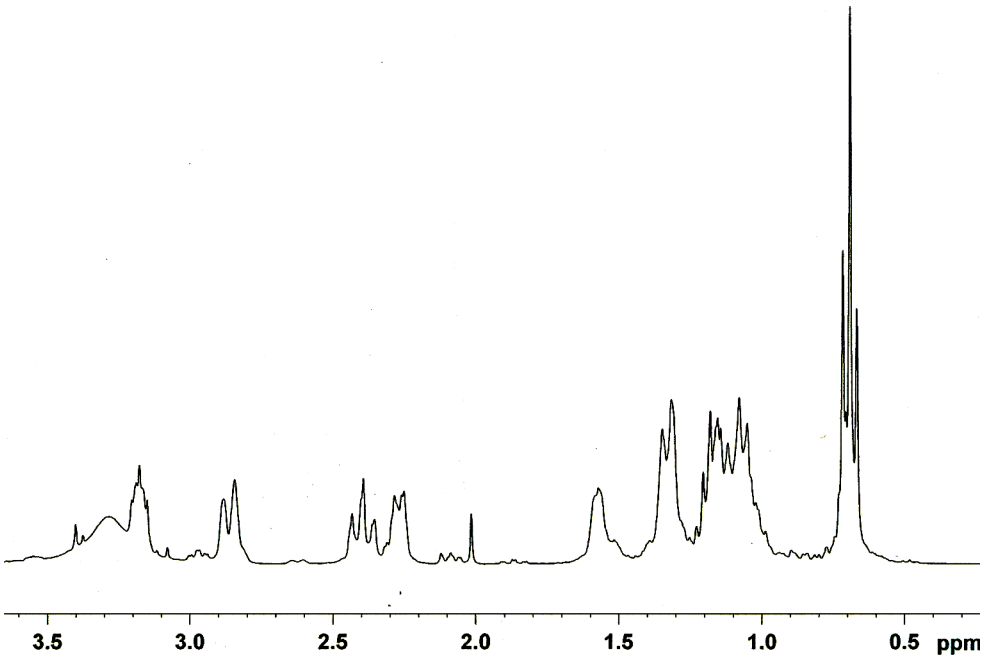
Spectral data for **(+)-**β-conhydrine



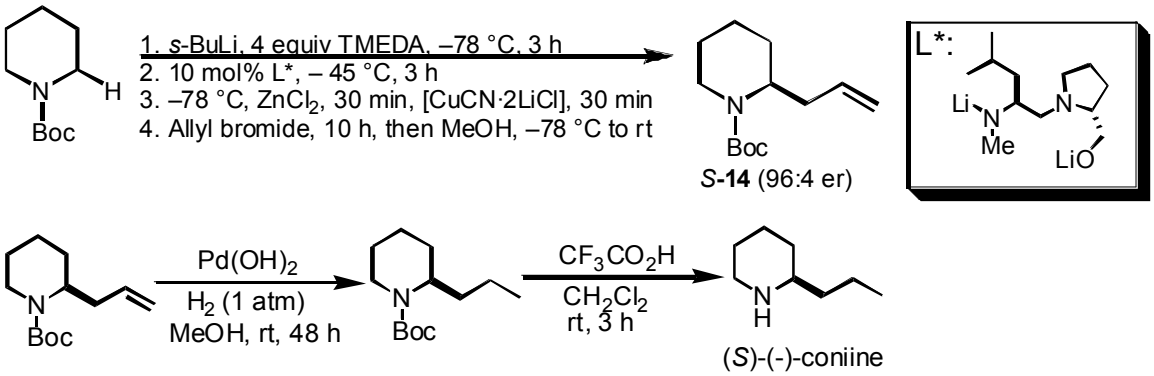
a. ^{13}C NMR spectrum



b.^{1}H NMR



4.17. Synthesis of (*S*)-(-)-coniine



Scheme 18. Synthesis of (*S*)-(-)-coniine

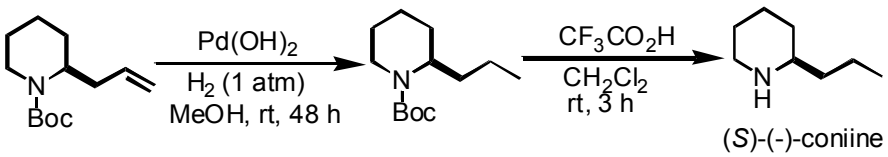
***tert*-Butyl 2-*N*-Propylpiperidine-1-carboxylate (*N*-Boc-(*S*)-(-)-coniine)**

$Pd(OH)_2$ (123 mg, 0.88 mmol, 40 mol%) was added to a solution of *S*-**14** (96:4 er; prepared by CDR using ligand **9**) (500 mg, 2.2 mmol, 1.0 equiv) in 20 mL of freshly distilled MeOH (20 mL) under hydrogen (1 atm) at room temperature. The reaction mixture was stirred for 2 days at this temperature, filtered through a plug of Celite and concentrated under reduced pressure to give 399 mg of *N*-Boc-(*S*)-(-)-coniine in 79% yield; spectroscopic data as reported.[16]

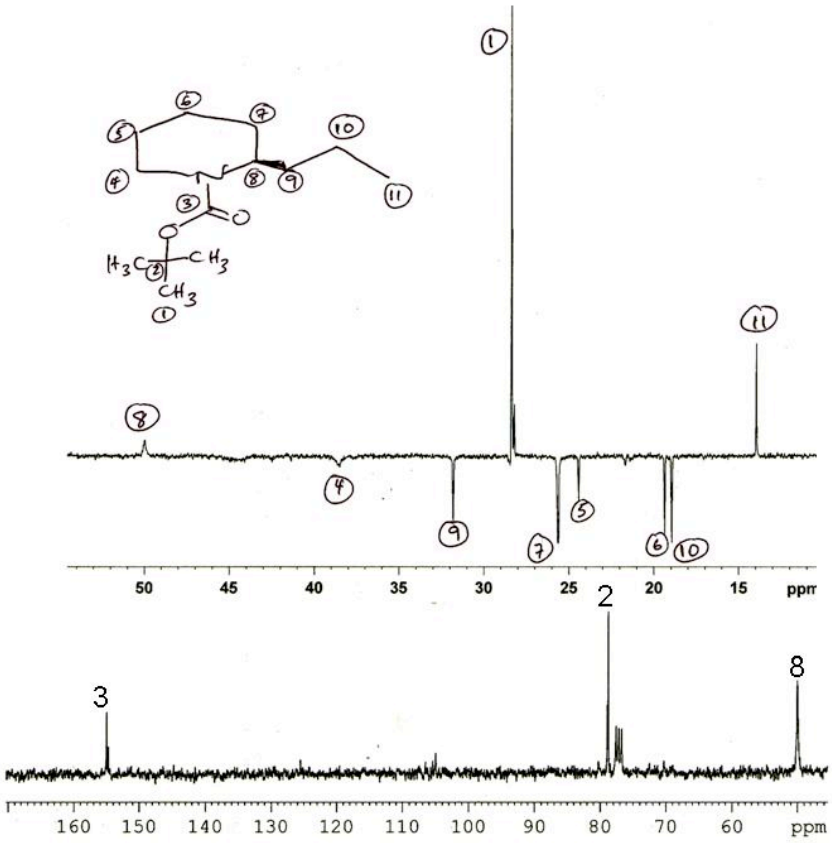
(*S*)-(-)-Coniine

To *N*-Boc-(*S*)-(-)-coniine (284 mg, 1.25 mmol) dissolved in CH_2Cl_2 (3.0 mL), was added CF_3CO_2H (2.0 mL) under argon at 0 ºC. The mixture was stirred for 3 h at this temperature and concentrated in vacuo to obtain the salt. The salt was basified to pH 10 – 12 with 20% $NaOH_{(aq)}$. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 5 mL). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure to give 158 mg of (*S*)-(-)-coniine in 100% yield. $[\alpha]_D^{22}$ –6.7 (*c* = 1.0, MeOH), lit.[16] $[\alpha]_D^{20}$ –7.3 (*c* = 1.0, MeOH). All other spectroscopic data as reported.[16a]

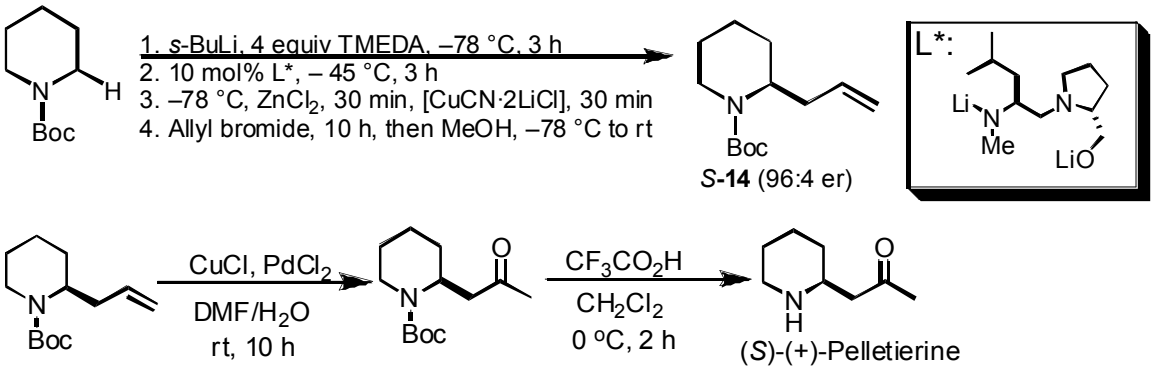
Spectroscopic data for *N*-Boc-(*S*)-(–)-coniine and (*S*)-(–)-coniine



a. ^{13}C NMR spectra



4.18. Synthesis of (*S*)-(+)-Pelletierine



Scheme 19. Synthesis of (*S*)-**(+)-**Pelletierine i) $PdCl_2$ (1.0 equiv), CuCl (10 mol%), O_2, DMF/H_2O (10:1), rt, 10 h, 88%, ii) CF_3CO_2H, CH_2Cl_2, 0 °C, 2 h, then 40% $NaOH_{aq}$, pH 10, 100%.

(*S*)-(2-Oxo-propyl)-piperidine-1-carboxylic acid tert-butyl ester: *N*-Boc-(*S*)-(+)-Pelletierine

CuCl (220 mg, 2.2 mmol, 1 equiv) and $PdCl_2$ (40 mg, 0.22 mmol, 10 mol%) were dissolved in 3 mL of DMF/H_2O (10:1) and the resulting suspension was stirred for 1 h at room temperature under an O_2.atmosphere. A solution of *S*-**14** (96:4 er; prepared by CDR using ligand **9**) (500 mg, 2.2 mmol, 1.0 equiv) in 2 mL of DMF/H_2O (10:1) was added to the reaction mixture and stirred for 10 h. After complete conversion of *S*-**14** as indicated by TLC analysis, the reaction mixture was quenched with 20% $KHSO_4$ (5 mL) and extracted with Et_2O (3 x 10 mL). The combined organic layers were washed with saturated $NaHCO_3$ (10 mL), then with brine (10 mL) and dried over Na_2SO_4. Concentration of the organic layer and purification by column chromatography on silica, eluting with hexane/EtOAc (80:20) afforded 475 mg of *N*-Boc-(*S*)-**(+)-**Pelletierine in 88% yield; spectroscopic data as reported.[17] $[\alpha]_D^{22}$ –11 (*c* = 0.2, $CHCl_3$), lit.[17] $[\alpha]_D^{25}$ –12.7 (*c* = 0.22, $CHCl_3$).

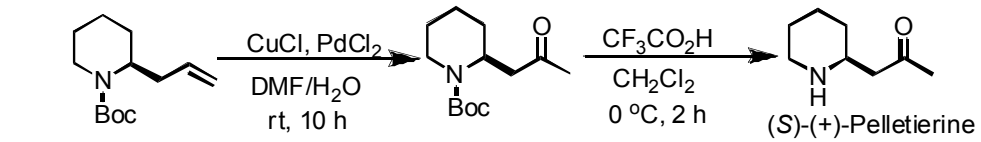
(*S*)-(2-Oxo-propyl)-piperidine: (*S*)-(+)-pelletierine

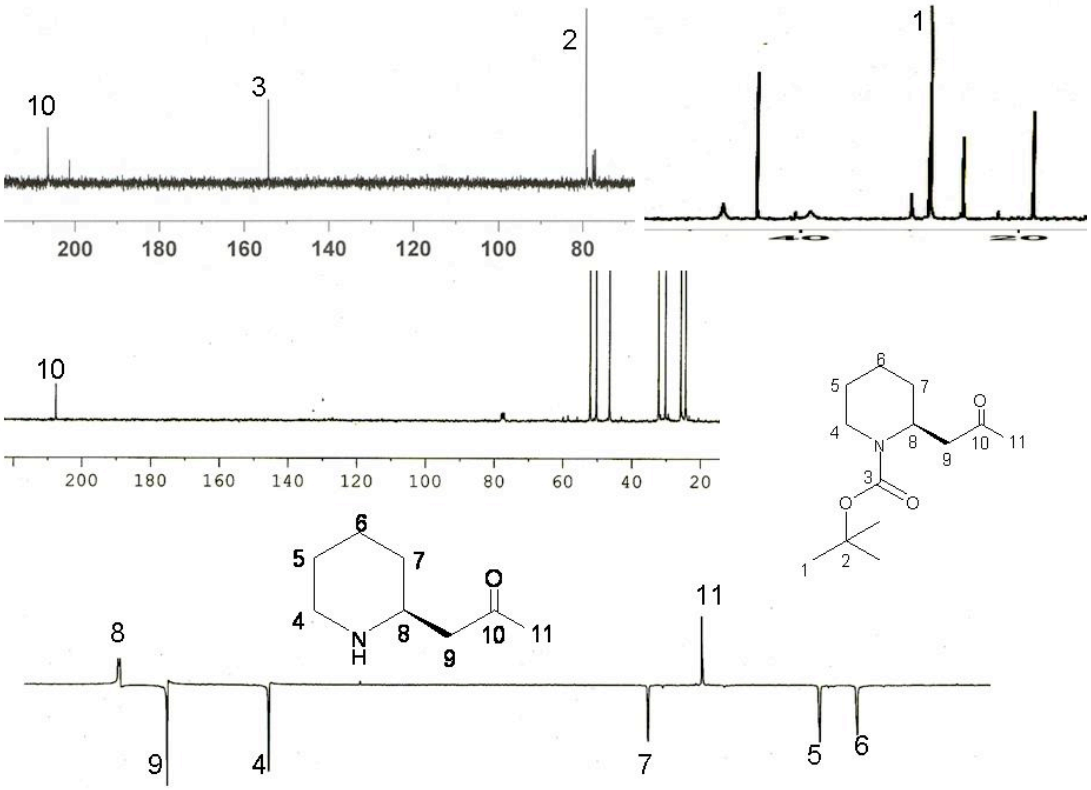
To *N*-Boc-(*S*)-**(+)-**Pelletierine (300 mg, 1.25 mmol) dissolved in CH_2Cl_2 (3.0 mL), was added CF_3CO_2H (2.0 mL) under argon at 0 °C. The mixture was stirred for 2 h at this temperature and concentrated in vacuo to obtain the salt. The salt was basified to pH 10 – 12 with 40% $NaOH_{(aq)}$. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 5 mL). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated under

reduced pressure to give 176 mg of (*S*)-**(+)-**Pelletierine in 100% yield. $[\alpha]_D^{22}$ +16.8 (*c* = 0.5, EtOH), lit.[17] $[\alpha]_D^{25}$ +19.4 (*c* = 0.47, EtOH).

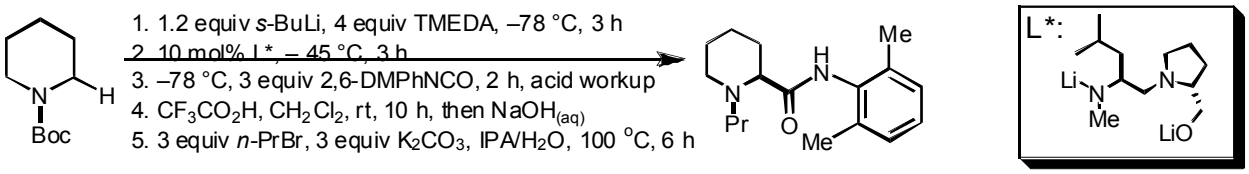
Spectral data for *N*-Boc-(*S*)-**(+)-**Pelletierine and (*S*)-**(+)-**Pelletierine

a. ^{13}C NMR spectra



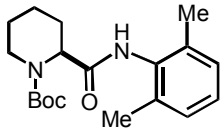


4.19. Synthesis of (*S*)-(-)-1-propyl-2',6'-pipecoloxylide: (*S*)-(-)-Ropivacaine



Scheme 18. Synthesis of (*S*)-(-)-ropivacaine**.** 1) *s*-BuLi (1.2 equiv), Et_2O, TMEDA (4.0 equiv), –78 °C, 3 h, 2) L* (ligand **9**, 10 mol%.), –45 °C, 3 h, 3) –78 °C, 2,6-dimethylphenyl isocyanate (3.0 equiv), 2 h, then MeOH, warm to rt, 69%, >99:1 er, 4) CF_3CO_2H, CH_2Cl_2, rt, 10 h, then NaOH, 100%, 5) isopropyl alcohol, 1-Bromopropane (3.0 equiv), K_2CO_3 (3.0 equiv), H_2O, 100 ºC, 6 h, 89%.

4.19.1 *(S)-N*-Boc-piperidine-2-carboxylic acid 2,6-dimethylphenyl amide: *S*-21



***S*-21**

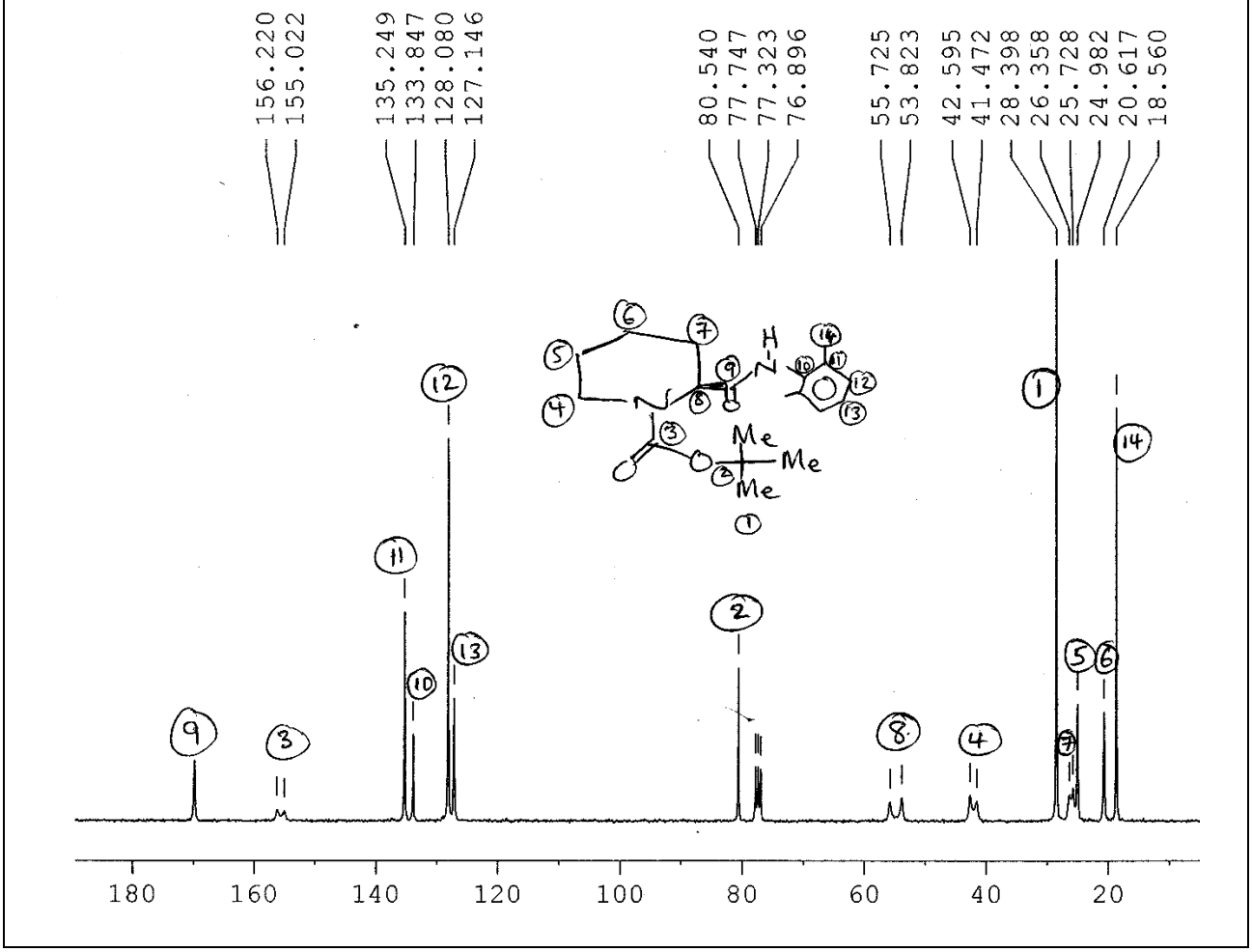
Using **General Procedure B**, *N*-Boc-piperidine (185 mg, 1.0 mmol, 0.25 M), freshly distilled TMEDA (0.6 mL, 4 mmol, 4.0 equiv) in freshly distilled Et_2O (4 mL), *s*-BuLi (1.0 M, 1.2 mL, 1.2 mmoL, 1.2 equiv), **9a** (precursor of **9**; 21.4 mg, 0.1 mmol, 10 mol%, in 0.5 mL Et_2O, pretreated with freshly titrated *s*-BuLi), freshly distilled 2,6-dimethylphenyl isocyanate (0.36 mL, 3 mmol, 3.0 equiv), MeOH (1 mL), gave the crude product as a yellowish solid. Purification by silica gel column chromatography eluting with hexane-EtOAc (90:10) afforded 230 mg of *S*-**21** in 69% yield and >99:1 er. $[\alpha]_D^{22}$ –57 (*c = 2*, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.01 (s, NH, 1H), 7.29-7.16 (m, 3H), 4.97 (s, 1H), 4.34-4.10 (m, 1H), 2.96 (m, 1H), 2.50-2.38 (m, 1H), 2.3 (s, 6H), 1.63-1.45 (m, 5H), 1.51. ^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 172.0 (C=O), δ = 156.2 (C=O), 135.2 and 135.0 (C), 133.7 (C), 127.7 and 127.4 (CH), 126.8 (CH), 80.7 (C), 54.7 (CH), 42.2 (CH_2), 28.1 (CH_3), 26.8 (CH_2), 24.7 (CH_2) and 20.3 (CH_2), 18.2 (CH_3).

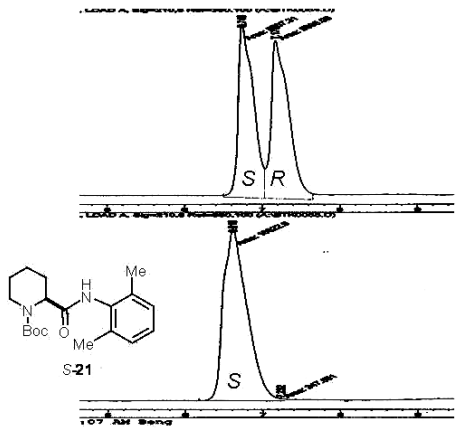
The enantiomers were resolved by CSP-SFC under the following conditions:

Column: Regis Technologies Pirkle-Whelk-O-1, **Chiral Stationary Phase**: 4-(3,5-dinitrobenzamido) tetrahydrophenanthrene, covalently bound to silica, **Flow Rate**: 3.0 mL/min, **Polarity Modifier %**: 3.2% Ethanol, Outlet Pressure **= 150 psi**, **Oven Temperature** = 35 ºC, *S*-**21** elutes before *R*-**21.**

Spectral data for CDR of **2**·and electrophilic quench with 2,6-dimethylphenyl isocyanate.

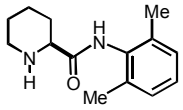
a. ^{13}C NMR spectrum





b. CSP-SFC traces

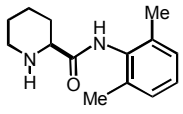
4.19.2 *(S)*-piperidine-2-carboxylic acid 2,6-dimethylphenyl amide *S*-22



S-**22**

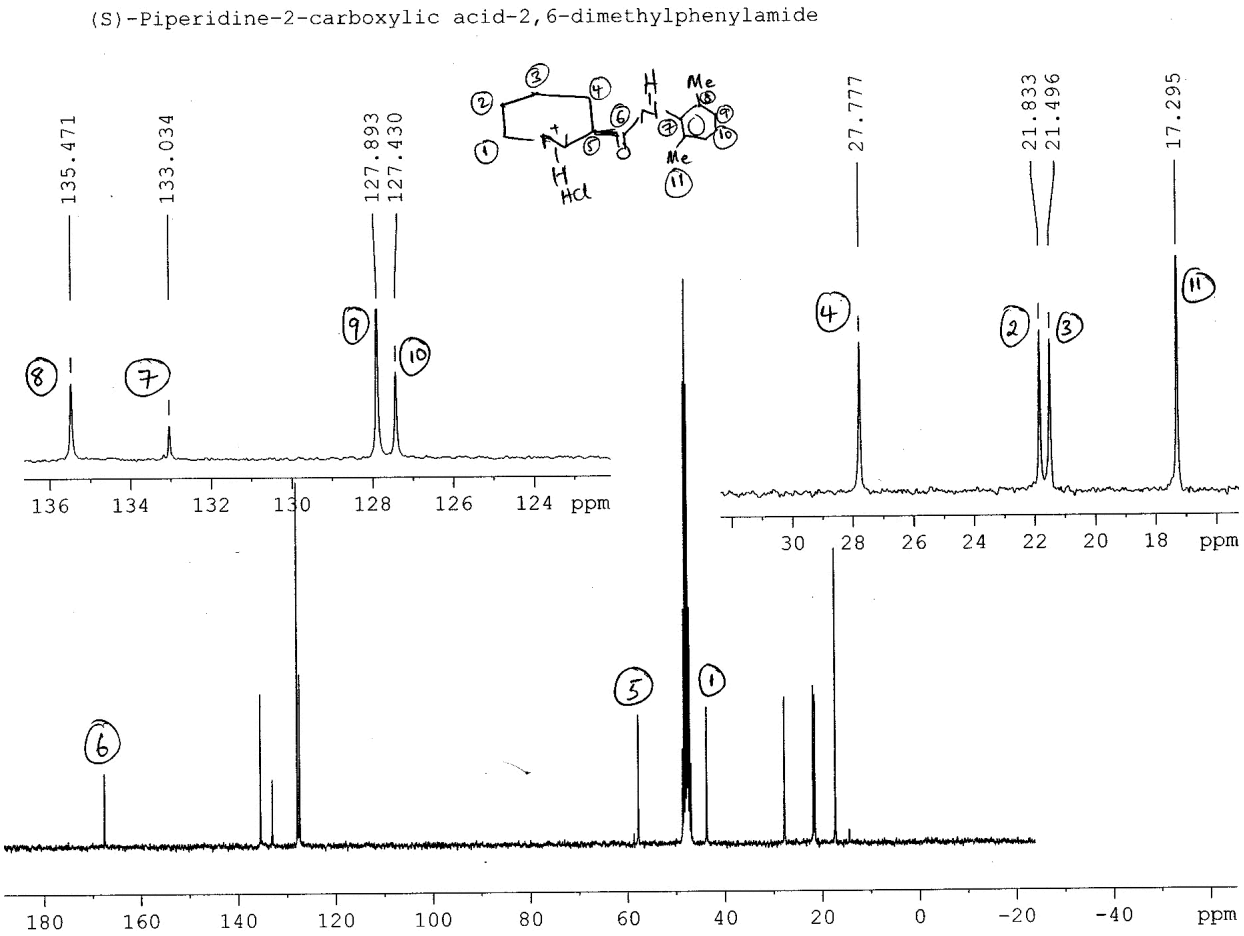
To *S*-**21** (200 mg, 0.6 mmol, 1.0 equiv) dissolved in freshly distilled CH_2Cl_2 (5.0 mL) was added dropwise CF_3CO_2H (1.0 mL) under argon at room temperature. The mixture was stirred for 10 h at this temperature and concentrated in vacuo to obtain the salt. Water (2 mL) was added and the mixture was basified to pH 10 – 12 with 40% $NaOH_{(aq)}$. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 5 mL). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure to give 139 mg of *S*-**22** as a white solid in 100% yield. $[\alpha]_D^{22}$ 33 (*c = 2*, HCl 1 M), mp 127–129 ºC. The literature values are as follows: *S* isomer $[\alpha]_D^{25}$ 35 (*c = 2*, HCl 1 M); *R* isomer $[\alpha]_D^{25}$ –46 (*c* = 2.3, HCl 2.3 M), mp 130 ºC).[18]

^{13}C NMR and GC-MS spectra for *S*-**22**



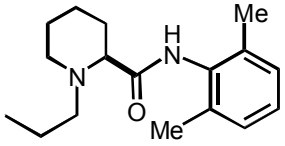
***S*-22**

a. ^{13}C NMR spectrum



Multiplet around 49 ppm is CD_3OD

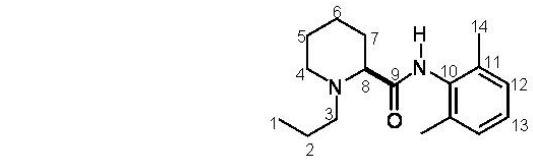
4.19.3 ***(S)-N*-propylpiperidine-2-carboxylic acid 2,6-dimethylphenyl amide: (*S*)-(-)-Ropivacaine**

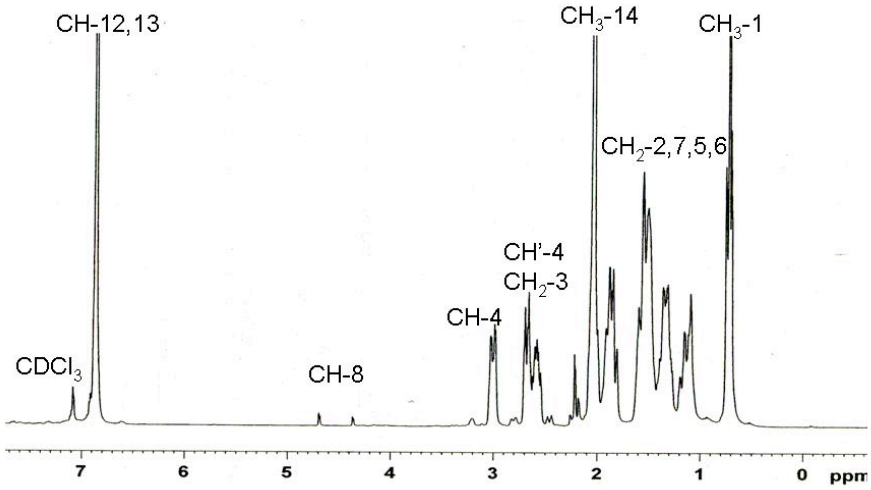


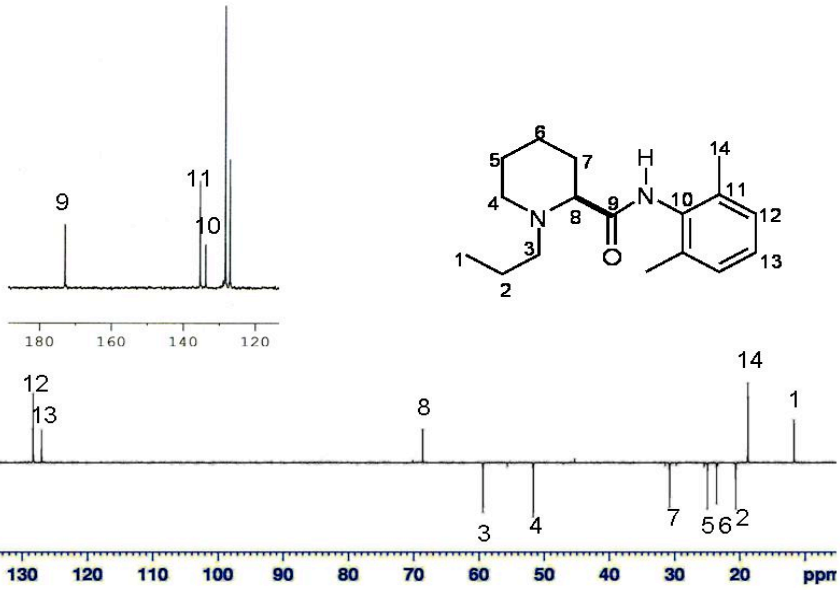
S-(-)-ropivacaine

1-Bromopropane (66 μL, 93 mg, 0.73 mmol, 3.0 equiv), K_2CO_3 (100 mg, 0.72 mmoL, 3.0 equiv) were added to a solution of *(S)*-**22** (55.7 mg, 0.24 mmoL, 1.0 equiv) in isopropyl alcohol (2 mL). Water (0.5 mL) was added and the mixture was stirred for 6 h at 100 ºC. The solvents were evaporated and the residue was treated with 2 mL of a toluene-water mixture (1:1 v/v) under gentle heating at 50 ºC. The layers were separated and the organic layer was washed with warm water at 40 ºC (2 x 2 mL). The organic layer was concentrated and stored in the refrigerator overnight. Vacuum filtration followed by washing of the crystals with cooled toluene and drying at 70 ºC afforded the crude product. Recrystallization of the crude product from toluene afforded 58.5 g of (*S*)-(**-**)-ropivacaine in 89% yield. $[\alpha]_D^{25}$ –80 (c = 2, MeOH), mp 145 – 147 ºC; lit. values are as follows: mp 144–146 ºC, $[\alpha]_D^{25}$ –82 (*c = 2*, MeOH).[18] ^{1}H NMR (300 MHz, $CDCl_3$), δ 0.95 (t, 3H), 1.68–2.10 (m, 7H), 2.19 (s, 6H), 2.40–2.46 (db, 1H), 3.10–3.19 (m, 3H), 3.70–3.75 (br d, 1H), 4.15–4.20 (br d, 1H), 4.78 (s, 3H), 7.17–7.28 (m, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$), δ 11.3 (CH_3), 17.9 (CH_2), 18.2 (2 × CH_3), 21.9 (CH_2), 23.3 (CH_2), 29.9 (CH_2), 53.1 (CH_2), 58.9 (CH_2), 66.8 (CH), 129.3 (2 × CH), 129.6 (CH), 132.8 (C), 137.0 (2 × C), 170.4 (C).

Spectral data for (*S*)-(**-**)-ropivacaine







4.20. Ligand Recovery Procedures

Some electrophiles, such as alkyl halides and isocyanates, react to consume the chiral ligand, while others do not (TMS-Cl, Bu_3SnCl, aldehydes and ketones). The following procedures may be used to recover the chiral ligand in either circumstance.

Procedure A: Recovery after reaction with electrophiles that do not consume the ligand

The resolved mixture of **2·8** was cooled to –78 °C and the electrophile was added The mixture was stirred for 2 – 4 h, prior to addition of MeOH (2 mL) and 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 Et_2O. The aqueous layer was then acidified to pH 3, washed with CH_2Cl_2 (2 x 10 mL), and basified to pH ~12 by dropwise addition of 50% KOH. The mixture was then extracted with CH_2Cl_2 (3 x 10 mL), dried over Na_2SO_4, and concentrated in vacuo to obtain a pale yellow oil. Kugelrohr distillation afforded the pure ligand.

Procedure B: Recovery using a sacrificial electrophile to protect the ligand during electrophilic quench.

The resolved mixture of **2·8** was cooled to –78 °C and Me_3SiCl (20 mol%) was added. After 5 min, the desired electrophile (e.g. PhNCO) was added and the mixture was stirred for 2 – 4 h, prior to addition of MeOH (2 mL). After warming to room temperature, 2 M HCl was added. The layers were separated and the aqueous layer was extracted with Et_2O (3 x 10 mL) The aqueous layer was further acidified to pH 3, washed with CH_2Cl_2 (2 x 10 mL), and basified to pH ~12 by dropwise addition of 50% KOH. The mixture was then extracted with CH_2Cl_2 (3 x 10 mL), dried over Na_2SO_4, concentrated in vacuo to obtain a pale yellow oil, which was Kugelrohr distilled to afford the pure ligand. The specific rotation was checked to ensure that there was no loss of optical purity.

4.20. References

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PhNCO quench 13

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Allylation 14

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Benzylation 15

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Cyclohexanone 16

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Benzaldehyde 17

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1-Naphthaldehyde 18

(13) None

Acetaldehyde 19

(14) None

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