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Dynamics and Catalytic Resolution of Selected Chiral Organolithiums

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DYNAMICS AND CATALYTIC RESOLUTION OF SELECTED CHIRAL ORGANOLITHIUMS

DYNAMICS AND CATALYTIC RESOLUTION OF SELECTED CHIRAL ORGANOLITHIUMS

A dissertation submitted in partial fulfillment
of the requirements for the degree of Doctor
of Philosophy in Chemistry

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ABSTRACT

One of the most important developments of the last decade has been the emergence of new methods to dynamically resolve racemic organolithiums using stoichiometric amounts of the chiral ligand. When this concept is implemented successfully, it obviates the need for covalently attached chiral auxiliary based methods, asymmetric deprotonation, and asymmetric synthesis of a precursor stannane as ways to access enantioenriched organolithium compounds for use in asymmetric synthesis. Since certain electrophiles consume the chiral ligand, it is desirable to render this process catalytic in the chiral ligand.

As part of a larger study on the amenability of chiral organolithiums to a catalytic dynamic resolution, N-trimethylallyl-2-lithiopyrrolidine, N-Boc-2-lithiopiperidine, and the ethylene ketal of N-Boc-2-lithio-4-oxopiperidine were selected. The barriers to racemization and dynamic thermodynamic resolution (DTR) of these compounds were measured in the presence of various diamine ligands. Using the thermodynamic parameters to guide us, the catalytic dynamic resolution (CDR) was then investigated on both heterocycles at temperatures where racemization is much slower than resolution. Enantiomer ratios as high as 93:7 and 99:1 were achieved for N-trimethylallyl-2-lithiopyrrolidine and N-Boc-2-lithiopiperidine respectively.

The CDR of N-Boc-2-lithiopiperidine using our newly discovered ligands was applied to the highly enantioselective synthesis of several piperidine alkaloids and medicinal compounds such as conhydrine, anabasine, ropivacaine, coniine, pipecolic acid, pelletierine, epipinidinone, lupetidine, and epidihydropinidine.

This dissertation is approved for
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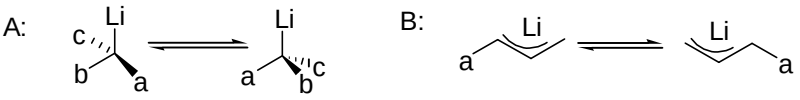
CHAPTER 1

INTRODUCTION

Organolithiums are arguably the most widely used organometallics in synthetic organic chemistry.[1] Their general usefulness derives from their versatility in mode of reactivity and diversity. There is a significant and growing interest in chiral organolithium species having an sp^3-hybridized carbanion center. It is not surprising that such interest coincides with the emergence of new methods to dynamically resolve chiral racemic organolithiums. The chirality element in organolithium compounds can be a stereogenic carbon bearing a lithium or η-allyl anion (Figure 1.1A & B). Because of the largely ionic character of the carbon-lithium bond of all organolithiums, it is best described as a close association rather than a covalent bond. Organolithium species that are substituted on the carbanion by a heteroatom such as nitrogen or oxygen are often referred to as functionalized organolithiums. The heteroatom may or may not be coordinated to the lithium. The solvents coordinated to the lithium can influence reactivity in a variety of ways. Therefore, in understanding the reactivity of organolithium compounds, it is important to understand not only the reactivity of the carbanionic species but also the effects of solvents and/or ligands coordinated to the lithium. One is therefore faced with a multitude of tasks that need investigating in order for organolithiums to be effectively utilized in asymmetric synthesis. These include, but are not limited to:

a) Stereoselective generation of the organolithium
b) Configurational stability of the organolithium
c) The barriers to inversion of the organolithium: racemization vs resolution
d) The predominant solution structure and reactive aggregation state of the organolithium
e) Subsequent electrophilic substitutions: invertive vs retentive.

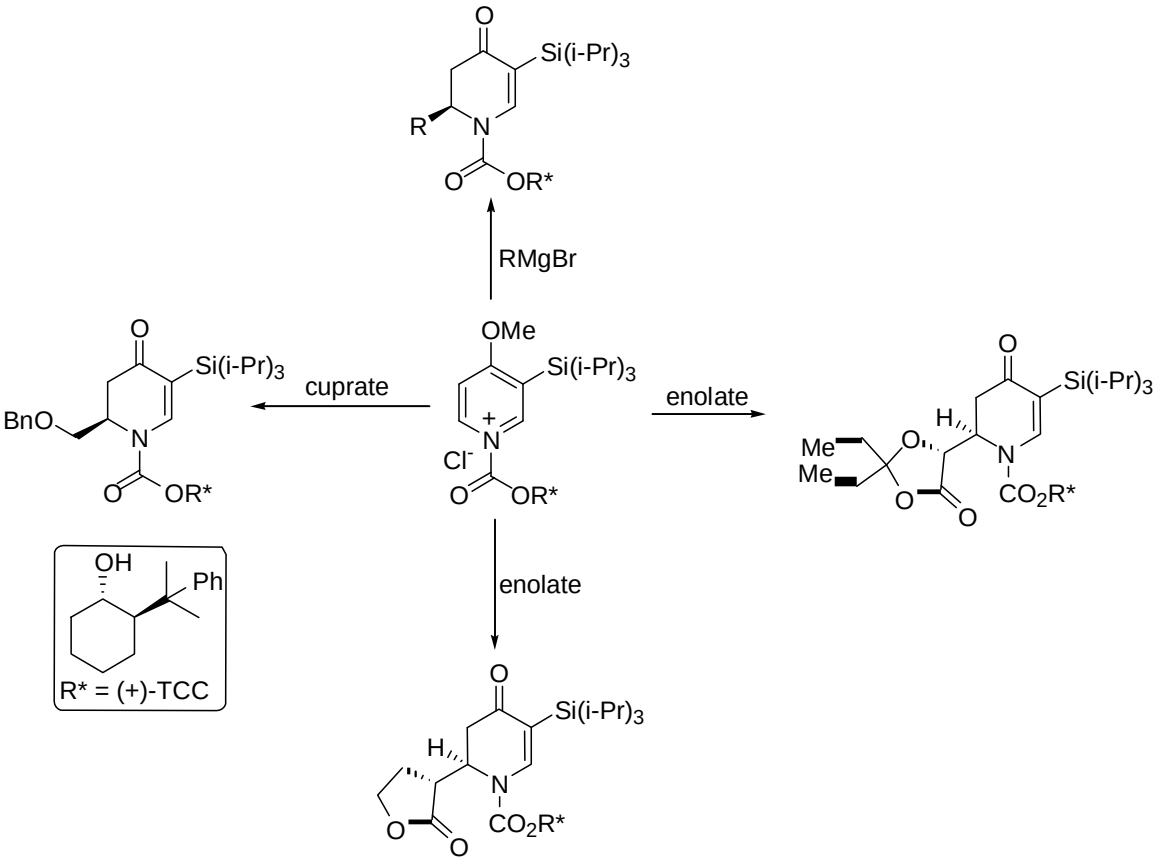
Figure 1.1. Chirality elements



1.1. Nucleophilic Methods for the Generation of Chiral Substituted Nitrogen Hetereocycles

A number of nucleophilic and electrophilic methods have been applied to induce asymmetry on nitrogen heterocycles. One of the nucleophilic methods involves addition of a nucleophile to an N-alkylpyridinium[2] or N-acylpyridinium[3-6] salt (Scheme 1.1).

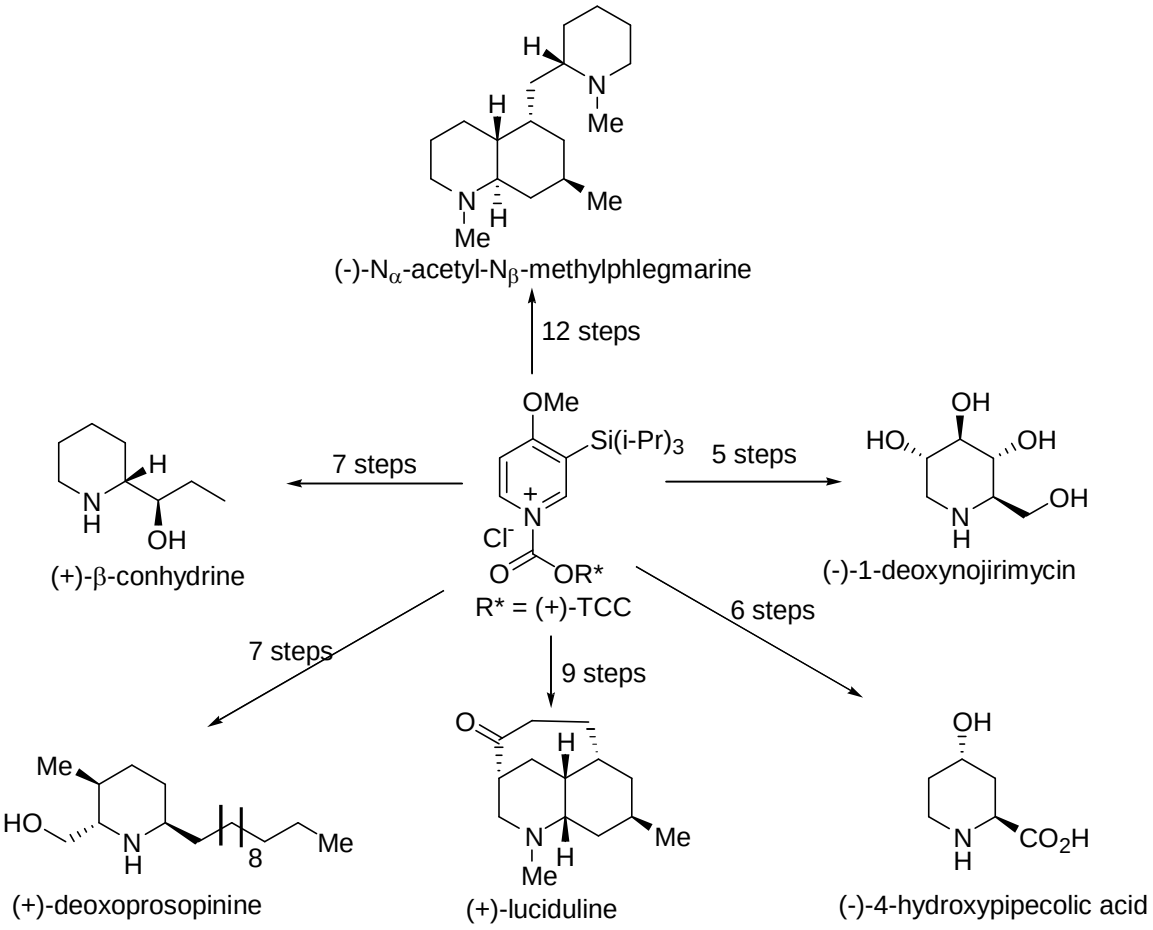
Scheme 1.1. Synthetic routes for the preparation of chiral 2,3-dihydropyridones.[4, 7-10]



The synthetic utility of 2,3-dihydropyridones has been demonstrated by Comins and other researchers.[8, 9, 11, 12] This versatile building block can undergo a variety of reactions including electrophilic substitution, 1,2- or 1,4-addition, enolate alkylation, and photochemically induced

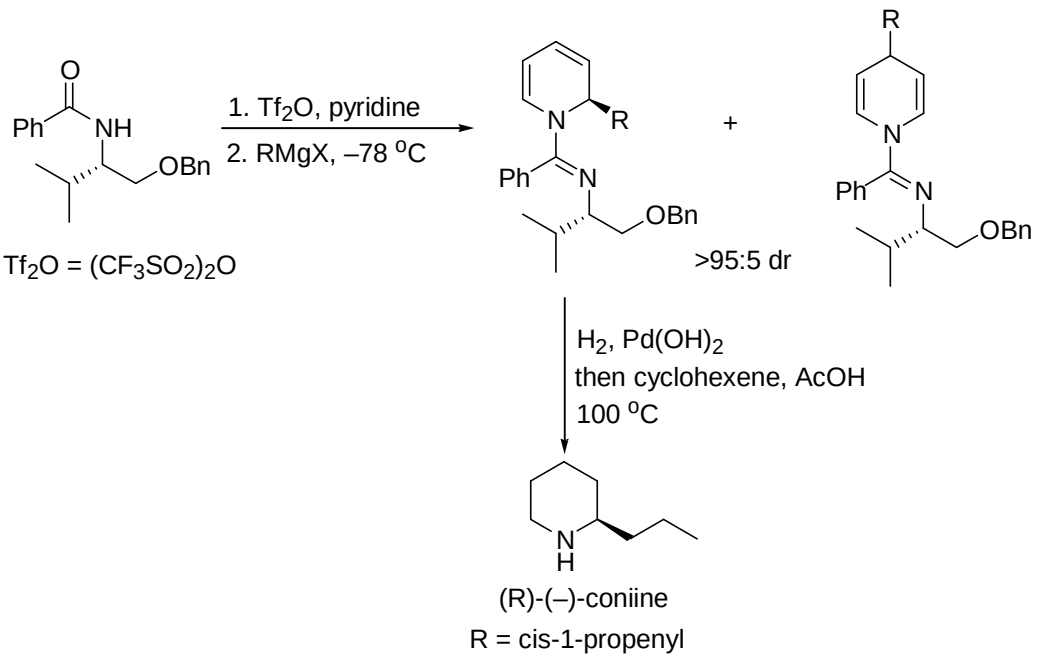
[2+2] cycloaddition reactions. Several piperidine alkaloids and natural products have been synthesized using 2,3-dihydropyridone as the key intermediate (Scheme 1.2).[4, 7-12]

Scheme 1.2. Synthetic utility of 2,3-dihydropyridones



In another nucleophilic approach, Charette et al utilized unsubstituted N-acylpyridinium salts to prepare 2-substituted dihydropyridines with high regio- and stereoselectivies. They noted that the approach relied on the stereoselective formation of the (E)-isomer of the N-pyridinium imidate. The authors further showed that the imidate lone pair effectively directs nucleophilic attack at C-2, and used this notion to synthesize (R)-(–)-coniine and other enantioenriched 2-substituted piperidines (Scheme 1.3).[13]

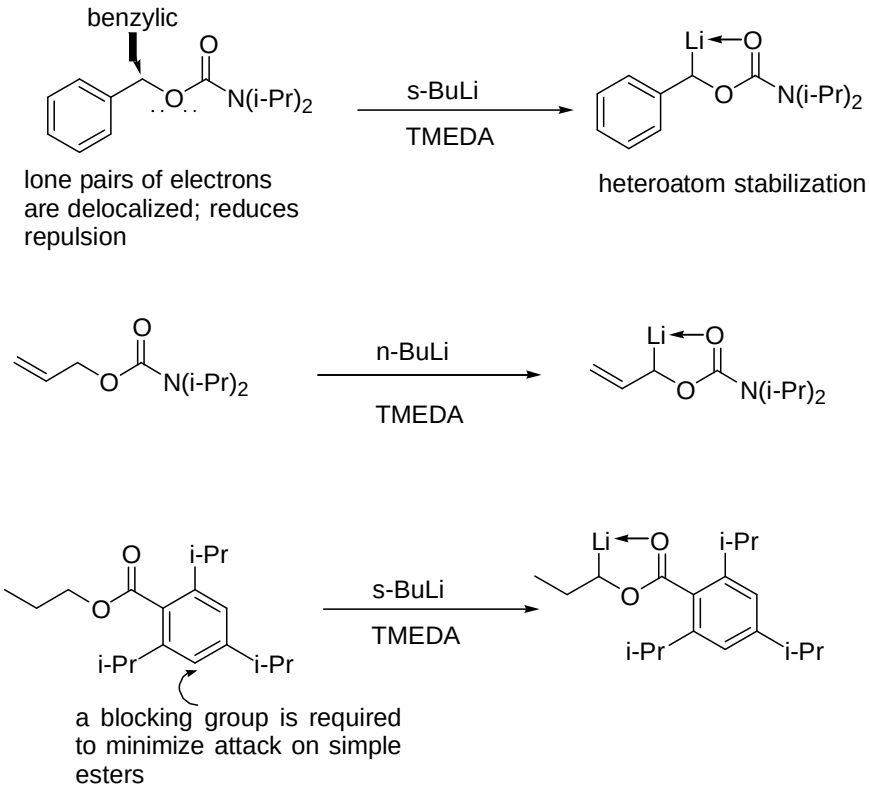
Scheme 1.3. Preparation of 2-substituted dihydropyridines and their application to the synthesis of enantioenriched 2-substituted piperidines.[13]



1.2. Electrophilic Methods for Inducing Asymmetry in Organolithium Compounds

There are two methods by which asymmetric induction can be promoted in organolithum chemistry. One approach is to prepare the organolithium species in enantioenriched form either by an asymmetric deprotonation or by a stereospecific transmetalation via tin-lithium exchange, under conditions that maintain the configurational stability of the organolithium species. The second approach is by an asymmetric substitution (dynamic resolution). Generally, deprotonations a to oxygen are unfavorable. The anti-bonding interaction of the lone pairs on oxygen with the carbon-lithium bonds overcomes the electron withdrawing effect of oxygen. In allylic and benzylic systems, the lone pairs on oxygen can be involved in delocalization thereby reducing repulsion (Scheme 1.4).

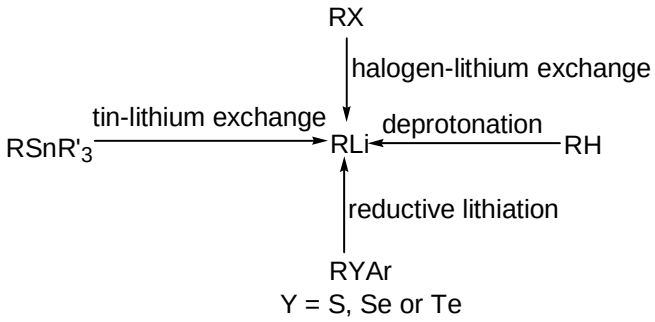
Scheme 1.4. Deprotonation using organolithium bases.[14]



A lithiation by deprotonation a to nitrogen is even less favorable than that a to oxygen. The anti-bonding interaction is much worse, such that delocalization becomes absolutely necessary. Therefore, in order for deprotonation to be useful, the conjugate acid has to be activated in some way that helps lower the kinetic barrier to deprotonation. In fact, significant advances in the use of chiral organolithium species were made with the discovery that certain dipole-stabilized a-alkoxy- and a-amino- organolithium species could be generated enantioselectively by asymmetric deprotonation with sec-butyllithium and (–)-sparteine as the chiral ligand.[15] These organolithium species are generally configurationally stable at low temperature. Stereoselective electrophilic quench of the chiral organolithium species then provides the enantioenriched product. Enantioselective deprotonations using chiral amines and lithium bases such as n-BuLi, s-BuLi, t-BuLi or chiral lithium amide bases are widely applicable in systems where the

Complex-Induced Proximity Effect (CIPE) provides a pathway for the lowering of the barrier to deprotonation.[16] Therefore enantioselective deprotonations are commonly observed in substrates with dipole stabilizing groups such as amides, carbamates, nitrosoamines, urethanes, oxazolines and formamidines. In the case of amides and carbamates, the equatorial hydrogen is preferably abstracted by the base as a result of the stabilization arising from the chelation of the lithium to the carbonyl oxygen as well as the HOMO-HOMO stereoelectronic repulsion in the axial anion. In addition to deprotonation and tin-lithium exchange, several other strategies have been employed to generate an organolithium (Figure 1.2). These include reductive lithiation[17-20] (reduction of halides, sulfides, selenides and tellurides) and reductive cyanation (in the case of a-amino tertiary organolithiums).[21]

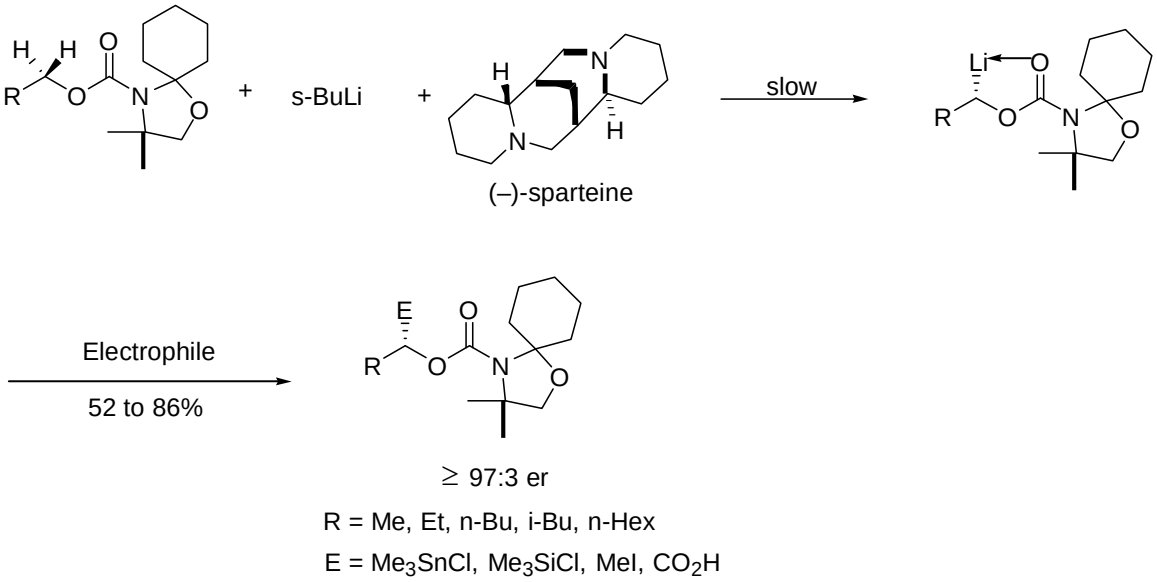
Figure 1.2. Possible strategies for generating organolithium compounds.[1, 21-24]



1.2.1. Asymmetric Deprotonation

In 1990, using hindered carbamates, Hoppe reported some examples of enantioselective deprotonations a to oxygen.

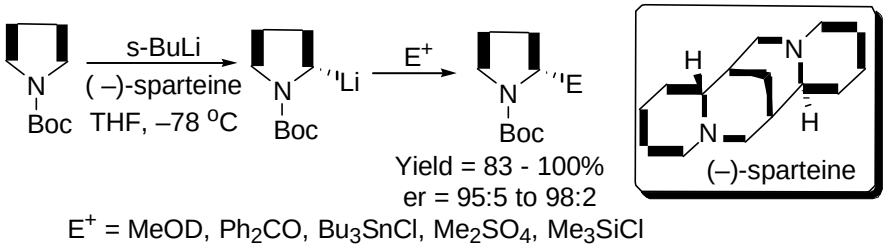
Scheme 1.5. Hoppe's enantioselective deprotonation of carbamates.[25]



Electrophilic quench of the resulting enantioenriched organolithium with Me_3SnCl, Me_3SiCl, MeI and CO_2 afforded products with ?_97:3 er (Scheme 1.5).[25] His findings marked the beginning of real progress in the field of asymmetric deprotonation.

In 1991, using an a-amino substrate, Beak showed that N-Boc-pyrrolidine can be deprotonated enantioselectively using the sec-butyllithium/(–)-sparteine complex.[15] The derived organolithium was also shown to react efficiently with a few electrophiles (Scheme 1.6).[15, 26, 27]

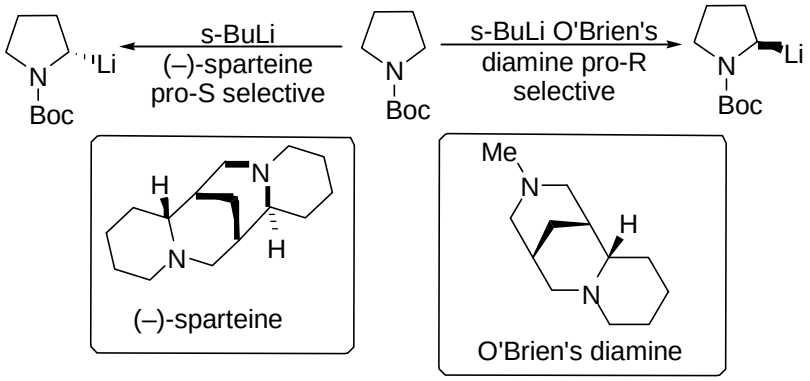
Scheme 1.6. Asymmetric deprotonation and electrophilic substitution of N-Boc-pyrrolidine.[15, 26, 27]



Two main limitations of Beak's asymmetric deprotonation methodology are (i) the organolithium does not react efficiently with some electrophiles, particularly alkyl halide electrophiles[1, 28, 29] and (ii) the method fails with N-Boc-piperidine.[30, 31] Since (–)-sparteine gives

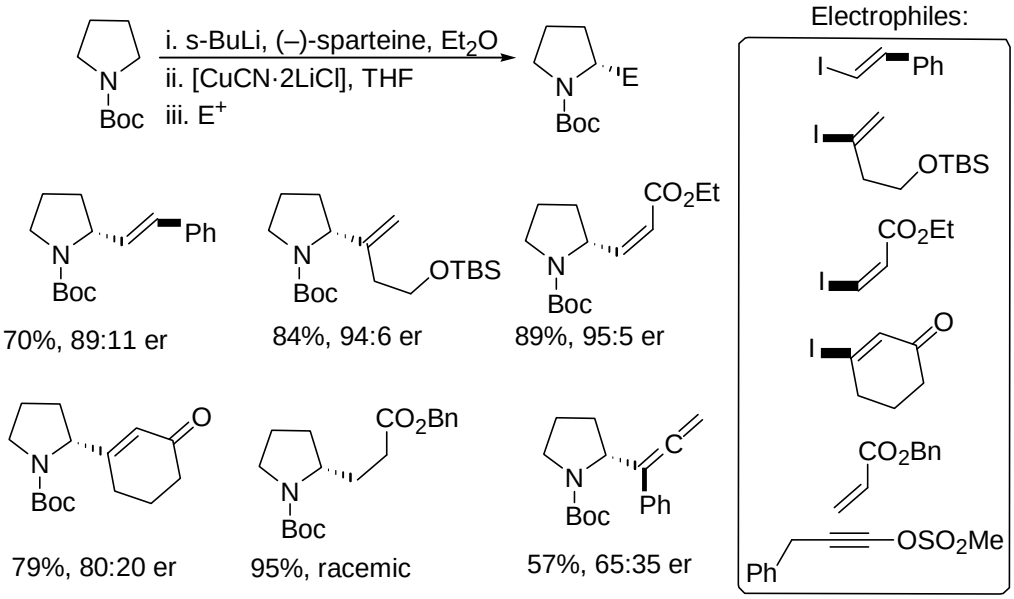
the S-organolithium, O'Brien synthesized the complementary (+)-sparteine surrogate and showed that it is pro-R selective.[32]

Scheme 1.7. Asymmetric deprotonation using s-BuLi and (–)-sparteine or O'Brien's diamine.[32]



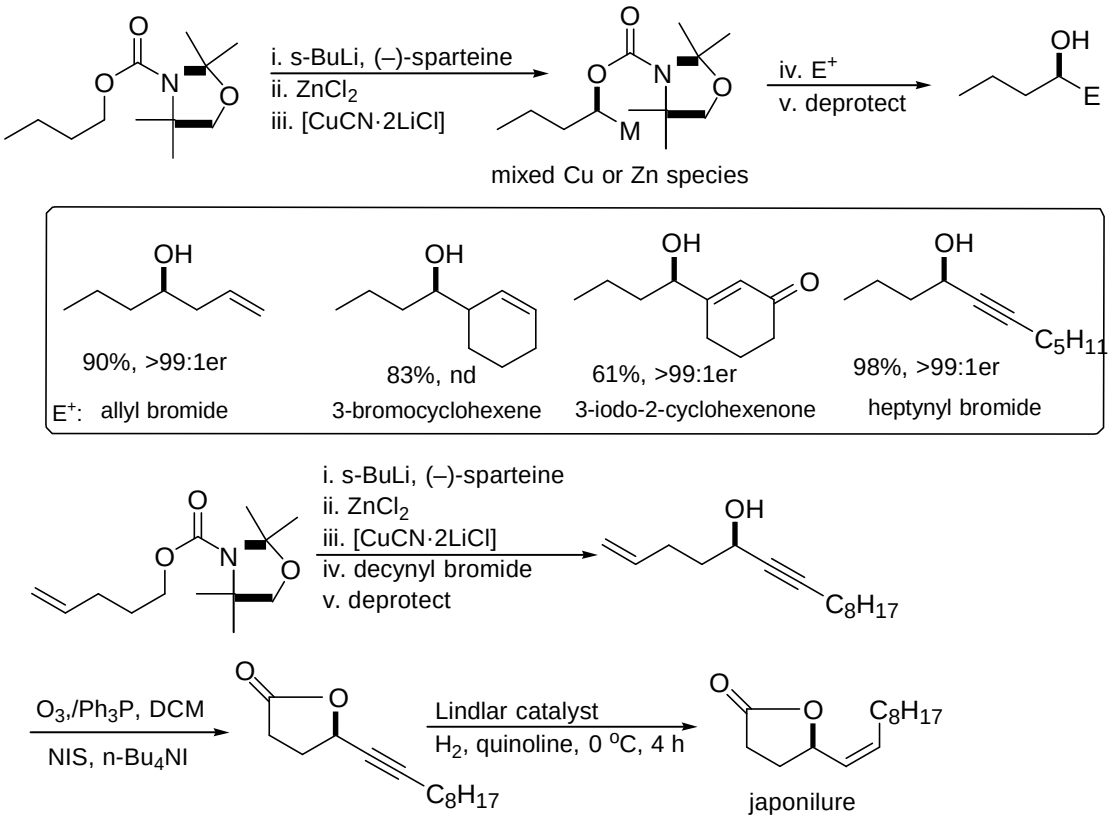
Dieter and coworkers showed that transmetalation from lithium to copper greatly extends the scope of electrophiles in the asymmetric lithiation of N-Boc-pyrrolidine. They were able to achieve enantioselective vinylation of N-Boc-pyrrolidine but there was some noticeable loss of er during some of the transmetalations (Scheme 1.8).[33]

Scheme 1.8. Dieter's conditions for copper-mediated enantioselective vinylation of N-Boc-pyrrolidine.[33]



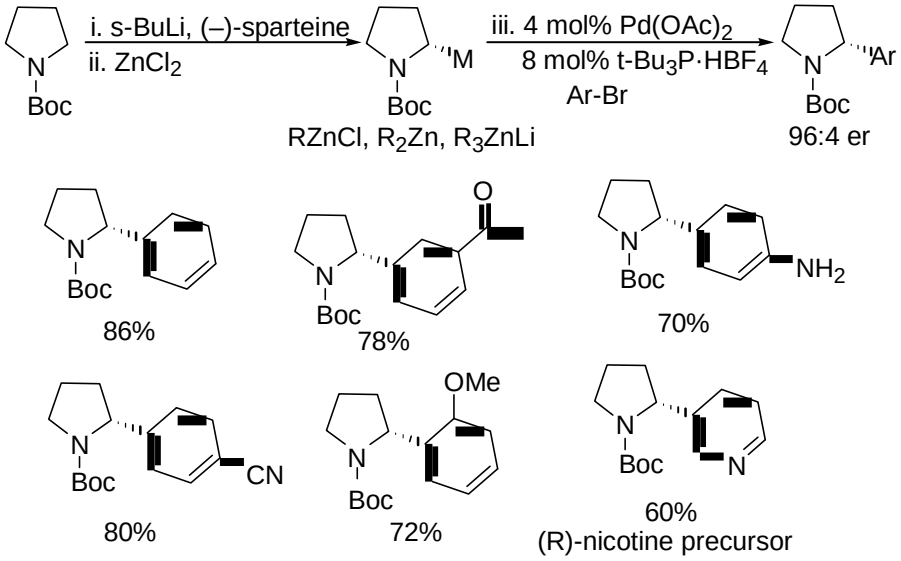
In 2002, Taylor et al utilized the lithiation-transmetalation methodology to synthesize allyl alcohols using a carbamate. Unlike with N-Boc-pyrrolidine, direct transmetalation from lithium to copper was unsuccessful. As such the authors transmetalated from lithium to zinc, then to copper prior to introducing the electrophile. Their approach was exemplified through the synthesis of the industrially important pheromone, japonilure (Scheme 1.9).[34]

Scheme 1.9. Taylor's conditions for enantioselective allylation, vinylation and alkynylation of a carbamate.[34]



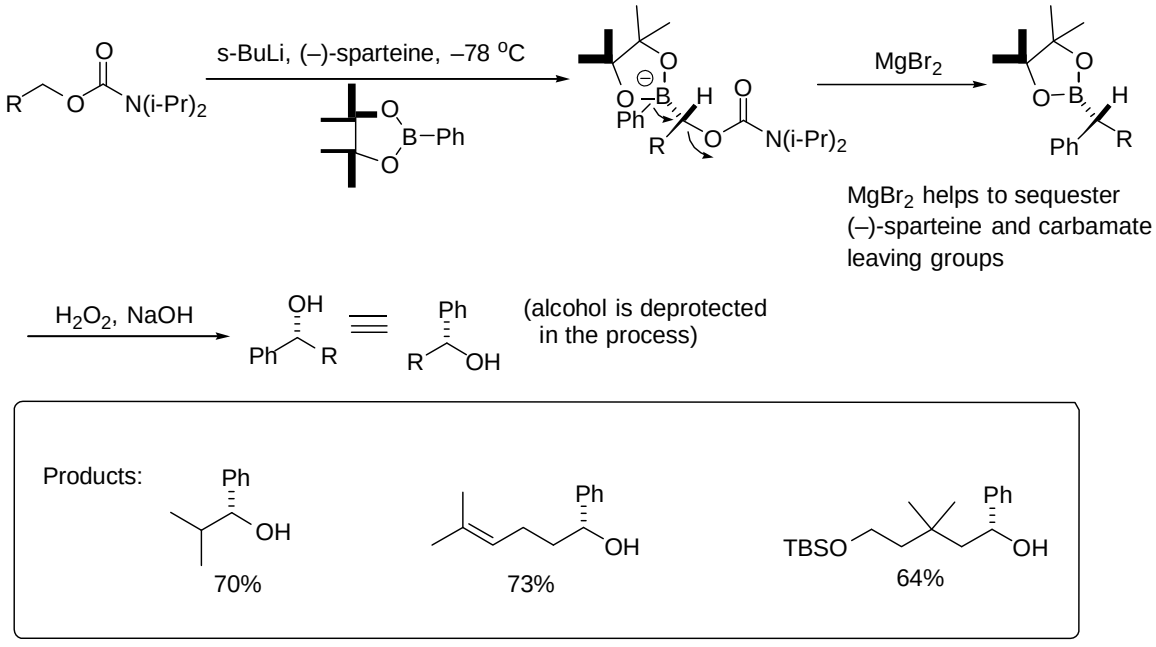
Neither Dieter nor Taylor's copper-mediated protocols were successful when applied to the enantioselective synthesis of 2-aryl-pyrrolidines. However, in 2006, Campos et al accomplished the direct enantioselective synthesis of 2-aryl-pyrrolidines by transmetalation of the enantioenriched N-Boc-2-lithiopyrrolidine to an organozinc species prior to entering into a palladium-catalyzed Negishi coupling with an aryl bromide (Scheme 1.10).[35]

Scheme 1.10. Campos' conditions for enantioselective arylation of N-Boc-pyrrolidine.[35]



In 2007, a lithiation-transmetalation followed by a 1,2-metalate rearrangement was reported starting from a carbamate (Scheme 1.11).[36]

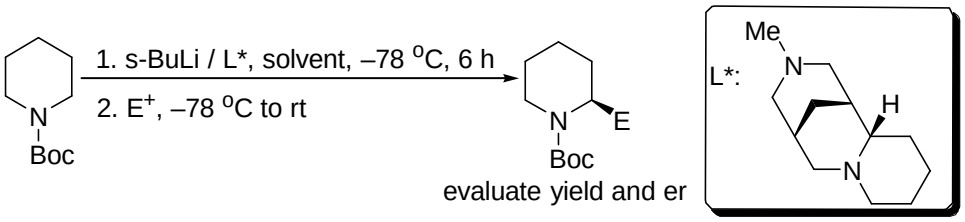
Scheme 1.11. Asymmetric lithiation, transmetalation and 1,2-metalate rearrangement.[36]



Very recently, O'Brien reported a successful asymmetric deprotonation of N-Boc-piperidine using s-BuLi and his chiral diamine (Scheme 1.12), achieving enantiomer ratios as

high as 88:12 in favor of the R-organolithium.[37] He also used the copper and palladium-catalyzed couplings to synthesize allylated and arylated piperidines respectively.[37]

Scheme 1.12. Asymmetric lithiation of N-Boc-piperidine using s-BuLi and O'Brien's chiral diamine ligand.[37]



Entry	Solvent	Electrophile	Yield (%)	er (S:R)
1[a]	Et_2O	Me_3SiCl	73	14:86
2[a]	Et_2O	Bu_3SnCl	82	12:88
3[a]	Et_2O	CO_2	92	88:12
4[a]	Et_2O	MeOCOCl	78	88:12
5[a]	MTBE	MeOCOCl	68	88:12
6[a]	Et_2O	$PhMe_2SiCl$	85	27:73
7[a]	Et_2O	MeI	45	64:36
8[a]	Et_2O	Me_2SO_4	45	60:40
9[b]	Et_2O	CH_2=$CHCH_2Br$	75	75:25
10[c]	Et_2O	3,4-$(OMe)_2$-C_6H_3-Br	33	82:18

[a] Reaction conditions: (i) 1.3 equiv of s-BuLi/L*, Et_2O or TBME, –78 °C, 6 h; (ii) E^+, –78 °C to rt, 16 h. [b] Reaction conditions: (i) 1.3 equiv of s-BuLi/L*, Et_2O, –78 °C, 6 h; (ii) CuCN 2LiCl, THF, –78 °C, 40 min; (iii) allyl-Br, -78 °C to rt, 16 h. [c] Reaction conditions (Negishi): (i) 1.3 equiv of s-BuLi/L*, Et_2O, –78 °C, 6 h; (ii) $ZnCl_2$, –78 °C, 30 min; (iii) –78 °C to rt, 35 min; (iv) 3,4-$(MeO)_2C_6H_3Br$, t-Bu_3PHBF_4, $Pd(OAc)_2$, rt, 16 h.

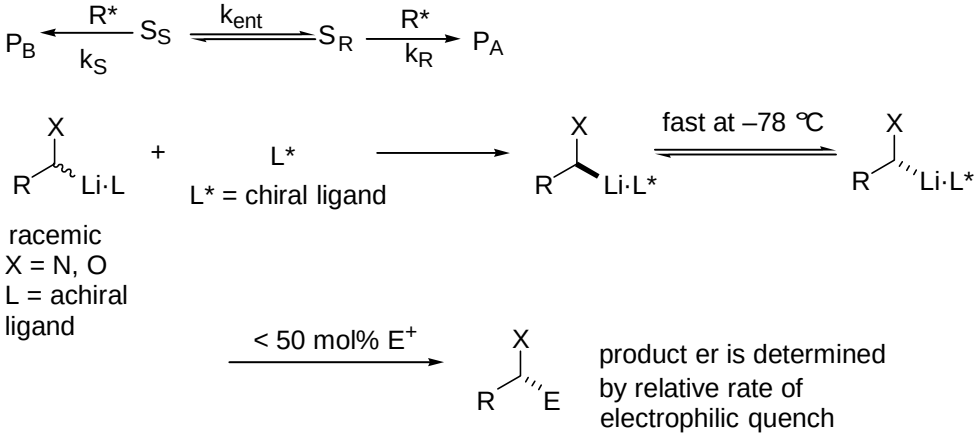
1.2.2. Asymmetric Substitution

An alternative approach to induce asymmetry in organolithium compounds is to use asymmetric substitution. An example of an asymmetric substitution is dynamic resolution.[38] In this scheme, a racemic organolithium is generated and a chiral ligand is added which resolves the organolithium dynamically. Subsequent quenching with the electrophile leads to formation of an enantioenriched product. It is necessary that the organolithium be configurationally labile at the equilibration temperature. The resolution can either be a dynamic kinetic, dynamic thermodynamic or a crystallization-induced resolution.

Dynamic Kinetic Resolution (DKR)

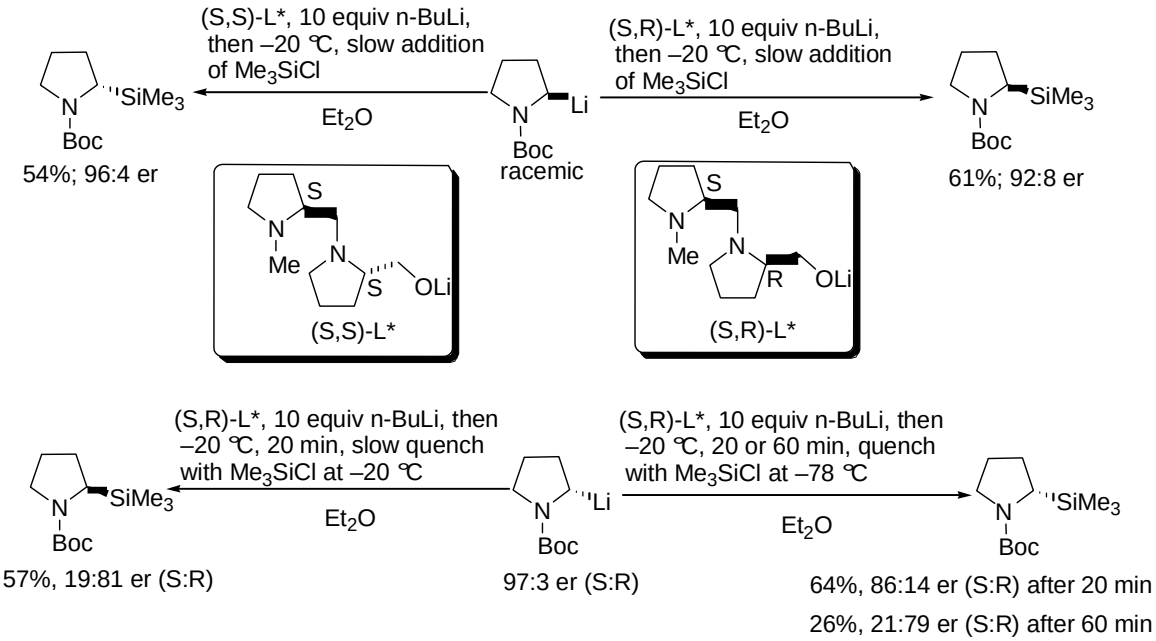
Dynamic kinetic resolution occurs when substrates, S, that are enantiomeric by definition interconvert with rate constant k_{ent}. The substrates are then allowed to react with a chiral reagent, R*, with rate constants k_R and k_S, for the R and S enantiomers, respectively, to give products P_A and P_B. The R-enantiomer is chosen as the faster reacting enantiomer for convenience (Scheme 1.13). If $k_{ent} >> k_R$, k_S, the product ratio P_A/P_B depends on the difference in transition state energies in accordance with the Curtin-Hammett principle.

Scheme 1.13. Dynamic Kinetic Resolution (DKR)



When k_{ent}, k_R and k_S are comparable, the product ratio is a function of relative rates as well as percent conversion to products. An example of a dynamic kinetic resolution of N-Boc-2-lithiopyrrolidine using diastereomeric, monolithiated diaminoalkoxide ligands, (S,S)-L* and (S,R)-L* was reported by Coldham.[39] Treatment of the racemic organolithium with (S,S)-L* at –20 °C for 20 min, followed by cooling to –78 °C and quenching with excess Me_3SiCl afforded the silane in 58:42 (R:S), indicating that the R·L* diastereomeric complex is slightly more stable than S·L*. However, quenching with a substoichiometric amount of the electrophile (0.4 equiv of Me_3SiCl) afforded the product in 81:19 er (S:R), suggesting that the S·L* complex is more reactive than the R·L* diastereomeric complex. High enantiomer ratios were also obtained when Me_3SiCl was added slowly at –20 °C in the presence of excess n-BuLi (Scheme 1.14), reflecting the improved relative rate of reaction between the diastereomeric complexes under the reaction conditions. With the diastereomeric ligand (S,R)-L*, the silane was obtained in 92:8 er (R:S). The authors treated the S-organolithium containing er 97:3 with (S,R)-L* for just 20 min at –20 °C before quenching slowly over 30 min at –20 °C with Me_3SiCl. Under these conditions, the silane was obtained in 81:19 er (R:S). Despite the fact that only 3% of the R-enantiomer of the organolithium was present at the start of the reaction, the high reactivity of the R·L* complex under these conditions led predominantly to the R-enantiomer of the product. The authors therefore concluded that the enhanced enantioselectivity arose from a dynamic kinetic resolution.

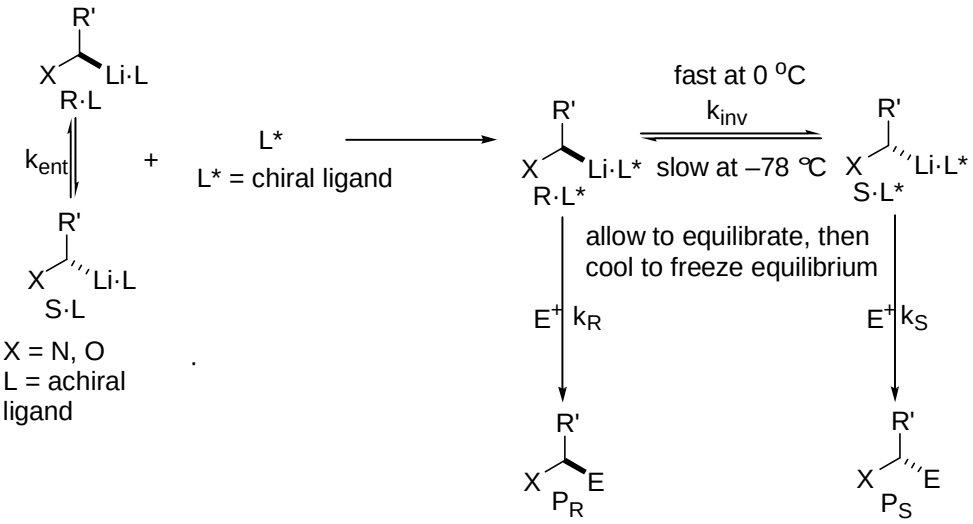
Scheme 1.14. Dynamic kinetic resolution of N-Boc-2-lithiopyrrolidine.[39]



Dynamic Thermodynamic Resolution (DTR)

Dynamic thermodynamic resolution (DTR) applies when the enantiomeric substrates, S·L and R·L (L is an achiral ligand) react with a chiral ligand, L* to afford a thermodynamic mixture of two diastereomers, S·L* and R·L* (Scheme 1.15).

Scheme 1.15. Dynamic Thermodynamic Resolution (DTR)

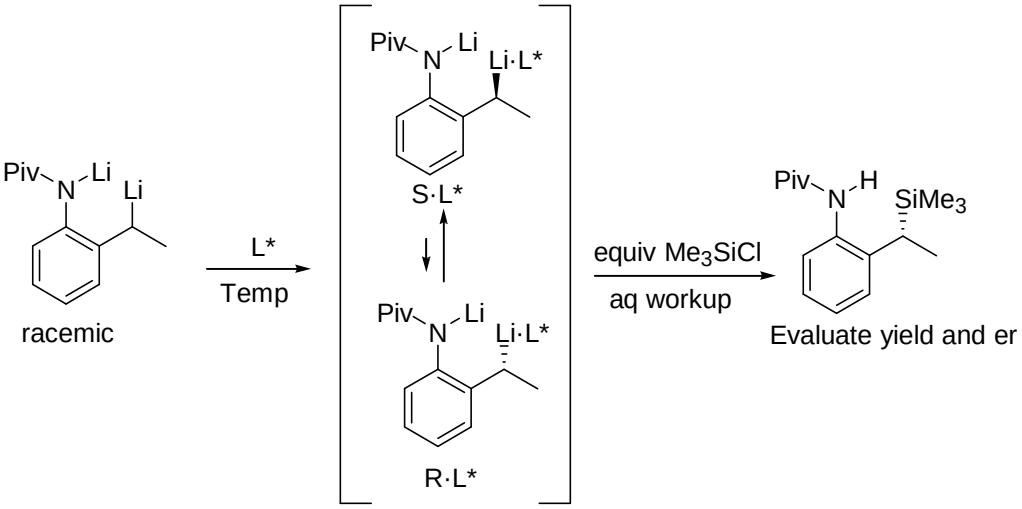


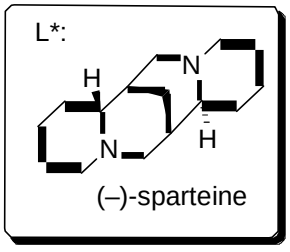
The diastereomers, R·L* and S·L* interconvert either by direct epimerization with rate constant k_{inv} or by dissociation of L* followed by enantiomerization with rate constant k_{ent}. The rates of product formation k_R, k_S are typically faster than the rate of interconversion of the equilibrating species, k_{inv} (i.e. k_R, $k_S > k_{inv}$). However, the relative rates, k_{inv}, k_{ent}, k_R, k_S, and the percent conversion to products might all influence the product ratio. If the diastereomeric complexes are trapped by an electrophile, E^+ and complete conversion to products P_R, P_S is attained, then the product ratio reflects the thermodynamic ratio of the two diastereomeric complexes, R·L* and S·L*. The rate of product formation depends on k_R[R·L*] and k_S[S·L*] respectively, not just k_R/k_S. The major product in a DTR depends on the magnitude of each of these terms.

A major advantage of DTR is that equilibration and resolution can be achieved in separate controllable steps. Using N-pivalolyl-o-ethylaniline, Beak and coworkers illustrated an example of an asymmetric lithiation-substitution (Scheme 1.16). After generating the racemic organolithium, addition of the chiral ligand, (–)-sparteine (L*) and equilibration at a certain temperature was followed by electrophilic quench with Me_3SiCl. The authors observed that the extent of enantioenrichment of the silane was dependent on reaction conditions. As shown in Scheme 1.16, when the initial reaction was kept at –78 °C, a low yield of nearly racemic silane was obtained. However, when the equilibration was carried out at –25 °C in the presence of (–)-sparteine and the solution was rapidly cooled to –78 °C prior to addition of the electrophile, the silane was obtained in high yield and in 90:10 er (R:S). Note that due to changes in CIP priority, S·L* affords the R-enantiomer of the silane. When the initial temperature was kept at –78 °C and quenched with a substoichiometric amount of the electrophile (0.1 equiv Me_3SiCl), the silane was obtained in 91:9 er (R:S). Finally, combining a cycling sequence of the warm/cool protocol with nine sequential additions of 0.1 equivalents of Me_3SiCl, afforded nearly

enantiopure R-silane (99:1 er) and in good yield.[40-42] The authors remarked that the above results are inconsistent with a dynamic kinetic resolution.

Scheme 1.16. Lithiation-substitution of N-pivalolyl-o-ethylaniline using s-BuLi/(–)-sparteine.[40-42]



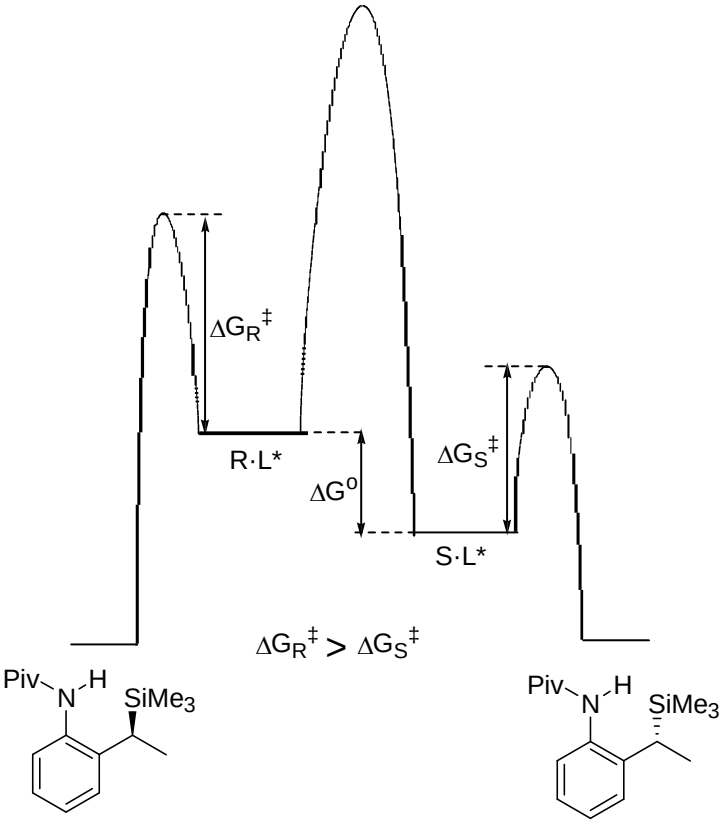


T (^{o}C)	equiv Me_3SiCl	% Yield	er (R:S)
–78	1	52	56:44
–25, –78	1	72	90:10
–78	0.1	nd	91:9
–25, –78	0.1*	70	99:1

* cycle repeated nine times

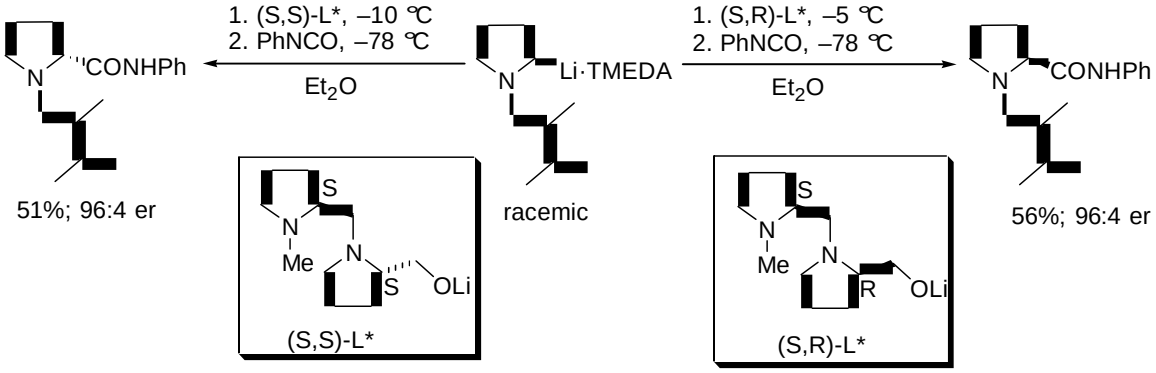
A reaction profile which provides an understanding of the observations made by the authors is a dynamic thermodynamic resolution as described in Figure 1.3.

Figure 1.3. Energy profile for lithiation-substitution of N-pivalolyl-o-ethylaniline via dynamic thermodynamic resolution.[40-42]



Coldham et al reported the dynamic resolution of an unstabilized a-aminoorganolithium using diastereomeric ligands to produce enantiomeric products (Scheme 1.17).[39] Tin lithium exchange in the presence of TMEDA afforded the racemic organolithium. After the addition of the chiral ligand, the mixture was warmed to –10 or –5 °C for 90 min, and rapidly cooled to –78 °C in order to freeze the equilibrium. Subsequent quenching with phenyl isocyanate afforded the anilide in 96:4 er. By using an enantioenriched organolithium, the authors showed that the electrophilic quench proceeds with retention of configuration at the metal bearing center.

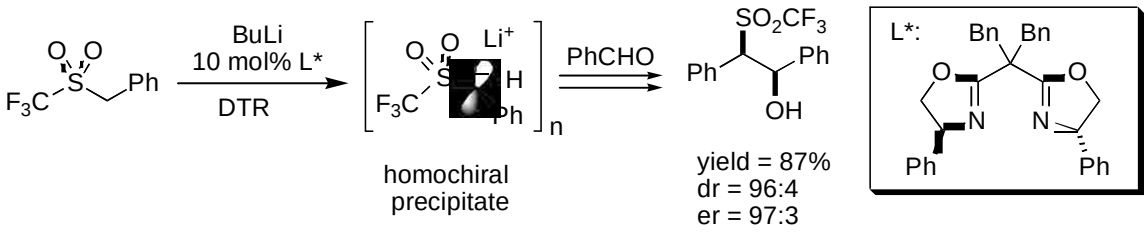
Scheme 1.17. DTR of N-trimethylallyl-2-lithiopyrrolidine using diastereomeric ligands.[39]



Crystallization-Induced Dynamic Resolution (CIDR)

It is possible to generate enantioenriched crystals when diastereomeric organolithium complexes interconvert on the timescale of the crystallization. The two requirements for this to be observed are (i) the ability for the organolithium to crystallize and (ii) preferential crystallization of a homochiral aggregate. It is also critical for the diastereoselective reaction leading to enantioenriched product to occur before loss of configuration. Optimization of a CIDR usually hinges on careful control of temperature, solvent, chiral ligand, and concentration. Hoppe and Boche[43, 44], Strohmann[45, 46], Livinghouse[47], and Evans[48] have all reported examples of CIDR's. In addition to the cited references, a review of CIDR was recently published.[49] With an example of a dynamic thermodynamic resolution using a substoichiometric amount of the chiral ligand, Toru and coworkers reported the dynamic thermodynamic resolution of planar-chiral organolithium enantiomers by a bisoxazoline ligand, (Scheme 1.18) followed by precipitation of homochiral aggregates (an asymmetric transformation of the second kind). When the aldehyde was added, the precipitate dissolved. After quenching with Me_3SiCl, the product was isolated in good yield, excellent diastereoselectivity and enantioselectivity. The authors noted that CIDR was operative.[50]

Scheme 1.18. Toru's CIDR using a substoichiometric amount of the chiral ligand.[50]



1.3. Racemization and Configurational Stability

A successful approach to promoting asymmetric induction with chiral organolithium species requires an understanding of the kinetics of enantiomerization and how these rates compare with the rate of electrophilic quench. Racemization is generally thought of as a thermodynamically favorable process as a result of the increase in entropy of mixing of two enantiomers. This assumes that the enthalpic contributions arising from S-S, R-R, and S-R interactions are negligible, which isn't often the case in organolithium chemistry where homochiral and heterochiral aggregates are common. Also, mixed aggregates may favor the formation of a single enantiomer from an equilibrating pair.[51] Organolithiums exhibit macroscopic and microscopic configurational stability. The presence of additives such as TMEDA and HMPA have been known to influence the configurational stability of various organolithium species.

Table 1.1: Configurational stability of several organolithium species[52-54]

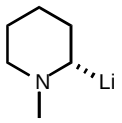
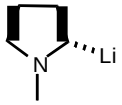
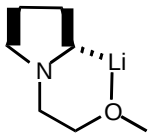
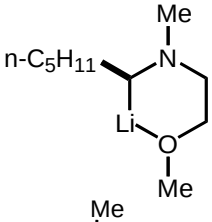
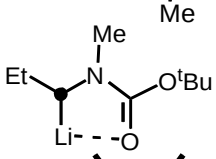
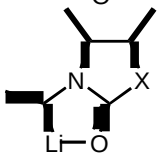
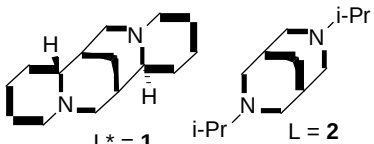
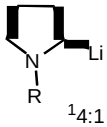
Entry	Substrate	Conditions for stability	Effect of additives
1		THF, –60 °C, 15 min	TMEDA retards racemization up to –40 °C
2		THF, –60 °C, 15 min	TMEDA retards racemization up to –40 °C
3		THF, –78 °C, 75 min	TMEDA retards racemization up to –60 °C
4		THF, –95 °C, 10 min	not determined
5		THF, –95 °C, 3 h	HMPA enhances racemization
6		X = O, 5 min	TMEDA enhances racemization
7		X = N, 45 min	

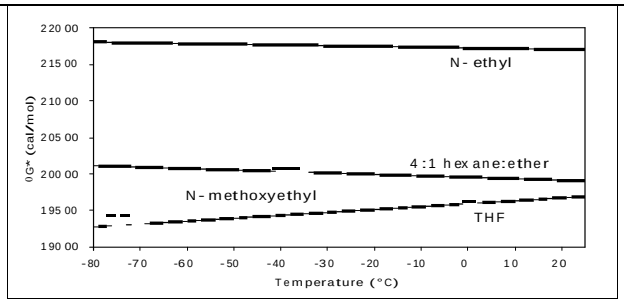
Figure 1.4. Thermodynamic paramaters and their effect on $\Delta G^{\ddagger}$ at various temperatures for racemization. All enthalpy values are in kcal/mol; all entropy values are in cal/mol·K. All kinetic measurements were done in Et_2O solvent unless otherwise noted. The additives employed are shown below:

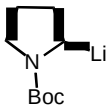




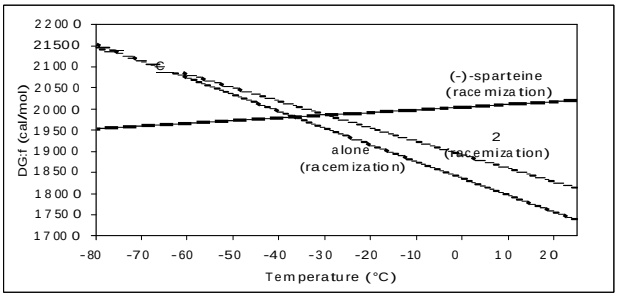
R	$\Delta H^{\ddagger}$	$\Delta S^{\ddagger}$
-Et[1]	22	1
$-(CH_2)_2OCH_3$[1]	20.5	2
$-(CH_2)_2OCH_3$[2]	18.5	-4

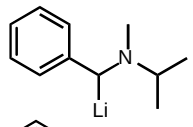
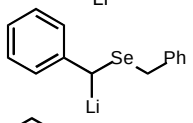
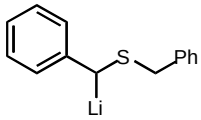
[1]4:1 Hexane:Et_2O
[2]THF

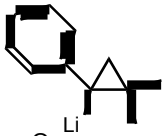
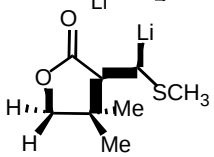
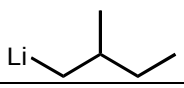




Additive	$\Delta H^{\ddagger}$	$\Delta S^{\ddagger}$
None	29.2	39.7
(–)-sparteine	18.3	-6.4
2	27.6	31.8



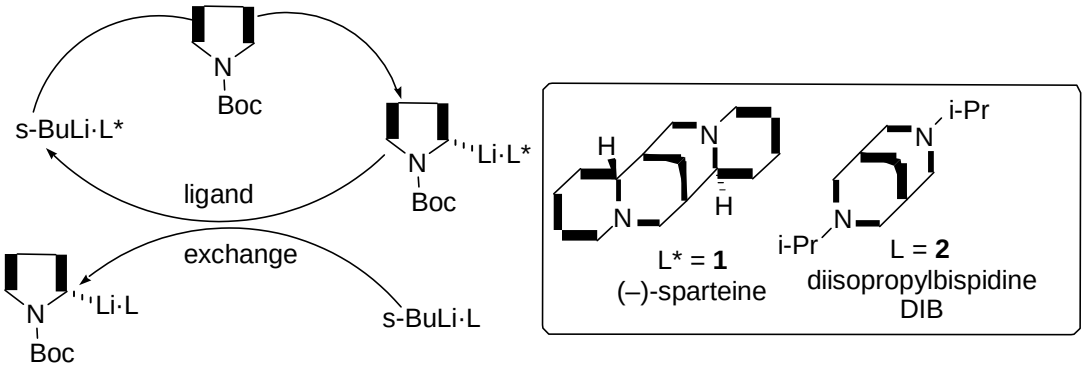
Organolithium	$\Delta G^{\ddagger}$ at 196 K (kcal/mol)
	9.0 ± 0.1
	9.5 ± 0.5
	9.9 ± 0.2

Organolithium	$\Delta G^{\ddagger}$ at 196 K (kcal/mol)
	13.3 ± 0.5
	10.8
	15

1.4. Catalytic Enantioselective Deprotonation and Catalytic Dynamic Resolution

Recently, O'Brien reported a catalytic, enantioselective deprotonation of N-Boc-pyrrolidine.[55] The process involves the use of a substoichiometric amount of the chiral ligand and a stoichiometric or higher amount of the achiral ligand. The authors reasoned that exchange of chiral and achiral ligands could render an enantioselective deprotonation catalytic. In their proposed catalytic cycle (Scheme 1.19), the sec-butyllithium-(–)-sparteine complex effects enantioselective deprotonation of N-Boc-pyrrolidine, giving N-Boc-2-lithiopyrrolidine, complexed to (–)-sparteine.

Scheme 1.19. O'Brien's proposed catalytic cycle for enantioselective deprotonation of N-Boc-2-lithiopyrrolidine by ligand exchange.[55]

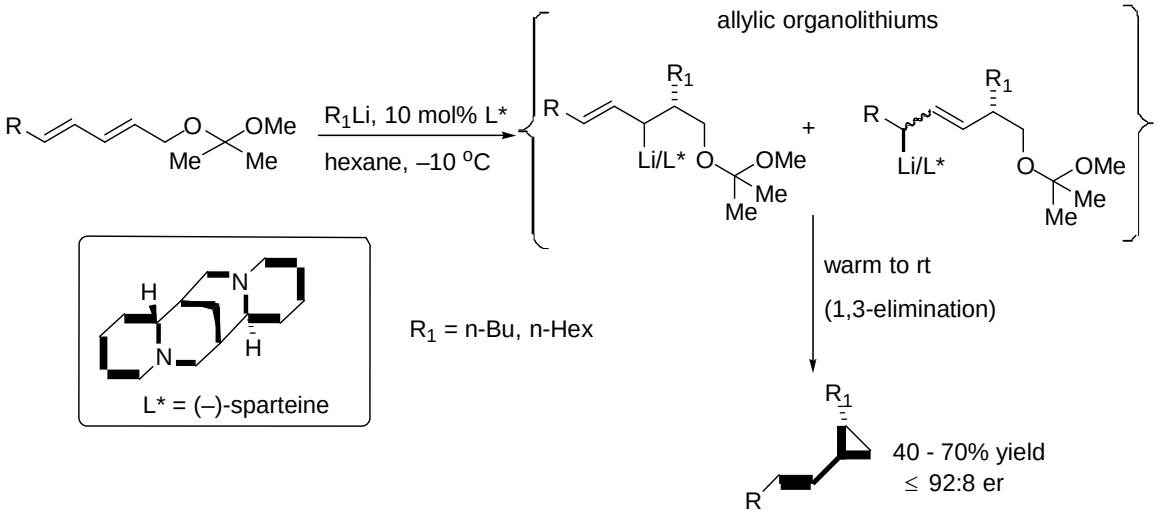


As noted previously, dynamic resolutions are very useful in synthetic organic chemistry because they minimize the need for an enantioselective deprotonation or an asymmetric synthesis of a precursor stannane. An undesirable feature of a DTR is that the chiral ligand might react irreversibly with the electrophile, such that the former is consumed; thereby complicating or preventing its recovery. Therefore, it is important to develop a catalytic variant whereby the use of a substoichiometric amount of the chiral ligand is desirable.

By using 10 mol% of (–)-sparteine, Marek et al showed that one can influence the course of a lithiation-substitution via DTR mechanism using less than one equivalent of the chiral ligand. The authors generated enantioenriched 1,2-disubstituted cyclopropanes in the presence

of (–)-sparteine. After the reaction mixture was warmed to room temperature, the configuration of the allyllithium was equilibrated and a 1,3-elimination provided the trans-disubstituted vinylcyclopropanes in up to 70% yield with er's as high as 92:8 (Scheme 1.20).[56] No comment was made by the authors about the driving force of such a resolution under substoichiometric control.

Scheme 1.20. Marek's catalytic asymmetric and stereoselective synthesis of vinylcyclopropanes by DTR using a substoichiometric amount of (–)-sparteine.

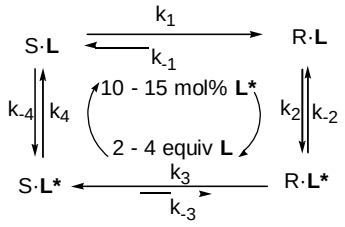


Consider the hypothetical catalytic cycle shown below, (Scheme 1.21) which represents the accumulation of the S organolithium enantiomer complexed to an achiral ligand, L. The top horizontal equilibrium represents racemization of the organolithium enantiomers. The bottom horizontal equilibrium represents a DTR using stoichiometric chiral ligand, L*. The vertical equilibria depict ligand exchanges. In a catalytic dynamic resolution, the organolithium substrate is in excess of the chiral ligand. The remainder of the substrate is presumably complexed to the achiral ligand.

We hypothesize that a minimum requirement for a system to be amenable to a catalytic dynamic resolution is that the barrier to racemization of the organolithium must be significantly higher

than the barrier to dynamic resolution. Therefore, careful control of temperature and time may be critical to developing a CDR. A second hypothesis is that the chiral and achiral ligands must both be involved in the resolution.

Scheme 1.21. Hypothetical catalytic cycle for dynamic resolution using substoichiometric amount of chiral ligand.



If an organolithium species has a low inversion barrier ($\Delta G^{\ddagger}$), it may be difficult to obtain a stoichiometric or catalytic resolution. Transmetalation from lithium to magnesium or zinc renders the metal-carbon bond more covalent. This could in turn increase the inversion barrier, hence the possibility of a DTR or CDR.

1.5. Statement of the Problem

The overall aim is to examine the enantiomerization and resolution dynamics of selected, synthetically important chiral organolithium compounds in the presence and absence of chiral and achiral ligands, and investigate the possibility of a catalytic dynamic resolution.

The specific goals are as follows:

- Determine the thermodynamic parameters for racemization and resolution of N-Boc-2-lithiopiperidine, the ethylene ketal of N-Boc-2-lithio-4-oxopiperidine, N-trimethylallyl-2-lithiopyrrolidine, and N-Boc-2-lithiopyrrolidine in the presence and absence of various diamine ligands.
- Determine the kinetic orders in both the achiral and chiral ligands involved in the inversion of N-Boc-2-lithiopiperidine.

- Investigate the possibility of a catalytic dynamic resolution; its mechanism, scope and limitations.
- Evaluate the range of electrophiles suitable for use in a stoichiometric and catalytic dynamic resolution.
- Apply catalytic dynamic resolution to the synthesis of several alkaloids, medicinal compounds, and natural products.

1.6. References

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CHAPTER 2

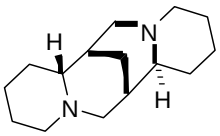
The Barriers to Enantiomerization and Dynamic Resolution of Selected α-aminoorganolithium Compounds

2.1. Introduction

A successful approach to promote asymmetric induction in chiral racemic organolithium compounds requires an understanding of the kinetics of enantiomerization and how these rates compare with the rate of electrophilic quench. A survey of the literature shows that there is very little information available on the barriers to inversion of α-aminoorganolithium compounds. Most reports on racemization are qualitative with some emphasis on the effects of solvents, the relative stability and the possible role of additives. The popular belief is that chiral organolithium compounds are generally configurationally labile but recent findings have revealed that some organolithium compounds exhibit unexpected configurational stability.[1-3] Organolithiums exhibit macroscopic and microscopic configurational stability.[1] The presence of additives such as TMEDA and HMPA are known to influence the configurational stability of various organolithium species. Using an N-Boc-N-(p-methoxyphenyl) benzylamine, Beak and coworkers showed that lithiation of the benzylic position in Et_2O at –78 °C, either by enantioselective deprotonation using s-BuLi/sparteine or by tin-lithium exchange in the absence of a ligand afforded a configurationally stable organolithium. The authors detected some charge delocalization by NMR spectroscopy but the configurational stability was unaffected. However, in the presence of TMEDA or THF, the configurational integrity was compromised. Changes in the stereoelectronics on the lithium-bearing center due to changes in aggregation and/or solvation might influence the dynamics of inversion of an organolithium species.

Some systematic, qualitative studies have been carried out on representative dipole-stabilized carbanionic species.[4-6] In these studies, the authors observed that a strongly coordinating solvent/additive such as HMPA or TMEDA lowers the barrier to inversion. Collum et al reasoned that such additives influence the inversion barrier by breaking up or weakening the chelation between lithium and the carbonyl oxygen or by stabilizing the transition state leading to carbanion inversion.[7] Conversely, using dipole-unstabilized systems such as N-methyl-2-lithiopyrrolidine and N-methyl-2-lithiopiperidine, Gawley et al showed that TMEDA retards racemization up to –40 °C.[8] Quantitative data for the inversion of some organolithium species have been measured using various techniques. Configurationally labile organolithium compounds may invert on the NMR timescale. Comparison of spectra obtained in a Dynamic Nuclear Magnetic Resonance (DNMR) experiment to those obtained through a computer modeling experiment can reveal the activation parameters.[9, 10] In general, such barriers are typically low (9 to 16 kcal/mol). Recently, some chemical protocols have been utilized to measure the thermodynamic parameters for enantiomerization of α-aminoorganolithium species.[11-13]

Figure 2.1. Structures of ligands, substrates, intermediates and products



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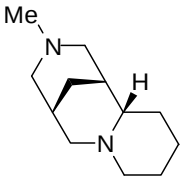
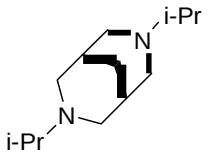


(+)-sparteine
surrogate



2
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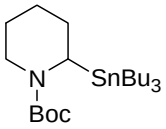
DIB



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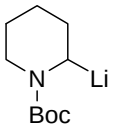

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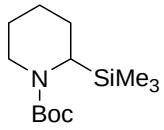
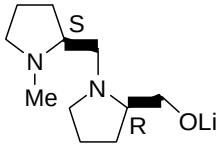
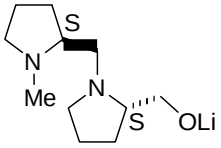


rac-**5**



(S,R)-**6**



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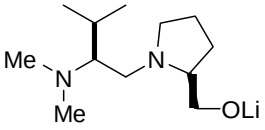

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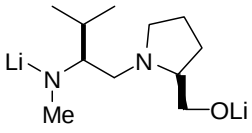

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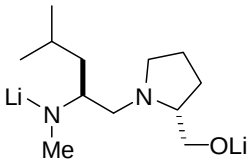

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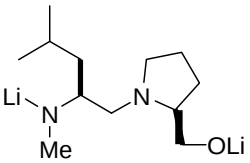

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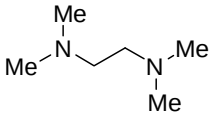
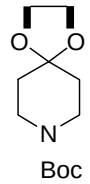


TMEDA



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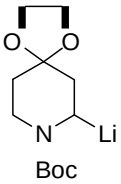

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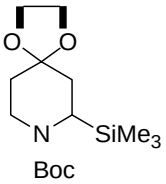

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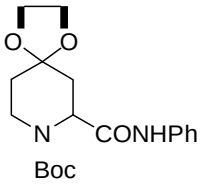

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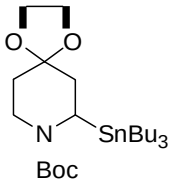

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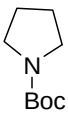
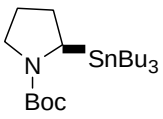


N-Boc-pyrrolidine



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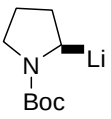

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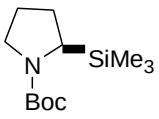

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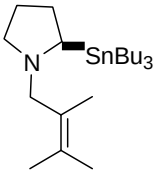

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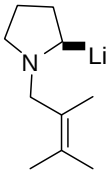

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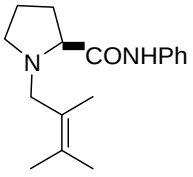

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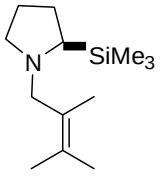


22

Case 1. N-Boc-2-lithiopiperidine

Objective: The specific goals of this section are as follows:

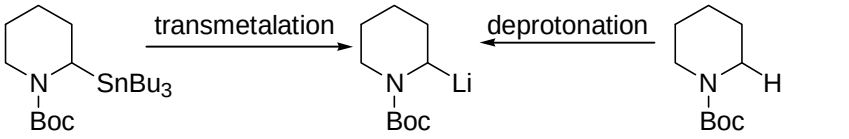
1. Determine the most efficient pathway for the generation of N-Boc-2-lithiopiperidine.
2. Investigate the configurational stability of enantioenriched N-Boc-2-lithopiperidine in the presence of selected diamine ligands.
3. Determine the thermodynamic parameters for racemization and dynamic resolution of N-Boc-2-lithiopiperidine in the presence or absence of selected diamine ligands.
4. Determine the rate laws for racemization and dynamic resolution of N-Boc-2-lithiopiperidine.
5. Improve the yields and enantioselectivities in the dynamic resolution of N-Boc-2-lithiopiperidine.

2.2. Results and Discussion

2.2.1. Formation of N-Boc-2-lithiopiperidine

Two different pathways were utilized to generate N-Boc-2-lithiopiperidine, namely deprotonation of N-Boc-piperidine and tin-lithium exchange of the corresponding stannane 3.

Scheme 2.1. Pathways for the generation of N-Boc-2-lithiopiperidine

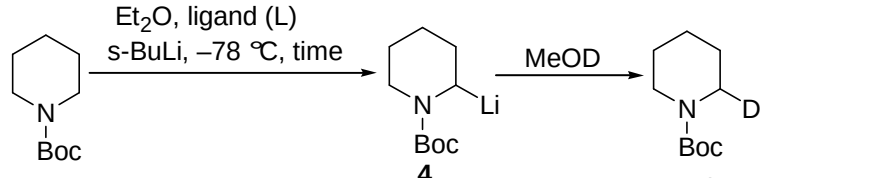


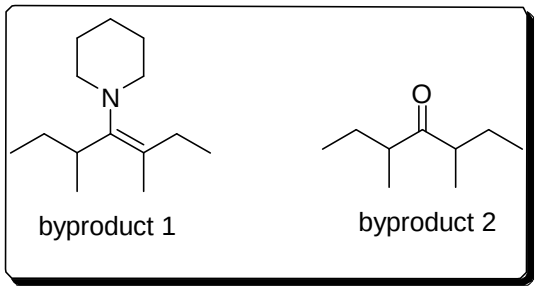
3 **4** N-Boc-piperidine

2.2.1a. Formation of N-Boc-2-lithiopiperidine by Deprotonation of N-Boc-piperidine

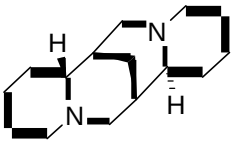
In order to optimize the process of formation of N-Boc-2-lithiopiperidine, deprotonation was carried in the presence and absence of selected diamine ligands. A solution containing N-Boc-piperidine in Et_2O and the desired diamine was cooled to –78 °C prior to addition of s-BuLi. The extent of deprotonation was monitored by quenching an aliquot of the reaction mixture with methanol-d_1 (CH_3OD), checking for deuterium incorporation by GC-MS, and calculating the integral ratio of the singly deuterated to undeuterated piperidine. The results are summarized in Table 2.1. In the absence of a ligand, after 10 h of treatment of N-Boc-piperidine with s-BuLi at –78 °C, quenching with MeOD showed no evidence of deuterium incorporation (Table 2.1, entry 1).[14] Due to the lengthy reaction time, two byproducts resulting from the attack of s-BuLi on the carbonyl carbon of the Boc-group were detected. In the presence of (–)-sparteine 1, 25% of the deuterated product was detected after 5 h (entry 2).[15] With diisopropylbispidine 2, and monolithiated diaminoalkoxide 6, no deprotonation was observed after 10 h (entries 3 and 4). However, in the presence of TMEDA, quenching with MeOD revealed complete deprotonation after 4 h (entry 5). These results indicate that TMEDA facilitates the deprotonation of N-Boc-piperidine. Full kinetic data for deprotonation in the presence of TMEDA are displayed in Appendix 1.

Table 2.1. Evaluation of the extent of deprotonation of N-Boc-piperidine in the presence of several diamines.

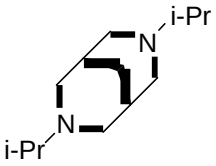




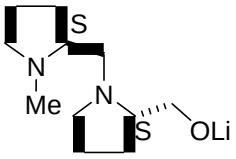
Entry	Ligand (1.0 equiv)	Time (h)	% deprotonation
1	None	10	~0
2	(–)-sparteine 1	4	25
3	2	10	~0
4	6	10	~0
5	TMEDA	4	Complete



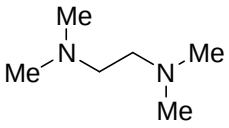
1
sparteine



2
diisopropylbispidine
DIB



6



TMEDA

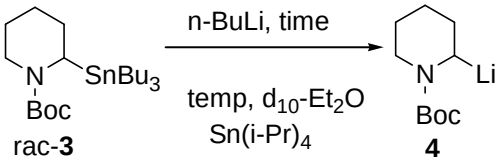
2.2.1b. Tin-Lithium Exchange Kinetics of N-Boc-2-(tributylstannyl) piperidine 3 by Low Temperature Nuclear Magnetic Resonance

The generation of the N-Boc-2-lithiopiperidine 4 by tin-lithium exchange from the corresponding stannane 3 was sometimes preferred in order to avoid the possibility of incomplete deprotonation of N-Boc-piperidine, which requires 4 h in the presence of TMEDA. We also hoped that this

would provide a means to generate 4 efficiently, in the absence of any ligands for possible examination of its solution structure.

The kinetics of tin-lithium exchange from 3 to 4 were measured using previously reported methods.[16] It was not possible to transmetalate 3 to 4 at –78 °C, but tin-lithium exchange was followed in d_{10}-ether from –60 °C to –20 °C using Sn(i-Pr)$_4$ as the internal calibrant in ^{119}Sn NMR (Scheme 2.2). In a typical NMR experiment, 0.25 M solutions of the stannane 3 and Sn(i-Pr)$_4$ in d_{10}-Et_2O were precooled to –40 °C and the initial ^{119}Sn spectrum was obtained prior to addition of freshly titrated n-BuLi at this temperature. After several time intervals, the ^{119}Sn NMR spectrum was recorded and the integral ratio of 3 to Sn(i-Pr)$_4$ was calculated.

Scheme 2.2. Transmetalation of 3 to 4 in the absence of a ligand in Et_2O.[16]



The exchange rate constants obtained from nonlinear parametric fits of the zero-order plots (see Appendix 2) for conversion of 3 to 4 in the absence of a ligand are shown in Figure 2.2. From the empirical equation

$$t_{1/2}(\text{min}) = 4.15 \times 10^{7} \exp(-0.06T) \qquad (2.1)$$

the half-life for conversion of 3 to 4 in the absence of a ligand at any given temperature can be estimated. Therefore, careful control of temperature allows for optimization of the tin-lithium exchange and minimizes organolithium decomposition, thereby improving the yields for the subsequent electrophilic substitution reactions.

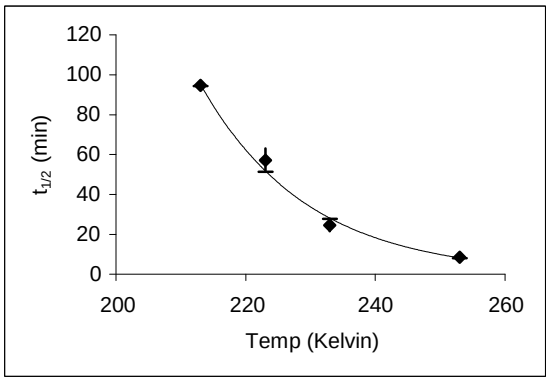
Figure 2.2. Half-lives ($t_{1/2}$) vs temperature for transmetalation of 3 to 4 in Et_2O. The data fits the following equation: $t_{1/2}\,(\text{min}) = 4.15 \times 10^{7} \exp(-0.06T)$

Sn/Li exchange rate constants

Temp (K)	k_{exc} (10^{-4} s^{-1})	$t_{1/2}$ (min)[a]
253	13.30 ± 0.81	8.7 ± 0.5
233	4.68 ± 0.51	24.7 ± 3.2
223	2.02 ± 0.24	57.2 ± 5.9
213	1.22 ± 0.01	94.7 ± 0.3

a. $t_{1/2} = \ln 2/k_{exc}$

$t_{1/2}$ vs temperature

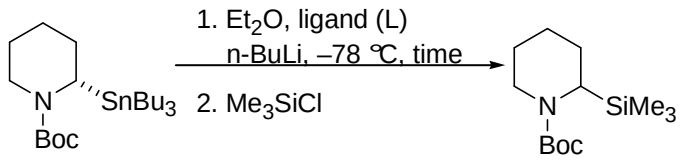


The extent of tin-lithium exchange at –78 °C in the presence of selected diamine ligands in diethylether was evaluated together with the configurational stability of N-Boc-2-lithiopiperidine as shown in the next section.

2.2.2. Configurational Stability of N-Boc-2-lithiopiperidine

As noted previously, the success of techniques such as enantioselective deprotonation and dynamic resolution rely on the varying degree of configurational stability of organolithiums at different temperatures. Therefore tin-lithium exchange of S-3 (73:27 er) was attempted at –78 °C in order to evaluate the configurational stability of N-Boc-2-lithiopiperidine 4 under several conditions (Scheme 2.3).

Scheme 2.3. Configurational stability of 4 at –78 °C in the presence of several diamines in Et_2O.



S-**3** (73:27 er)

5

Evaluate er

After 5 hours of treatment of 3 with n-BuLi at –78 °C, quenching with Me_3SiCl produced a mixture of mostly unreacted 3 (due to slow transmetalation from tin to lithium) and the silylated product 5, but the latter was racemic. This indicates a lack of configurational stability of 4, even at this low temperature (Table 2.2, entry 1). The rapid racemization of 4 in the absence of any ligands therefore precluded any quantitative kinetic measurements of the barrier to enantiomerization of 4 alone.[17] In the presence of (–)-sparteine, TLC and CSP-SFC monitoring showed that transmetalation of S-3 (73:27 er) to 4 was complete after 5 h. However, quenching with Me_3SiCl afforded racemic 5. Although the rapid racemization is in contrast to an 87:13 er of 5 after deprotonation by s-BuLi in the presence of (–)-sparteine[18], it reflects the differences in the mechanisms for the formation of 5. Tin-lithium exchange affords unligated 5, which racemizes before (–)-sparteine can coordinate the lithium. With diisopropylbispidine 2, transmetalation of S-3 (73:27 er) to 4 was also complete after 5 h and rapid racemization was observed. These findings indicate that neither ligand stabilizes the configuration of 5. (S)-N-Boc-2-lithiopiperidine racemizes in less than ten minutes at –78 °C in the absence of a ligand and in the presence of (–)-sparteine or diisopropylbispidine (entries 2 and 3). Intriguingly, after treatment of 3 with n-BuLi for only 30 min at –78 °C in the presence of 1.0 equivalent of TMEDA, quenching with Me_3SiCl revealed complete transmetalation, and S-5 was obtained in 73:27 er (entry 4). Thus, TMEDA facilitates an otherwise recalcitrant transmetalation and stabilizes the anion configuration of N-Boc-2-lithiopiperidine.

Table 2.2. Configurational stability of S-4 (73:27 er) in the presence of various ligands

Entry	Ligand (1.0 equiv)	Time (h)	Extent of tin-lithium exchange	er (S:R)
1[a]	None	5	Incomplete	50:50
2[a]	(–)-sparteine	5	Complete	50:50
3[a]	2	5	Complete	50:50
4	TMEDA	0.5	Complete	73:27

[a]Complete racemization was observed even after 10 min.

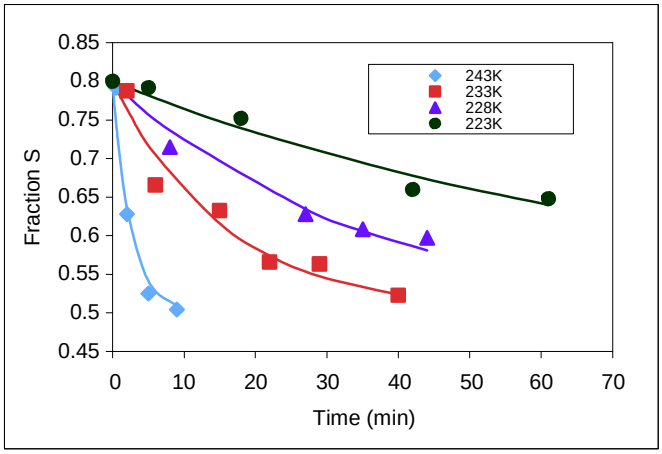
2.2.3. Enantiomerization of (S)-N-Boc-2-lithiopiperidine in the presence of TMEDA

Knowing that TMEDA facilitates the formation of N-Boc-2-lithiopiperidine either by deprotonation or transmetalation, and stabilizes its configuration, we decided to determine the barrier to racemization of N-Boc-2-lithiopiperidine in the presence of varying amounts of the TMEDA. Thus the rate of racemization of N-Boc-2-lithiopiperidine was followed by generating the organolithium 4 using tin–lithium exchange in Et_2O at –78 °C with n-BuLi and TMEDA, followed by warming to the desired temperature for different time periods, then cooling to –78 °C and quenching with excess Me_3SiCl. The rate constants were determined by nonlinear fits to the zero-order plots using SOLVER statistics on MS Excel. The zero-order plots are shown in Figure 2.3.

Figure 2.3. Zero order plots for enantiomerization of S-4 with varying [TMEDA]

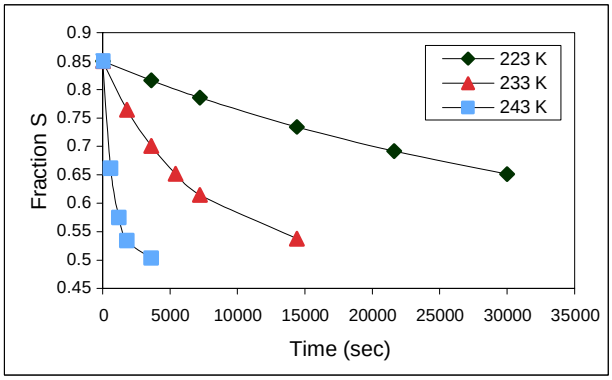
(a). Enantiomerization of S-4 (80:20 er) with 1.0 equiv TMEDA

$$(S)_t = 0.5 + (0.80 - 0.50)\left(e^{-k_{rac}t}\right)$$



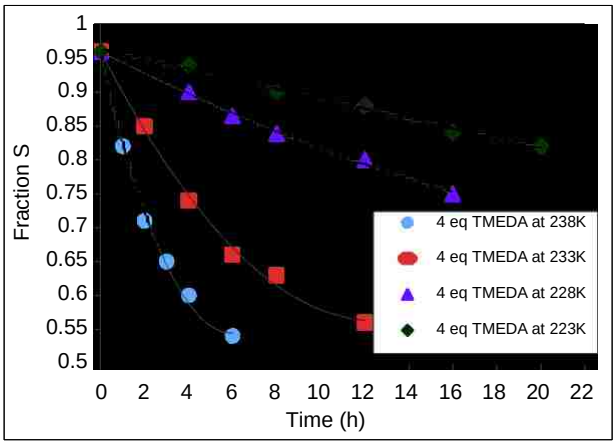
(b). Enantiomerization of S-4 (85:15 er) with 2.0 equiv TMEDA

$$(S)_t = 0.5 + (0.85 - 0.50)\left(e^{-k_{rac}t}\right)$$

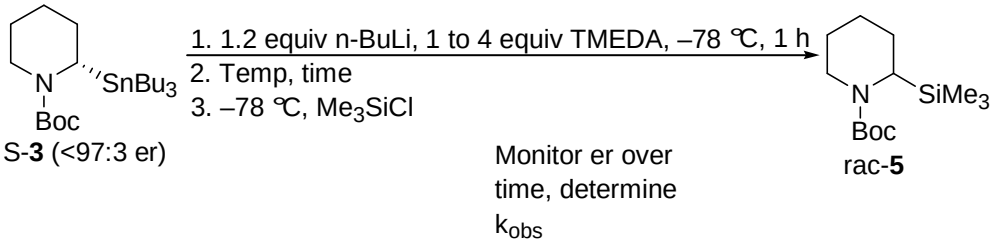


(c). Enantiomerization of S-4 (96:4 er) with 4.0 equiv TMEDA

$$(S)_t = 0.5 + (0.96 - 0.50)\left(e^{-k_{rac}t}\right)$$



Scheme 2.4. Generalized scheme for enantiomerization of N-Boc-2-lithiopiperidine in the presence of TMEDA in Et_2O



With four equivalents of TMEDA, the fraction of the S-enantiomer starting from S-3 (96:4 er) as a function of time (t), is given by:

$$(S)_t = 0.5 + (0.96 - 0.50)\left(e^{-k_{rac}t}\right) \qquad (2.2)$$

where k_{rac} is the observed rate constant for the racemization.

Table 2.3. Rate constants at their respective temperatures for enantiomerization of S-4 with varying [TMEDA]

(a) 1.0 equiv TMEDA

Temp (K)	k_{rac} (x 10^{-4} s^{-1})	$-\ln(k_{ent}/T)^a$
243	66.3 ± 2.5	11.203
233	10.6 ± 0.8	12.996
228	4.9 ± 0.4	13.733
223	2.1 ± 0.2	14.578

(b) with 2.0 equiv TMEDA

Temp (K)	k_{rac} (x 10^{-5} s^{-1})	-ln(k_{ent}/T)
243	129 ± 7	12.840
233	15.5 ± 0.6	14.916
223	2.80 ± 0.07	16.585

(c) 4.0 equiv TMEDA

Temp (K)	k_{rac} (x 10^{-5} s^{-1})	-ln(k_{ent}/T)[a]
238	10.52 ± 0.3	15.325
233	4.22 ± 0.06	16.217
228	1.00 ± 0.02	17.635
223	0.45 ± 0.007	18.407

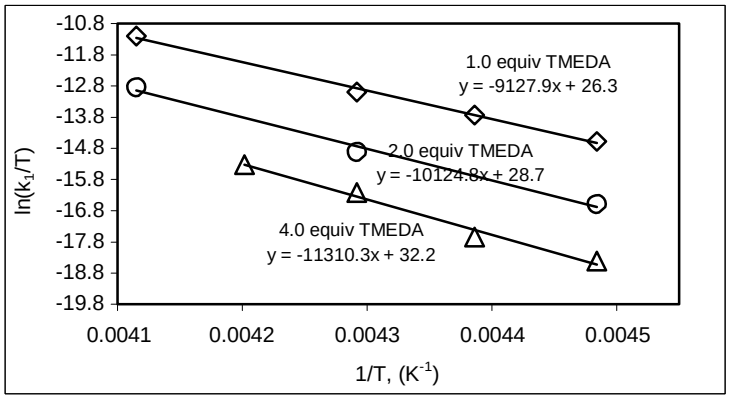
Eyring analysis of the rate constants at their respective temperatures using equation 2.3 provided the thermodynamic parameters listed in Figure 2.4c.

$$\ln \frac{k_{ent}}{T} = -\frac{\Delta H^{\ddagger}}{RT} + \ln \frac{k_B}{h} + \frac{\Delta S^{\ddagger}}{R} \qquad (2.3)$$

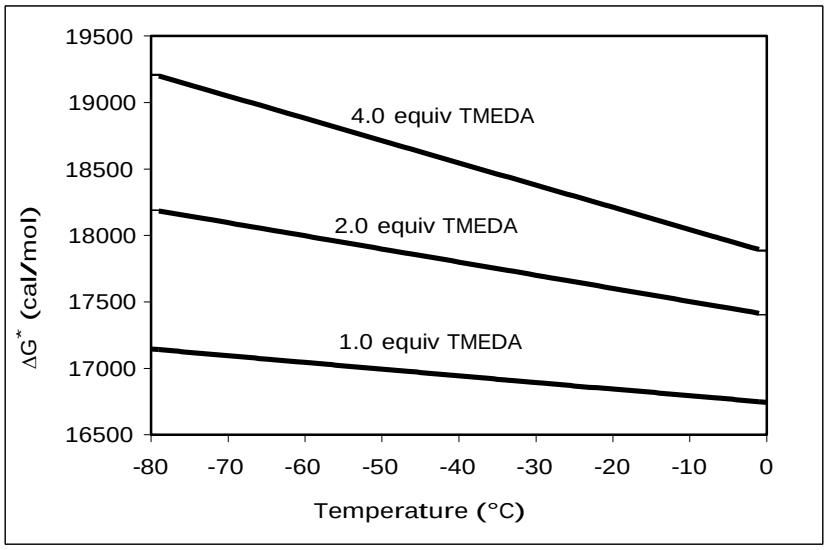
k_{ent} = rate constant for the enantiomerization (S to R), T = absolute temperature, $\Delta H^{\ddagger}$ = enthalpy of activation, R = molar gas constant, k_B = Boltzmann's constant, h = Planck's constant, $\Delta S^{\ddagger}$ = entropy of activation.

The analysis of the Eyring plots shown in Figure 2.4a is based on the assumption that A (the Arrhenius pre-exponential factor), E_a (the activation energy), and $\Delta H^{\ddagger}$ are independent of temperature.[19] This approximation is generally considered valid over a small temperature range, such as used in these experiments. Our findings reveal that both $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ increase with an increase in [TMEDA]. Thus excess TMEDA retards racemization.

Figure 2.4. (a) Eyring plots (b) The relationship between $\Delta G^{\ddagger}$ and temperature (c) Thermodynamic parameters for enantiomerization of S-4 with TMEDA (1.0 equiv, 2.0 equiv, 4.0 equiv). $\ln \frac{k_{ent}}{T} = -\frac{\Delta H^{\ddagger}}{RT} + \ln \frac{k_B}{h} + \frac{\Delta S^{\ddagger}}{R}$, $k_{ent} = k_{rac}/2$, $\Delta H^{\ddagger} = -\text{slope} \cdot x\ R$, $\Delta S^{\ddagger} = (\text{Intercept} \cdot x\ R) - (R \times \ln(k_B/T))$.



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

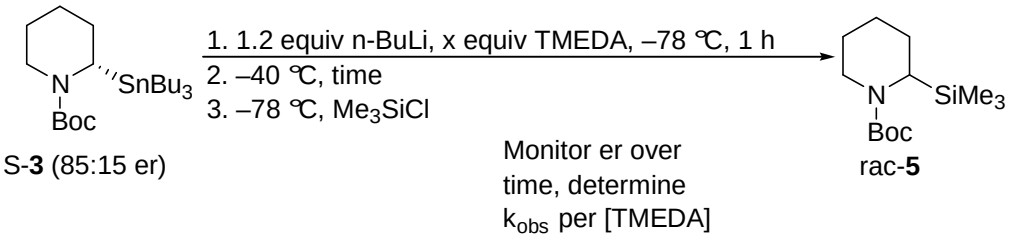


Racemization of 4 with TMEDA	$\Delta H^{\ddagger}$ (kcal/mol)	$\Delta S^{\ddagger}$ (R→S) (cal/mol·K)
1.0 equiv	18.1 ± 0.8	5.0 ± 3.2
2.0 equiv	20.1 ± 1.8	9.9 ± 7.6
4.0 equiv	22.5 ± 2.0	16.7 ± 8.8

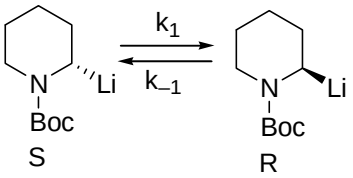
2.2.4. Kinetic order in TMEDA for Racemization of N-Boc-2-lithiopiperidine

Because we observed rapid racemization in the absence of TMEDA and slow racemization in the presence of excess TMEDA, we decided to follow the progress of the reaction in the presence of limiting (catalytic) and excess amounts of TMEDA at a particular temperature in an attempt to measure the kinetic order. Thus the rate of racemization with varying amounts of TMEDA was measured at –40 °C and the kinetic order in TMEDA was determined.

Scheme 2.5a. Racemization of S-4 in the presence of TMEDA



Consider the following equilibrium in the absence of any ligands:



$[R]_0$ = concentration of R at time = 0, $[S]_0$ = concentration of S at time = 0

$[R]_{eq}$ = concentration of R at equilibrium, $[S]_{eq}$ = concentration of S at equilibrium

$$\text{Rate of Reaction} = \frac{d[R]}{dt} = -\frac{d[S]}{dt} = k_1[S] - k_{-1}[R] \qquad (2.4)$$

Both [S] and [R] are changing with time; so we must express differential equation in terms of one variable in order to solve.

By conservation of matter:

$$[R]_0 + [S]_0 = [R] + [S] = [R]_{eq} + [S]_{eq} \qquad (2.5)$$

At equilibrium,

$$k_1[R]_{eq} = k_{-1}[S]_{eq} \tag{2.6}$$

Solving for [R] in equation (2.5) gives

$$[R] = [R]_{eq} + [S]_{eq} - [S] \tag{2.7}$$

Rearranging equation (2.6) to solve for $[R]_{eq}$ gives

$$[R]_{eq} = \left(\frac{k_1}{k_{-1}}\right)[S]_{eq} \tag{2.8}$$

Substituting equation (2.8) into equation (2.7) gives

$$[R] = [S]_{eq} + \left(\frac{k_1}{k_{-1}}\right)[S]_{eq} - [S] \tag{2.9}$$

Substituting the right hand side of equation (2.9) into equation (2.4) gives

$$\frac{d[S]}{dt} = -k_1[S] + k_{-1}\left([S]_{eq} + \left(\frac{k_1}{k_{-1}}\right)([S]_{eq} - [S])\right) \tag{2.10}$$

Expanding equation (2.10) and grouping like terms together gives

$$\frac{d[S]}{dt} = (k_1 + k_{-1})([S]_{eq} - [S]) \tag{2.11}$$

Separation of variables and integration of equation (2.11) yields

$$-\ln\left(\frac{[S]_t - [S]_{eq}}{[S]_0 - [S]_{eq}}\right) = (k_1 + k_{-1})t \tag{2.12}$$

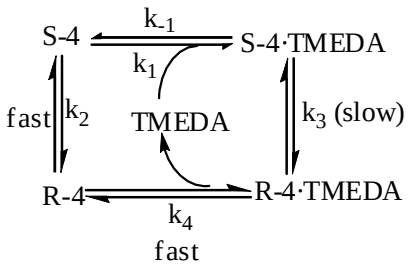
Equation (2.12) can be written in its exponential form as

$$[S]_t = [S]_{eq} + ([S]_0 - [S]_{eq})\exp - k_{obs}t \tag{2.13}$$

where $k_{obs} = k_1 + k_{-1}$ is the observed rate constant.

Now consider the racemization in the presence of a TMEDA as shown below:

Scheme 2.5b. Proposed kinetic profile for racemization



Starting from S-4, the inverstion to R-4 can occur through the pathway that is dependent on TMEDA (top horizontal through the right vertical to bottom horizontal equilibria) and through the TMEDA-independent pathway via k_2. We know that the TMEDA-independent pathway is fast since rapid racemization was observed in the absence of TMEDA even at –78 °C (see Table 2.2). Assuming that the inversion step is the slow step in the presence of TMEDA, then the overall rate of formation of R-4 is given by the parallel processes

$$\text{Rate} = \frac{d[R-4]}{dt} = k_2[S-4] + k_3[S-4.TMEDA] \tag{2.14}$$

$$\frac{d[S-4{\cdot}TMEDA]}{dt} = k_1[S-4][TMEDA] - k_{-1}[S-4{\cdot}TMEDA] - k_3[S-4{\cdot}TMEDA] \approx 0 \tag{2.15}$$

such that

$$[S-4.TMEDA] = \frac{k_1}{k_{-1}+k_3}[S-4][TMEDA] \tag{2.16}$$

and…

$$\frac{d[R-4]}{dt} = \frac{k_1 k_3}{k_{-1}+k_3}[S-4][TMEDA] + k_2[S-4] \tag{2.17}$$

Equation (2.17) can be re-written in the form

$$\frac{d[R-4]}{dt} = k_{ent}[S-4] \tag{2.18}$$

where the observed rate constant for enantiomerization, k_{ent} is given by

$$k_{ent} = k_2 + \frac{k_1 k_3}{k_{-1} + k_3}[\text{TMEDA}] \qquad (2.19)$$

k_{ent} corresponds to half the measured rate constant for racemization, k_{rac}.

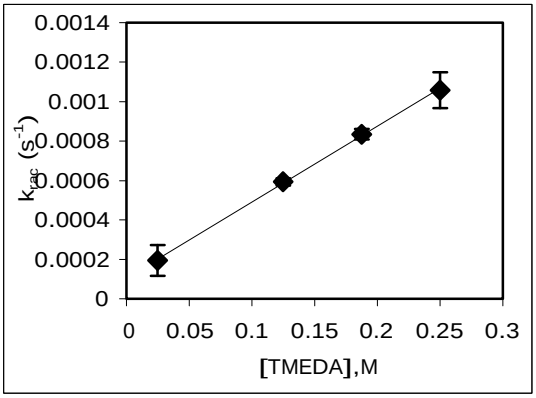
$k_{rac} = k_{SR} + k_{RS} = 2k_{ent}$

Figure 2.5. Effect of varying [TMEDA] on the rate enantiomerization of 4 in Et_2O at 233 K.

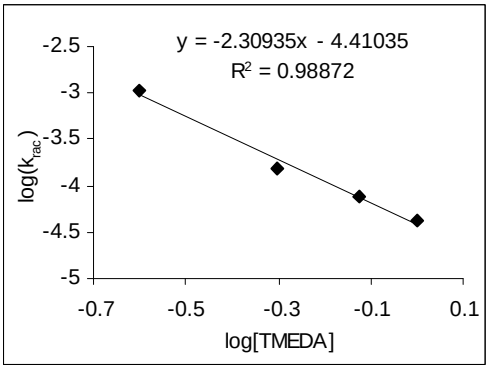
[4] = 0.25 M in Et_2O

Equiv. TMEDA	k_{obs} (x 10^{-5} s^{-1})
0.10	19.4 ± 0.78
0.50	59.4 ± 1.8
0.75	83.5 ± 2.7
1.00	105.8 ± 10.4
2.00	15.5 ± 0.6
3.00	7.81 ± 0.30
4.00	4.22 ± 0.21

a) Zero to one equivalent of TMEDA[17]
$k_{rac} = k_x[\text{TMEDA}]^n$; specific order, n = 0.995; $k_x = 4.56 \times 10^{-3}$ $M^{-1}s^{-1}$



b) One to four equivalents: Linear plot
Slope = order in TMEDA = –2.31 ± 0.17



c) One to four equivalents: Non linear plot

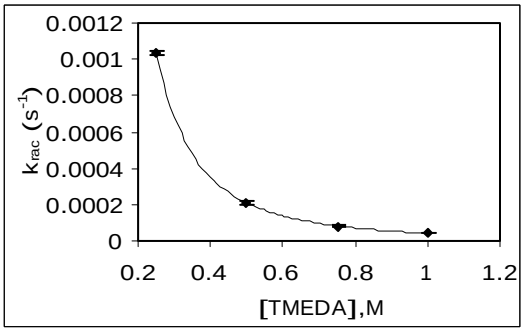


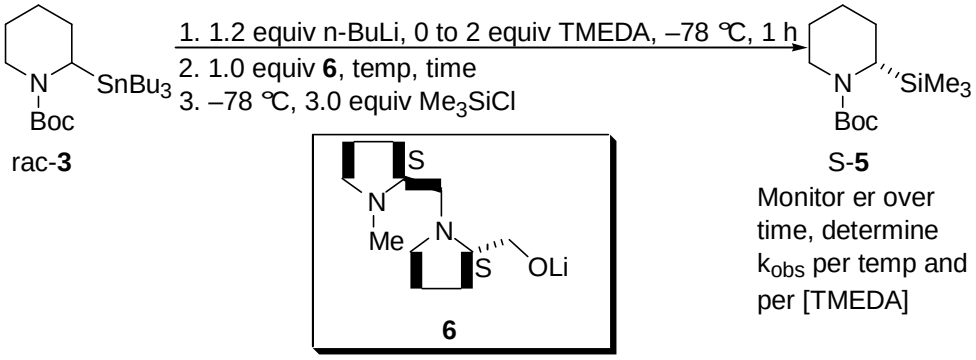
Figure 2.5 shows the racemization rate constants plotted against [TMEDA] from 0.10 to 1.0 and from 1.0 to 4.0 equivalents. A fit of the equation $k_{rac} = k_x[\text{TMEDA}]^n$ (specific order, n = 0.995; rate coefficient, $k_y = 4.56 \times 10^{-3}$ $M^{-1}s^{-1}$) reveals a first-order dependence of rate on [TMEDA] from 0.10 to 1.0 equivalent. Beyond one equivalent of TMEDA, we observed an

inverse dependence on the rate of racemization on [TMEDA]. Therefore, although TMEDA catalyzes the racemization of 4 up to one equivalent, excess TMEDA exhibits a stabilizing effect on the anion configuration.

2.2.5. Activation Parameters for Dynamic Thermodynamic Resolution (DTR) of N-Boc-2-lithiopiperidine in the Presence of 6 with and without TMEDA

Dynamic thermodynamic resolution was followed by generating rac-4 using tin–lithium exchange in Et_2O at –78 °C with n-BuLi with TMEDA, addition of 1.0 equivalent of the chiral ligand, followed by warming to the desired temperature for different time periods, then cooling to –78 °C and electrophilic quench with excess TMSCl. The rate constants for the resolution were obtained from nonlinear fits of the zero-order plots.

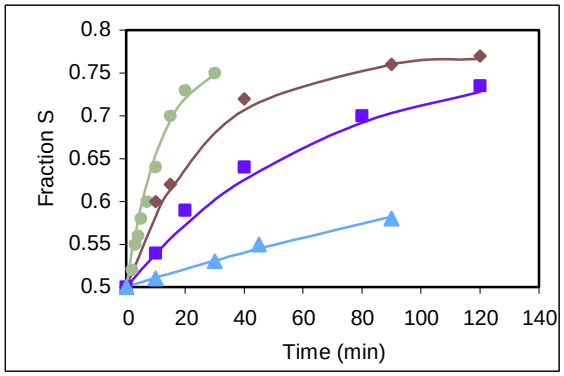
Scheme 2.6. DTR of 4·6 with and without TMEDA



Dynamic thermodynamic resolution of 4 with a stoichiometric amount of 6 in the absence of TMEDA was not observed at temperatures below –30 °C. However, at higher temperatures it was possible to obtain reasonable kinetic data. The observed rate constants at their respective temperatures for the resolution of 4 in the presence of 6 alone and in the presence of 2 equiv TMEDA are shown in Table 2.4. Ligand 6 resolves 4 with a thermodynamic preference for the S-diastereomeric complex (S-4·6:R-4·6 = 77:23) following electrophilic quench with Me_3SiCl.[20]

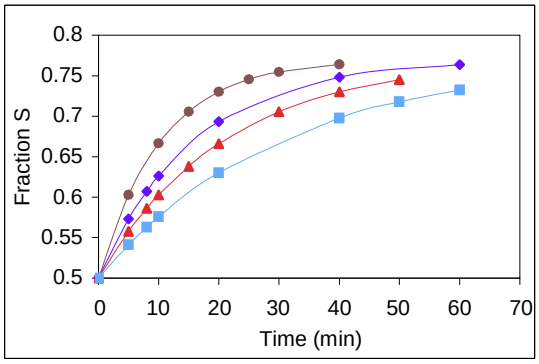
Table 2.4. DTR of 4 (0.06 M) in the presence of 6 (1.0 equiv) in Et_2O

a) Zero-order plots for DTR in the absence of TMEDA



KEY: 20 °C; circles, 10 °C; diamonds, 2 °C; squares, –10 °C; triangles.

b) Zero-order plots for DTR in the presence of 2 equiv TMEDA



KEY: –2 °C; circles, –10 °C; diamonds, –20 °C; triangles, –30 °C; squares.

Temp (K)	1/T (K^{-1})	k_{obs} (x $10^{-4}s^{-1}$)
293	0.003413	14.2 ± 1.92
283	0.003534	6.07 ± 0.31
275	0.003636	2.59 ± 0.14
263	0.003802	0.675 ± 0.03

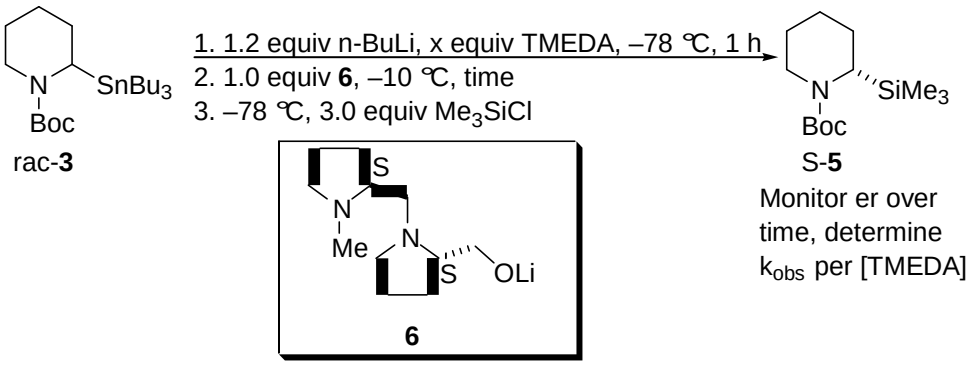
Temp (K)	1/T (K^{-1})	k_{obs} (x $10^{-4}s^{-1}$) [a]
271	0.00369	15.97 ± 1.44
263	0.00380	10.51 ±1.12
253	0.003952	7.98 ± 0.41
243	0.004115	5.49 ± 0.30

$k_{obs} = k_1 + k_{-1}$ for DTR $K_{eq} = \frac{k_1}{k_{-1}} = \frac{[S]_{eq}}{[R]_{eq}} = \frac{77}{23} = 3.3$ $k_1 = \frac{k_{obs}K_{eq}}{1+K_{eq}}$ and $k_{-1} = A\left(1 - \frac{K_{eq}}{1+K_{eq}}\right) = k_{obs}$

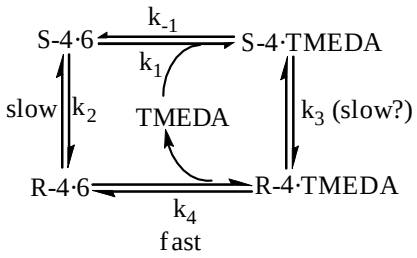
2.2.6. Effect of varying [TMEDA] on the Rate of Dynamic Resolution of 4·6

In order to determine the kinetic order in TMEDA for DTR of 4·6, the racemic organolithium 4 was generated using tin–lithium exchange in Et_2O at –78 °C with n-BuLi and 0.1, 0.5, 0.75, 1.0, 2.0 equiv of TMEDA. After one hour at –78 °C, 1.0 equiv 6 was added followed by warming to –10 °C for different time periods, then cooling to –78 °C and quenching with excess Me_3SiCl.

Scheme 2.7a. DTR of S-4·6 in the presence of varying [TMEDA]



Scheme 2.7b. Kinetic profile for DTR of S-4·6 in the presence of varying [TMEDA]



The formation of S-4·6 is dependent on TMEDA going through k_3 and independent of TMEDA in the parallel pathway via k_2. The rate of formation of S-4·6 is given by

$$\text{Rate} = \frac{d[S-4\cdot6]}{dt} = k_2[R-4\cdot6] + k_3[R-4\cdot6\cdot\text{TMEDA}] \tag{2.20}$$

Assuming that the ternary complex, R-4·6·TMEDA is formed and consumed immediately such that it does not become observable, we can apply the steady state approximation

$$\frac{d[R-4\cdot6\cdot\text{TMEDA}]}{dt} = k_1[R-4\cdot6][\text{TMEDA}] - k_{-1}[R-4\cdot6\cdot\text{TMEDA}] - k_3[R-4\cdot6\cdot\text{TMEDA}] \approx 0$$

such that

$$[R-4\cdot6\cdot\text{TMEDA}] = \frac{k_1}{k_{-1}+k_3}[R-4\cdot6][\text{TMEDA}] \tag{2.21}$$

and…

$$\frac{d[S-4{\cdot}6]}{dt} = \frac{k_1}{k_{-1}+k_3}[R-4{\cdot}6][TMEDA] + k_2[R-4{\cdot}6] \qquad (2.22)$$

Equation (2.22) can be re-written in the form

$$\frac{d[S-4{\cdot}6]}{dt} = k_{obs}[R-4{\cdot}6] \qquad (2.23)$$

where the observed rate constant, k_{obs} is given by

$$k_{obs} = k_2 + \frac{k_1 k_3}{k_{-1}+k_3}[TMEDA] \qquad (2.24)$$

The mechanism reduces to the simple form…..

$$R-4{\cdot}6 + TMEDA \longrightarrow \text{product} \qquad (2.25)$$

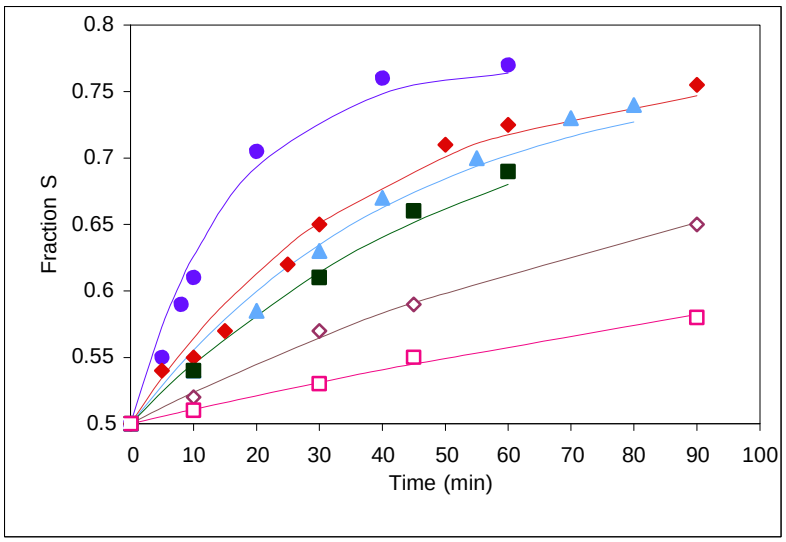
$$R-4{\cdot}6 \longrightarrow \text{product} \qquad (2.26)$$

Figure 2.6 shows the DTR rate constants plotted against [TMEDA] from 0.00 to 2.0 equivalents. A fit of the equation $k_{obs} = k' + k''[TMEDA]^n$ (specific order, n = 1.053; rate coefficient, k' = 6.94×10^{-5} s^{-1}, k'' = 1.07×10^{-2} $M^{-1}s^{-1}$) reveals a first-order dependence of rate on [TMEDA]. The k' term indicates DTR uncatalyzed by TMEDA, corresponding to the intercept on the vertical axis of Figure 2.6c. The value is in good agreement with the experimentally observed value of 6.74×10^{-5} s^{-1} for DTR in the absence of TMEDA. Therefore, parallel pathways for the DTR are implicated. One of the pathways is fast and TMEDA-dependent while the other is slow and independent of TMEDA. The proposed kinetic profile is consistent with our results where k' equal k_2 and k'' equals the multitude of rate constants $\frac{k_1 k_3}{k_{-1}+k_3}$ (equation 2.24).

Figure 2.6. Effect of varying [TMEDA] on the DTR of 4 (0.25 M) in the presence of 6 in Et_2O

$k_{obs} = k' + k''[TMEDA]^n$; It follows (from eqn 2.24) that $k' = k_2$, $k'' = \frac{k_1 k_3}{k_{-1} + k_3}$

(a) Zero order plots

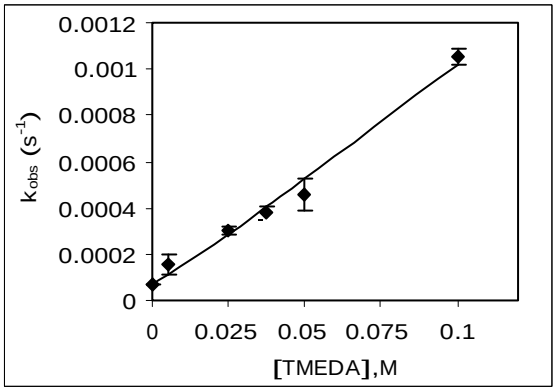


KEY: (a) 0.00 equiv; open squares, 0.10 equiv; open diamonds, 0.50 equiv; squares, 0.75 equiv; triangles, 1.0 equiv; diamonds, 2.0 equiv; circles

(b) Observed rate constants

Equiv TMEDA	k_{obs} (x $10^{-4}s^{-1}$)
0.0	0.674 ± 0.02
0.10	1.523 ± 0.02
0.50	3.05 ± 0.12
0.75	3.84 ± 0.11
1.0	4.55 ± 0.16
2.0	15.97 ± 0.56

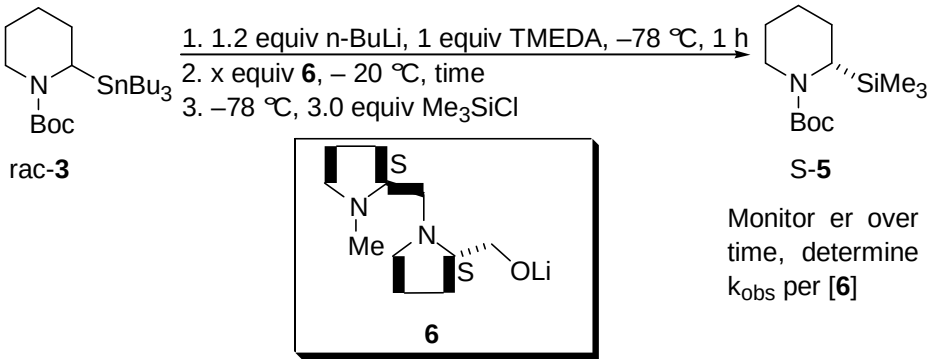
(c) $k_{obs} = k' + k''[TMEDA]^n$



2.2.7. Effect of varying [6] on the Rate of Dynamic Resolution of 4·6

Having determined the kinetic order in the achiral ligand, TMEDA, our next goal was to measure the order in the chiral ligand 6 for DTR in the presence of TMEDA. This was followed by generating the racemic organolithium 4 using tin–lithium exchange in Et_2O at –78 °C with n-BuLi and one equivalent of TMEDA, addition of varying amounts of 6 (0.25 to 4.0 equiv) followed by warming to –20 °C for different time periods, then cooling to –78 °C and quenching with excess Me_3SiCl.

Scheme 2.8. Effect of varying [6] on dynamic resolution of 4



The fraction of the S-enantiomer for the dynamic resolution with stoichiometric 6, starting from a racemate, as a function of time (t), is given by

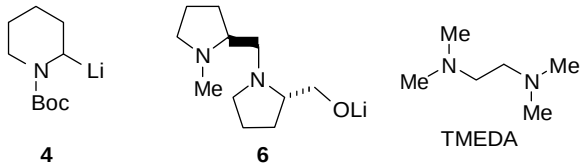
$$(S)_t = 0.77 + (0.50 - 0.77)\exp(-k_{obs}t) \qquad (2.27)$$

where k_{obs} is the observed rate constant for equilibration obtained from a nonlinear fit of the zero-order plots.

The rate of resolution increases with an increase in [6] up to one equivalent and decreases upon addition of excess 6. The downward curvature observed in Figure 2.7a from zero to one equivalent is indicative of a fractional dependence of rate on [6], which is emblematic of deaggregation in organolithium chemistry.[21] A nonlinear fit of the equation $k_{obs} = k_x[6]^n$ (specific order, n = 0.503; rate coefficient, $k_x = 1.59 \times 10^{-3}$ $M^{-1/2}s^{-1}$) confirms the half-order

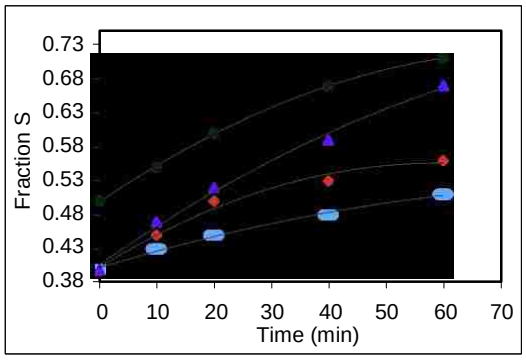
dependence of rate on [6] from zero to one equivalent (Figure 2.7a). Similarly, a fit of the equation $k_{obs} = k_y[6]^n - c$ ($k_y = 1.61 \times 10^{-4}$ $M^{-1/2}s^{-1}$, $c = 2.41 \times 10^{-4}$ s^{-1}, n = specific order in 6 = –0.499) indicates an inverse half-order dependence of rate on [6] from one to four equivalents. Blackmond and Collum separately noted that several factors might cause a rate deceleration with an increase in concentration of an organolithium species. Some of these factors include product inhibition, catalyst deactivation, and a change in the observable form of the intermediate as concentration increases.[21-23] As the concentration is increased beyond one equivalent, it may be possible that less reactive, higher-order aggregates are favored.

Figure 2.7. k_{obs} vs [6] for DR of 4 (0.06 M) in the presence of TMEDA (0.06 M, 1.0 equiv) at 253 K in Et_2O.; (b) 1.0-4.0 equiv 6.



4 **6**

(a) When 6 is limiting over 4



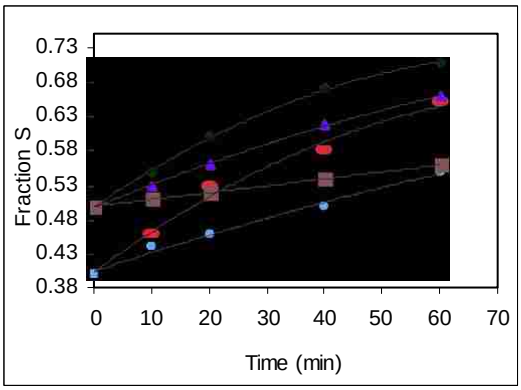
KEY: 0.25 equiv; squares, 0.50 equiv; diamonds, 0.75 equiv; triangles, 1.0 equiv; circles

Equiv. 6	k_{obs} (x 10^{-5} s^{-1})
0.00	0.00 ± 0.00
0.25	18.3 ± 1.2
0.50	27.7 ± 1.0
0.75	32.7 ± 2.5
1.00	40.1 ± 0.8

$k_{obs} = k_x[6]^n$

$k_x = 1.62 \times 10^{-3}$ $M^{-1/2}s^{-1}$

(b) When 6 is in excess of 4



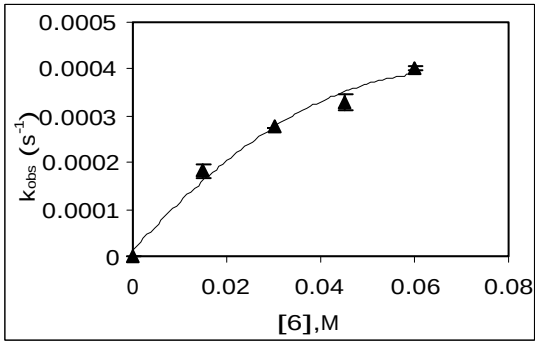
KEY: 1.0 equiv; diamonds, 1.50 equiv; squares, 2.0 equiv; triangles, 3.0 equiv; circles, 4.0 equiv; stars

Equiv. 6	k_{obs} (x 10^{-5} s^{-1})
1.00	40.1 ± 0.8
1.50	30.7 ± 1.9
2.00	23.9 ± 0.8
3.00	14.2 ± 0.75
4.00	6.82 ± 0.14

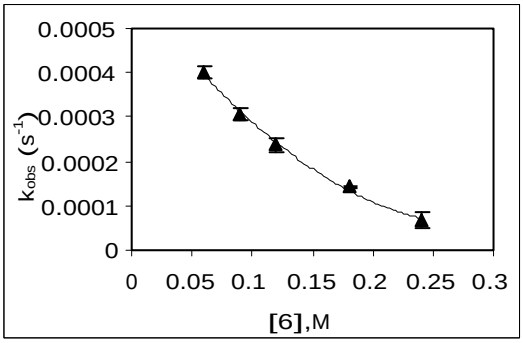
$k_{obs} = k_y[6]^n - c$

$k_y = 1.61 \times 10^{-4}$ $M^{-1/2}s^{-1}$, $c = 2.41 \times 10^{-4}$ s^{-1}

n = specific order in 6 = 0.5003



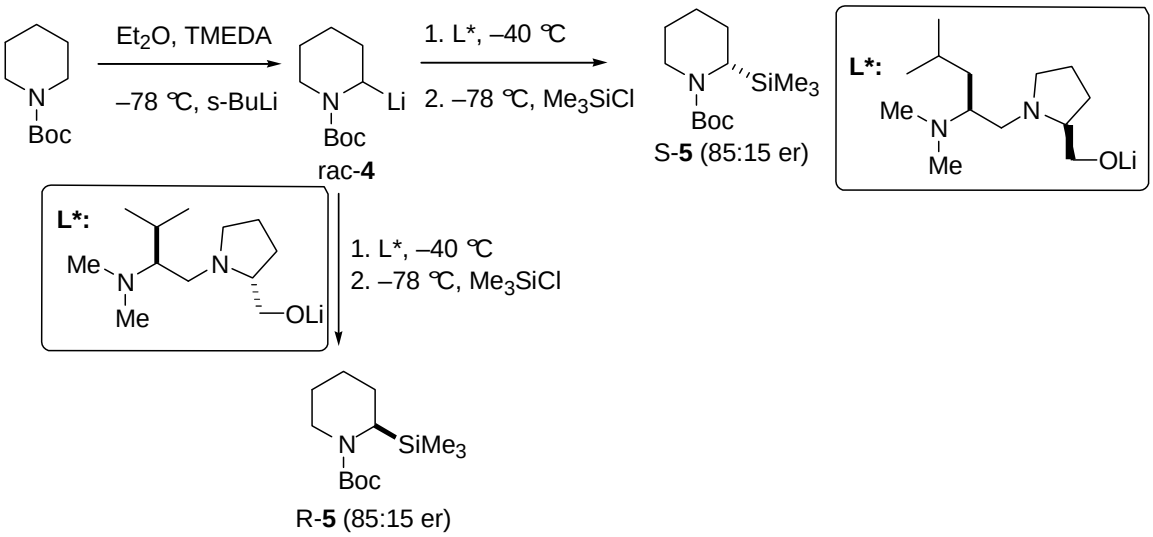
n = specific order in 6 = –0.499



2.2.8. Dynamic Thermodynamic Resolution of N-Boc-2-lithiopiperidine in the Presence of TMEDA and dilithiated diaminoalkoxide Ligands

As noted previously, Coldham et al showed that N-Boc-2-lithiopiperidine 4 can be resolved dynamically in the presence of several monolithiated diamino alkoxide ligands such as 6.[20, 24] Although they obtained either enantiomer of 4, the maximum enantiomer ratio was 85:15 er (Scheme 2.9). The authors observed that addition of salts such as lithium isopropoxide aided the yield of product 5. This observation alludes to changes in aggregation of the organolithium complexes in solution and suggests that a dilithiated diamino alkoxide ligand might improve the DTR of 4. At about the same time and using an asymmetric deprotonation methodology, O'Brien showed that R-4 can be obtained in er's as high as 88:12, using his (+)-sparteine surrogate (see Figure 2.1 for its structure).[25] However, this method is limited to one enantiomer and variable yields were reported when R-4 was trapped with several electrophiles.

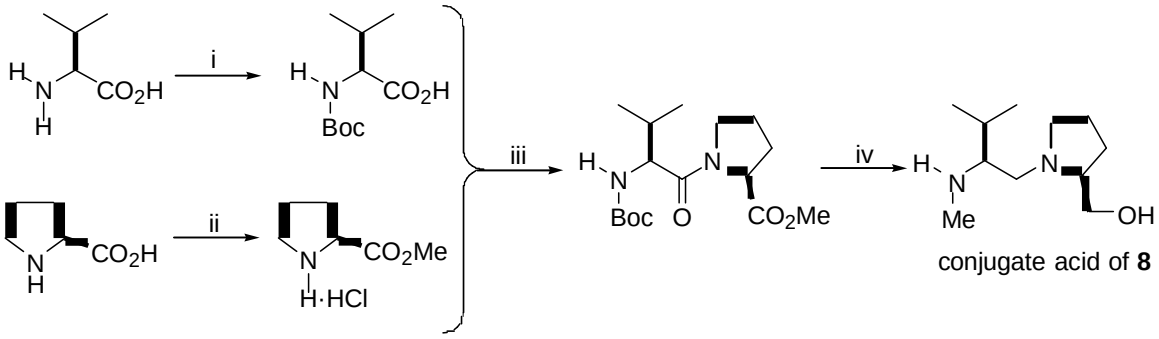
Scheme 2.9. DTR of 4 in the presence of TMEDA in Et_2O using Coldham's most efficient chiral ligands.[24, 26]



We decided to synthesize the alcohol precursors of several dilithiated diamino alkoxide ligands (see Experimental Section for details).

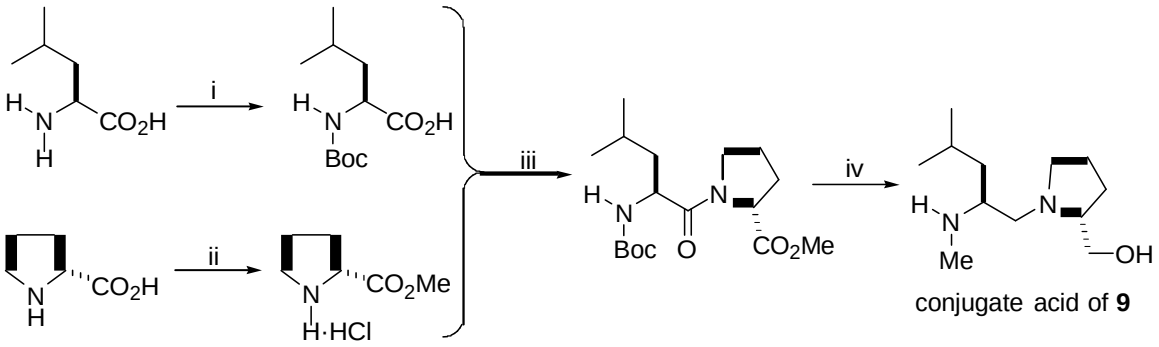
Scheme 2.10. Preparation of the alcohol precursors of our dilithiated diamino alkoxide ligands

A. Conjugate acid of ligand 8



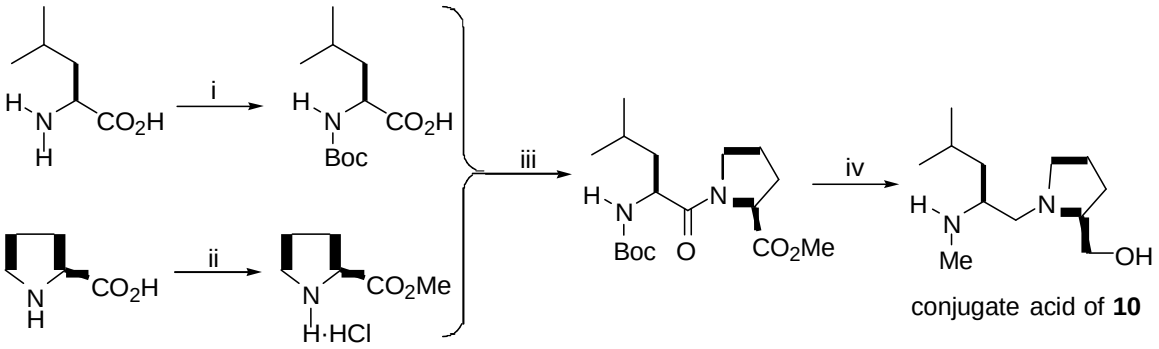
i) NaOH (2 M), Boc_2O (1.2 equiv in CH_2Cl_2), rt, 18 h; 96%, ii) $SOCl_2$ (1.1 equiv), MeOH, 0 ^oC, 2 h, 100%, iii) EDCI, HOBt, Et_3N, $CHCl_3$), rt, 10 h; 92%, iv) $LiAlH_4$, THF, 0 ^oC, then heat at reflux, 16 h; 86%.

B. Conjugate acid of ligand 9



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%, $[a]^{22}_D$ 18 (c = 0.20, MeOH), iv) $LiAlH_4$, THF, 0 ^oC, then heat at reflux, 16 h; 85%, $[a]^{22}_D$ 66.25 (c = 2.0, MeOH).

C. Conjugate acid of ligand 10



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; 88%, $[a]^{22}_D$ –2.8 (c = 0.25, MeOH), iv) $LiAlH_4$, THF, 0 ^oC, then heat at reflux, 16 h; 82%, $[a]^{22}_D$ 18.15 (c = 2.0, MeOH).

The dilithiated ligands were tested under the DTR conditions. This was followed by generating rac-4 using tin–lithium exchange in Et_2O at –78 °C with n-BuLi (1.2 equiv) and TMEDA (2.0 equiv), followed by addition of the desired dilithiated diaminoalkoxide (1.0 equiv), transferring to a second thermostatted bath at –30 °C for 2 h, cooling to –78 °C, addition of 3 equiv Me_3SiCl and stirring for 4 h (Scheme 2.11). Note that the conjugate acid of the ligand was

deprotonated separately using s-BuLi (2.2 equiv) at the same time that tin–lithium exchange of 3 to 4 was carried out. Note also that the deprotonation was carried out in the adjacent bath at –30 °C for convenience and the mixture was added to that at –78 °C via cannula. After workup, CSP-SFC analysis of the silanes revealed that ligands 8 and 10 showed a thermodynamic preference for the S-diastereomeric complex (S-4·8:R-4·8 = 92:8 er; S-4·10:R-4·10 = 96:4 er) following electrophilic quench with Me_3SiCl whereas ligand 9 favored the R-diastereomeric complex (R-4·9:S-4·9 = 98:2 er). Similar er's were obtained after cooling and quenching of the resolved mixture of 4·10 with Bu_3SnCl. No resolution was observed at –78 °C after electrophilic quench with excess Me_3SiCl. When a resolved mixture of 4·10 was quenched rapidly with Me_3SiCl at the equilibration temperature of –30 °C, S-5 of 90:10 er was obtained. Also, after rac-4·TMEDA was generated at –78 °C, addition of 1.0 equiv of 10 and stirring for 2 h, then quenching with 0.4 equiv Me_3SiCl afforded R-5 in 62:38 er. A reaction profile which provides an understanding of these observations is a dynamic thermodynamic resolution as described in Figure 2.8. When the racemic organolithium reacts with 10 at –78 °C, a one-to-one mixture of epimers at the lithium-bearing carbon is formed as non-equilibrating diastereomeric complexes. Treatment with excess TMSCl then traps all of the carbanionic species to give a racemic product. When the reaction is warmed to –30 °C prior to the addition of TMSCl, equilibration occurs. After 2 h, the diastereomeric complexes achieve thermodynamic equilibrium. Rapid cooling to –78 °C freezes the equilibrium and maintains this ratio. Addition of excess electrophile and subsequent reaction affords the enantiomeric products with the high enantiomeric ratio thus reflecting the population of the equilibrated species. The 62:38 enantiomer ratio obtained when the mixture at –78 °C is quenched with a substoichiometric amount of the Me_3SiCl reflects the fact that the activation energies for the reaction of each of the diastereomeric complexes with

Me_3SiCl are different. The fact that the R-enantiomer is favored in this case reveals that the less stable diastereomer is the more reactive one.

Scheme 2.11. DTR of 4 in Et_2O using dilithiated diaminoalkoxide ligands

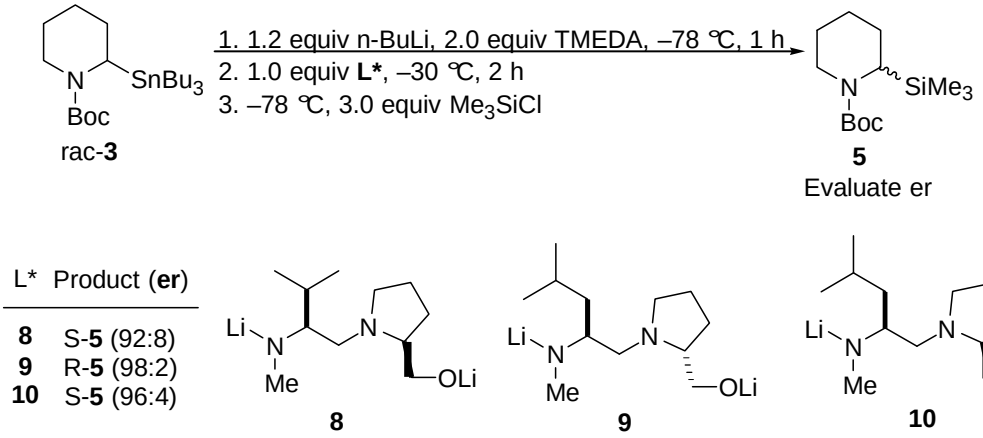
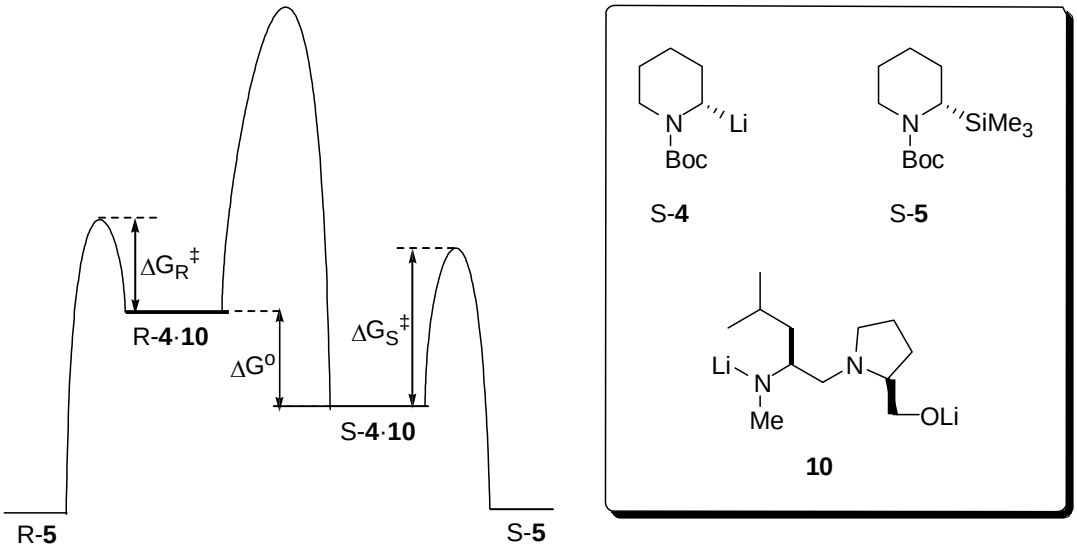


Figure 2.8. Energy profile for DTR of 4·10 in the presence of TMEDA in Et_2O and electrophilic quench with Me_3SiCl.

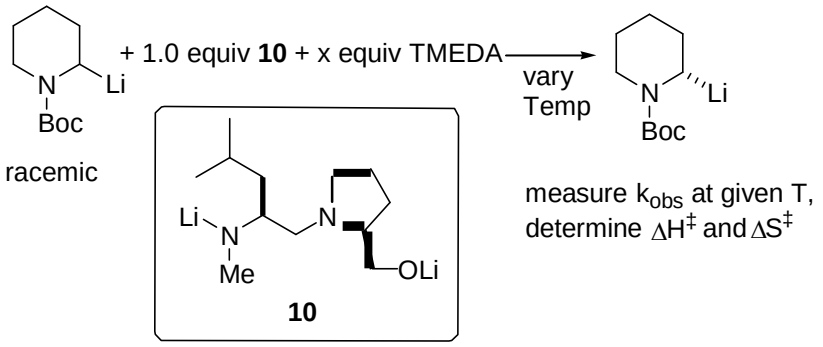


2.2.9. Activation Parameters for Dynamic Thermodynamic Resolution of 4·10 in the presence of TMEDA

This was followed by generating the organolithium 4 using tin–lithium exchange in Et_2O at –78 °C with n-BuLi and TMEDA, followed by addition of 10 (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.

Scheme 2.12. Dynamic resolution of 4 in the presence of 10 and TMEDA in Et_2O

DTR:



The inversion of 4 in the presence of 10 converges to 96:4. The equilibrium constant is therefore 96:4 in favor of the S-enantiomer. The rate constants were determined from nonlinear fits of the zero-order plots using the equation

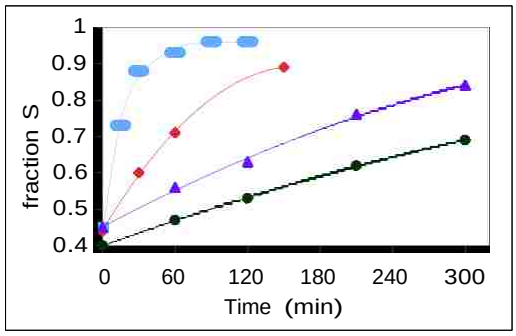
$$(S)_t = 0.96 + ((S_0) - 0.96)\exp(-k_{obs}t) \qquad (2.28)$$

where k_{obs} = observed rate constant for inversion and (S_0) = initial fraction of the S-enantiomer.

Figure 2.9. DTR of 4 (0.06 M) in the presence of 10 (1.0 equiv) and varying [TMEDA] in Et_2O.

a) 2.0 equiv TMEDA

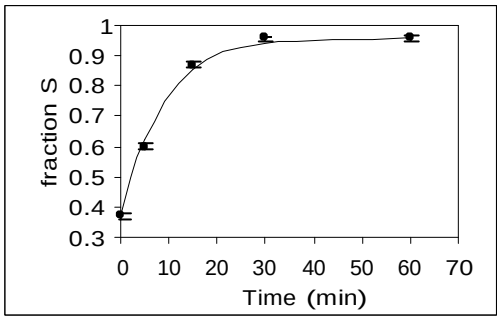
Zero-order plots.



KEY: 245 K; squares, 233 K; diamonds, 223 K, triangles, 213 K, circles

Fitted equation at T = 253 K

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

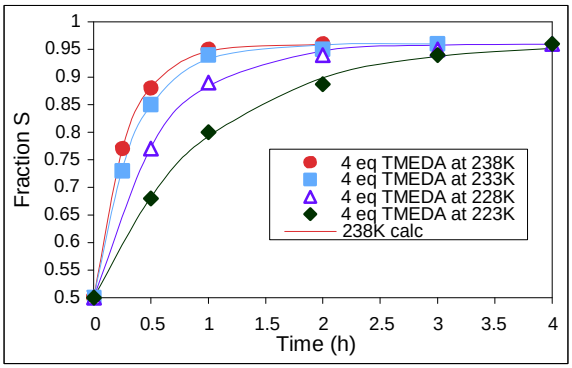


Rate constants

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

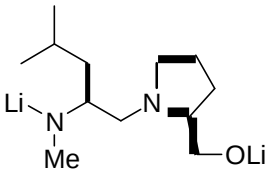
b) 4.0 equiv TMEDA

Zero-order plots.

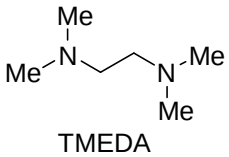


Rate constants

Temp (K)	k_{obs} (x 10^{-4} s^{-1})
223	2.80 ± 0.07
228	4.99 ± 0.04
233	7.89 ± 0.23
238	9.81 ± 0.06



10



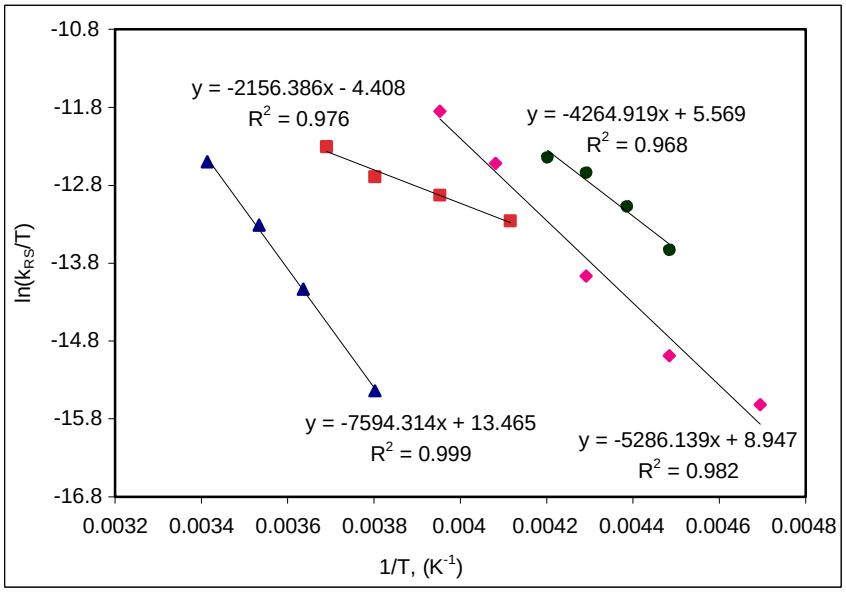
TMEDA

Eyring analysis of the rate constants at their respective temperatures for the DTR of 4·6 (Section 2.2.5) and 4·10 with varying TMEDA provided the plot in Figure 2.10a from which the thermodynamic parameters listed in Figure 2.10b were obtained. The R→S parameters are

calculated from forward rate constants, $k_{R\rightarrow S}$ and the S→R parameters are calculated from reverse rate constants, $k_{S\rightarrow R}$. The errors in $\Delta H^{\ddagger}$, $\Delta S^{\ddagger}$, and $\Delta G^{\ddagger}$ are calculated using standard error propagation rules.

Figure 2.10. a) Eyring plots for DTR of 4 in the presence of 6 (triangles), 6 + 2.0 equiv TMEDA (squares), 10 + 2.0 equiv TMEDA (diamonds) 10 + 4.0 equiv TMEDA (circles) (b) Thermodynamic parameters for DTR of 4

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

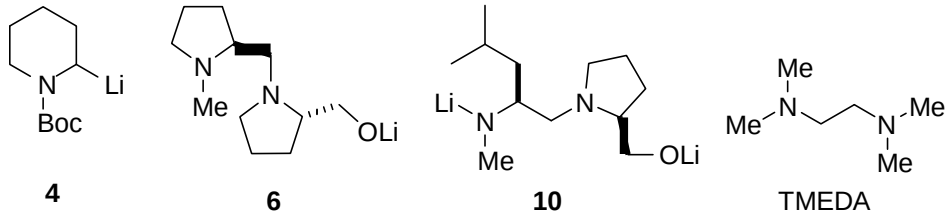


b) Thermodynamic parameters

RLi·L	Description	$\Delta H^{\ddagger}$ (kcal/mol)	$\Delta S^{\ddagger}$ (R→S) (cal/mol·K)
4·6	DTR of 4 with 6	15.1 ± 0.4	-20.4 ± 1.4
4·6·TMEDA	DTR of 4 with 6 and 2 equiv TMEDA	4.3 ± 0.5	–55.9 ± 1.8
4·10·TMEDA	DTR of 4 with 10 and 2 equiv TMEDA	10.5 ± 0.9	-29.3 ± 3.7
4·10·TMEDA	DTR of 4 with 10 and 4 equiv TMEDA	8.5 ± 1.1	-36.1 ± 4.7

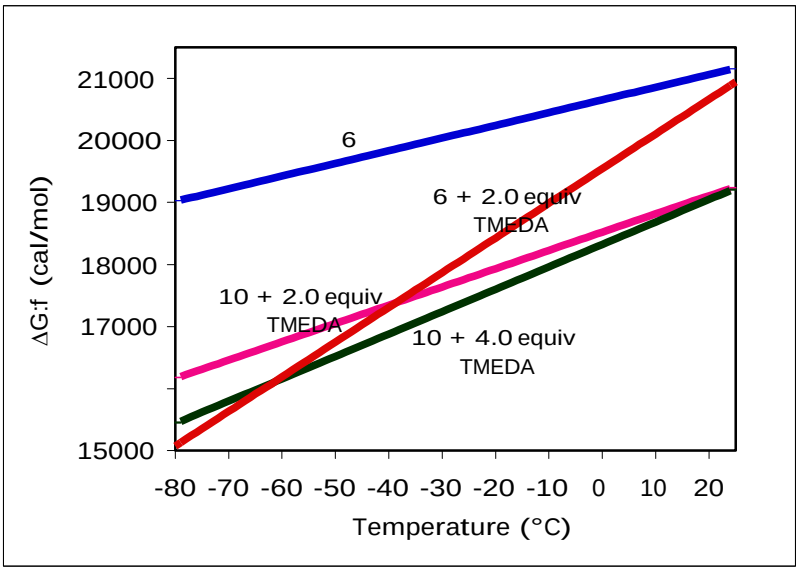
Plots of the relationship between the free energy of activation and temperature for DTR of 4·6 and 4·10 are shown in Figure 2.11. The DTR is mostly entropy controlled with large negative entropies such that $\Delta G^{\ddagger}$ increases with an increase in temperature although the rate constants also increase with an increase in temperature.

Figure 2.11. The relationship between $\Delta G^{\ddagger}$ and temperature for DTR of 4·6 and 4·10



4 **6** **10** TMEDA

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

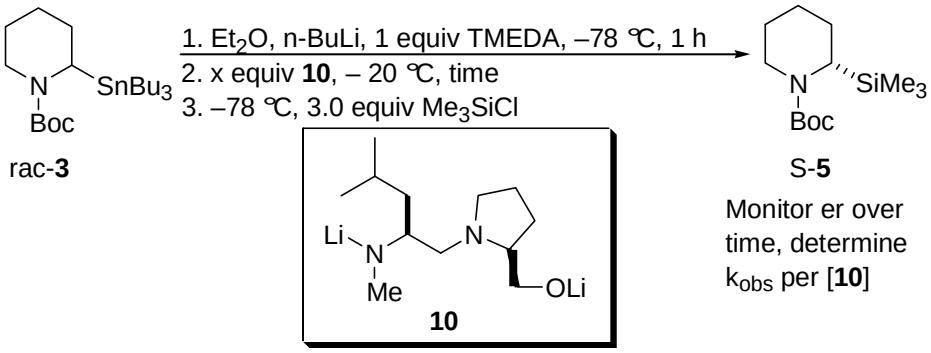


2.2.10. Effect of varying [10] on the Rate of Dynamic Resolution of 4·10

In order to determine the kinetic order in 10, the organolithium 4 was generated using tin–lithium exchange in Et_2O at –78 °C with n-BuLi (1.2 equiv) and TMEDA (1.0 equiv), followed by addition of varying amount of 10 (10 mol% to 100 mol%) and warming to –20 °C for various time intervals, then cooling to –78 °C prior to addition of 3 equiv Me_3SiCl and stirring for 4 h (Scheme 2.13). The zero-order plots for the resolution with varying amounts of

10 and the observed rate constants at their respective concentrations are shown in Figure 2.12. With 10, 25 and 50 mol% 10, the rate constants were determined starting from R-4 (80:20 er). However, with 75 and 100 mol% 10, the rate constants were determined starting from rac-4.

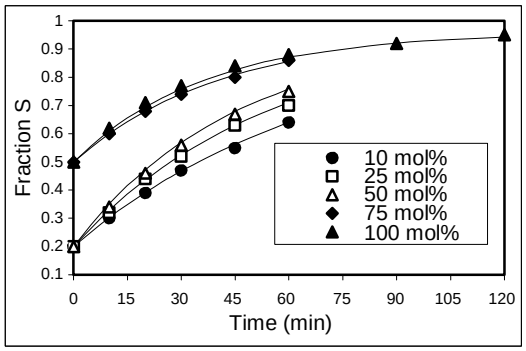
Scheme 2.13. Effect of varying [10] on dynamic resolution of 4



The rate of resolution increases nonlinearly with an increase in [10]. The downward curvature observed in Figure 2.12c reveals a fractional dependence of rate on [10]. A nonlinear fit of the equation $k_{obs} = k_x[10]^n$ (where k_x is the ligand-dependent rate coefficient and n is the specific order in 10) reveals that the kinetic order in 10 is approximately one-fourth ($n = 0.265 \pm 0.022$; rate coefficient, $k_x = 9.45 \times 10^{-4}\ M^{-1/4}s^{-1}$).

Figure 2.12. k_{obs} vs [10] for dynamic resolution of 4 (0.06 M) in the presence of TMEDA (1.0 equiv) at –20 °C in Et_2O

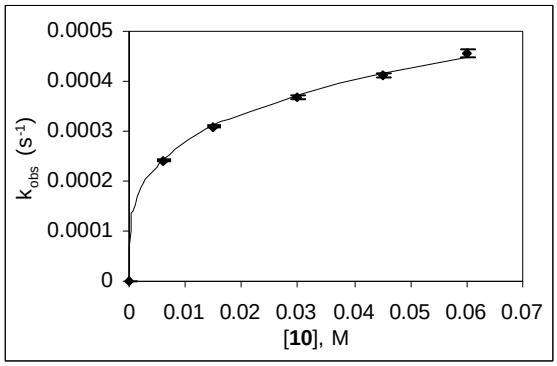
(a) Zero order plots



(b) Observed rate constants

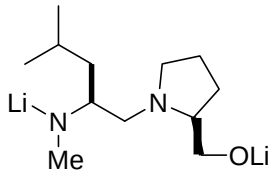
Amount of 10 (mol%)	k_{obs} (x 10^{-4} s^{-1})
0.00	0.00 ± 0.00
10	2.41 ± 0.06
25	3.10 ± 0.03
50	3.69 ± 0.04
75	4.12 ± 0.05
100	4.56 ± 0.08

(c) non linear plot of k_{obs} vs [10]



$k_{obs} = k_x[10]^n$, $k_x = 9.45 \times 10^{-4}$ $M^{-1/4}s^{-1}$

n = specific order in 10 = 0.265 ± 0.022

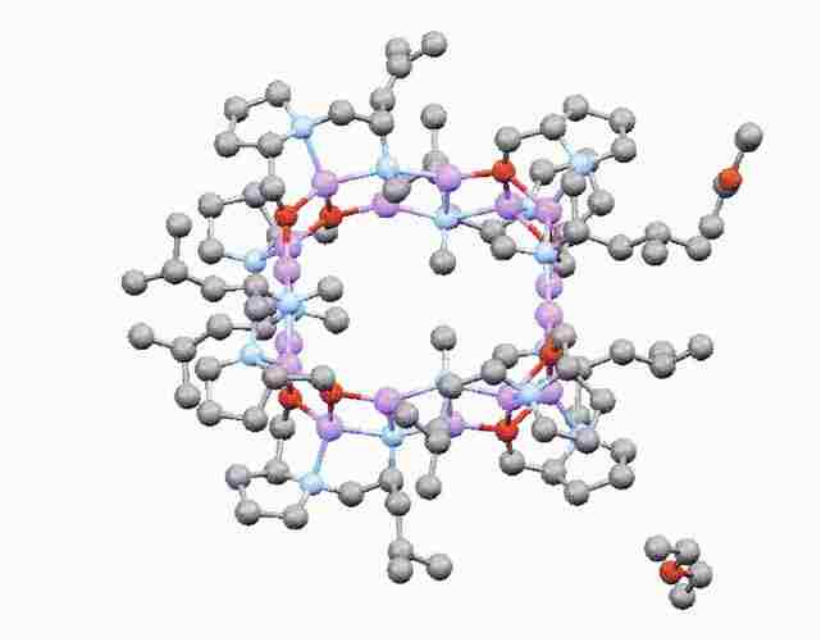


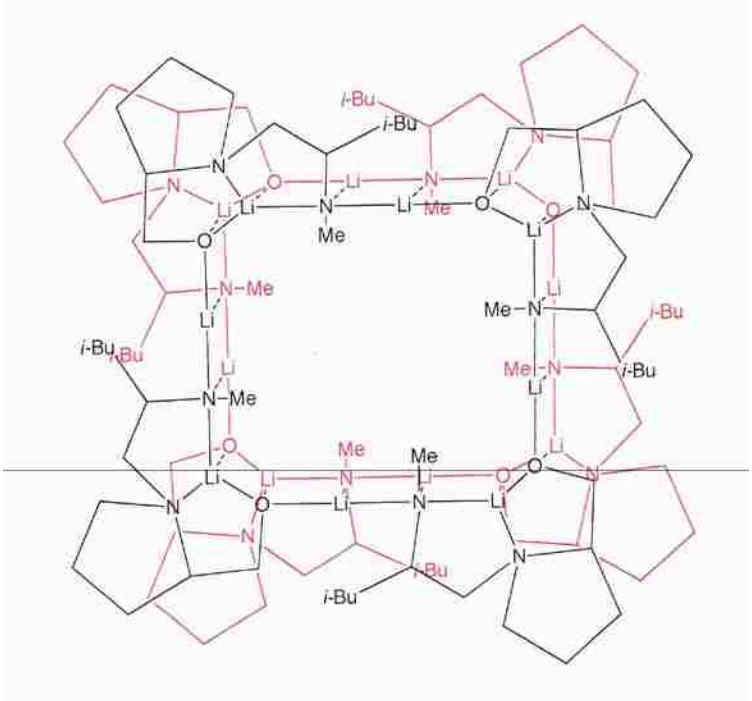
10

In a collaborative effort, the Williard group obtained the X-ray crystal structure of 10 in Et_2O and showed that it is an octomer in its resting state (Figure 2.13). Therefore, a kinetic order of n = 0.265 ± 0.022 implicates deaggregation of the octomer. Henceforth, the structure of 10 will be drawn as a monomer for simplicity.

Figure 2.13. X-ray crystal structure of 10 in Et_2O (obtained by Dr Paul Williard)

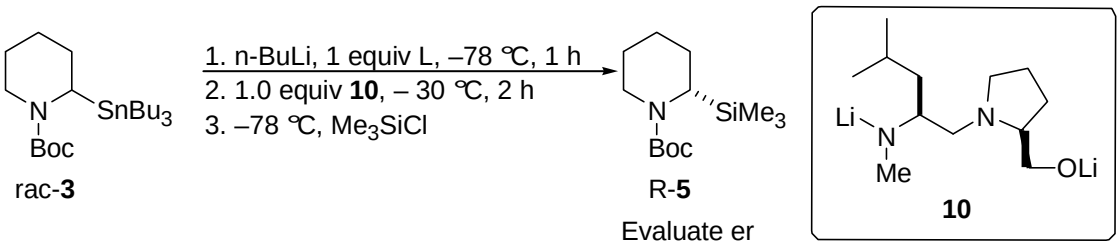
Key: Grey = carbon, red = oxygen, purple = lithium, light blue = nitrogen





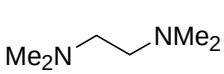
2.2.11. Dynamic Thermodynamic Resolution of N-Boc-2-lithiopiperidine in the Presence of 10 and other Achiral Ligands

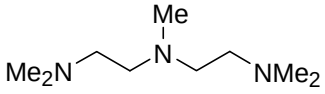
Scheme 2.14. DTR of 4·10 in the presence of other achiral ligands (1.0 equiv) in Et_2O

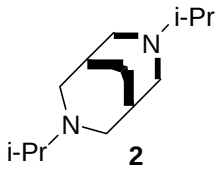


The effect of the achiral ligand on the enantioselectivities and yields obtained in a DTR was followed by generating the organolithium 4 using tin–lithium exchange in Et_2O at –78 °C with n-BuLi (1.2 equiv) and an additional achiral ligand, followed by addition of 10 (1.0 equiv) and warming to –30 °C for 2 h, cooling to –78 °C, addition of 3 equiv Me_3SiCl and stirring for 4 h. Ligand 10, with four equivalents of TMEDA, promotes dynamic resolution under thermodynamic control to give the product S-5 in 74% yield and 96:4 er (Table 2.5, entry 1). However, without TMEDA, no DTR was observed after 120 min at this temperature and racemic silane was produced (entry 2). Gradual enantioenrichment upon warming to higher temperatures was observed but the yield of the silane was very low. The bulky pentamethyl diethylenetriamine (PMDTA) gave rather low selectivity (entry 3). Diisopropylbispidine 2 gave reasonable yield of S-5 with a high enantioselectivity (entry 4). However, its presence complicates recovery of 10 (acid workup affords the protonated forms of 2 and 10 in the aqueous layer) and its synthesis from N-isopropylpiperidone via a Mannich reaction, followed by a Wolf-Kishner reduction, proceeds in low yield.[27]

Table 2.5. Resolution of 4 in the presence of 10 and other ligands in Et_2O







2

Entry	Ligand (1.0 equiv)	Yield (%) 5	er (S:R)
1	TMEDA	74	96:4
2	None	40	50:50
3	PMDTA	63	73:27
4	2	46	96:4

Based on the overall yields and selectivities, the results indicate that other achiral ligands do not enhance the DTR of 4 as effectively as TMEDA.

2.3. Summary and Mechanistic Hypotheses

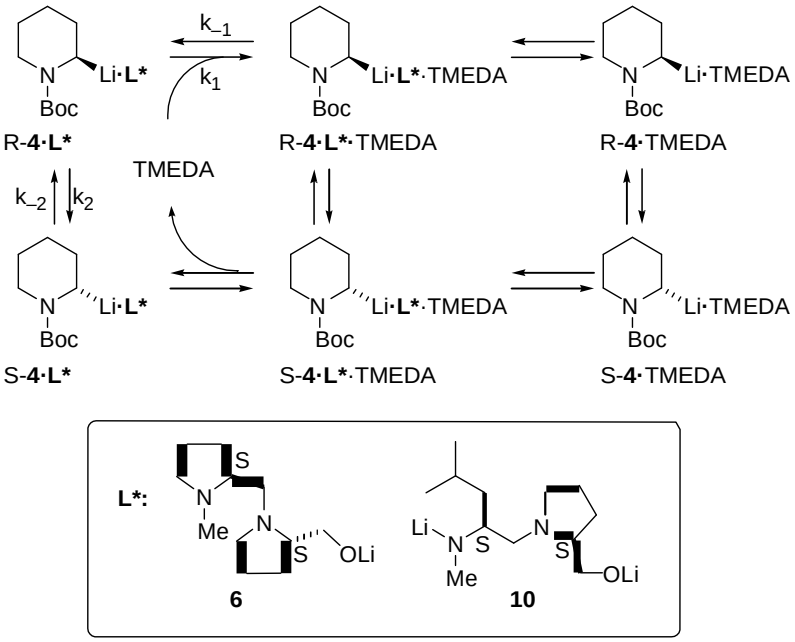
The following mechanistic insights have emerged from our kinetic studies:

1. TMEDA facilitates the generation of N-Boc-2-lithiopiperidine 4 by deprotonation at low temperatures. The deprotonation of 4 in the absence of TMEDA or in the presence of (–)-sparteine, 2, 6, 10 occurs very slowly at –78 °C.
2. Transmetalation of 3 to 4 occurs slowly and 4 exhibits loss of configurational stability in the absence of any ligands even at –78 °C. The rate of racemization of N-Boc-2-lithiopiperidine 4 is at a maximum when the ratio 4:TMEDA = 1. Racemization is first order in [TMEDA] from 0.1 to 1 equivalent of TMEDA but there an inverse concentration dependence when TMEDA is in excess of 4. Therefore, excess TMEDA stabilizes the anion configuration of 4. The free energy barrier to racemization therefore increases with an increasing amount of TMEDA.
3. TMEDA accelerates the DTR. The stoichiometric DTR is first order in [TMEDA] from 0.1 to 2 equiv. Two parallel pathways for the DTR have been revealed by the kinetics.

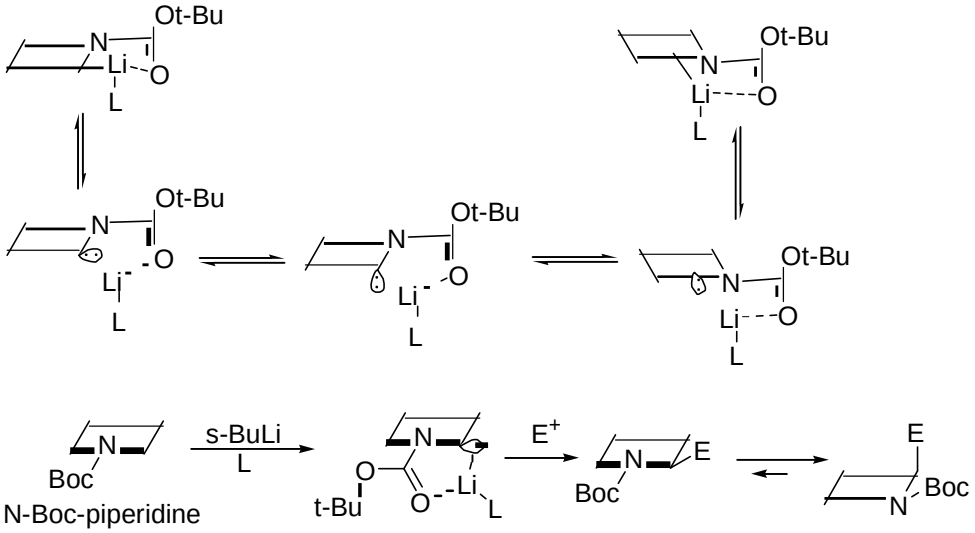
One of the pathways is slow and has a zero-order dependence on TMEDA whereas the other is fast and is catalyzed by TMEDA. The free energy barrier to DTR drops significantly with an increase in [TMEDA]. Based on the overall yields and selectivities, the results indicate that other achiral ligands do not enhance the DTR of 4 as effectively as TMEDA.

4. Excess chiral ligand 6 retards DTR. The rate of DTR of 4 is at a maximum with the ratio 4:6 = 1. The kinetic order for DTR of 4 is inverse half-order in [6] when the latter is in excess, such that the rate of DTR decreases with increasing [6].
5. The rate law for the DTR, using excess monolithiated diaminoalkoxide 6, is: $\frac{d[S\text{-}\mathbf{4}]}{dt} = k_{DTR}[R\text{-}\mathbf{4}][TMEDA][\mathbf{6}]^{-0.5}$
6. DTR of 4 by 6 or 10, in the presence of TMEDA, is mostly entropy controlled.
7. DTR of 4 by 10 and electrophilic quench with Me_3SiCl gratifyingly gives enantiomer ratios as high as 96:4 while diastereomic ligand 9 yields the opposite enantiomer, R-5 in 98:2 er.
8. The kinetic order in 10 for dynamic resolution of 4 in the presence of up to one equivalent of 10 is 0.265 ± 0.022, such that the rate increases nonlinearly with increasing [10].
9. The X-ray crystal structure of 10 reveals that 10 is an octomer in its resting state in Et_2O such that deaggregation to the dimer is implicated.

Scheme 2.15a. Proposed mechanism for DTR of 4



Scheme 2.15b. Conducted tour mechanism for inversion of 4



Scheme 2.15a illustrates possible mechanisms that could operate in the inversion dynamics of 4 with or without TMEDA. The enantiomerization in the presence of TMEDA is characterized by a 1st-order dependence in TMEDA when it is present in limiting amounts, and an inverse dependence in the presence of excess TMEDA over 4. The left vertical equilibrium depicts the

DTR uncatalyzed by TMEDA. The kinetics of inversion are slow and the DTR barrier is high. The yields of the products obtained following electrophilic quench are very low due to the low thermal stability of the organolithiums at the high temperatures where the dynamics were measured. The second vertical equilibrium from left to right describes a DTR that is catalyzed by TMEDA with a 1^{st}-order dependence. The thermodynamic parameters for DTR in the absence or presence of TMEDA are very surprising (Figure 2.10b). The DTR is mostly entropy controlled with large negative entropies that signify high order in the transition state leading to carbanion inversion, consistent with the formation of the ternary complexes. The large negative entropies could also be as a result of multiple pre-equilibria involved as a consequence of deaggregation of 6_n or 10_8.

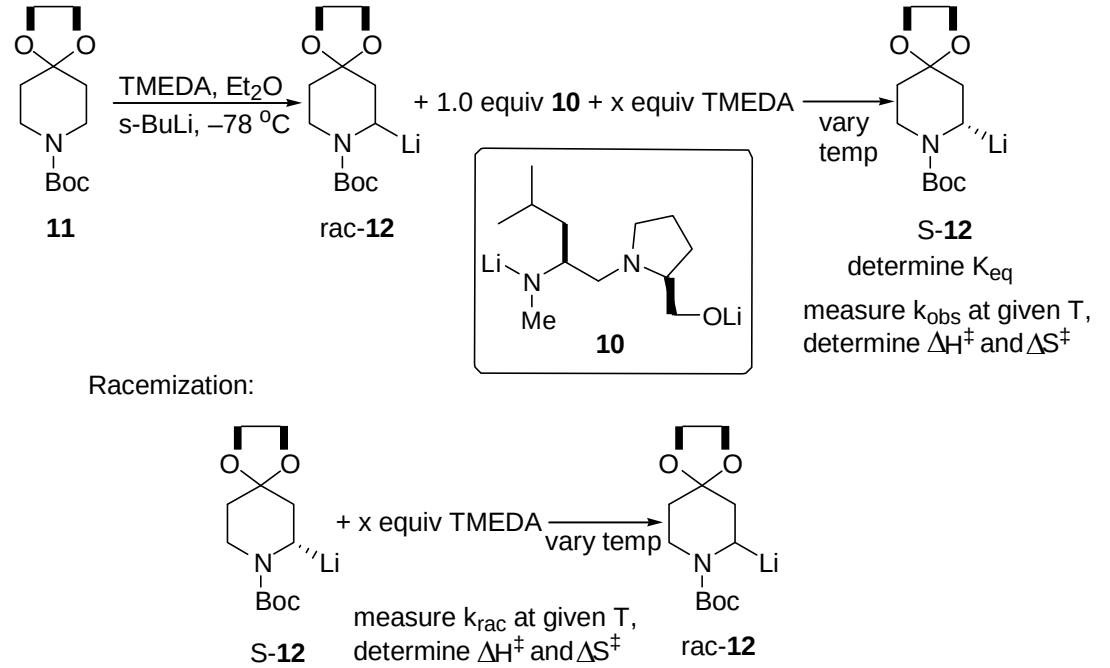
These results have implications in catalytic dynamic resolution chemistry and we are interested in understanding the crucial role played by the ligand exchange processes between the chiral and achiral ligands.

Case 2: Ethylene ketal of N-Boc-2-lithio-4-oxopiperidine 12

Objective: The specific goals of this section are as follows:

1. Determine the equilibrium constant for the dynamic resolution of 12 in the presence of 10 and TMEDA
2. Determine the thermodynamic parameters for racemization and dynamic resolution of 12 in the presence of TMEDA.

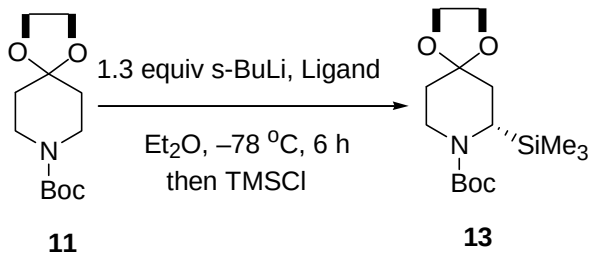
Scheme 2.16. Generalized scheme for DTR of 12·10 and racemization of 12 in the presence of TMEDA in Et_2O



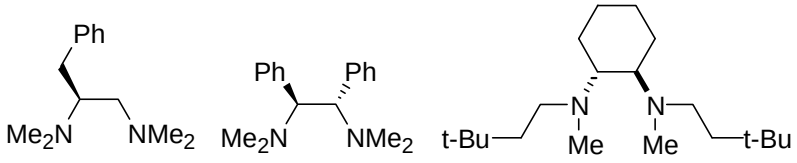
In 1990, Beak showed that using 11, rac-12 can be conveniently generated by deprotonation using s-BuLi and TMEDA. Subsequent alkylation of 12 with methyl iodide provided the 2,4-disubstituted adduct.[28] Later, Laha showed that treatment of rac-12 with Me_3SiCl followed by another lithiation-silylation provided a 2,4,6-trisubstituted product but the relative configuration was unspecified. The 2,4,6-trisubstituted product then served as an intermediate for the synthesis of various cocaine antagonists.[29] In 2007, the O'Brien and

Coldham groups jointly reported the first attempt to generate 12 enantioselectively by deprotonation using s-BuLi and one of several chiral diamine ligands (Scheme 2.17).[14] After quenching with Me_3SiCl, the maximum er reported by the authors was 60:40 in favor of the S-enantiomer of the silane.

Scheme 2.17. Coldham's conditions for enantioselective deprotonation of 11.[14]



11 **13**

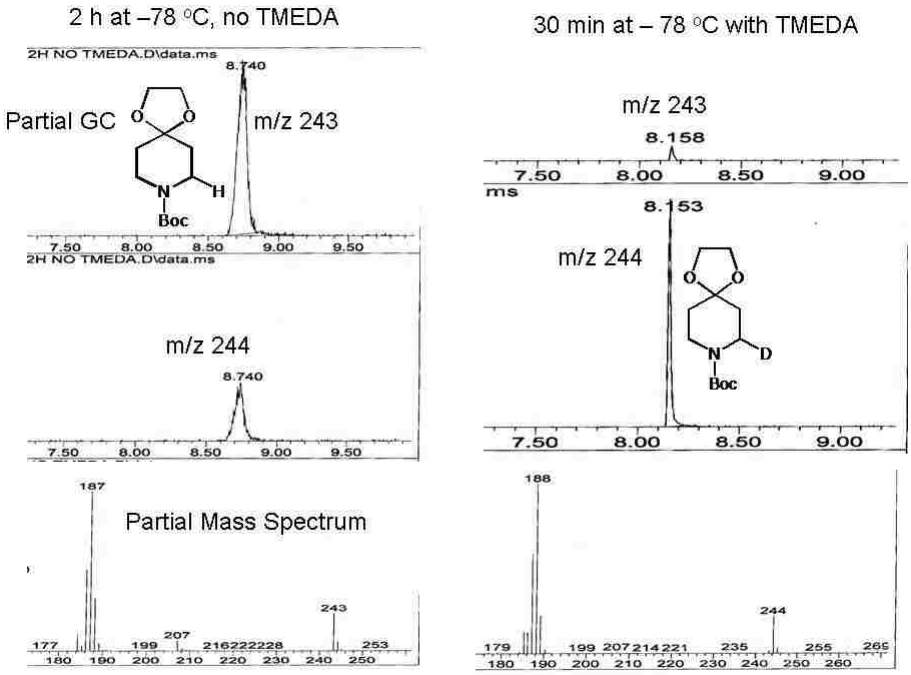
Ligand			
Yield (%)	47	6	53
er of **13** (S:R)	60:40	60:40	47:53

2.4. Activation parameters for resolution of 12 in the presence of 10 and TMEDA

As mentioned previously, an alternative approach to induce asymmetry on the 2-position of a piperidine heterocycle is by electrophilic quench of the resolved 2-lithiated derivative obtained by dynamic resolution. We began by investigating the extent of deprotonation of 11 in the absence of a ligand and in the presence of TMEDA. In the absence of a ligand, ~20% deprotonation was observed after 2 h at –78 °C. It should be recalled that no deprotonation of N-Boc-piperidine was observed after 10 h. In the presence of TMEDA, deprotonation of 11 was complete after an hour at –78 °C (Figure 2.14). The extent of deprotonation of 11 in the presence of TMEDA is therefore three times faster than that of N-Boc-piperidine, which requires

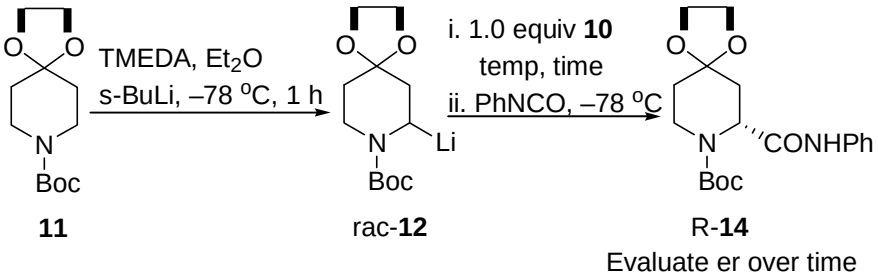
at least three hours under identical conditions. The MS traces are obtained from electron impact ionization.

Figure 2.14. Partial GC and MS traces for deprotonation of 11 in the absence (left) and in the presence of TMEDA (right)



Our initial optimization of the DTR of 12 started with the previously optimized conditions for DTR of N-Boc-2-lithiopiperidine (see Scheme 2.11). Thus in oven-dried septum capped tubes, 11 (0.06 M in Et_2O) and TMEDA (4.0 equiv) were treated with s-BuLi at –78 °C to effect deprotonation, affording rac-12·TMEDA. (Scheme 2.18). A stoichiometric amount of the preformed dilithio diaminoalkoxide 10, was added to each of the tubes at –78 °C and the tubes were quickly transferred to a second thermostatted bath at –30 °C (see Experimental Section for details). At various time intervals, a tube was cooled to –78 °C and quenched with excess phenyl isocyanate. CSP-SFC analysis provided the enantiomer ratio of the anilides. The above procedure was repeated at –40 °C, –45 °C and –50 °C.

Scheme 2.18. DTR of 12·10 in the presence of 4 equiv TMEDA in Et_2O



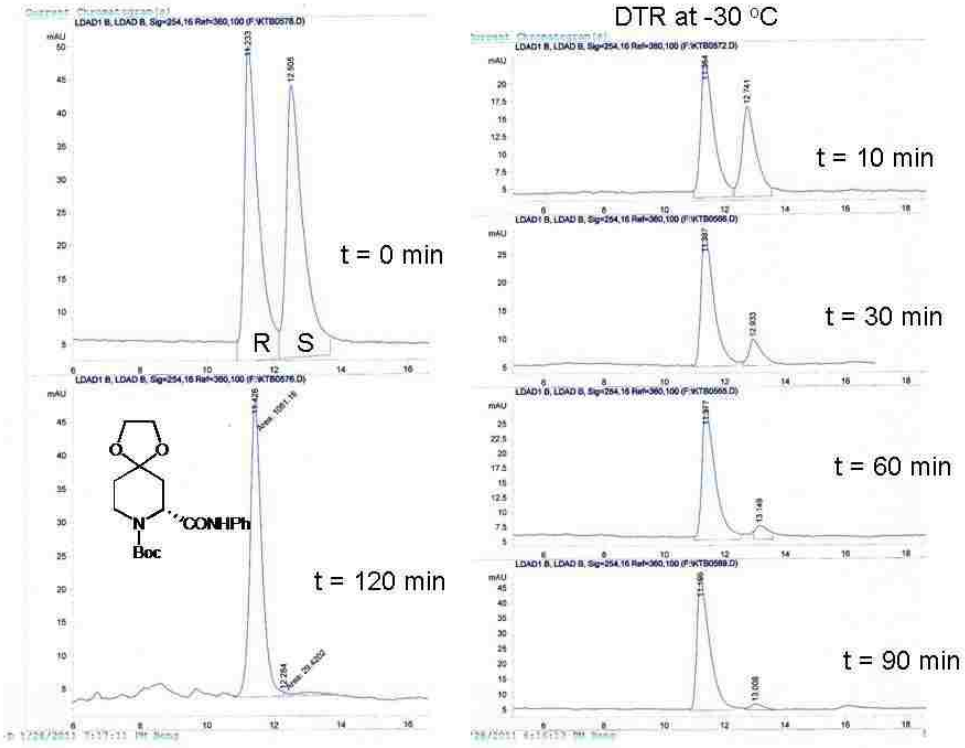
In duplicate experiments, the inversion of 12 in the presence of 10 at –30 °C converged to 98:2 er in favor of the S-organolithium. Longer reaction times and higher temperatures (–20 °C and –10 °C) did not change the er of R-14. In addition, when a resolved mixture of 12·10 was quenched with methyl chloroformate, the ester was obtained with no loss of enantioselectivity. These findings reveal that ligand 10 has a preference for one diastereomeric complex (S-12·10:R-12·10 = 98:2).

Note that S-12 affords R-14 due to change in CIP priority. Using reversible first-order kinetics,[19] the fraction of the major enantiomer in a DTR (S in this case), starting from a racemate, as a function of time (t), is given by:

$$(S)_t = (S)_{eq} + (0.5 - (S)_{eq})\left(e^{k_{obs}t}\right) \qquad (2.29)$$

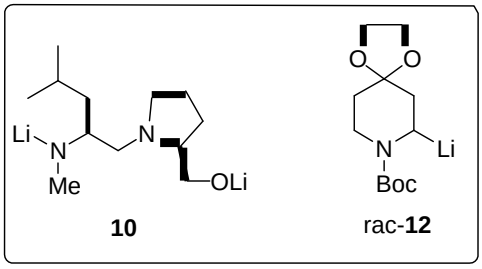
where k_{obs} is the observed rate constant for equilibration. Knowing the equilibrium constant for the resolution of 12·10, the observed rate constants at the respective temperatures were obtained from nonlinear fits of the zero-order plots using the above equation, where $(S)_{eq} = 0.98$ and the results are shown in Figure 2.16.

Figure 2.15. CSP-SFC traces for product 14 formed by DTR of 12·10 in the presence of 4 equiv TMEDA at 243 K in Et_2O.

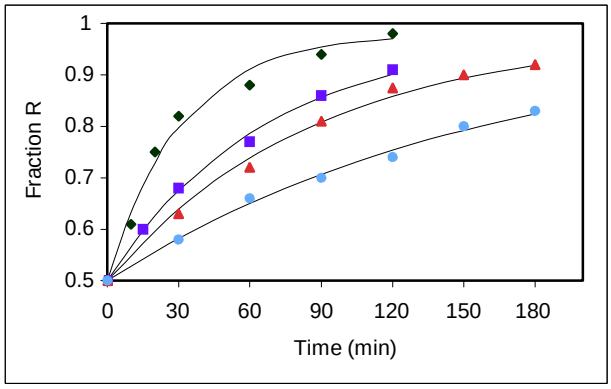


Since we did not observe any deprotonation of N-Boc-piperidine in the absence of TMEDA at –78 °C,[17] it was unsurprising that the formation of 12 from 11 in the absence of TMEDA required elevated temperatures but when a DTR was attempted at –30 °C for 2 h, rac-14 was obtained. Thus TMEDA facilitates the deprotonation and also catalyzes the DTR of 12 by 10.

Figure 2.16. DTR of 12 (0.06 M) in the presence of 10 (1.0 equiv) and TMEDA (4.0 equiv) in Et_2O.



a) Zero order plots.



KEY: 243 K; diamonds, 233 K; squares, 228 K, triangles, 223 K, circles

b) Rate constants

Temp (K)	k_{obs} (x 10^{-4} s^{-1})
243	5.389
233	2.514
228	1.906
223	1.04

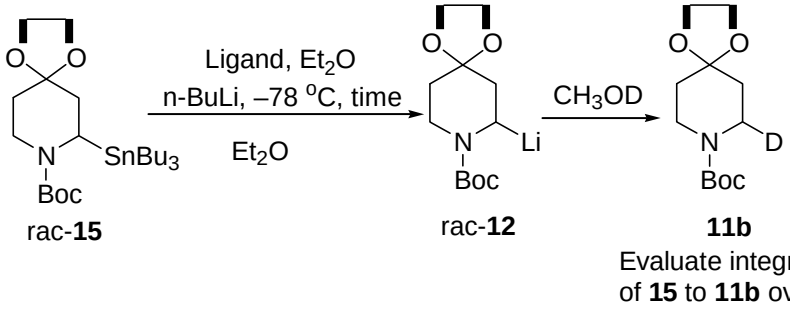
2.5. Activation Parameters for Enantiomerization of S-12 (93:7 er) in the Presence of TMEDA

In order to examine the kinetics of enantiomerization of 12, the stannane S-15 was prepared in 93:7 er by DTR using ligand 10 and the thermodynamic parameters for racemization of 12 were measured in the presence of four equivalents of TMEDA, using previously reported methods.[11, 30]

The extent of formation of 12 from 15 by tin-lithium exchange was followed by generating 12 using n-BuLi, zero or four equivalents of TMEDA at –78 °C in Et_2O. After several time

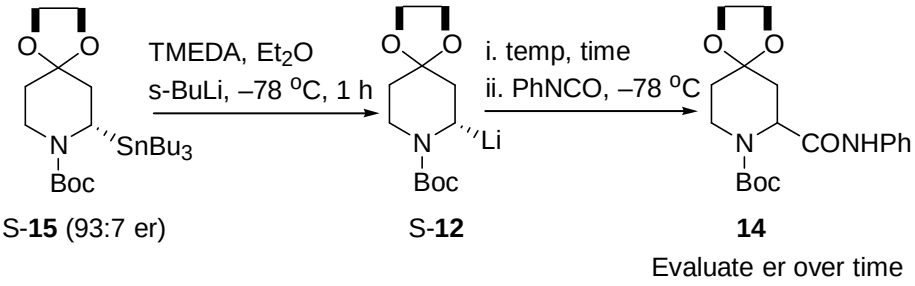
intervals, 12 was trapped with MeOD, and the amount of 12 formed was estimated by comparing the integral ratio of unreacted 15 to that of the singly deuterated piperidine, 11b.

Scheme 2.19. Transmetalation of rac-15 in the presence or absence of TMEDA



After 1 hour of treatment of 15 with n-BuLi (1.2 equiv) at –78 °C, quenching with MeOD revealed only 5% deuteration. Formation of 12 was 50% complete after three hours. However, in the presence of TMEDA (4 equiv), complete transmetalation was observed after just thirty minutes. These findings reveal that (i) TMEDA enhances the transmetalation of 15 to 12 in Et_2O; (ii) in the absence of a ligand, formation of the organolithium 12 by tin-lithium exchange is relatively faster ($t_{1/2}$ ~3 h) than the formation of N-Boc-2-lithiopiperidine 4 under identical conditions ($t_{1/2}$ ~5.8 h at –78 °C, see equation 2.1).

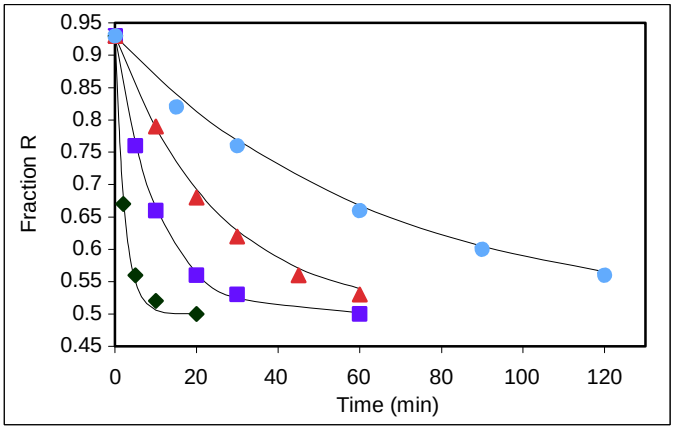
Scheme 2.20. Racemization of S-12 (93:7 er) in the presence of 4 equiv TMEDA



Transmetalation of S-15 (93:7 er, 0.06 M in Et_2O) at –78 °C in the presence of 4 equiv of TMEDA, then stirring at temperatures from –50 to –30 °C, followed by cooling to –78 °C and electrophilic quench with phenyl isocyanate afforded 14 whose er was evaluated by CSP-SFC.

Figure 2.17. Enantiomerization of S-12 (93:7 er, 0.06 M) in the presence of TMEDA (4.0 equiv) in Et_2O.

a) Zero order plots.



KEY: 243 K; diamonds, 233 K; squares, 228 K, triangles, 223 K, circles

b) Rate constants

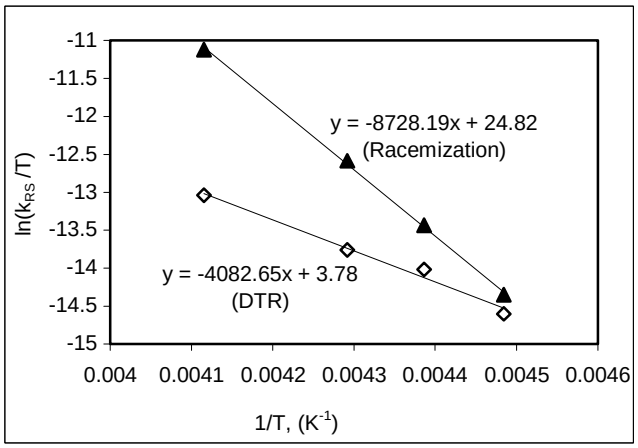
Temp (K)	k_{rac} (x 10^{-4} s^{-1})
243	71.923
233	15.936
228	6.679
223	2.614

Table 2.6. Thermodyamic parameters for inversion of 12

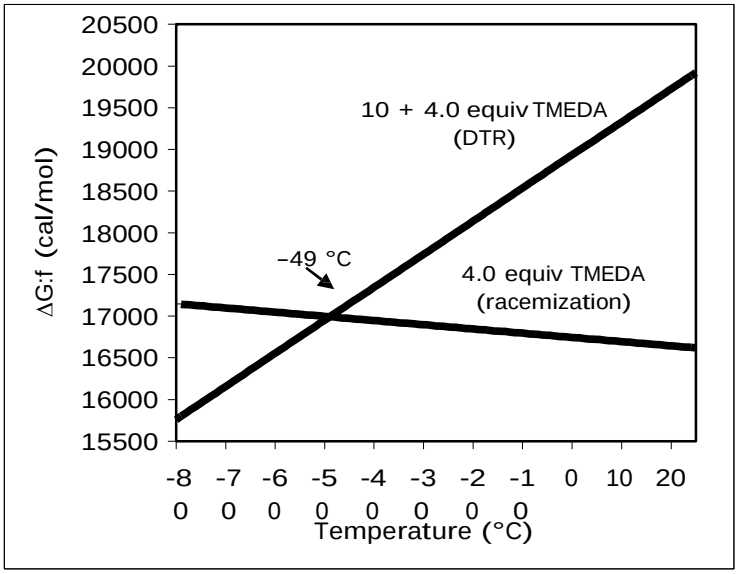
RLi·L	Description	$\Delta H^{\ddagger}$ (kcal/mol)	$\Delta S^{\ddagger}$ (R→S) (cal/mol·K)
12·10·TMEDA	DTR of 12 with 10 and 4 equiv TMEDA	8.1 ± 0.7	-39.7 ± 3.0
12·TMEDA	Racemization of 12 with 4 equiv TMEDA	17.3 ± 0.4	2.1 ± 0.1

Figure 2.18. (a) Eyring plots (b) The relationship between $\Delta G^{\ddagger}$ and temperature for racemization of S-12 and DTR of 12·10, both in the presence of 4.0 equiv TMEDA.

$$\ln \frac{k_{RS}}{T} = -\frac{\Delta H^{\ddagger}}{RT} + \ln \frac{k_B}{h} + \frac{\Delta S^{\ddagger}}{R}$$



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



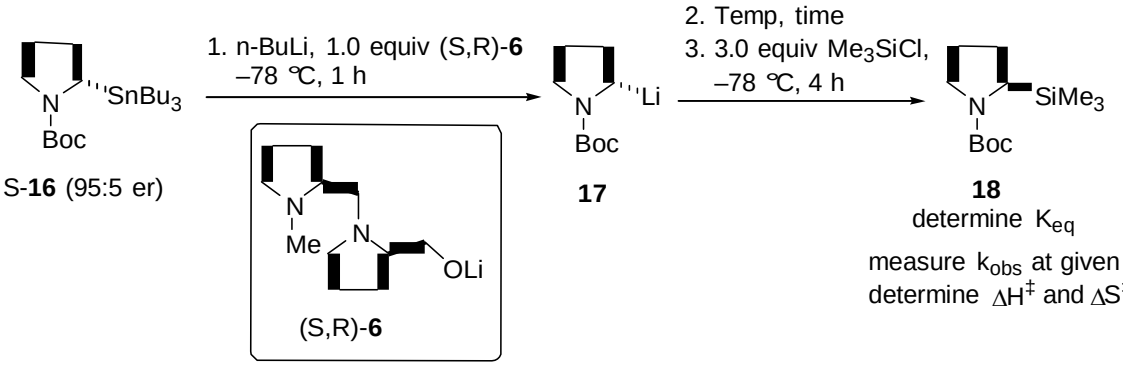
Case 3. N-Boc-2-lithiopyrrolidine 17

The asymmetric synthesis of 2-substituted pyrrolidines has been the focus of many research groups in the last few decades.[31-36] Beak and coworkers showed that stoichiometric chiral ligands such as (–)-sparteine 1, when complexed to sec-butyllithium, form a chiral base that is capable of enantioselective deprotonation of N-Boc-pyrrolidine.[37] Later, O'Brien demonstrated that substoichiometric amounts of 1, in combination with diisopropylbispidine 2 are also capable of asymmetric deprotonation.[38] Our approach to asymmetric synthesis using chiral racemic organolithiums employs dynamic thermodynamic resolution (DTR).

Statement of the Problem: The specific goal of this section is to determine the thermodynamic parameters for racemization and dynamic resolution of N-Boc-2-lithiopyrrolidine in the presence or absence of selected diamine ligands.

2.6. Enantiomerization of N-Boc-2-lithiopyrrolidine 17 in the presence of (S,R)-6

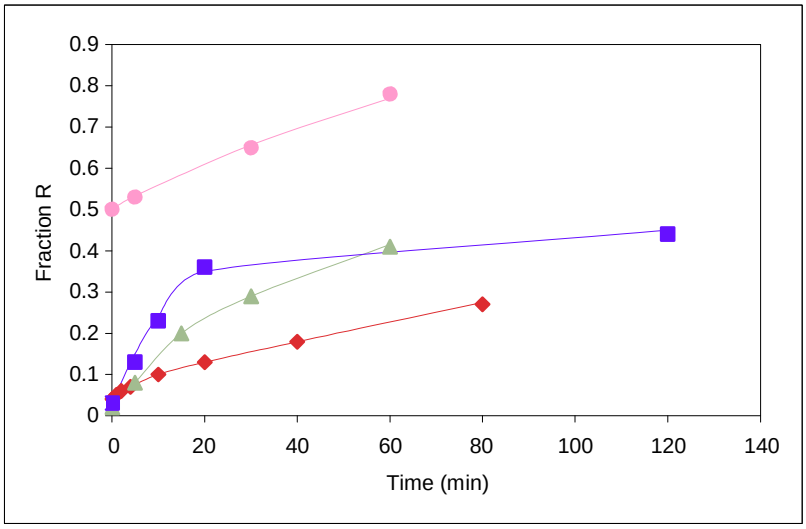
Scheme 2.21. Enantiomerization of S-17 (95:5 er) in the presence of (S,R)-6



Transmetalation of S-16 (95:5 er) with n-BuLi (1.2 equiv) in the presence of one equivalent of (S,R)-6 at –78 °C for an hour and quenching with Me_3SiCl afforded S-18 of 95:5 er. When 17·(S,R)-6 of 95:5 er was warmed to –20 °C for 60 minutes, cooling to –78 °C and quenching with excess Me_3SiCl afforded R-18 in 83:17 er. Stirring for an additional 60 minutes at –20 °C did not change the enantiomer ratio and R-18 of 83:17 er was obtained.

Transmetalation of rac-16 at –78 °C for an hour followed by addition of one equivalent of (S,R)-6, warming to –20 °C for 5, 30 and 60 min, then cooling to –78 °C and quenching with excess Me_3SiCl afforded R-18 in 53:47, 65:35, and 78:22 er respectively. When the resolution was performed at –5 °C for 1 to 4 hours, cooling to –78 °C and quenching with excess Me_3SiCl afforded R-18 in 83:17 er. Thus the inversion of 17 in the presence of (S,R)-6 converges to 83:17 er (R:S). The equilibrium constant is therefore 83:17 in favor of the R-enantiomer.

Figure 2.19. (a) Zero-order plots for DTR of rac-17 at 253 K (circles) and for enantiomerization of S-17 (95:5 er) in the presence of 1.0 equiv (S,R)-6 in Et_2O at 246 K (squares), 241 K (triangles) and 235 K (diamonds).



(b) Observed rate constants

Temp (K)	k_{obs} (10^{-5} s^{-1})
253	82.9 ± 6.45
246	22.3 ± 0.74
241	8.99 ± 0.83
235	3.48 ± 0.17

Knowing the equilibrium constant, the enantiomerization dynamics were carried out at 235 K, 241 K, 246 K and 253 K and the observed rate constants at their respective temperatures were determined from nonlinear fits of the zero-order plots (Figure 2.19) using the equation

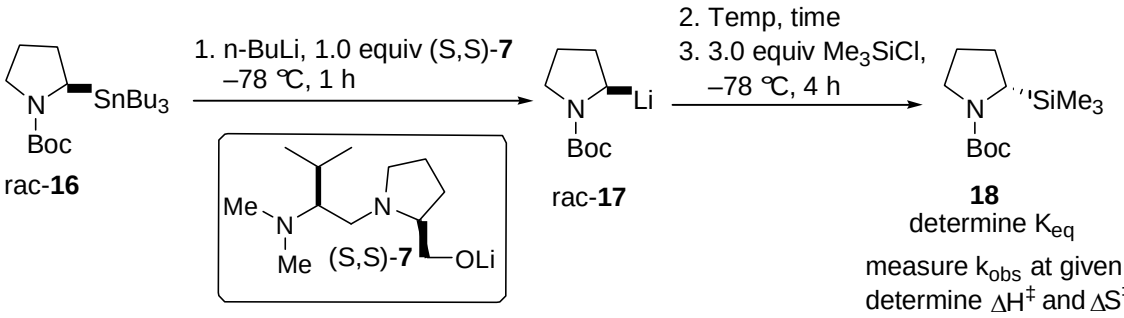
$$(R)_t = 0.83 + ((0.05 - 0.83)\exp(-k_{obs}t)$$

where k_{obs} = observed rate constant for inversion, 0.05 = initial fraction of the R-enantiomer, 0.83 = fraction of the R-enantiomer at equilibrium.

2.7. Dynamic Thermodynamic Resolution of 17 in the presence of (S,S)-7

Dynamic thermodynamic resolution was followed by generating the racemic organolithium 16 using tin–lithium exchange in Et_2O at –78 °C with n-BuLi and 1.0 equivalent of (S,S)-7, followed by warming to the desired temperature for different time periods, then cooling to –78 °C and quenching with excess Me_3SiCl.

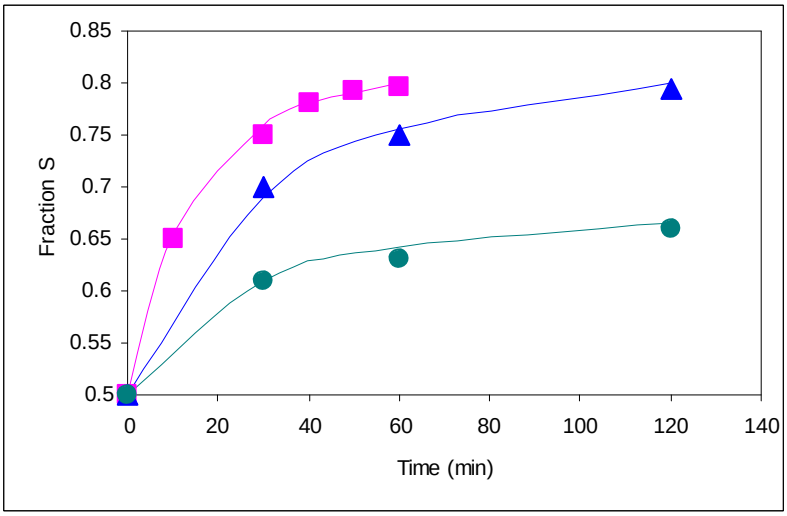
Scheme 2.22. DTR of rac-17 (0.06 M) in the presence of (S,S)-7 in Et_2O



The observed rate constants at their respective temperatures were obtained from nonlinear fits of the zero-order plots as previously described.[17]

$$(S)_t = 0.80 + ((0.50 - 0.80)\exp(-k_{obs}t)$$

Figure 2.20. (a) Zero-order plots and observed rate constants for DTR of rac-17 in the presence of 1.0 equiv (S,S)-7 in Et_2O at 263 K (circles), 276 K (triangles) and 283 K (squares).



(b) Observed rate constants

Temp (K)	k_{obs} ($10^{-4}s^{-1}$)
283	6.33 ± 0.38
276	2.83 ± 0.31
263	0.281 ± 0.01

For all the enantiomerization and resolution data, Eyring analysis of the rate constants at their respective temperatures provided the thermodynamic parameters listed in Table 2.7. Plots of the relationship between free energy of activation and temperature for inversion of 17 are shown in Figure 2.21.

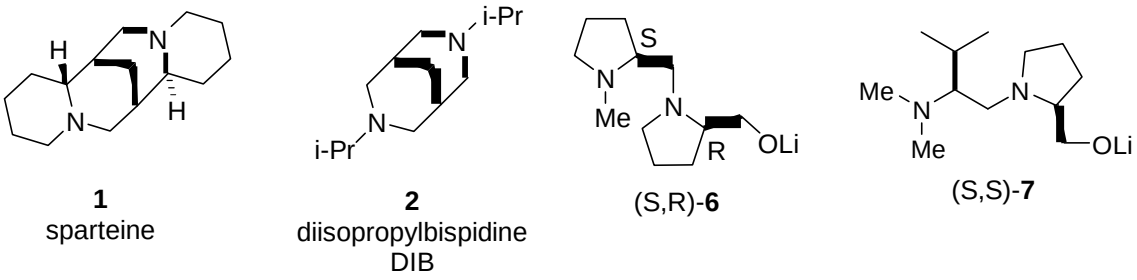
Table 2.7. Thermodynamic parameters for inversion of 17 in the presence of various diamine ligands.[11]

Ligand	$\Delta H^{\ddagger}$ (R→S) = (S→R) (kcal/mol)	$\Delta S^{\ddagger}$ (R→S) (cal/mol.K)	$\Delta S^{\ddagger}$ (S→R) (cal/mol.K)
None	29.4 ± 4.1[a]	39.5 ± 16.4	39.5 ± 16.4
1	18.2 ± 0.71[a]	-7.8 ± 2.8	-7.8 ± 2.8
2	27.6 ± 1.1[a]	30.4 ± 4.2	30.4 ± 4.2
(S,S)-7	22.5 ± 3.5	6.3 ± 2.7	3.5 ± 2.7
(S,R)-6	20.3 ± 1.0	4.5 ± 3.9	8.0 ± 3.9

[a]The thermodynamic parameters are taken from previously reported data.[11]

For N-Boc-2-lithiopyrrolidine, the free energy barrier decreases with an increase in temperature in the presence of 2, (S,R)-6, (S,S)-7 and in the absence of a ligand. These systems are mostly enthalpy controlled. However, the free energy barrier increases with an increase in temperature for racemization in the presence of 1. This difference reveals the effect of negative entropy in this system, suggesting a higher degree of organization in the transition state leading to carbanion inversion (Figure 2.21).

Figure 2.21. Relationship between free energy of activation and temperature for inversion of 17 in the presence of various diamine ligands

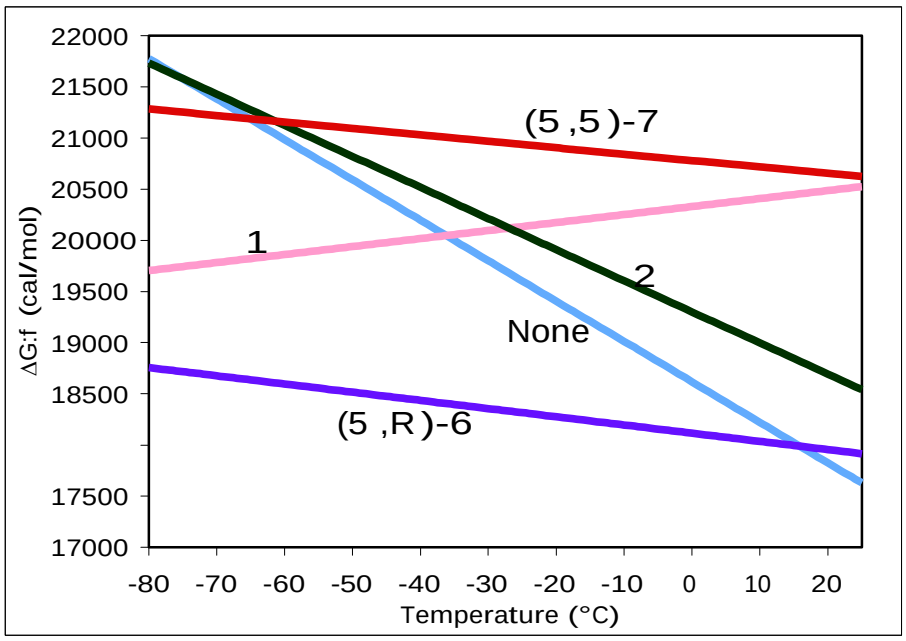


1
sparteine

2
diisopropylbispidine
DIB

(S,R)-**6**

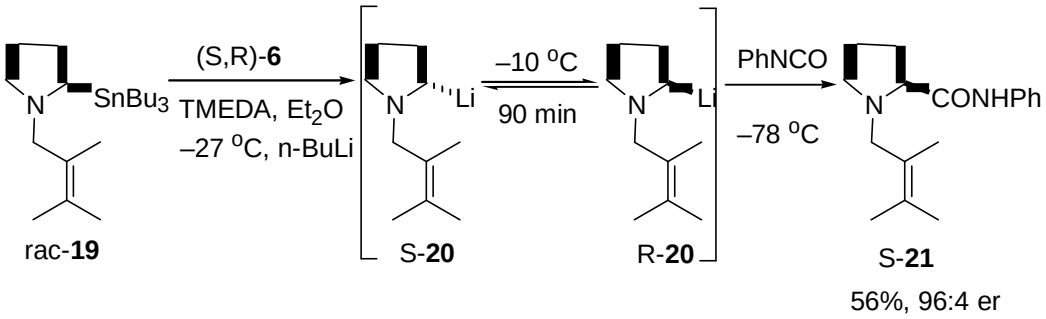
(S,S)-**7**



2.8. Thermodynamic Parameters for Inversion of N-trimethylallyl-2-lithiopyrrolidine

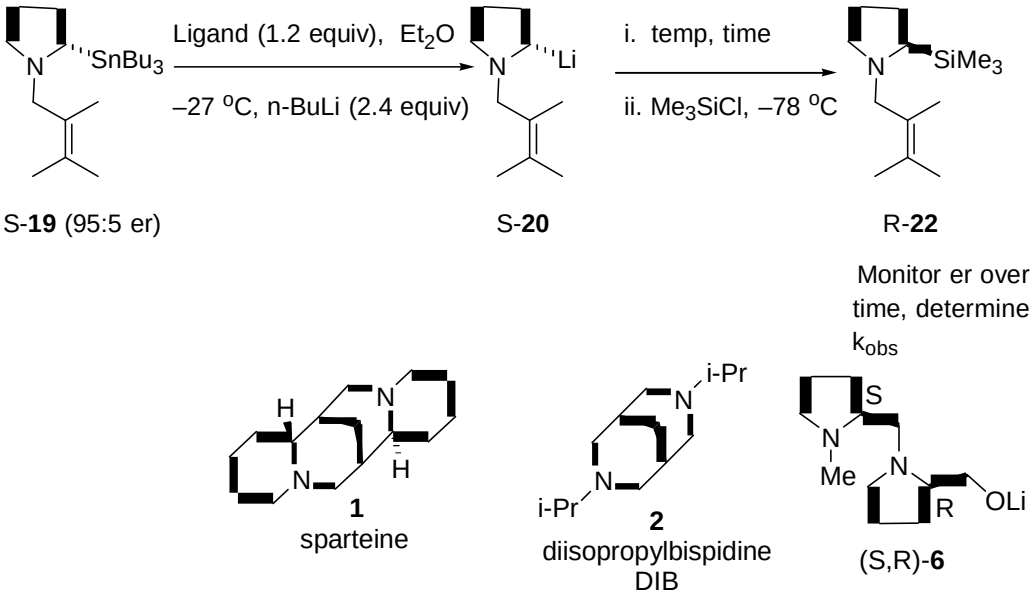
In 2006, Coldham and coworkers reported that ligand (S,R)-6 resolves N-trimethylallyl-2-lithiopyrrolidine 20 with a thermodynamic preference for the R-organolithium, affording enantiomer ratios as high as 96:4 er when quenched at –78 °C with phenyl isocyanate (Scheme 2.23).[39] They obtained 20 from the corresponding stannane 19 by transmetalation at a relatively high temperature (–10 °C).

Scheme 2.23. DTR of N-trimethylallyl-2-lithiopyrrolidine 20.[39]



The thermodynamic parameters for inversion of 20 were determined by a coworker in our group, Dr. Yousaf Taher. The results are summarized in Table 2.8.

Table 2.8. Thermodynamic parameters for inversion of S-20 (95:5 er) in the presence of 1, 2, and (S,R)-6



System	$\Delta H^{\ddagger}$ (S→R) (kcal/mol)	$\Delta S^{\ddagger}$ (S→R) (cal/mol.K)	$\Delta H^{\ddagger}$ (R→S) (kcal/mol)	$\Delta S^{\ddagger}$ (R→S) (cal/mol.K)
20·1[a]	19.9 ± 2.2	-7.4 ± 7.7	19.9 ± 2.2	-10.3 ± 7.7
20·2	25.1 ± 1.4	8.1 ± 5.0	25.1 ± 1.4	8.1 ± 5.0
20·(S,R)-6[b]	25.1 ± 1.7	14.2 ± 6.1	25.1 ± 1.7	7.9 ± 6.1

[a]Calculated using K_{eq} = 4.26 (81:19 er), [b]Calculated using K_{eq} = 24 (96:4 er)

2.9. Experimental Section

General Experimental 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 chiral ligands were purified by Kugelrohr distillation. Commercial N,N,N',N'-tetramethylethylene diamine (TMEDA), tributyltin chloride, trimethylsilyl chloride, 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.[40] 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. Typical Procedures

2.9.1. Kinetics of Deprotonation of N-Boc-piperidine

In an oven-dried, septum-capped 25 mL round bottom flask equipped with a stir bar, N-Boc-piperidine (185 mg, 1.0 mmol) and distilled TMEDA (0.6 mL, 2.6 mmol, 4.0 equiv) were dissolved in freshly distilled Et_2O (10 mL) under argon. The solution was cooled to –78 °C and treated with freshly titrated s-BuLi (1.2 equiv). At various time intervals (0 to 4 h) an aliquot was drawn and immediately quenched with MeOD. The layers were separated and the organic layer was filtered through a plug of Celite using a Pasteur pipette. The sample was placed in a vial and analyzed for deuterium incorporation by GC-MS using chemical ionization. The integral ratio of the base peaks for both N-Boc-piperidine (m/z 130) and singly deuterated N-Boc-piperidine (m/z 131) were used to calculate the concentration of unreacted N-Boc-

piperidine over time. The rate constant was determined by nonlinear fits to the zero-order plots using SOLVER statistics on MS Excel (see Appendix 1).

2.9.2. Tin-Lithium Exchange Kinetics in the absence of a Ligand[16]

The stannane 3 (0.3 mL, 0.25 M in freshly distilled Et_2O) and $Sn(i\text{-}Pr)_4$ (0.3 mL, 0.25 M in Et_2O) were mixed in a dry NMR tube under argon. The sample was then introduced into the NMR probe, which had been precooled to –40 °C. When the temperature had equilibrated after ca 10 minutes, an initial ^{119}Sn spectrum was obtained prior to addition of freshly titrated n-BuLi (1.2 equiv) at –40 °C. After several time intervals, the ^{119}Sn NMR spectrum was recorded and the integral ratio of 3 to $Sn(i\text{-}Pr)_4$ was calculated. Because the total integration and relative chemical shift position of tetraisopropyltin is unaffected by the addition of n-BuLi, it was used as an internal calibrant, both for integration and chemical shift. The procedure was repeated at –60 °C, –50 °C and –20 °C. The exchange rate constants at the respective temperatures were obtained from the x-coefficient of the nonlinear fits of the time-dependent plots (see Appendix 2).

2.9.3. Configurational Stability of N-Boc-2-lithiopiperidine

In 8 oven-dried septum capped tubes (two tubes per ligand) equipped with a stir bar, S-3 (73:27 er, 0.06 M in Et_2O) and the desired ligand (1.0 equiv) were treated with n-BuLi (1.2 equiv) at –78 °C under argon. After a specified length of time (depending on the ligand), a tube was cooled to –78 °C and quenched with excess Me_3SiCl. After 4 h, MeOH (2 mL) was added and the mixture was extracted into Et_2O. The organic layer was filtered through a plug of Celite and the enantiomer ratio of the crude mixture was analyzed by CSP-SFC monitoring at 210 nm.

2.9.4. Enantiomerization of (S)-N-Boc-2-lithiopiperidine 4 in the presence of TMEDA

In 8 oven-dried septum capped tubes equipped with a stir bar, S-3 (85:15 er, 0.25 M in Et_2O) and TMEDA (2.0 equiv) were treated with n-BuLi (1.2 equiv) at –78 °C for 60 min under nitrogen to

effect tin-lithium exchange. The tubes were quickly transferred to a second thermostatted bath and warmed to the desired temperature. At various time intervals, a tube was cooled to –78 °C and quenched rapidly with excess Me_3SiCl. After 4 h, MeOH (2 mL) was added and the mixture was extracted into Et_2O. The organic layer was filtered through a plug of Celite and the enantiomer ratio of the silanes was analyzed by CSP-SFC monitoring at 210 nm. The experiments were repeated using one and four equivalents of TMEDA at various temperatures. The observed rate constants were determined by nonlinear fits to the zero-order plots.

2.9.5. Kinetic order in TMEDA for Racemization of (S)-N-Boc-2-lithiopiperidine 4

In 8 oven-dried septum capped tubes equipped with a stir bar, S-3 (85:15 er, 0.25 M in Et_2O) and the desired amount of TMEDA (0.1, 0.50, 0.75, 1.0, 2.0, 3.0 or 4.0 equiv) were treated with n-BuLi (1.2 equiv) at –78 °C for 60 min under nitrogen to effect tin-lithium exchange. The tubes were quickly transferred to a second thermostatted bath at –40 °C. At various time intervals, a tube was cooled to –78 °C and quenched rapidly with excess Me_3SiCl. After 4 h, MeOH (2 mL) was added and the mixture was extracted into Et_2O. The organic layer was filtered through a plug of Celite and the enantiomer ratio of the silanes was analyzed by CSP-SFC monitoring at 210 nm. The observed rate constants were determined by nonlinear fits to the zero-order plots.

2.9.6. Dynamic Thermodynamic Resolution (DTR) of N-Boc-2-lithiopiperidine 4 in the presence of TMEDA

In 8 oven-dried septum capped tubes equipped with a stir bar, rac-3 (0.25 M in Et_2O) and TMEDA (4.0 equiv) were treated with n-BuLi (1.2 equiv) at –78 °C for 60 min under nitrogen to effect tin-lithium exchange, affording rac-4·TMEDA. The diaminoalcohol (precursor of 10) was treated with s-BuLi (2.2 equiv) at –45 °C for an hour. The preformed alkoxide was added to the flask at –78 °C and the tubes were quickly transferred to a second thermostatted bath and

warmed to –45 °C. At various time intervals, a tube was cooled to –78 °C and quenched rapidly with excess Me_3SiCl. After 4 h, MeOH (2 mL) was added. The mixture was warmed to room temperature and HCl (2 M, 2 mL) was added followed by extraction with Et_2O (2 mL). The organic layer was filtered through a plug of Celite and the enantiomer ratio of the silanes was analyzed by CSP-SFC monitoring at 210 nm. The procedure was repeated at four other temperatures and the observed rate constants were determined by nonlinear fits to the zero-order plots.

Note: The above procedure was used to evaluate DTR using ligand 6 in the absence and presence of TMEDA.

2.9.7. Kinetic order in [6] for DTR of N-Boc-2-lithiopiperidine 4 in the presence of TMEDA.

Stock solutions (0.25 M) of rac-3 (592 mg, 1.25 mmol in 5.0 mL Et_2O), TMEDA (145 mg, 1.25 mmol, in 5 mL Et_2O), and the diaminoalcohol of 6 (250 mg, 1.25 mmol in 5 mL Et_2O) were prepared. To each of five oven-dried, septum-capped tubes, the following amounts of each stock solution were added: 0.4 mL of 3, 0.4 mL of TMEDA, and the corresponding amount of 6 (0.25, 0.5, 0.75, 1.0, 1.50, 2.0, 3.0, and 4.0 equiv). Transmetalation of rac-3 to 4 was effected by addition of n-BuLi (1.2 equiv) at –78 °C for 1 h in the presence of TMEDA (1.0 equiv). The diaminoalcohol (precursor of 6) was treated with s-BuLi (1.2 equiv) at –20 °C for an hour. The preformed alkoxide was added to the flask at –78 °C and the tubes were quickly transferred to a second thermostatted bath at –20 °C. After a measured time period (between 0 and 60 min), the mixture was cooled to –78 °C and Me_3SiCl (3.0 equiv) was added. After 4 h, MeOH (2 mL) was added. The mixture was warmed to room temperature and HCl (2 M, 2 mL) was added followed by extraction with Et_2O (2 mL). The organic layer was filtered through a plug of Celite and the enantiomer ratio of the silanes was analyzed by CSP-SFC monitoring at 210 nm.

Note: The above procedure was used to determine the kinetic order in ligand 10.

2.9.8. Effect of varying [TMEDA] on DTR of N-Boc-2-lithiopiperidine with 6.

In oven-dried septum capped tubes equipped with a stir bar, rac-3 (0.25 M in Et_2O) and the desired amount of TMEDA (0.1, 0.50, 0.75, 1.0, 2.0 equiv) were treated with n-BuLi (1.2 equiv) at –78 °C for 60 min under nitrogen to effect tin-lithium exchange. The diaminoalcohol (precursor of 6) was treated with s-BuLi (1.2 equiv) at –10 °C for 10 min. The preformed alkoxide was added to the flask at –78 °C and the tubes were quickly transferred to a second thermostatted bath at –10 °C. At various time intervals, a tube was cooled to –78 °C and quenched rapidly with excess Me_3SiCl. After 4 h, MeOH (2 mL) was added. The mixture was warmed to room temperature and HCl (2 M, 2 mL) was added followed by extraction with Et_2O (2 mL). The organic layer was filtered through a plug of Celite and the enantiomer ratio of the silanes was analyzed by CSP-SFC monitoring at 210 nm. The observed rate constants were determined by nonlinear fits to the zero-order plots.

2.9.9. Progress of Deprotonation of 11

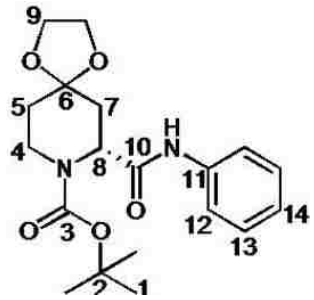
In an oven-dried, septum-capped 25 mL round bottom flask equipped with a stir bar, freshly distilled 11 (2 mmol, 1.0 equiv) and freshly distilled TMEDA (8 mmol, 4.0 equiv) were dissolved in freshly distilled Et_2O under argon. The solution was cooled to –78 °C and s-BuLi (2.4 mmol, 1.2 equiv) was added slowly by means of a syringe, down the side of the flask, over a 10-min period. CH_3OD (0.1 mL), stored over molecular sieves, was placed in an oven-dried vial and the vial was capped rapidly. At various time intervals (every 15 min), an aliquot (ca 0.1 mL) of the deprotonating mixture was drawn using a syringe equipped with an oven-dried needle, and rapidly placed in the vial containing the CH_3OD. The mixture was diluted with freshly distilled Et_2O (ca 1 mL). The ethereal layer was filtered through Celite. The sample was placed in a GC

vial and analyzed by GC-MS for deuterium incorporation. Electron impact (EI) was used. When the deprotonation is complete, there is a noticeable shift of the molecular ion peak from m/z 243 for the starting material to m/z 244 for the singly deuterated product.

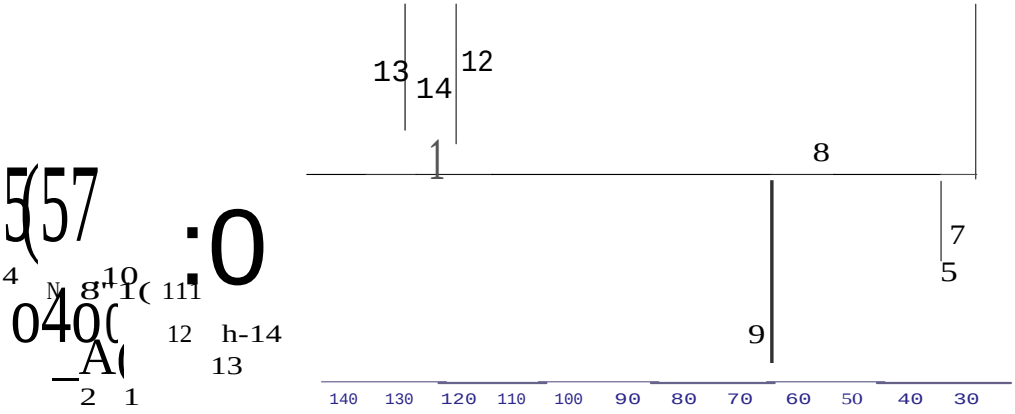
2.9.10. Dynamic Thermodynamic Resolution (DTR) of 12 in the presence of TMEDA

In 8 oven-dried septum capped tubes equipped with a stir bar, 11 (0.06 M in Et_2O) and TMEDA (4.0 equiv) were treated with s-BuLi (1.2 equiv) at –78 °C for 60 min under nitrogen to effect deprotonation, affording rac-12·TMEDA. The diaminoalcohol (precursor of 10) was treated with s-BuLi (2.2 equiv) at –30 °C for an hour. The preformed alkoxide was added to the flask at –78 °C and the tubes were quickly transferred to a second thermostatted bath at –30 °C. At various time intervals, a tube was cooled to –78 °C and quenched rapidly with excess phenyl isocyanate After 1 h, MeOH (2 mL) was added followed by filtration through Celite. The enantiomer ratio of the anilides was analyzed by CSP-SFC monitoring at 210 nm and/or 254 nm. The procedure was repeated at three other temperatures (–40 °C, –45 °C, –50 °C) and the observed rate constants were determined by nonlinear fits to the zero-order plots. The enantiomers of 14 were resolved by CSP-SFC under the following conditions:

Column: Pirkle Whelk-O-1, Flow Rate = 2.5 mL/min, Polarity Modifier = 2.5% Ethanol; Outlet Pressure = 150 psi, Oven Temperature = 35 ^{o}C, R-14 elutes after ~11.5 min and S-14 elutes after ~13 min.


9
O
O
5
6
7
4
N
8
10
H
N
11
O
O
3
O
12
13
14
2
1

H13,14,12
H9
H5
H8
H4
H4'
H7
85 80 75 70 65 60 55 50 45 40 35 30 25 20 15 10 05 ppm


13
14
12
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8
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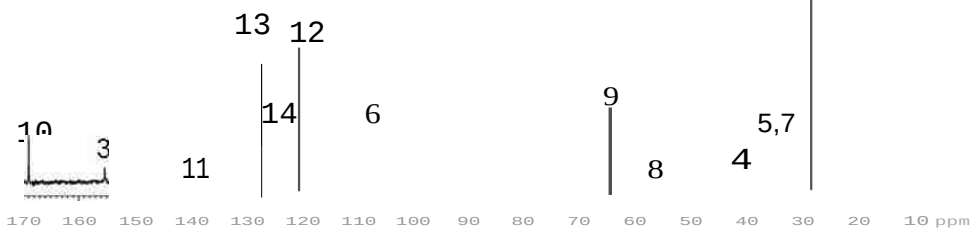
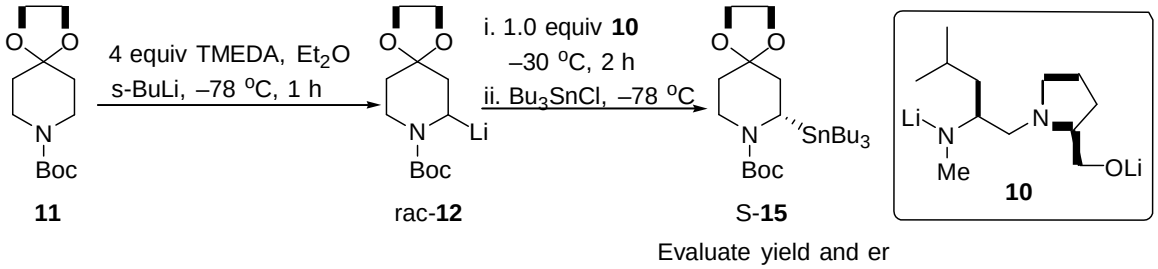
140 130 120 110 100 90 80 70 60 50 40 30


13
12
14
6
9
5,7
11
8
4
3
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

2.9.11. Enantiomerization of S-12 in the presence of TMEDA

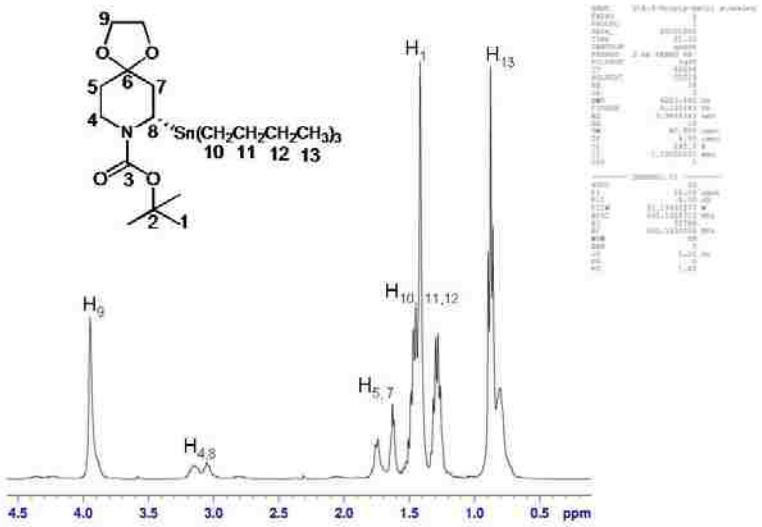
In 8 oven-dried septum capped tubes equipped with a stir bar, the stannane S-15 (93:7 er, 0.06 M in Et_2O) and TMEDA (4.0 equiv) were treated with n-BuLi (1.2 equiv) at –78 °C for 60 min under nitrogen to effect tin-lithium exchange. The tubes were quickly transferred to a second thermostatted bath at –50 °C. At various time intervals, a tube was cooled to –78 °C and quenched rapidly with excess phenyl isocyanate (3.0 equiv). After 1 h, MeOH (2 mL) was added followed by filtration through Celite. The enantiomer ratio of the anilides was analyzed by CSP-SFC monitoring at 210 nm and/or 254 nm. The procedure was repeated at three other temperatures (–45 °C, –40 °C, –30 °C) and the observed rate constants were determined by nonlinear fits to the zero-order plots.

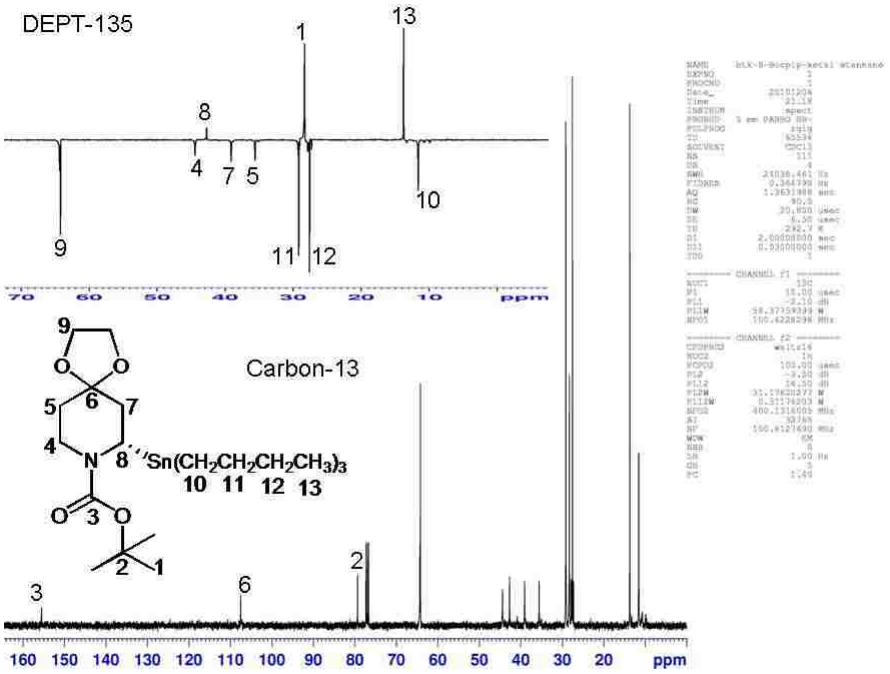
2.9.12. Synthesis of S-15



In an oven-dried, septum-capped 50 mL round bottom flask equipped with a stir bar, freshly distilled 11 (486 mg, 2.0 mmol, 0.25 M, 1.0 equiv) and freshly distilled TMEDA (1.2 mL, 8 mmol, 4.0 equiv) were dissolved in freshly distilled Et_2O (8 mL) under argon. The solution was cooled to –78 °C and s-BuLi (2.4 mL, 1.0 M, 2.4 mmol, 1.2 equiv) was added slowly by means of a syringe, down the side of the flask, over a ten minute period. The mixture was stirred for 1 h to effect deprotonation, affording rac-12·TMEDA. The extent of deprotonation was monitored by quenching an aliquot of the reaction mixture with methanol-d_1 (CH_3OD) and checking for deuterium incorporation by GC-MS. Freshly distilled diamino alcohol, precursor of 10 (428 mg, 2.0 mmol, 0.25 M in 8 mL Et_2O, 1.0 equiv) was treated with s-BuLi (4.8 mL, 1.0 M, 4 mmol, 2.0 equiv). After complete deprotonation of 11 as noted by GC-MS (there is a shift in the molecular ion peak from m/z 243 to m/z 244 after deuterium incorporation), the preformed alkoxide 10 was added and the flask was quickly transferred to a second thermostatted bath at –30 °C, and allowed to stir for 2 h. The solution was cooled to –78 °C and quenched rapidly with Bu_3SnCl, precooled to –78 °C (1.6 mL in 3 mL Et_2O, 6 mmol, 3.0 equiv). After 4 h, MeOH (2 mL) was added and the mixture was allowed to slowly warm to room temperature overnight. Purification by silica gel chromatography eluting with hexane-EtOAc (99:1) afforded 724 mg of S-15 as a colorless oil in 68% yield and 93:7 er. The enantiomers were resolved by CSP-SFC under the following conditions: Column: Pirkle Whelk-O-1, Flow Rate = 1.0 mL/min, Polarity Modifier

= 1.0% Ethanol; Outlet Pressure = 150 psi, Oven Temperature = 35 ^{o}C, R-15 elutes after 11.8 minutes and S-15 elutes after 12.2 minutes.





2.9.13. DTR of 17 (0.06 M in Et_2O) in the presence of 1.0 equiv 7

Typical kinetic run: In 8 oven-dried septum capped tubes equipped with a stir bar, rac-16 (0.06 M in Et_2O) and 7 (1.0 equiv) were treated with n-BuLi (1.2 equiv) at –78 °C for 1 hour under argon to effect tin-lithium exchange. The tubes were quickly transferred to a second thermostatted bath at a warmer temperature. At various time intervals a tube was cooled to –78 °C and rapidly quenched with excess Me_3SiCl. After 4 h, 10% H_3PO_4 (2 mL) was added and the mixture was extracted into Et_2O. The silanes were subsequently analyzed by CSP-GC.

2.9.14: General Procedure A: Synthesis of alcohol precursors to dilithiated ligands

i) N-Boc-protection of (S)-Leucine

To a solution of (S)-leucine (1.0 equiv) in 2 M $NaOH_{(aq)}$, di-tert-butyl dicarbonate (1.2 equiv) was added slowly. The mixture was stirred for 18 h at room temperature prior to addition of CH_2Cl_2. The layers were separated and the aqueous layer was acidified with citric acid and extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered and evaporated to give N-Boc-(S)-leucine as an oil.

ii) (S)-Proline methyl ester hydrochloride

To a solution of (S)-proline (1.0 equiv) in anhydrous MeOH at 0 °C, was added $SOCl_2$ (1.1 equiv) dropwise over a five minute period. The mixture was stirred for 2 h and then concentrated under high vacuum to give the desired product.

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

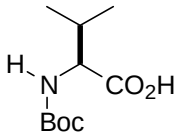
To a stirred solution of N-Boc-(S)-leucine (1.0 equiv) in $CHCl_3$ was added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide, EDCI (1.0 equiv) and 1-hydroxybenzotriazole, HOBt (1.0 equiv). The suspension was stirred for 10 min and (S)-proline methyl ester hydrochloride (1.0 equiv) in Et_3N:$CHCl_3$ (1:5) was added. After 10 h at room temperature, the solvents were

evaporated. Ethylacetate was added and the mixture was stirred for 30 min. The solution was filtered and the filtrate was washed with 10% citric acid and then with 10% $NaHCO_3$. The organic layer was dried over Na_2SO_4 and evaporated to give the pure dipeptide ester as a pale yellow oil.

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

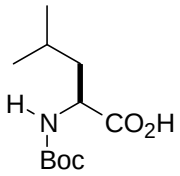
To a stirred suspension of $LiAlH_4$ (7.7 equiv) in THF, cooled to 0 °C, was added dropwise a solution of the dipeptide ester (1.0 equiv) in THF. The mixture was stirred for 10 min at room temperature and then heated under reflux for 16 h. The mixture was cooled to 0 °C and Et_2O was added. The mixture was carefully quenched by slow addition of $NaOH_{(aq)}$, 2 M 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 $HCl_{(aq)}$. The aqueous layer was then basified with 50% KOH (aq) to pH 14 and extracted with Et_2O. The combined organic layers were dried over Na_2SO_4 and evaporated to give the crude product. Purification by Kugelrohr distillation gave the alcohol (conjugate acid of 10) as a colorless oil.

(S)-N-Boc-Valine



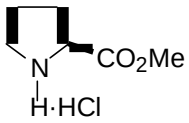
Using General Procedure A(i), (S)-Valine (10 g, 85.4 mmol) in 2 M NaOH (200 mL), di-tert-butyl dicarbonate (22.4 g, 102.5 mmol, 1.2 equiv) gave 17.8 g of the N-Boc-protected amino acid in 96% yield as an oil, data as reported.[24]

(S)-N-Boc-Leucine



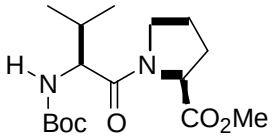
Using General Procedure A(i), (S)-Leucine, (10 g, 76.2 mmol) in 2 M NaOH (200 mL), di-tert-butyl dicarbonate (20 g, 91.5 mmol, 1.2 equiv) gave 17.1 g of the N-Boc-protected amino acid in 97% yield as an oil, data as reported.[24] $[\alpha]_D^{23} = -10.9$ (c = 1, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) ll = 10.80 (1H, br s), 5.00 (1H, d, NH), 4.43–3.97 (1H, m, CH), 1.87–1.50 (3H, m, CH_2 and CH), 1.44 (9H, s, t-Bu), 0.95 (6H, d, 2 x CH_3)

(S)-Proline methyl ester hydrochloride



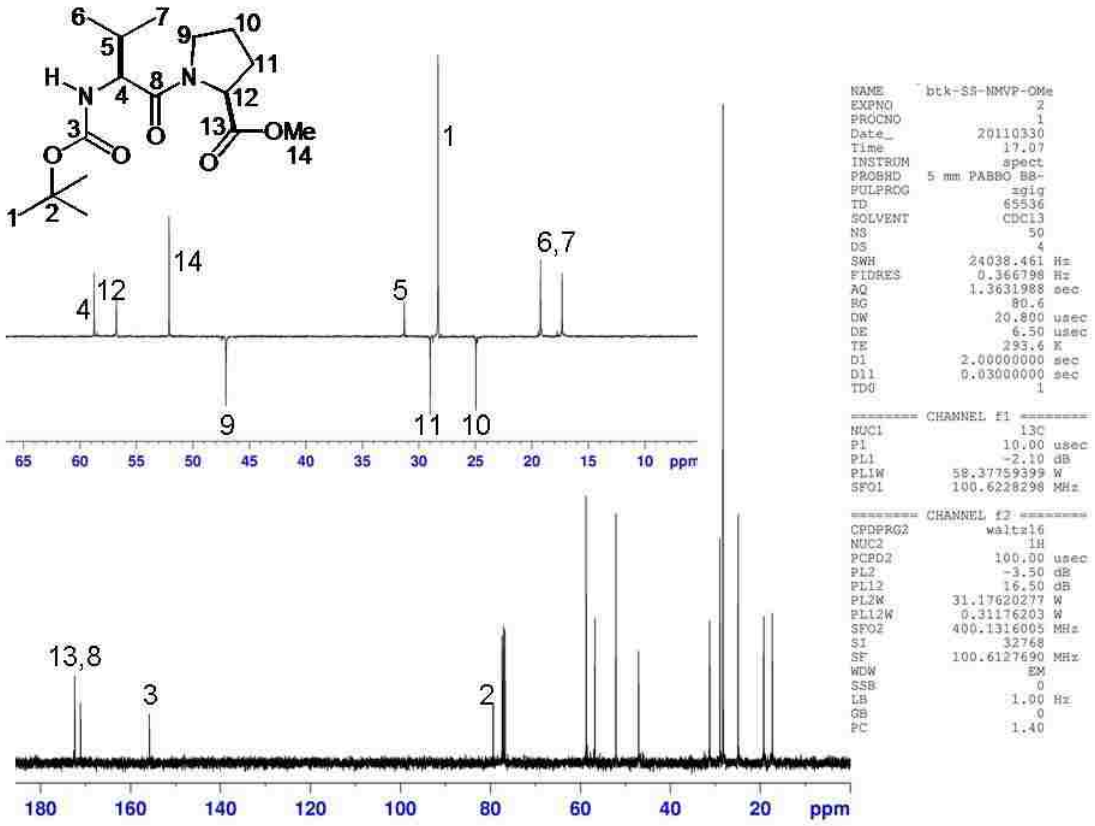
Using General Procedure A(ii), (S)-Proline (5.8 g, 50.0 mmol), anhydrous MeOH (35 mL) and $SOCl_2$ (4.0 mL, 55 mmol, 1.1 equiv) gave 8.28 g of the desired product in 100% yield, data as reported.[24] ^1H NMR (400 MHz, $CDCl_3$) ll = 10.73 (1H, br, s, HCl), 9.28 (1H, br, s, NH), 4.60–4.41 (1H, br, m, NCH), 3.85 (3H, s, CH_3), 3.71–4.43 (2H, br m, CH_2), 2.53–2.32 (1H, br m, CH), 2.28–1.98 (3H, m, CH_2 and CH).

(S,S)-N-Boc-Val-Pro-OMe

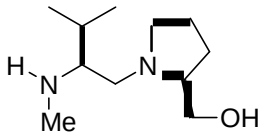


Using General Procedure A(iii), N-Boc-(S)-valine (5.43 g, 25 mmol, 1.0 equiv), $CHCl_3$ (100 mL), EDCI (4.9 g, 25 mmol, 1.0 equiv), HOBt (3.8 g, 25 mmol, 1.0 equiv), (S)-proline methyl ester hydrochloride (4.14 g, 25 mmol, 1.0 equiv) in Et_3N (10 mL) / $CHCl_3$ (50 mL) gave 7.54 g of the pure dipeptide ester as a pale yellow oil in 92% yield, data as reported [24] ^{13}C NMR (75.5

MHz, $CDCl_3$) (mixture of rotamers) ll = 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).

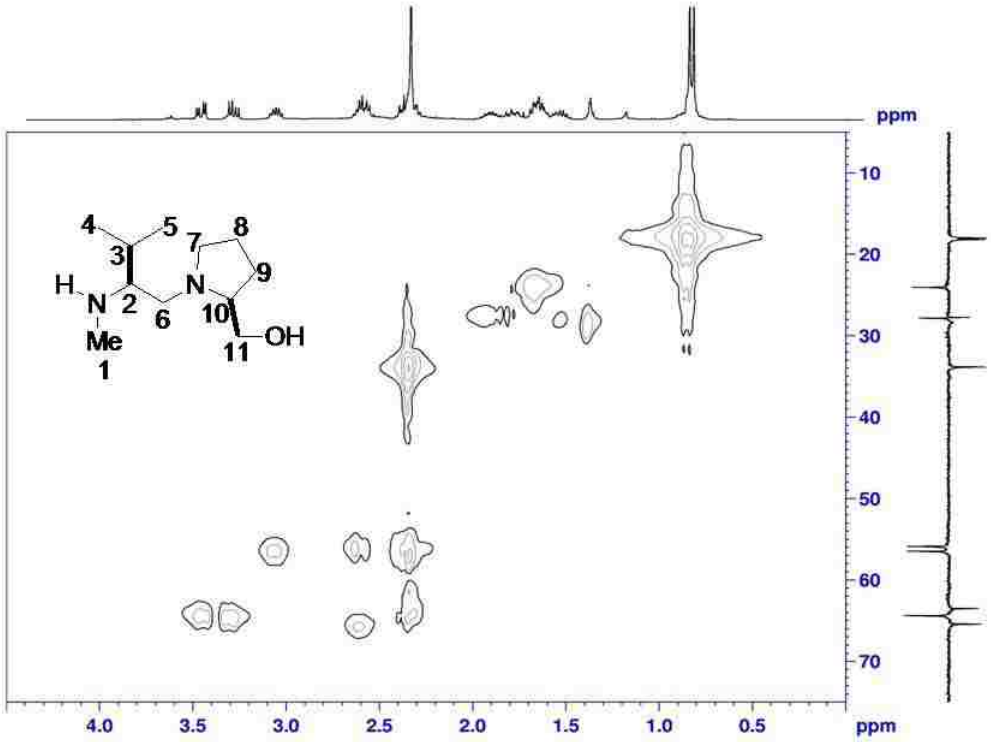


((S)-1-((S)-3-methyl-2-(methylamino)butyl)pyrrolidin-2-yl) methanol, conjugate acid of ligand 8

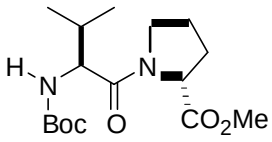


Using General Procedure A(iv), $LiAlH_4$ (6.0 g, 158 mmol, 7.7 equiv) in THF (50 mL), the dipeptide, (S,S)-N-Boc-Val-Pro-OMe (6.84 g, 20 mmol, 1.0 equiv) in THF (100 mL) gave 3.44 g of the desired alcohol of 8 as a colorless oil in 86% yield. ^{13}C NMR (75.5 MHz, $CDCl_3$) ll =

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).

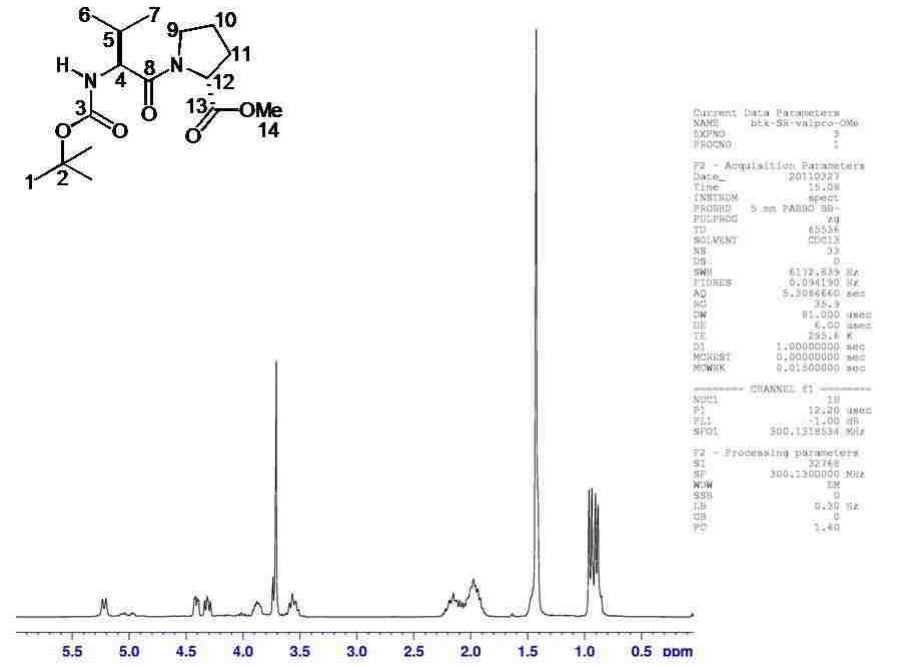


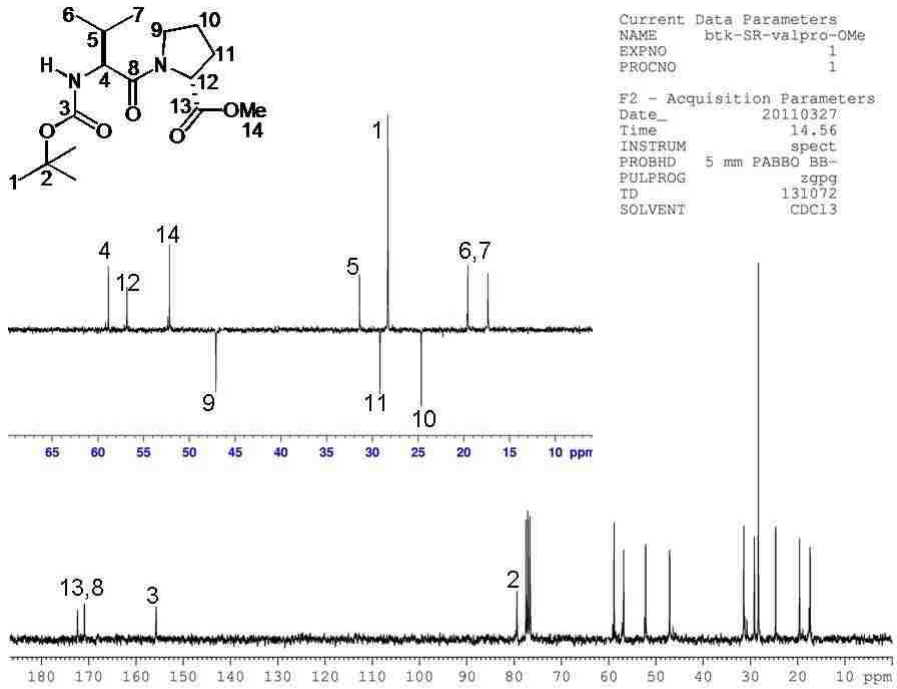
(S,R)-N-Boc-Val-Pro-OMe



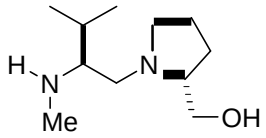
Using General Procedure A(iii), N-Boc-(S)-valine (2.18 g, 10 mmol, 1.0 equiv), $CHCl_3$ (50 mL), EDCI (1.96 g, 10 mmol, 1.0 equiv), HOBt (1.52 g, 10 mmol, 1.0 equiv), (R)-proline methyl ester hydrochloride (1.66 g, 10 mmol, 1.0 equiv) in Et_3N (5 mL) / $CHCl_3$ (25 mL) gave 2.95 g of the pure (S,R)-dipeptide ester as a pale yellow oil in 90% yield, data as reported. ^{13}C NMR (75.5 MHz, $CDCl_3$) (mixture of rotamers) ll = 172.6 (C=O of ester), 170.1 (C=O of amide), 155.8 (C=O of carbamate), 79.3 (C), 59.2 and 58.9 (CH), 56.8 (CH), 52.4 and 52.2 (CH_3), 47.1 and

46.4 (CH_2), 31.4 and 31.2 (CH), 29.2 (CH_2), 28.3, (3 x CH_3), 24.7 (CH_2), 19.6 (CH_3), 17.6 and 17.4 (CH_3).

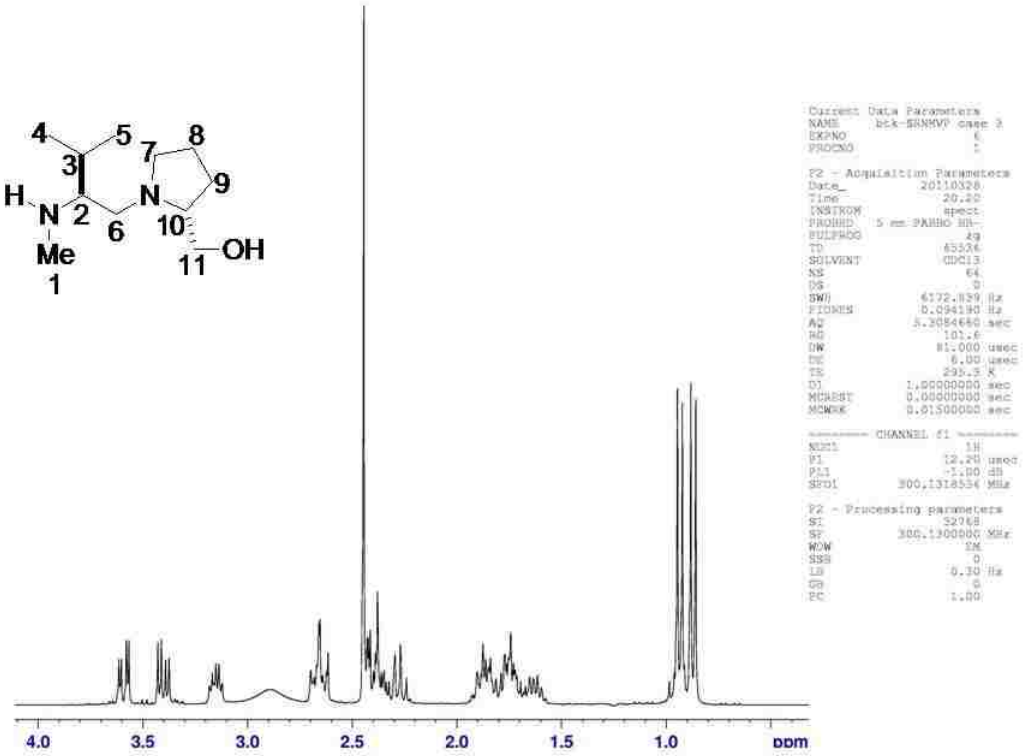


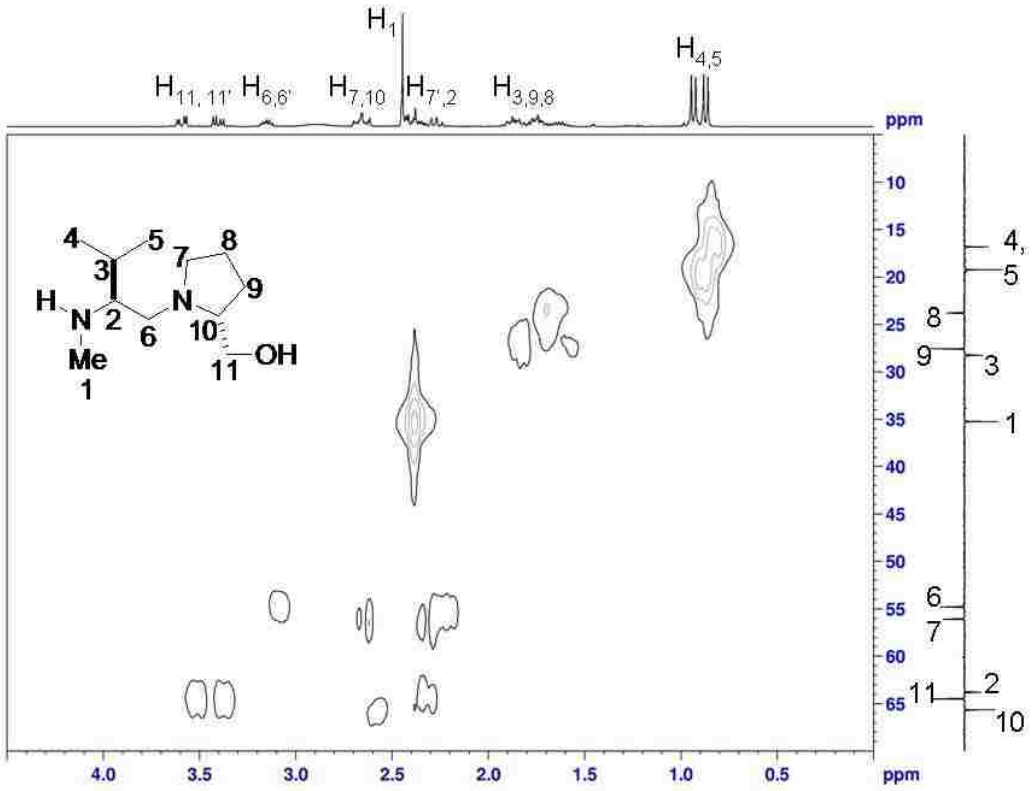


Conjugate acid of ligand (S,R)-8



Using General Procedure A(iv), $LiAlH_4$ (2.49 g, 65.5 mmol, 7.7 equiv) in THF (50 mL), the dipeptide, (S,R)-N-Boc-Val-Pro-OMe (2.90 g, 8.5 mmol, 1.0 equiv) in THF (50 mL) gave 1.53 g of the desired alcohol of (S,R)-8 as a colorless oil in 90% yield. $[a]^{22}_{D}$ +105 (c = 2.0, MeOH); ^{13}C NMR (75.5 MHz, $CDCl_3$) ll = 65.7 (CH), 64.5 (CH_2), 63.8 (CH), 56.1 (CH_2), 54.8 (CH_2), 35.2 (CH_3), 28.2 (CH), 27.6 (CH_2), 23.8 (CH_2), 19.2 (CH_3) and 16.8 (CH_3).



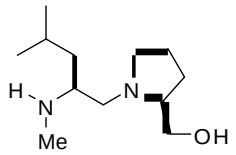


(S,S)-N-Boc-Leu-Pro-OMe

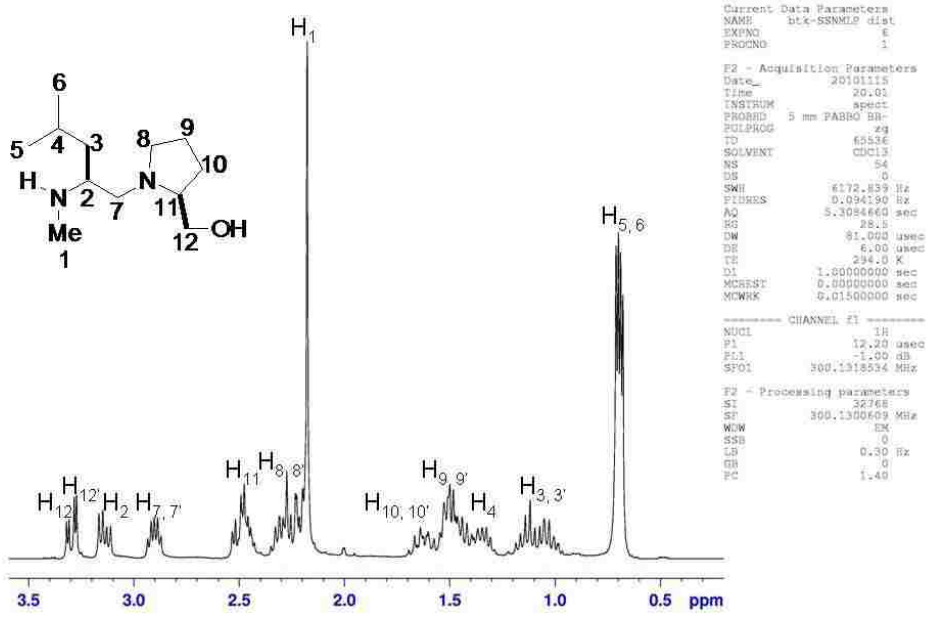
Using General Procedure A(iii), N-Boc-(S)-leucine (5.8 g, 25 mmol, 1.0 equiv), $CHCl_3$ (100 mL), EDCI (4.9 g, 25 mmol, 1.0 equiv), HOBt (3.8 g, 25 mmol, 1.0 equiv), (S)-proline methyl ester hydrochloride (4.14 g, 25 mmol, 1.0 equiv) in Et_3N (10 mL) / $CHCl_3$ (50 mL) gave 7.52 g of the pure dipeptide ester as a pale yellow oil in 88% yield, data as reported $[a]^{22}_D$ -2.8 (c = 0.25, MeOH); ^{13}C NMR (75.5 MHz, $CDCl_3$) (mixture of rotamers) ll = 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; (20:80).

[(S)-1-((S)-2-Methylamino-4-methylpentyl)pyrrolidin-2-yl]methanol, conjugate acid of ligand 10



Using General 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 10 as a colorless oil in 82% yield. $[a]^{22}_D$ +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, $CDCl_3$) ll = 3.41 (1H, dd, CHOH), 3.24 (1H, dd, CHOH), 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, $CDCl_3$) ll = 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).

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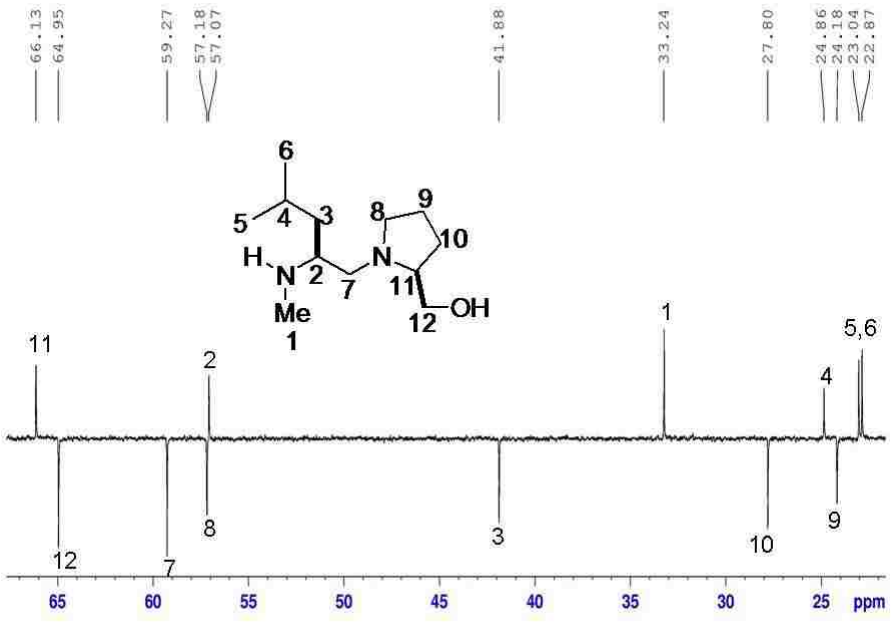

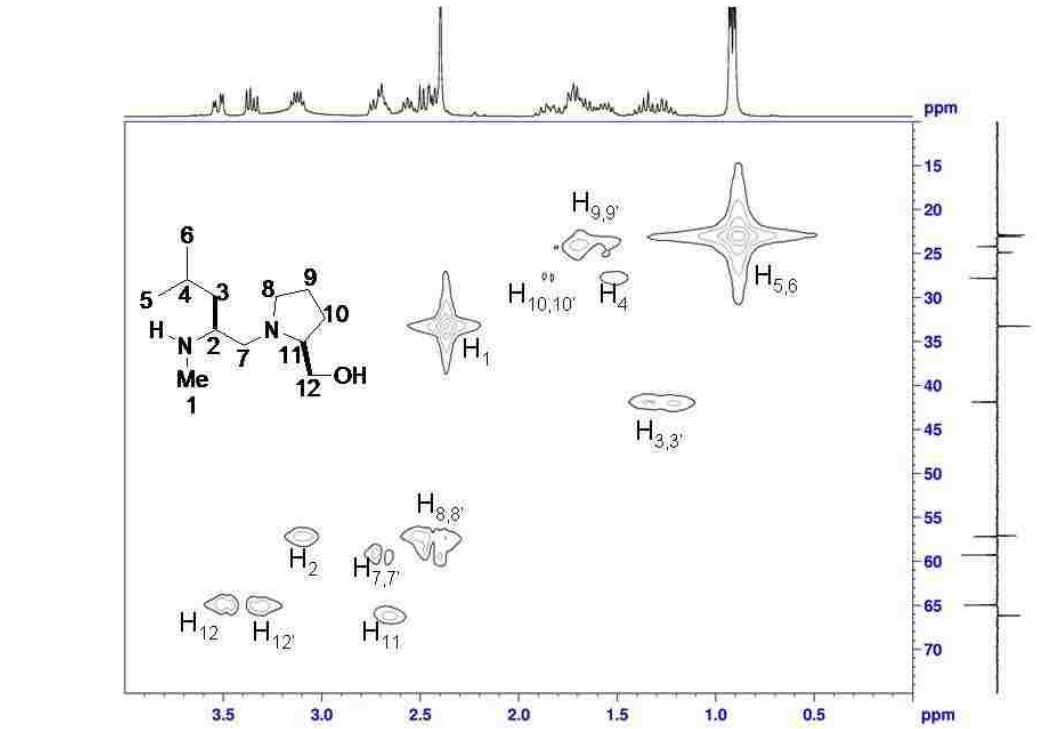
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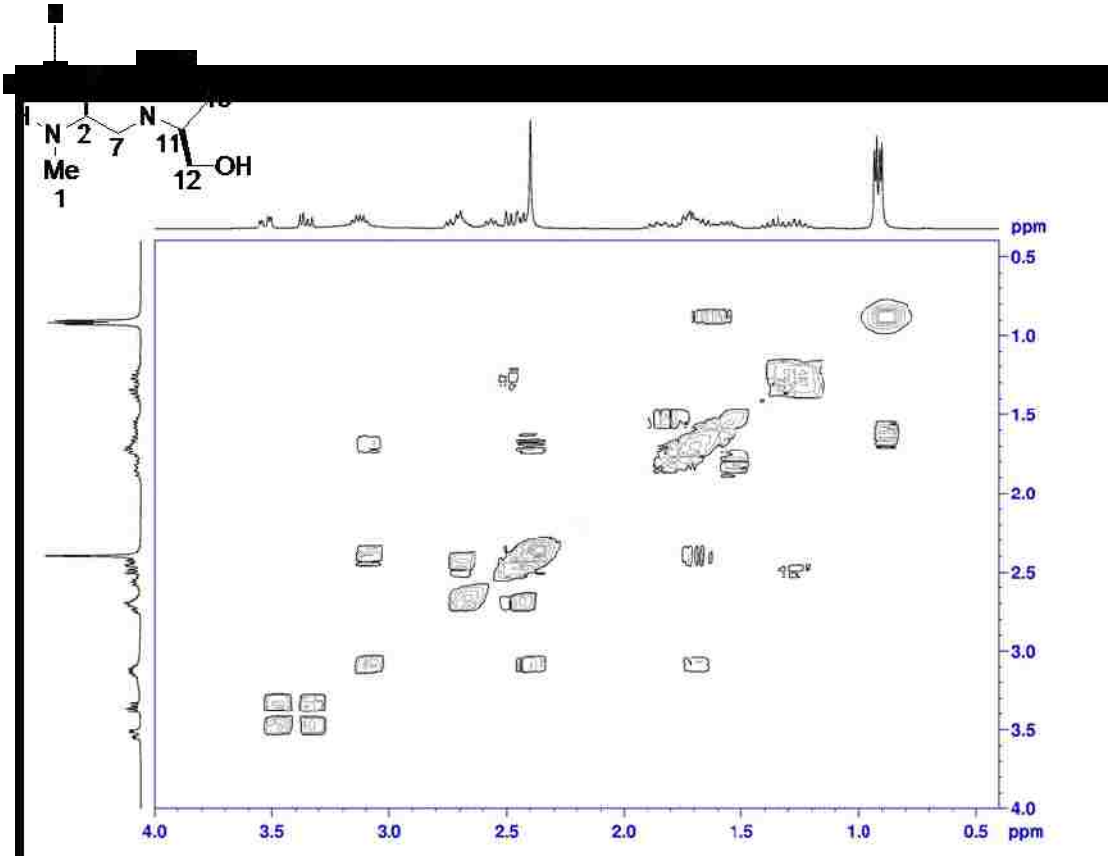
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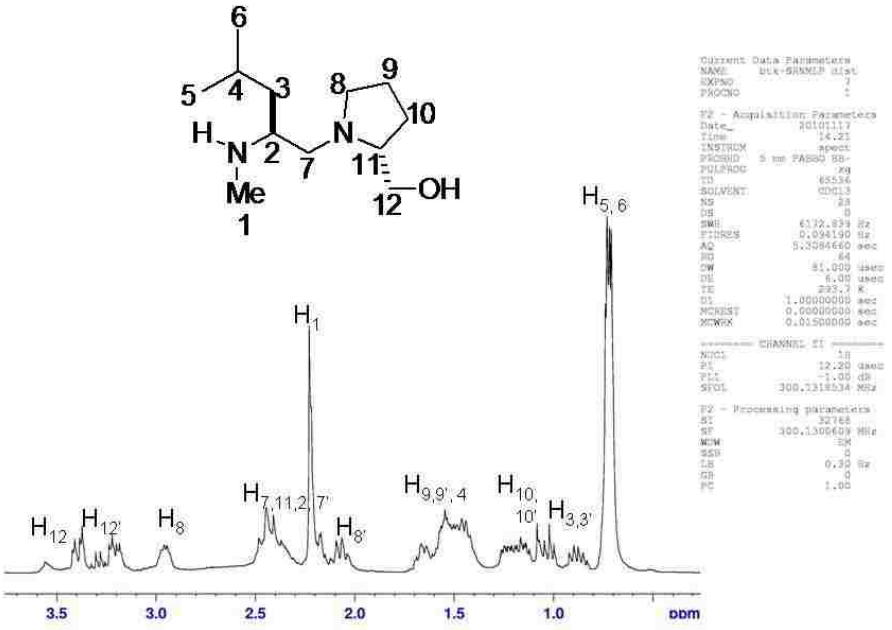
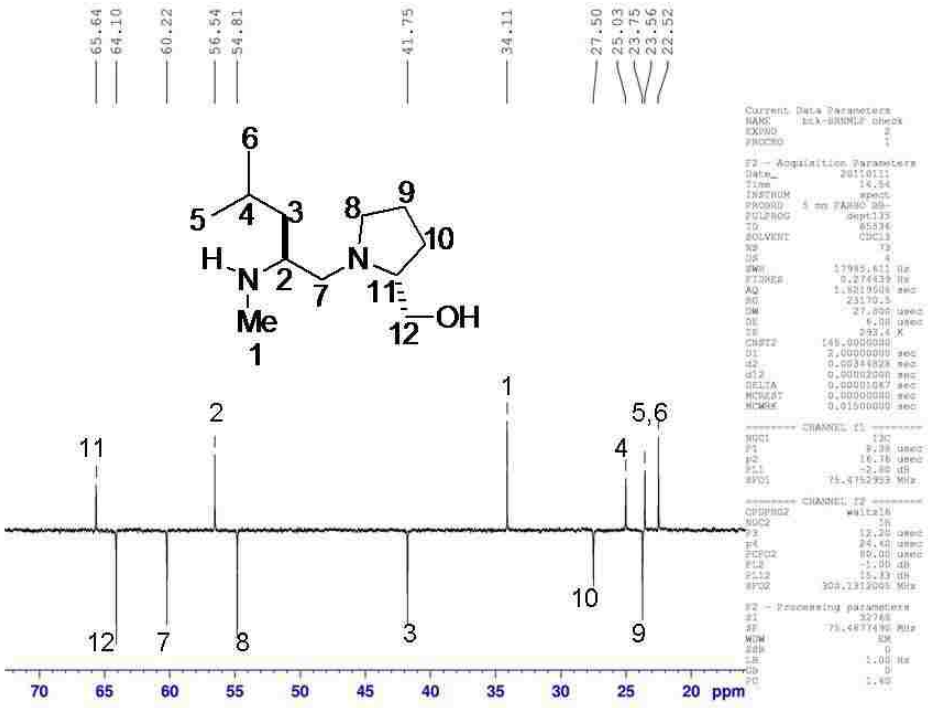
((R)-1-((S)-4-methyl-2-(methylamino)pentyl)pyrrolidin-2-yl) methanol, conjugate acid of ligand 9

Using General Procedure A(iv), $LiAlH_4$ (6.0 g, 158 mmol, 7.7 equiv) in THF (50 mL), (S,R)-dipeptide ester (7.0 g, 20 mmol, 1.0 equiv) in THF (100 mL) gave 3.64 g of the desired alcohol of 10 as a colorless oil in 85% yield. $[a]^{22}_{D}$ +66.25 (c = 2.0, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) ll = 3.6-3.1 (2H, CHOH), 2.95 (1H, m) 2.5–2.3-2.0 (8H, m), 1.75–1.3 (3H, m), 1.25-0.8 (4H, m), 0.80 (6H, m) ^{13}C NMR (100 MHz, $CDCl_3$) ll = 65.8 (CH), 64.1 (CH_2), 60.0 (CH_2), 56.5 (CH), 54.7 (CH_2), 41.7 (CH_2), 34.0 (CH_3), 27.5 (CH_2), 25.0 (CH), 23.8 (CH_2), 23.5 (CH_3) and 22.5 (CH_3).

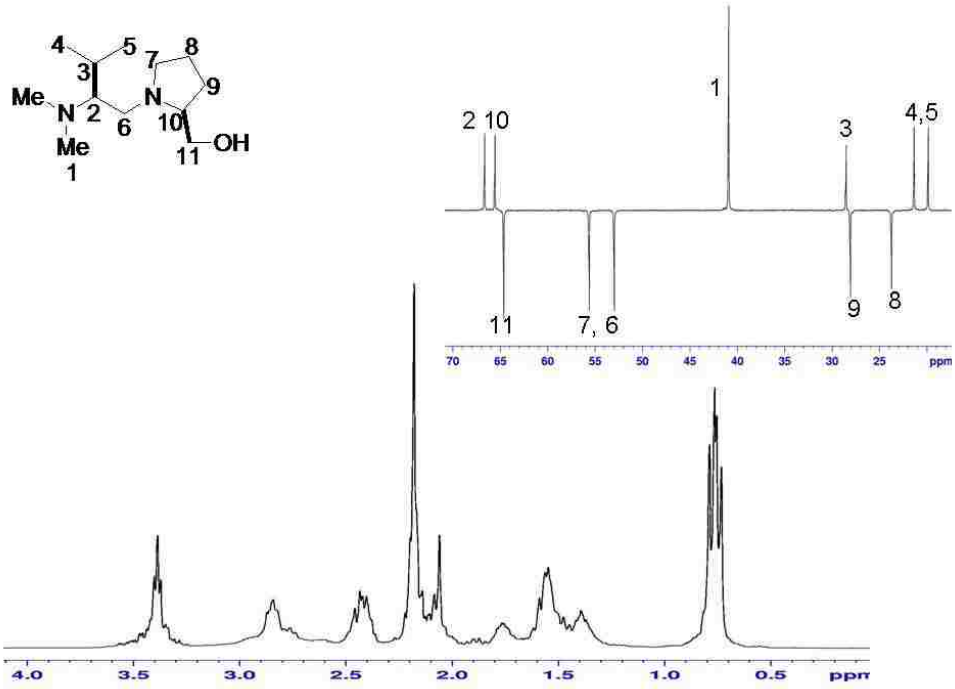




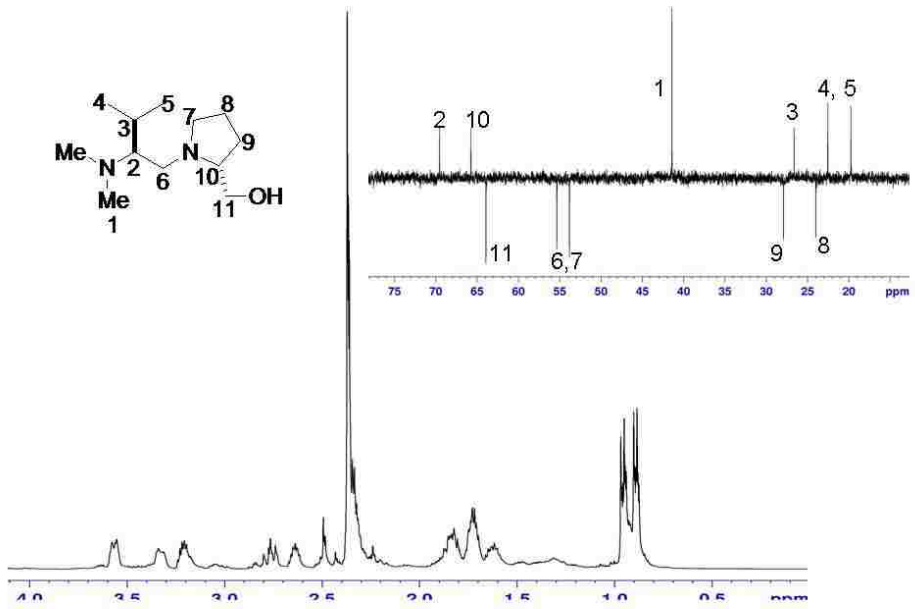
[(S)-1-((S)-2-Dimethylamino-3-methylbutyl)pyrrolidin-2-yl]methanol, conjugate acid of ligand (S,S)-7

To formic acid (95%, 2.6 g, 50 mmol, 5.0 equiv) in a 100 mL round bottom flask was added slowly (S,S)-8 (2.0 g, 10 mmol, 1.0 equiv) at 0 ^{o}C. To the resulting clear solution were added a solution of formaldehyde (37% w/v, 2.3 mL, 30 mmol, 3.0 equiv) and a small boiling stone. The flask was connected to a reflux condenser and was placed in an oil bath preheated to 90 ^{o}C. After 3 min (as soon as vigorous evolution of CO_2 began), the flask was removed from the hot bath and kept at 0 ^{o}C for 20 min (until the gas evolution stopped). The flask was then returned to the oil bath and heated at reflux at a temperature of 100 ^{o}C for 12 h. The solution was cooled and 2 M $HCl_{(aq)}$ (5 mL) was added and the mixture was concentrated in vacuo. The pale yellow syrupy residue was dissolved in water (5 mL) and 20% $NaOH_{(aq)}$ (5 mL) was added, liberating the organic base. The layers were separated and the aqueous layer was extracted with Et_2O (3 x

10 mL). The combined Et_2O layers were dried over Na_2SO_4 and evaporated to give the crude product as an oil. Purification by Kugelrohr distillation at 150 ^oC afforded 1.9 g of the diaminoalchohol, precursor of (S,S)-7 as a colorless oil in 89% yield. $[a]_D^{22}$ −22.0 (c = 1.0, EtOH). ^{13}C NMR (300 MHz, C_6D_6) ll = 66.4 (CH), 65.3 (CH), 64.4 (CH_2), 55.4 (CH_2), 52.8 (CH_2), 40.7 (CH_3), 28.3 (CH), 27.8 (CH_2), 23.5 (CH_2), 21.1 (CH_3) and 19.6 (CH_3). ^1H NMR (400 MHz, $CDCl_3$) ll = 3.46 to 3.1 (3H, m, 2CHOH and CHN), 2.75–2.25 (5H, m, 5 x CHN), 2.23 (6H, s, 2 x CH_3N), 2.13–1.60 (4H, m, CH_2 + 2 x CH), 1.64–1.42 (1H, m, CH), 0.91 to 0.90 (6H, d, 2 x CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) ll = 66.1 (CH), 64.6 (CH), 64.5 (CH_2), 56.2 (CH_2), 52.9 (CH_2), 40.7 (2 x CH_3), 27.8 (CH_2), 26.9 (CH), 24.1 (CH_2), 21.9 (CH_3), 19.5 (CH_3).



The diaminoalcohol of (S,R)-7 was synthesized in the same way as (S,S)-7, starting from (S,R)-8.



2.10. References

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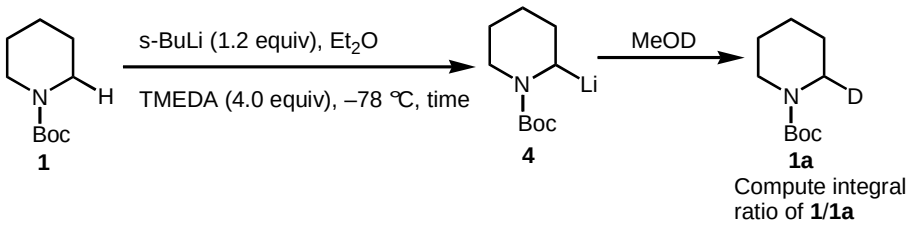
Appendix 1. Kinetics of deprotonation of N-Boc-piperidine in the presence of TMEDA (4.0 equiv)



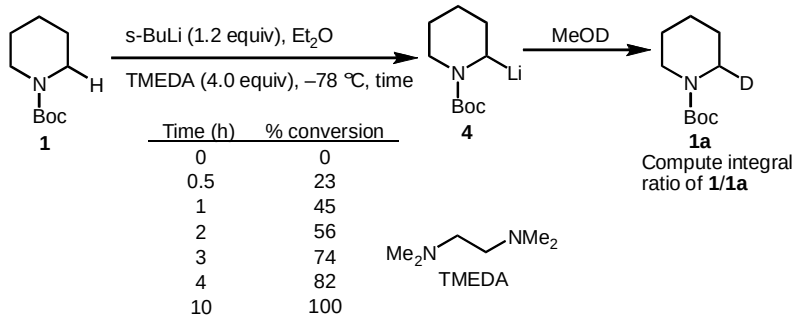
The rate of disappearance of 1 is given by

$$\text{Rate} = -\frac{d[1]}{dt} = -k_{dep}[1] \qquad \text{(A.1)}$$

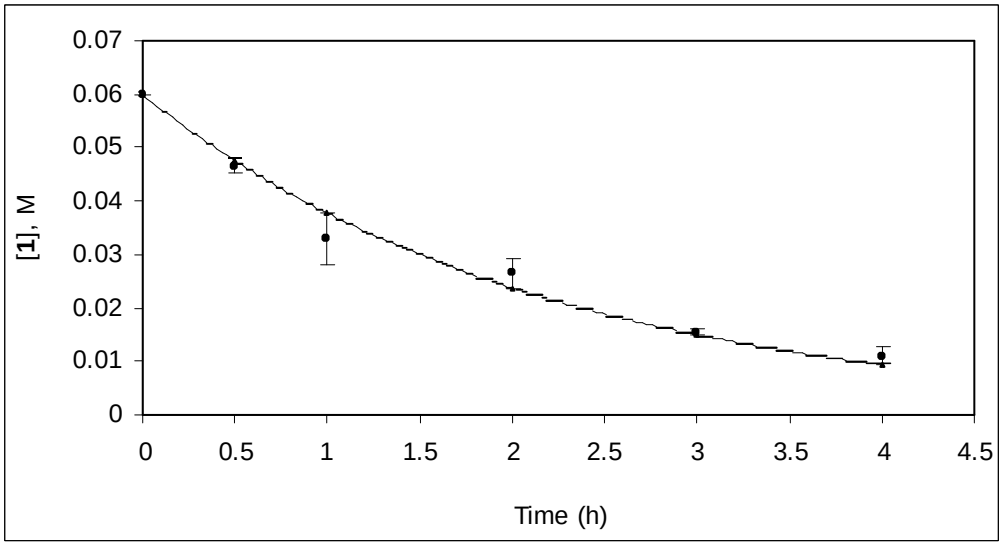
Integrating Eq. (2.1) gives

$$[1]_t = [1]_0 \exp(-k_{dep}t) \qquad \text{(A.2)}$$

where k_{dep} is the observed rate constant for the deprotonation obtained from a nonlinear fit of Eq. (A.2)

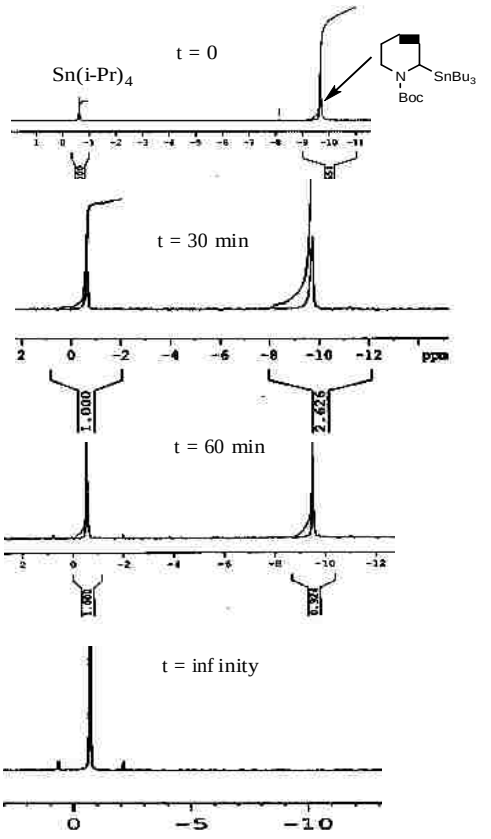


Time (h)	% conversion
0	0
0.5	23
1	45
2	56
3	74
4	82
10	100

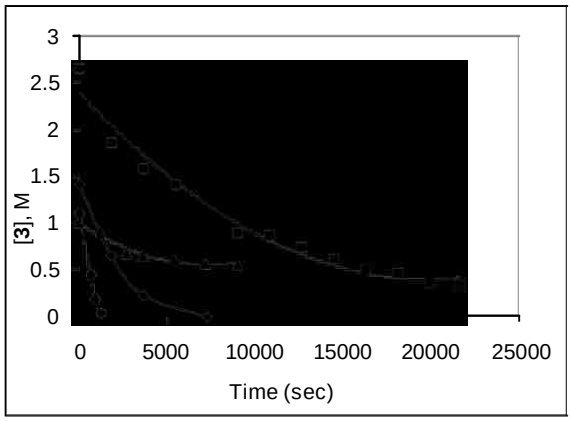


Appendix 2. (i) Sn-119 NMR spectra for conversion of 3 to 4 at 233 K (ii) Transmetalation of 3 to 4 in the absence of a ligand at 213 K (triangles), 223 K (squares), 233 K (diamonds), and 253 K (circles) in Et_2O. Fitting equation: $y = ax^2 - bx + c$, where a, b and c are adjustable parameters. y represents [3] and x represents time

i)



ii)



Fitting parameters using $y = ax^2 - bx + c$

T (Kelvin)	a (10^{-3} Ms^{-2})	b (10^{-4} Ms^{-1})	c (M)
253	360.8	13.30	1.11
233	38.0	4.68	1.40
223	5.10	2.02	2.39
213	8.40	1.22	0.99

Appendix 3. DTR of 4·10 with TMEDA in Et_2O at different temperatures

Appendix 3a. DTR with 2 equiv TMEDA

A). T = 253 K

$k_{obs} = 1.88 \pm 0.08 \times 10^{-3}\ s^{-1}$

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

B). T = 245 K

$k_{obs} = 9.32 \pm 0.48 \times 10^{-4}\ s^{-1}$

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

$k_{obs} = 2.09 \pm 0.03 \times 10^{-4}\ s^{-1}$

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

D). T = 223 K

$k_{obs} = 6.94 \pm 0.32 \times 10^{-5}\ s^{-1}$

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

E). T = 213 K

$k_{obs} = 3.65 \pm 0.05 \times 10^{-5}\ s^{-1}$

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

Appendix 3b. Eyring plot parameters for DTR of 4 in the presence of 1.0 equiv 10 and 2.0 equiv TMEDA

Temp (K)	1/T (K^{-1})	K_{eq}	k_{obs} (x 10^{-4} s^{-1})[a]	ln(k_{obs}/T)	ln(k_{RS}/T)	ln(k_{SR}/T)
253	0.003952	24	18.84 ± 0.08	-12.5008	-12.5416	-15.7197
245	0.00408	24	9.32 ± 0.48	-12.4794	-12.5202	-15.6983
233	0.004292	24	2.09 ± 0.03	-13.9230	-13.9642	-17.1423
223	0.004484	24	0.72 ± 0.03	-14.9829	-15.0237	-18.2018
213	0.004695	24	0.36 ± 0.05	-15.5799	-15.6207	-18.7987

Appendix 3c. DTR of 4 in the presence of 1.0 equiv 10 and 4.0 equiv TMEDA

A). T = 238 K

k_{obs} = 9.81 ± 0.06 x 10^{-4} s^{-1}

Time (h)	er (S:R)
0	50:50
0.25	77:23
0.5	88:12
1	95:5
2	96:4

B). T = 233 K

k_{obs} = 7.89 ± 0.23 x 10^{-4} s^{-1}

Time (h)	er (S:R)
0	50:50
0.25	73:27
0.5	85:15
1	94:6
2	95:5
3	96:4

C) T = 228 K

k_{obs} = 4.99 ± 0.04 x 10^{-4} s^{-1}

Time (h)	er (S:R)
0	50:50
0.5	77:23
1	89:11
2	94:6
3	95:5
4	96:4

C) T = 223 K

k_{obs} = 2.80 ± 0.07 x 10^{-4} s^{-1}

Time (h)	er (S:R)
0	50:50
0.5	68:32
1	80:20
2	89:11
3	94:6
4	96:4

Appendix 3d. Eyring plot parameters for DTR of 4 with 10 and 4.0 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)
223	0.00448	2.80 ± 0.07	13.588	13.628	16.807
228	0.00438	4.99 ± 0.04	13.032	13.073	16.251
233	0.00429	7.89 ± 0.23	12.596	12.636	15.814
238	0.00420	9.81 ± 0.06	12.399	12.439	15.618

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 an Eyring plot,

$\Delta H^{\ddagger} = -\text{slope}\cdot R$

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

Similarly, $\Delta S^{\ddagger} = \text{Intercept}\cdot R - R\ln(k_B/T)$

$$\frac{\text{Err}(\Delta S)}{\Delta S} = \sqrt{\left(\frac{\text{err(intercept)}}{\text{intercept}}\right)^2 + \left(\frac{\text{err}(R)}{R}\right)^2} = \sqrt{\left(\frac{\text{err(intercept)}}{\text{intercept}}\right)^2}$$

$$\frac{}{T\Delta S} \quad \sqrt{\frac{}{T}^2 \quad \left(\frac{}{\Delta S}\right)^2}$$

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

Appendix 4. Evolution of er for DTR of 12·10 in the presence of 4 equiv TMEDA

A). T = –30 °C

k_{obs} = 5.39 ± 0.06 x 10^{-4} s^{-1}

Time (min)	er (S:R)
0	50:50
10	61:39
20	75:25
30	82:18
60	88:12
90	94:6
120	98:2

B). T = –40 °C

k_{obs} = 2.51 ± 0.23 x 10^{-4} s^{-1}

Time (min)	er (S:R)
0	50:50
15	60:40
30	68:32
60	77:23
90	86:14
120	91:9

C) T = –45 °C

k_{obs} = 1.91 ± 0.04 x 10^{-4} s^{-1}

Time (min)	er (S:R)
0	50:50
30	63:37
60	72:28
90	81:19
120	88:12
150	90:10
180	92:8

D) T = –50 °C

k_{obs} = 1.04 ± 0.07 x 10^{-4} s^{-1}

Time (min)	er (S:R)
0	50:50
30	58:42
60	66:34
90	70:30
120	74:26
150	80:20
180	83:17

CHAPTER 3

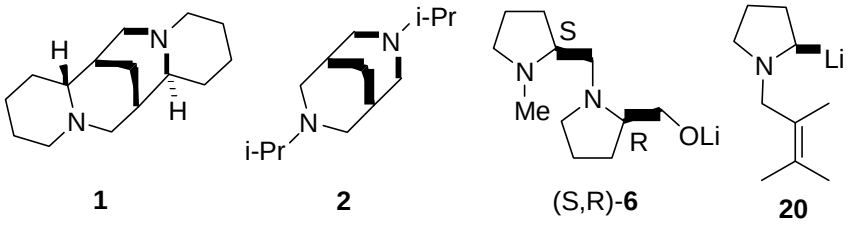
Catalytic Dynamic Resolution of N-trimethylallyl-2-lithiopyrrolidine and N-Boc-2-lithiopiperidine

3.1. Introduction

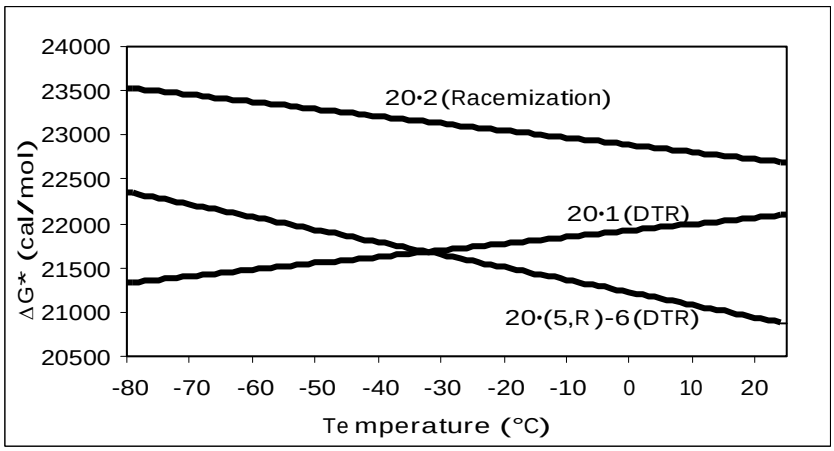
An undesirable feature of a dynamic thermodynamic resolution (DTR) is that the chiral ligand might react irreversibly with the electrophile, such that the former is consumed; thereby complicating or preventing its recovery. Therefore, it is important to develop a catalytic variant whereby the use of a substoichiometric amount of the chiral controller is desirable.

Case 1: Catalytic Dynamic Resolution of N-trimethylallyl-2-lithiopyrrolidine 20

Figure 3.1. The relationship between $\Delta G^{\ddagger}$ and temperature for inversion of 20



1 **2** (S,R)-**6** **20**



The enthalpic and entropic parameters (Chapter 2, Table 2.8) for the DTR of 20·1 and 20·(S,R)-6 revealed that these are entropy and enthalpy-controlled processes, respectively. The negative entropy for DTR using 1 implies that the difference in free energy, $\Delta(\Delta G^{\ddagger})$, between racemization in the presence of 2 and DTR in the presence of 1 increases as the temperature is

lowered. The barrier for DTR of 20·1 is lower than the barrier for racemization of 20·2 at the temperature range of interest (20 °C to –80 °C; Figure 3.1). At 0 °C, the barrier for DTR using 1 is 21.9 kcal/mol, whereas the racemization barrier with 2 is 22.9 kcal/mol. These barriers correspond to half-lives of equilibration of 5.9 h and 37.5 h, respectively. On the contrary, the positive entropy for DTR using (S,R)-6 and for racemization in the presence of 2 implies that the $\Delta(\Delta G^{\ddagger})$ between racemization and DTR increases as the temperature is increased. The barrier for DTR of 51·(S,R)-6 is lower than the barrier for racemization of 20·2 at all temperatures (Figure 3.1). At 0 °C, the DTR barrier using (S,R)-6 is 21.2 kcal/mol corresponding to a half-life of 1.6 h. Since at very low temperatures, carbanion inversion is too slow to be observed, and at high temperatures, the organolithiums are not thermally stable, the temperature chosen for the investigation of a resolution using a substoichiometric amount of ligand was 0 °C. Having no knowledge of the ligand exchange dynamics and the exact concentration of the achiral ligand 2 required for the studies, we carried out a series of experiments.

3.2.1. Time Evolution of 20 for Dynamic Resolution in the presence of 2 and 1 or (S,R)-6 (15 mol%)

The evolution of er in the catalytic resolution was followed by generating the racemic organolithium 20 (0.06 M in Et_2O) by tin–lithium exchange in Et_2O using n-BuLi (1.2 equiv) and 2 (1.2 equiv) at 0 °C for 2 hours to afford rac-20·2. The chiral ligand 1 or (S,R)-6 (15 mol%) was added and after several hours at 0 °C, the tubes were quickly transferred to the –78 °C bath and quenched rapidly with excess Me_3SiCl (Scheme 3.1). After workup, the enantiomer ratio of the silane was evaluated by CSP-GC.

Scheme 3.1. Evolution of er in the catalytic dynamic resolution of rac-20

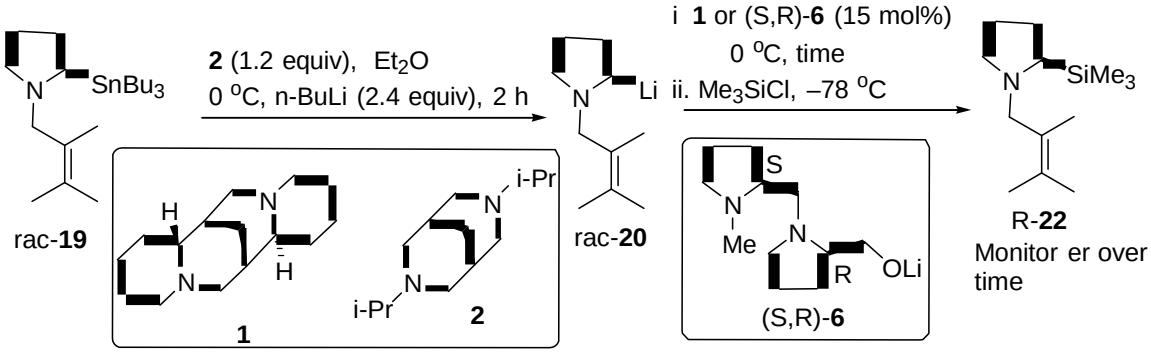
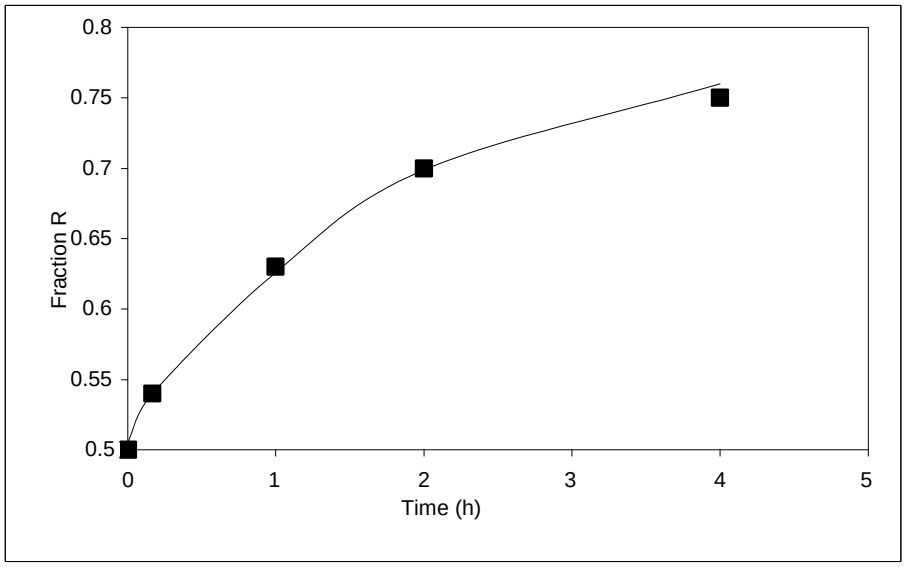


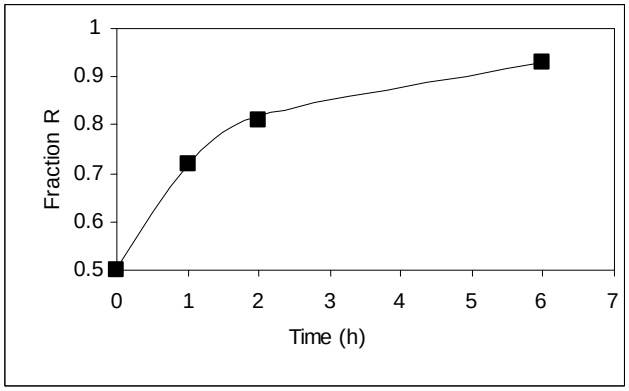
Figure 3.2. Time evolution for CDR of 20 in the presence of 2 (1.2 equiv) and 1 (15 mol%) at 0 ^{o}C in Et_2O.



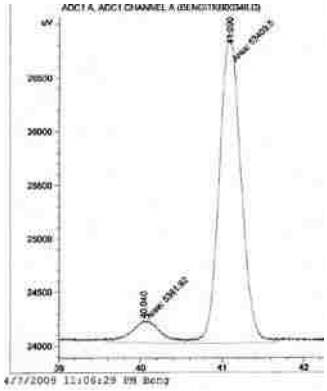
The zero-order plot (Figure 3.2) shows a buildup of the R-organolithium over time under the reaction conditions. R-22 (75:25 er) was achieved after 4 h, equaling the ratio obtained when a stoichiometric amount of 1 was employed in the DTR. The observed rate constant for a resolution with 15 mol% of 1 was obtained by a nonlinear fit of the zero-order plot; k_{obs} = 5.90 ± 0.45 x 10^{-5} s^{-1}. Using 15 mol% of (S,R)-6, R-22 of 93:7 er was achieved after 6 h (k_{obs} = 6.01 ± 0.43 x 10^{-5} s^{-1}). In 2006, Coldham showed that a stoichiometric amount of (S,R)-6 resolves 20 with a thermodynamic preference for the R-diastereomeric complex (R-20·(S,R)-6:S-20·(S,R)-6 = 96:4 er) following electrophilic quench with phenyl isocyanate. For a resolution under

thermodynamic control, if 15% of 20·(S,R)-6 resolves to 96:4 while the remaining 85% of 20 or 20·2 gives racemic product, the enantiomer ratio will be 57:43 (R:S). The fact that we observed er's as high as 93:7 suggests that catalysis might be occuring.

Figure 3.3. Time evolution for CDR of 20 in the presence of 2 (1.2 equiv) and (S,R)-6 (15 mol%) at 0 °C in Et_2O

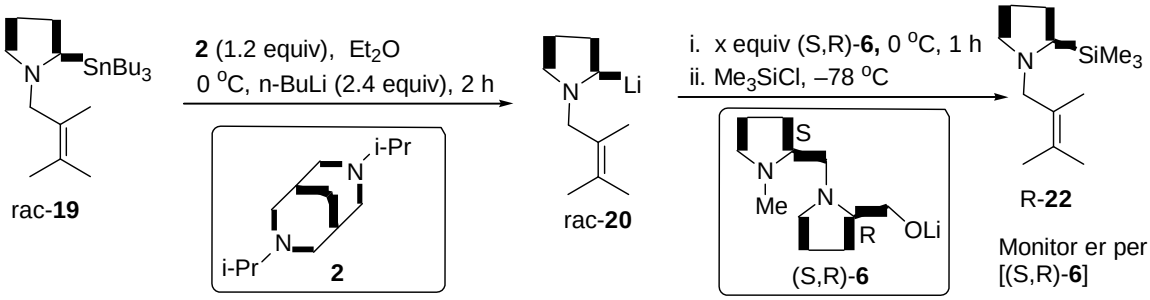


CSP-GC trace for R-22 (93:7 er) obtained after 6 h at 0 °C



3.2.2. Effect of varying [(S,R)-6] on the resolution of 20 in the presence of 2

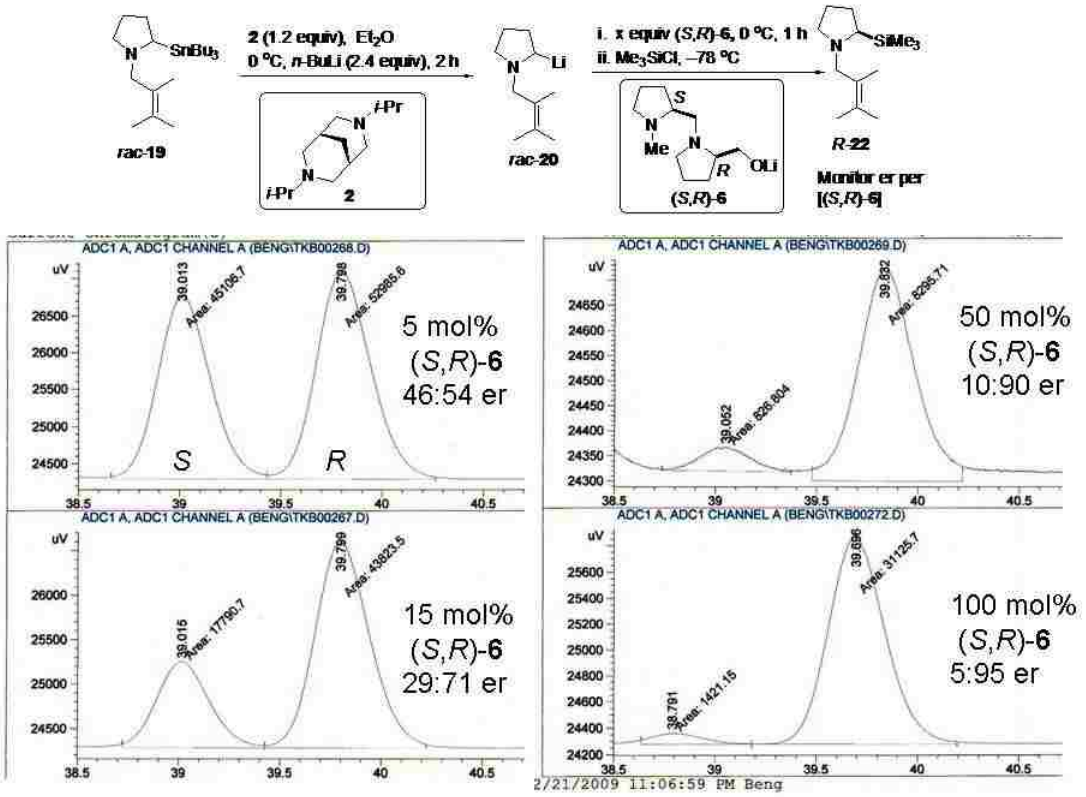
Scheme 3.2. Dynamic resolution of 20 with varying amounts of (S,R)-6 at 0 °C in Et_2O for 1 h



Dynamic resolution of rac-20 in the presence of varying amounts of (S,R)-6 was followed by treating rac-19 (0.06 M in Et_2O) with n-BuLi (1.2 equiv) and 2 (1.2 equiv) at 0 °C for 1 hour under argon to effect tin-lithium exchange, affording rac-20·2. The concentration of (S,R)-6 was varied (0.0 to 100 mol%). After 1 h at this temperature, the tubes were transferred to the bath at

–78 °C and quenched with excess Me_3SiCl. CSP-GC analysis of the silanes provided the data in Figure 3.4.

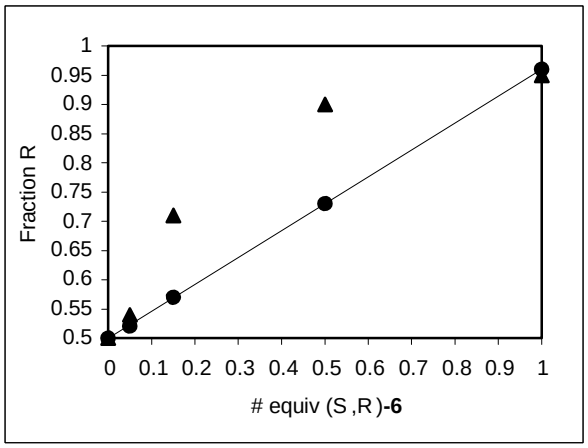
Figure 3.4. Effect of varying [(S,R)-6] on resolution of 20 with 2 (1.2 equiv) at 0 °C in Et_2O for 1 h.



Enantiomer ratios for varying [(S,R)-6]. Predicted er assumes that 20·2 is racemic and 20·(S,R)-6 is resolved to a an er of 96:4.

# equiv (S,R)-6	Predicted er (R:S)	Observed er (R:S)
0.00	50:50	50:50
0.05	52:48	54:46
0.15	57:43	71:29
0.50	73:27	90:10
1.00	96:4	95:5

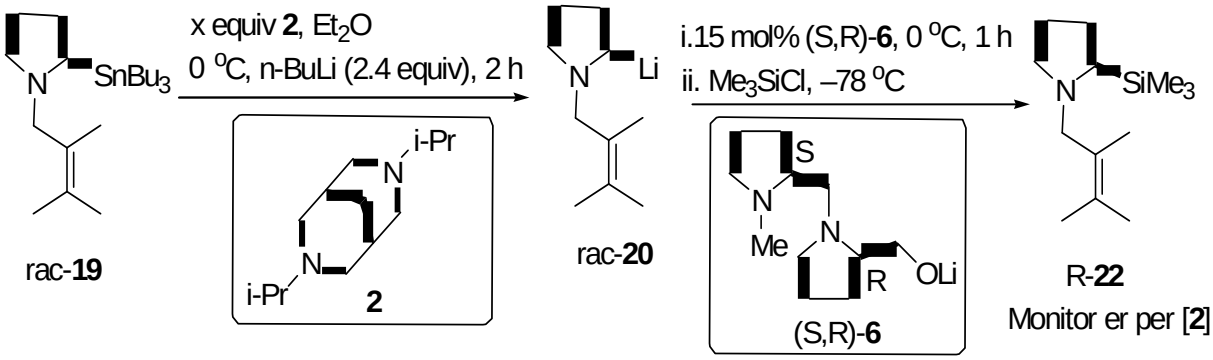
Observed er; diamonds, predicted er at thermodynamic equilibrium; circles)



Using 5, 15, 50, and 100 mol% of (S,R)-6, after stirring for 1 h at 0 °C, cooling to –78 °C and quenching with Me_3SiCl afforded R-22 of 54:46, 71:29, 90:10 and 95:5 er respectively. (Figure 3.4, triangles). This reveals that there is a nonlinear dependence of the evolution of the R-enantiomer on the catalyst loading.

3.2.3. Effect of [2] on the CDR of 20 in the presence of (S,R)-6

Scheme 3.3. Catalytic dynamic resolution of 20 with varying [2] at 0 °C in Et_2O for 1 h



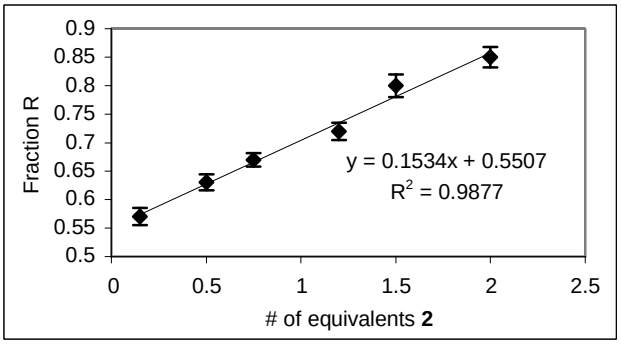
The time evolution of S-20 under CDR conditions in the presence of varying amounts of 2 (zero to two equivalents) was followed as described in Scheme 3.3 and the results are shown below.

Figure 3.5. (a) Enantiomer ratios at varying [2] for CDR of 20 with (S,R)-6 (15 mol%) at 0 °C in Et_2O for 1 h. (b) Plot of fraction R vs [2] for CDR of 20.

(a)

# equiv 2	er (R:S)
0.15	57:43
0.50	63:37
0.75	67:33
1.20	72:28
1.50	80:20
2.00	85:15

(b)

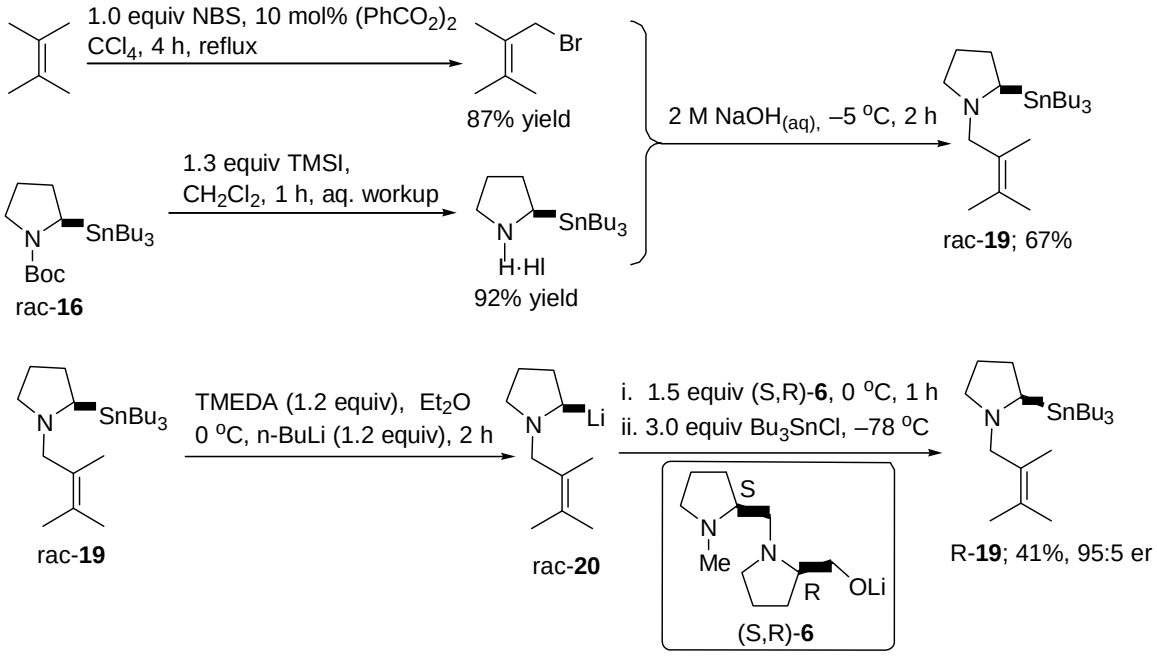


When a resolution was conducted using a stoichiometric amount of (S,R)-6 in the absence of 2, R-22 of 88:12 er was obtained after an hour at 0 °C. However, when the resolution was

repeated in the presence of 1.2 equivalents of 2, the er of R-22 improved to 95:5. Quantitative kinetic measurements revealed that in addition to promoting tin-lithium exchange, 2 accelerates the CDR of 20 by both 1 and (S,R)-6. The enantiomer ratio for catalytic dynamic resolution in the absence of 2 can be obtained from the intercept of Figure 3.5 (55:45 in favor of R). Note that if 15% of 20·(S,R)-6 resolves to 96:4 while the remaining 85% of 20·2 gives racemic product, the enantiomer ratio will be 57:43 in favor of the R-enantiomer. Therefore, the achiral ligand 2 is required for a CDR to be operative. The ligand exchange processes between the achiral and chiral ligands are not fully understood at this point but the results clearly indicate that for the purpose of developing a CDR, the achiral and chiral ligands must be involved.

3.2.4. Time Evolution of R-20 (95:5 er) under CDR conditions in the presence of 2 (1.2 equiv) and (S,R)-6 (15 mol%)

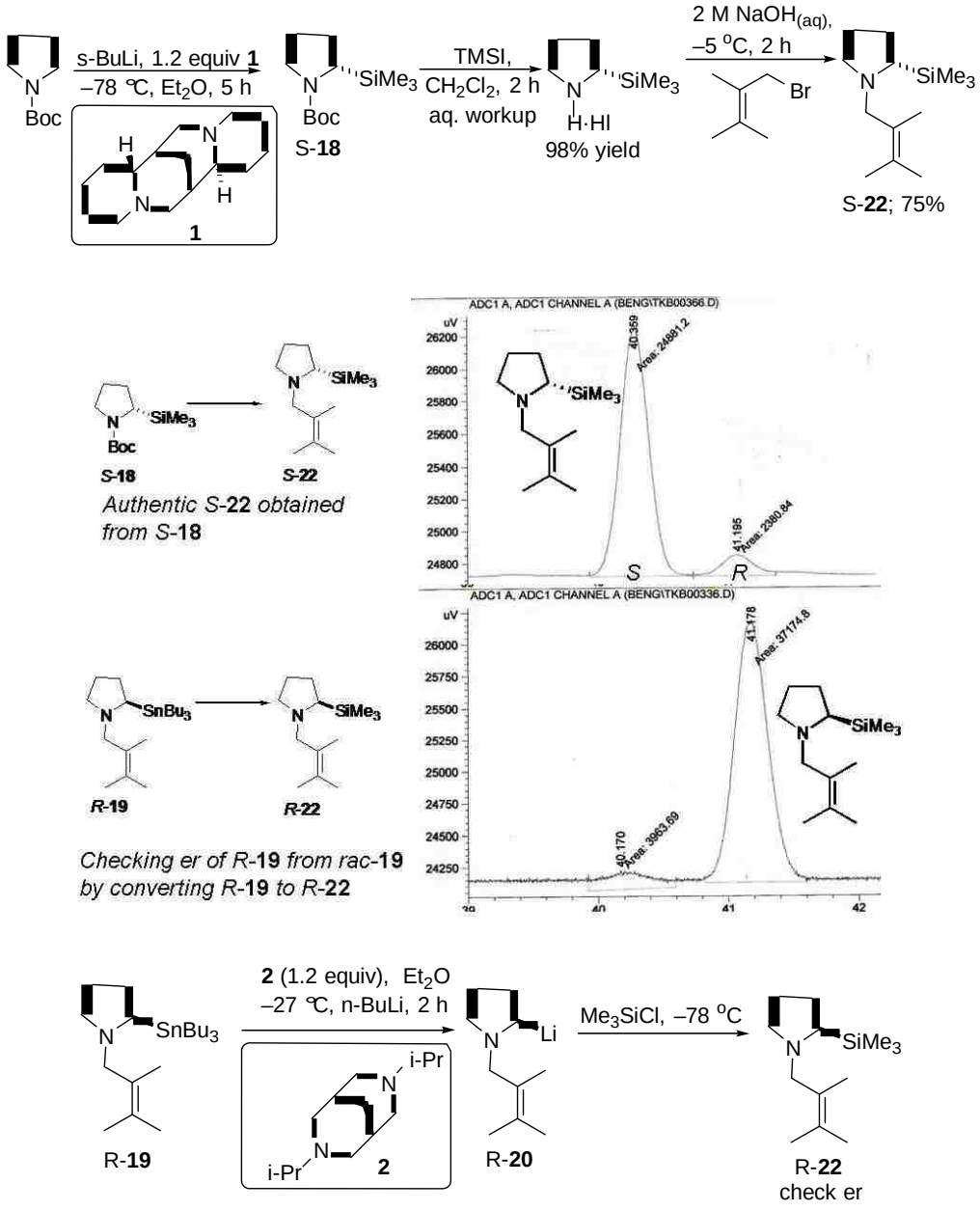
Scheme 3.4. Synthesis of R-19 by DTR in the presence of TMEDA[1]



From the thermodynamic values in Chapter 2, Table 2.8, less than 1% inversion of 20·2 at 0 °C is anticipated in the course of an hour. In an attempt to investigate the rate of the reverse processes (R to S) and also test the configurational stability of R-20·2 under the catalytic

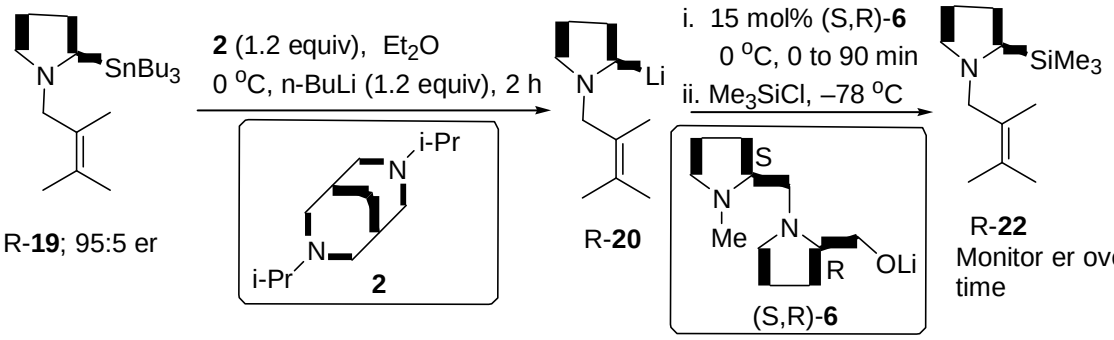
conditions, R-19 was prepared by stoichiometric DTR using the Coldham conditions (Scheme 3.4).[1]

Figure 3.6. Establishing the faster eluting enantiomer of 22 on CSP-GC and evaluating the er of R-19 by converting it to 22



We established whether the S or R-enantiomer of 22 eluted first on our CSP-GC column by obtaining S-22 from S-18, prepared using Beak's asymmetric deprotonation methodology[2] with the chiral base s-BuLi/(–)-sparteine (Figure 3.6). Knowing that S-22 elutes faster than R-22, we evaluated the er of R-19 by converting it to R-22 under conditions that ensured the configurational stability of R-20 (Figure 3.6). R-19 of 95:5 er was converted to R-20·2 and subjected to the catalytic conditions as illustrated in Scheme 3.5.

Scheme 3.5. Testing the configurational stability of R-20 (95:5 er) in the CDR of 20·(S,R)-6



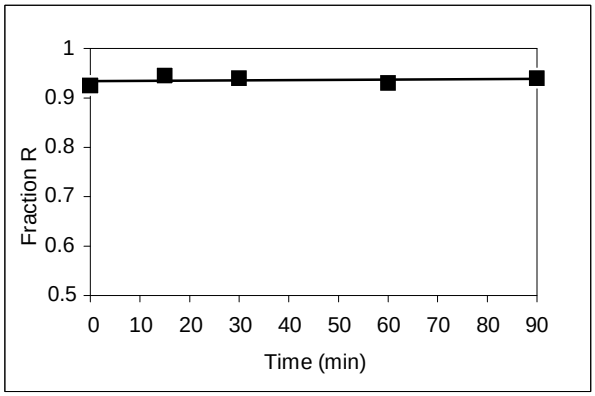
In duplicate experiments, the er was monitored over the course of 90 min to see whether it is maintained under the catalytic conditions, or whether it drops to the thermodynamic value of 57:43 (R:S). After 15, 30, 60 and 90 min, R-22 of 94:6, 95:5, 92:8 and 94:6 er was obtained respectively.

Figure 3.7 shows that no loss of enantiopurity was observed over the course of 90 min, indicating that the conversion of R-20·2 to S-20·2 does not occur under these conditions.

Figure 3.7. Evolution of er in the CDR of R-20 (95:5 er) with (S,R)-6 (15 mol%) in the presence of 2 (1.2 equiv)

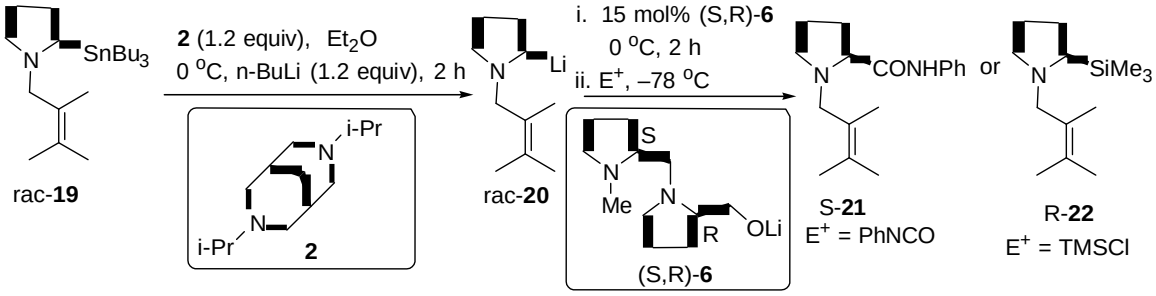
time (min): 0, 15, 30, 60, 90

er (R:S): 95:5, 94:6, 95:5, 92:8, 94:6



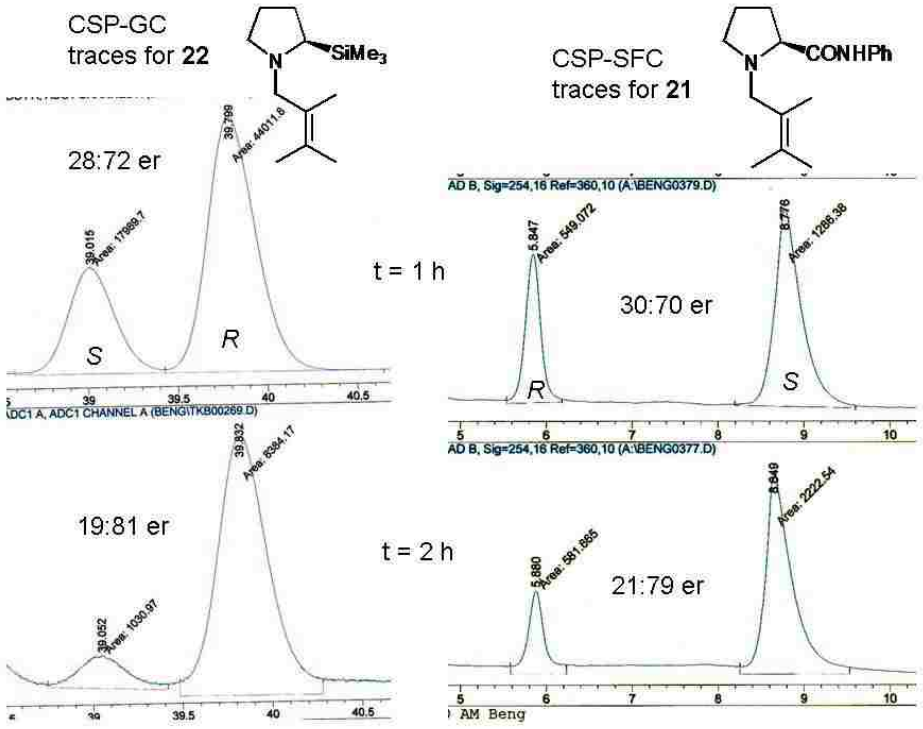
3.2.5. Variation of the Electrophile

Scheme 3.6. CDR of 20·(S,R)-6 with varying electrophiles



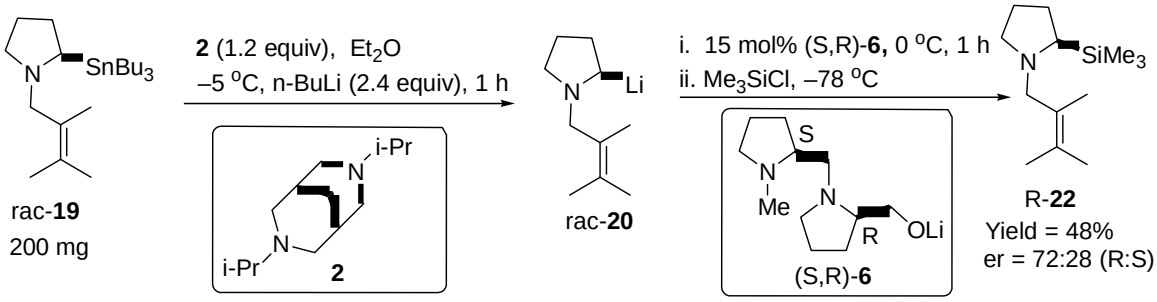
This was followed by generating the racemic organolithium 20 using tin–lithium exchange in Et_2O at 0 °C with n-BuLi and 2, followed by addition of (S,R)-6 and stirring at 0 °C for two hours, then cooling to –78 °C and electrophilic quench with either Me_3SiCl or phenyl isocyanate. Quenching with phenyl isocyanate afforded S-21 in 70:30 er after 1 h and 79:21 er after 2 h. With Me_3SiCl, R-22 was obtained in 72:28 er after 1 h and 81:19 er after 2 h.

Figure 3.8. CDR of 20·(S,R)-6 with varying electrophiles



3.2.6. Optimized Yields

Scheme 3.7. Optimized yield for CDR of 20·(S,R)-6 in the presence of 2 in Et_2O

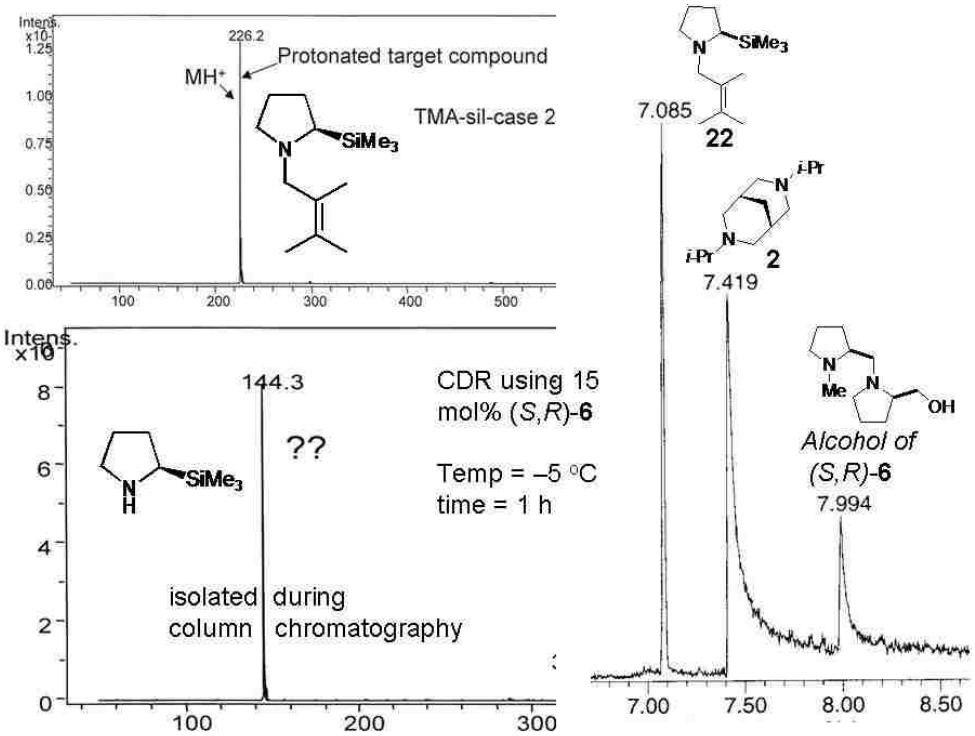


Starting with rac-19 (200 mg, 0.54 mmol), 1.2 equiv 2, 15 mol% (S,R)-6, stirring at 0 °C for 1 h and electrophilic quench with Me_3SiCl afforded 48 mg of R-22 as a colorless oil in 48% yield and 72:28 er. As we performed this experiment, we were also interested in analyzing the crude mixture containing all three amines (silane 22, achiral ligand 2, and chiral ligand (S,R)-6). We decided to determine the % conversion by GC using 2 as an internal calibration standard.

Thus five drops of the crude mixture were placed in a vial, diluted with Et_2O and analyzed for yield on a GC-MS column.

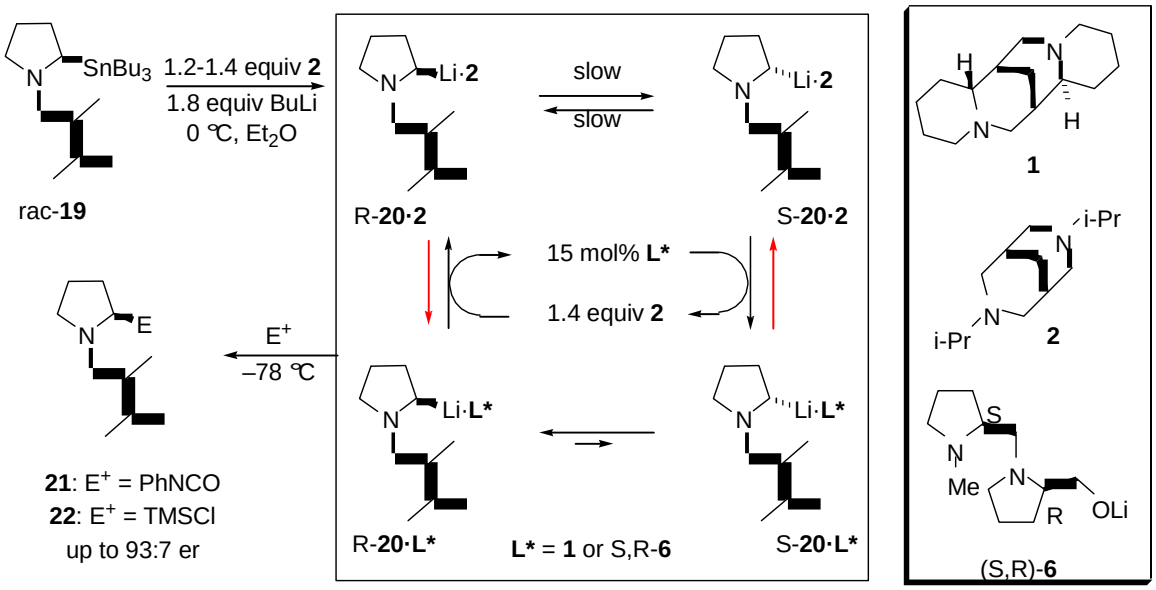
The top left trace in Figure 3.9 shows the ESI-MS of R-22 in its protonated form. The bottom left trace is that of deallylated silane that was formed as a byproduct. The GC trace on the right of Figure 3.9 is that of the crude mixture. The retention times of 7.08, 7.42, and 7.99 min correspond to the silane 22, achiral ligand 2, and the diamino alcohol of (S,R)-6 respectively. From the integral ratio of 2 to 22, the % conversion by GC was estimated at 52%. Knowing that the ratio of 2 to (S,R)-6 at the start of the experiment was eight (120 mol% 2:15 mol% (S,R)-6), and after comparing the integral ratio of 2 to (S,R)-6 after workup, we were pleased to observe internal consistency (2:(S,R)-6 = 7.7).

Figure 3.9. Determination of % conversion by GC in the CDR of 20·(S,R)-6 in the presence of 2 in Et_2O



3.2.7. Mechanistic Hypothesis

Scheme 3.8. Proposed catalytic cycle for CDR of 20



Scheme 3.8 summarizes how a catalytic dynamic resolution might operate. The aggregation states of 20 and (S,R)-6 in Et_2O are unknown. They are drawn as monomers for simplicity. We know that the N-methyl analog of 20 is a homochiral dimer and the N-ethyl analog is a mixture of aggregates.[1, 3] There has been one previous report of a DTR using substoichiometric amount of chiral ligand. The authors showed that the resolution was driven by the well known process of crystallization induced resolution (see Chapter 1, Scheme 1.18).[4, 5] In our case, the solution remains homogeneous throughout, indicating that aggregation is not the driving force for the catalytic resolution. Starting from rac-20, there is a buildup of R-20·2 under the CDR conditions (Figure 3.2). The kinetic studies have revealed that 2 catalyzes the CDR. It is worth noting that alkylation of rac-20·(S,R)-6 at –78 °C with substoichiometric electrophile gives S-21 (65:35 er) and R-22 (62:38 er) but this kinetic preference alone cannot account for the observed er's in the CDR. We have tested the configurational stability of R-20·2 (95:5 er) under the catalytic conditions and found that it retains configurational integrity under

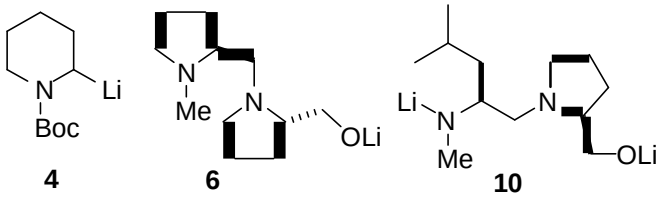
the CDR conditions. This reveals that there is no apparent pathway to racemization through the enantiomeric complexes, i.e. the enantiomerization from R-20·2 to S-20·2 does not occur under the CDR conditions. The CDR works equally well with PhNCO giving er values similar to those obtained with TMSCl. The measured er after 1 h at 0 °C using 5, 15, 50 and 100 mol% catalyst, shows that the effect is nonlinear (Figure 3.4). This is not a nonlinear effect in the standard sense of the word. The er of the catalyst has not been changed, only its loading. Therefore, to avoid confusion, we do not call it a nonlinear effect. The isolated yield of 48% for purified 22 bears some significant mechanistic implications. If the (S,R)-6-containing complex reacted faster than the uncomplexed or the 2-containing complex, then the isolated yield would have to be ~15% or less for us to achieve er's as high as 93:7 er; but it isn't. Also, if the enantiomeric complexes were thermally less stable than the diastereomeric complexes such that selective decomposition occurs, then enhanced er's would be possible. However, Figure 3.9 shows that the ratio of 2 to (S,R)-6 is retained throughout thus implying that selective decomposition does not occur.

Detailed mechanistic studies are however hampered by the instability of 20 due to the fragility of the trimethylallyl group and its ability to undergo proton transfer reactions (intra- and intermolecular). Also, the presence of ligand 2 complicates recovery of the chiral ligand and the synthesis of 2 proceeds in low yield.[6]

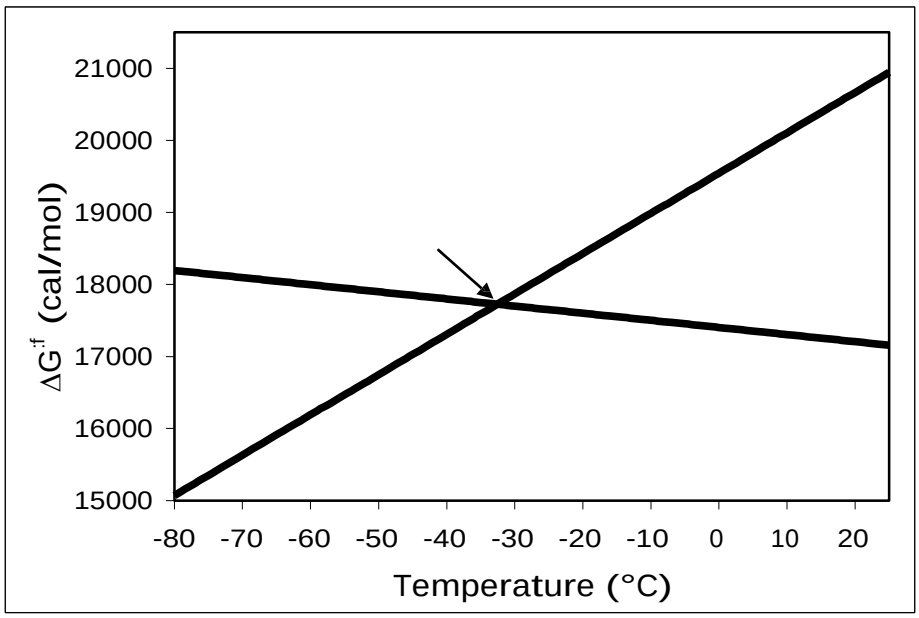
Case 2: Catalytic Dynamic Resolution of N-Boc-2-lithiopiperidine 4.

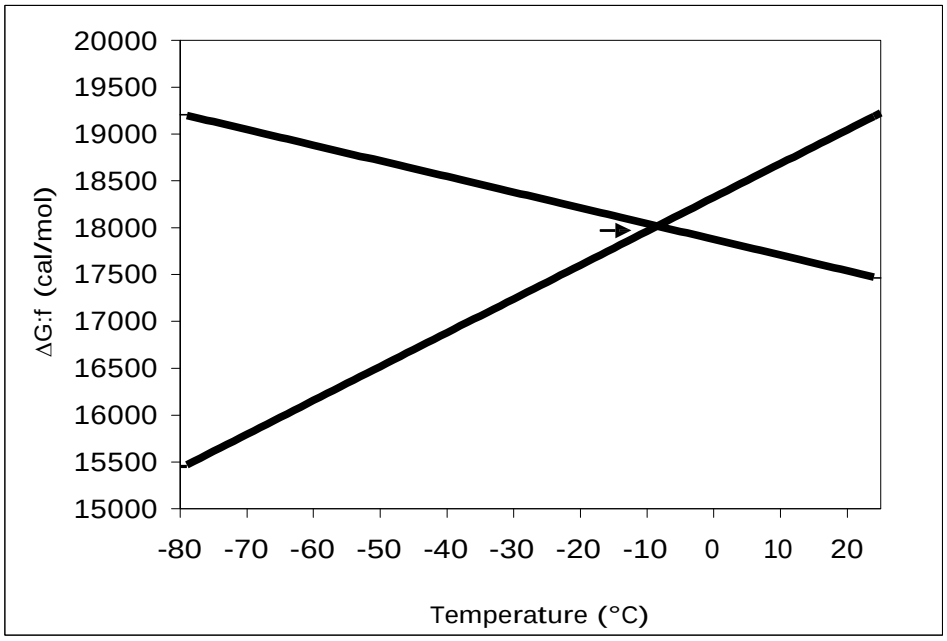
The unusual enthalpic and entropic parameters for the DTR of 4·6 and 4·10 in the presence of TMEDA (Chapter 2, Figure 2.10) have revealed that these are mostly entropy-controlled processes, and the free energy barrier drops significantly at low temperature. The difference in free energy, $\Delta(\Delta G^{\ddagger})$ between racemization and DTR increases as the temperature is lowered. The barrier for DTR of 4·6 in the presence of two equivalents of TMEDA is lower than the barrier for racemization below –33 °C (Figure 3.10). At –55 °C, the DTR barrier is 16.47 kcal/mol, whereas the racemization barrier is 17.95 kcal/mol. These barriers correspond to half-lives of equilibration of 1.1 h and 21.5 h, respectively. Similarly, the barrier for DTR of 4·10 in the presence of four equivalents of TMEDA is lower than that for racemization below –8 °C. At –45 °C, the DTR barrier is 16.70 kcal/mol and the racemization barrier is 18.63 kcal/mol corresponding to half-lives of equilibration of 24 min and 15 h, respectively. Since at very low temperatures, carbanion inversion is too slow to be observed, and at high temperatures, the organolithiums are not thermally stable, the temperature range chosen to evaluate the possibility of a catalytic dynamic resolution is –45 °C to –55 °C. Having no knowledge of the ligand exchange dynamics and the exact concentration of the achiral ligand TMEDA required for the catalytic dynamic resolution, we tried the following experiments:

Figure 3.10. The relationship between $\Delta G^{\ddagger}$ and temperature for inversion of 4



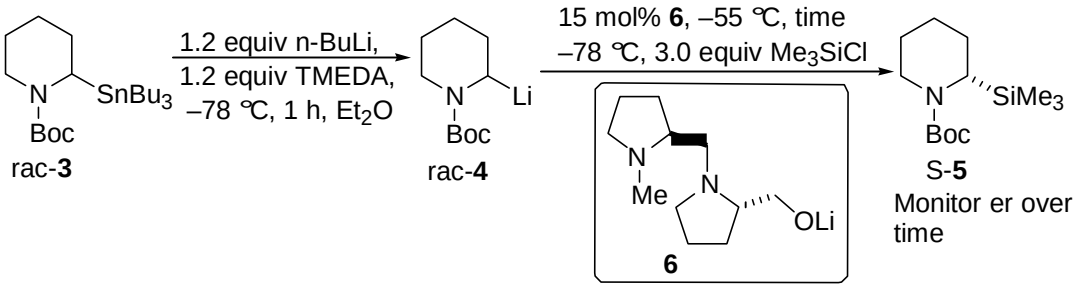
4 **6** **10**





3.3.1. Time Evolution of 4 for CDR in the presence of TMEDA and 6 (15 mol%)

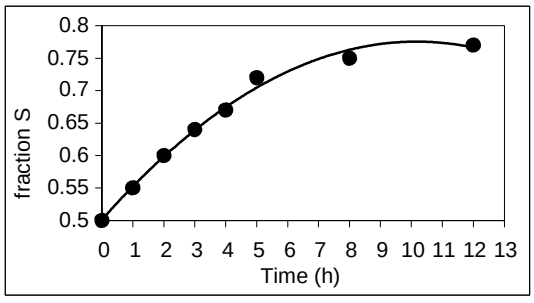
Scheme 3.9. Time evolution of er in the CDR of 4 in the presence of 6 and TMEDA

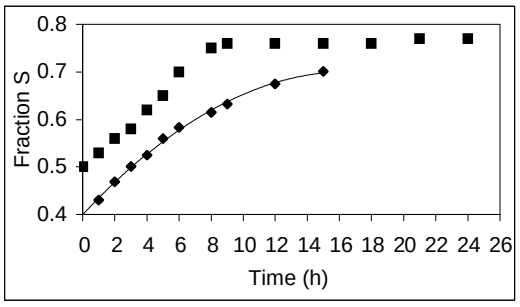


The time evolution for catalytic dynamic resolution of rac-4 was evaluated as illustrated in Scheme 3.9. In oven-dried vials, rac-3 was treated with n-BuLi and 1.2 equiv of TMEDA at –78 °C for 1 h to effect tin-lithium exchange, affording rac-4·TMEDA. The chiral ligand 6 (15 mol%) was then added and the vials were transferred to a second bath thermostatted at –55 °C. At various time intervals over 24 h, a vial was cooled to –78 °C, quenched with Me_3SiCl and the er measured by CSP-GC. Figure 3.11 shows the results obtained from duplicate experiments.

Figure 3.11. (a) Evolution of er in the DTR of 4 with 6 (1.0 equiv) in the presence of TMEDA (1.2 equiv) at –55 °C. The curve fits the equation $(S)_t = 0.77 + (0.5 - 0.77)\exp(-k_{obs}t)$ where k_{obs} is the observed rate constant. (b) Evolution of er in the CDR of 4 with 6 (15 mol%) in the presence of TMEDA (1.2 equiv). The lower curve fits the equation $(S)_t = 0.77 + (0.4 - 0.77)\exp(-k_{obs}t)$

a) $k_{obs} = 7.48 \pm 0.32 \times 10^{-5}\ s^{-1}$ b) $k_{obs} = 3.057 \pm 0.03 \times 10^{-5}\ s^{-1}$

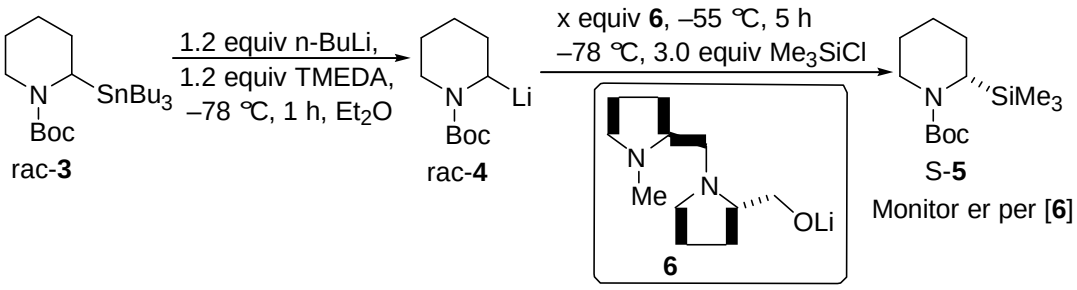




The upper curve in Figure 3.11b reveals that there is a buildup of the S-organolithium over time, followed by maintenance of configurational stability for at least 12 hours under the reaction conditions. Intriguingly, the observed rate constant for a resolution with only 15 mol% of 6 (k_{obs} = 3.057 ± 0.03 x 10^{-5} s^{-1}) is approximately twice as small as that observed in a stoichiometric DTR (k_{obs} = 7.48 ± 0.32 x 10^{-5} s^{-1}). This amplification of the resolution suggests that catalysis is occurring.

3.3.2. Effect of varying [6] on Dynamic Resolution of N-Boc-2-lithiopiperidine in the presence of TMEDA in Et_2O

Scheme 3.10. Dynamic resolution of 4 with varying [6] at –55 °C

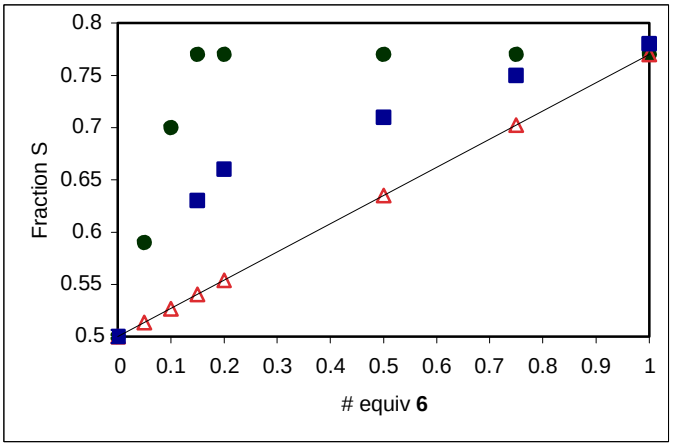


To evaluate the effect of varying amounts of chiral ligand 6 on dynamic resolutions, our initial experiments were conducted using 1.2 equivalents of TMEDA and 15, 20, 50, 80 and 100 mol% catalyst (Scheme 3.10). After 5 h at –55 °C, enantiomer ratios for 5 of 63:37, 66:34, 71:29, 75:25, and 78:22 were observed at the respective concentrations (Figure 3.12, squares). Using 4 equivalents of TMEDA and 5, 10, 15, 20, 50, 75, and 100 mol% of 6, stirring for 4 h at –55 °C then cooling to –78 °C and quenching with Me_3SiCl afforded S-5 of 59:41, 70:30, 77:23, 77:23, and 77:23, 77:23, 77:23 er respectively (Figure 3.12a, circles). Both plots reveal a nonlinear dependence of the evolution of the S-enantiomer on the catalyst loading. The observed er is always higher than that predicted if the system is at thermodynamic equilibrium (4·TMEDA being racemic and 4·6 having 77:23 er). This indicates that catalysis is occuring. The largest

difference between the observed er and the predicted er occurred with 15 mol% of 6. Therefore, this amount of chiral ligand was used to further investigate the dynamics of CDR. A quantitative study of the effect of the rate of resolution of 4 with substoichiometric 6 revealed a half-order dependence of rate on [6], thus implicating deaggregation of 6 (see Chapter 2, Figure 2.7). Similarly, with 4 equivalents of TMEDA and using 5, 10, 20, 50, 75, 100 mol% of 10, after 3 h at –45 °C, cooling to –78 °C and quenching with Me_3SiCl afforded S-5 of 73:27, 94:6, 96:4, 96:4, 96:4 and 96:4 er (Figure 3.12b).

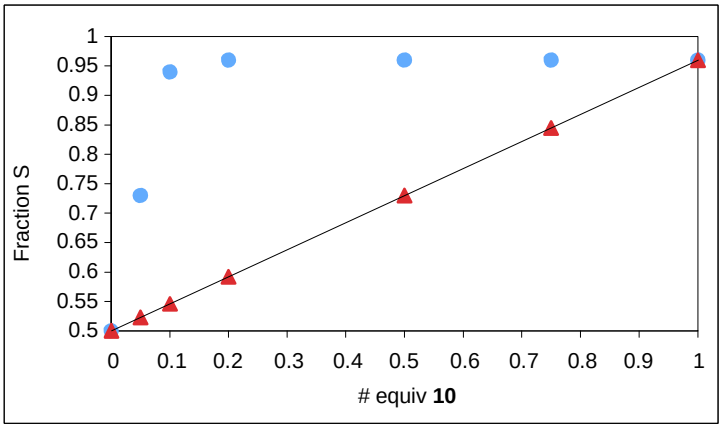
Figure 3.12. Effect of varying [L*] on dynamic resolution of 4 with TMEDA in Et_2O

(a) L* = 6, T = 218 K



KEY: predicted er; triangles, Observed er after 5 h using 1.2 equiv TMEDA; squares, Observed er after 4 h using 4 equiv TMEDA; circles.

(b) With chiral ligand 10 and 4.0 equiv TMEDA for 3 h at –45 °C



KEY: predicted er; triangles, Observed er after 3 h using 4 equiv TMEDA; circles.

3.3.3. Effect of [TMEDA] on CDR of N-Boc-2-lithiopiperidine in the presence of 15 mol% of 6

We observed a 1st-order dependence on the rate of racemization and stoichiometric dynamic resolution of 4 on [TMEDA] up to one equivalent of TMEDA (see Chapter 2, sections 2.2.4 and 2.2.6). We also observed an inverse dependence on the rate of racemization when TMEDA is in excess of 4. In addition, we noticed a significant difference in the plots shown in Figure 3.12a for the dependence of rate on [6] as the amount of TMEDA was varied from 1.2 to 4 equivalents. Because of these striking differences, we decided to measure the kinetic order in TMEDA under CDR conditions. The time evolution of S-4 under CDR conditions in the presence of varying amounts of TMEDA (zero to four equivalents) was evaluated as illustrated in Scheme 3.11.

Scheme 3.11. CDR of 4·6 with varying [TMEDA] at –55 °C in Et_2O

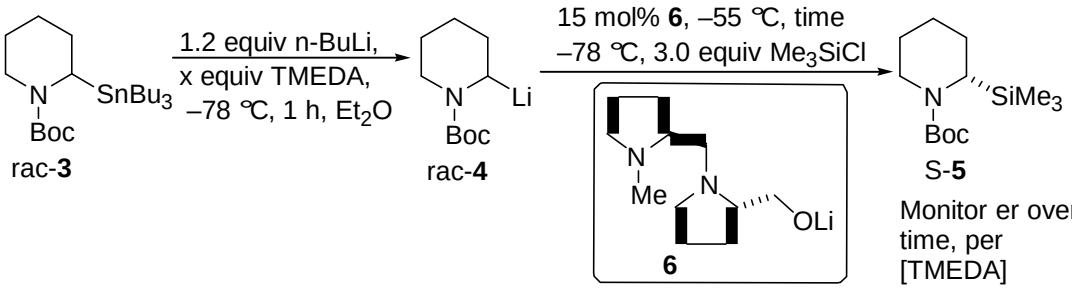
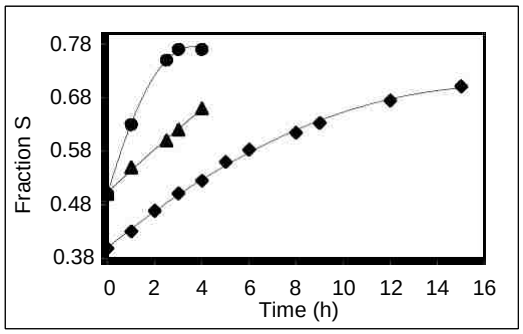


Figure 3.13b shows the observed rate constants for CDR of 4·6 plotted against [TMEDA]. The upward curvature is emblematic of a higher order dependence of rate on [TMEDA]. A nonlinear fit of the equation $k_{obs} = k_x[TMEDA]^n$ (specific order, n = 1.99; rate coefficient, $k_x = 4.02 \times 10^{-3}$ $M^{-2}s^{-1}$) reveals a 2nd-order dependence of rate on [TMEDA]. This indicates that the transition structure of the rate limiting step in the catalytic cycle contains two TMEDA molecules. Therefore, not only does excess TMEDA beneficially retard racemization and enhance DTR with a 1st-order dependence, it also mediates CDR with a 2nd-order dependence.

Figure 3.13. (a) Time evolution of 4 for CDR with varying [TMEDA] in the presence of 6 (15 mol%) in ether at 218 K for 4 h (b) k_{obs} vs [TMEDA] for CDR of 4 with 6 (15 mol%) at 218 K in Et_2O.

a) $(S)_t = 0.77 + (S(0) - 0.77)\exp(-k_{obs}t)$, S(0) = Initial fraction S,

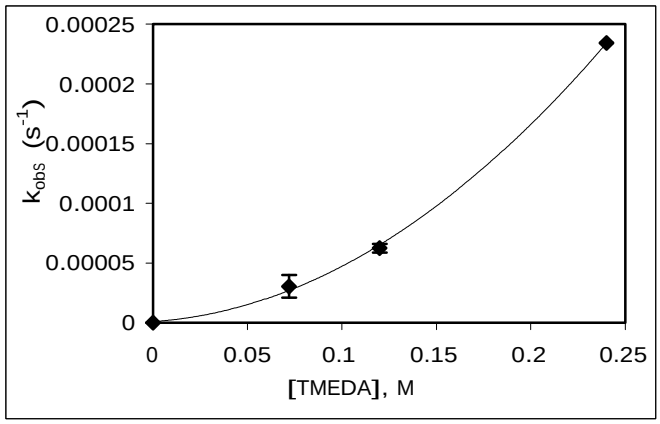
KEY: 1.2 equiv; diamonds, 2.0 equiv; triangles, 4.0 equiv; circles



Equiv TMEDA	k_{obs} (x 10^{-5} s^{-1})
0.00	0.00 ± 0.00
1.20	3.06 ± 0.03
2.00	6.24 ± 0.45
4.00	23.4 ± 2.1

(b) $k_{obs} = k_x[TMEDA]^n$, k_x = overall rate coefficient = 4.02 x 10^{-3} $M^{-2}s^{-1}$

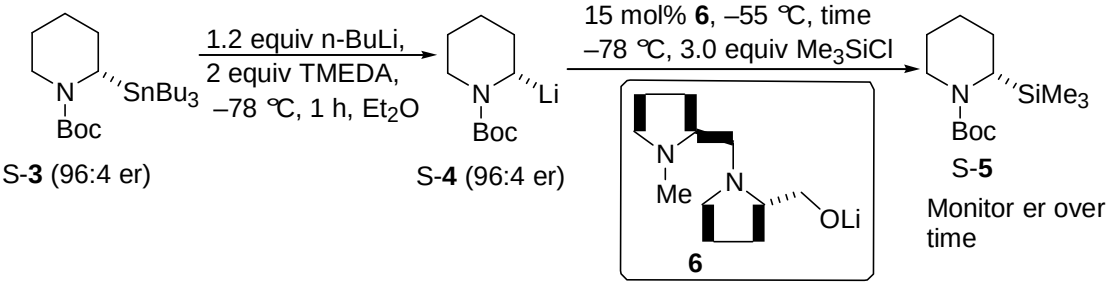
n = specific order in TMEDA = 1.99



3.3.4. Time Evolution of S-4 (96:4 er) and R-4 (72:28 er) in the presence of TMEDA (2.0 equiv) and 6 (15 mol%)

Starting from rac-4, the zero order plots of the CDR and DTR using ligand 6 converge at the equilibrium er value of 77:23 (K_{eq} = 3.35), representing a buildup of the S-enantiomer under the CDR conditions. In order to investigate whether the buildup is a consequence of configurational stability or a reflection of slow reverse reactions, S-3 of 96:4 er was synthesized using ligand 10. S-3 was then subjected to the catalytic conditions (15 mol% 6, 2 equiv TMEDA, –55 °C), and the time evolution of er was followed as shown in Scheme 3.12.

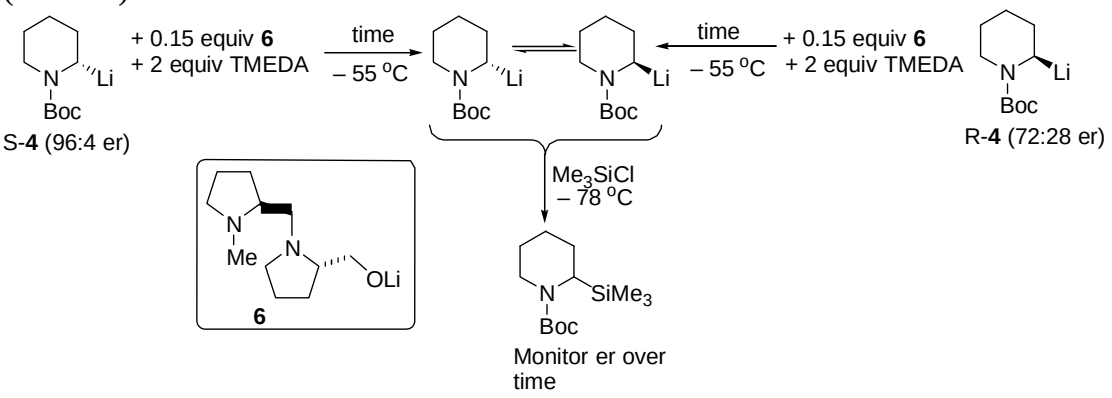
Scheme 3.12. Time evolution of S-4 (96:4 er) under CDR conditions



The er was monitored closely to see whether it is maintained under the catalytic conditions, or whether it dropped to 77:23, the value that is observed for CDR starting with rac-3 or R-3 (72:28 er). Figure 3.14a shows a gradual decrease in the enantiomer ratio over a 30-hour period until convergence at er 77:23 (S:R). The observed rate constant, $k_{SR,}$ for equilibration of S-4 (96:4 er) with 2 equiv TMEDA and 15 mol% 6 is 1.93±0.11 $\asymp 10^{-5}$ s^{-1}. Similarly, the rate constant, $k_{RS,}$

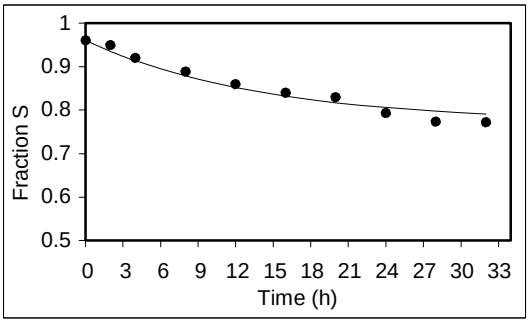
for equilibration of R-3 (72:28 er) is 6.24±0.45 $\asymp 10^{-5}$ s^{-1}. The ratio k_{RS}/k_{SR} is 3.23, which is similar to the ratio of S-4·6 to R-4·6 in a DTR (K_{eq} = 77:23 = 3.35). These findings indicate that the reverse reactions that convert S-4 to R-4 occur very slowly.

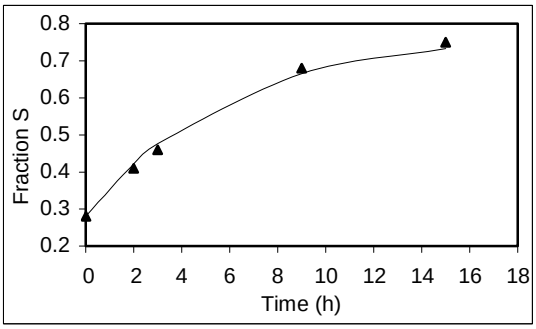
Figure 3.14. Evolution of er under CDR condition for a) S-4 (96:4 er) and b) R-4 (72:28 er)



$(S)_t = 0.77 + (0.96 - 0.77)\exp(-k_{obs}t)$ $(S)_t = 0.77 + (0.28 - 0.77)\exp(-k_{obs}t)$

$k_{SR} = 1.93 \pm 0.11 \times 10^{-5}\ s^{-1}$ $k_{RS} = 6.24 \pm 0.45 \times 10^{-5}\ s^{-1}$

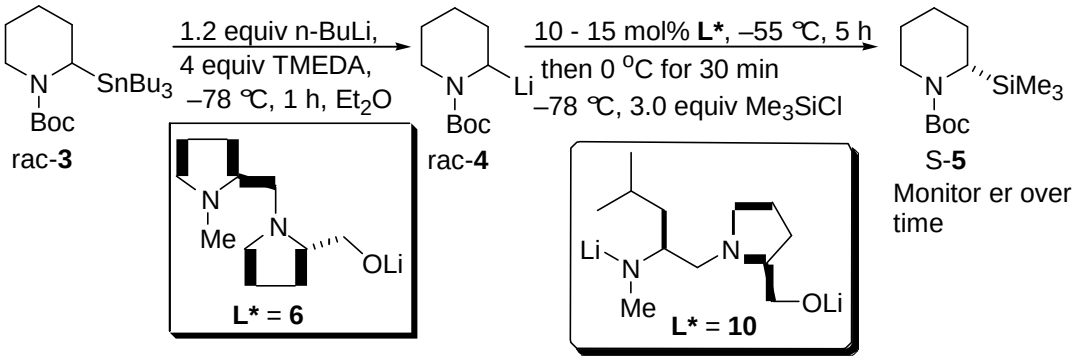




3.3.5. Importance of temperature control in developing a CDR

The negative entropy of activation for DTR of 4·6 in the presence of TMEDA implies that the free energy barrier increases with an increase in temperature, although the rate increases as temperature increases. Recall that from the Eyring equation, there is a direct proportionality between k_{obs} and temperature, but the relationship between $\Delta G^{\ddagger}$ and k_{obs} is complex since the $\Delta G^{\ddagger}$ in turn depends on $\Delta H^{\ddagger}$, $\Delta S^{\ddagger}$, and on temperature. With two equivalents of TMEDA, the DTR barrier is lower than the barrier to racemization below –33 °C. To demonstrate how proper control of temperature might influence the feasibility of a CDR, several experiments were carried out and the results are summarized below.

Scheme 3.13. CDR of 4·L* in the presence of TMEDA (4.0 equiv) at –55 °C followed by warming to 0 °C.



Transmetalation of rac-3 with n-BuLi (1.2 equiv) in the presence of TMEDA (4.0 equiv) at –78 °C for an hour afforded rac-4·TMEDA. Addition of 6 (15 mol%) followed by warming to 0 °C for 30 minutes, then cooling to –78 °C and quenching with Me_3SiCl afforded S-5 in 54:46 er.

Figure 3.15a. Evolution of er for CDR of 4 in the presence of TMEDA (4.0 equiv) at (a) 218 K for 3 h, then rapid warming to 273 K for 30 min

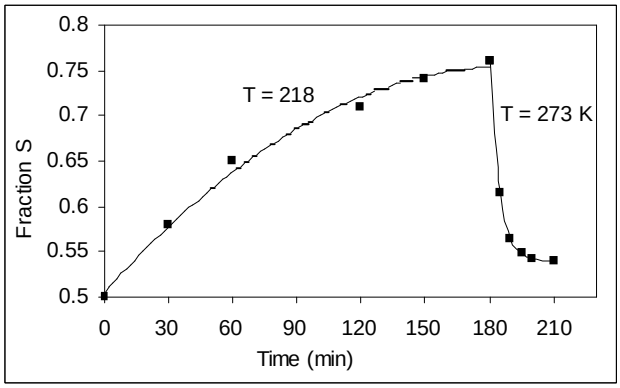
T = 218 K

Time (h)	er (S:R)
0.0	50:50
0.5	58:42
1.0	65:35
2.0	71:29
2.5	74:26
3.0	76:24

T = 273 K

Time (min)	er (S:R)
0.0	76:24
5.0	62:38
10.0	56:44
15.0	55:45
20.0	54:46
30.0	54:46

Equilibration at 218 K for 3 h, followed by warming to 273 K for 30 min.



Transmetalation of rac-3 with n-BuLi (1.2 equiv) in the presence of TMEDA (4.0 equiv) at –78 °C for an hour was accompanied by addition of the chiral ligand 6 (15 mol%), then stirring at –55 °C for 3 hours. The enantiomer ratio of S-5 was measured at several time intervals until it

reached 76:24, (k_{obs} = 2.25±0.3 $\asymp$ 10^{-4} s^{-1}). When equilibration at –55 °C for 3 hours in the presence of 6 (15 mol%) was accompanied by rapid warming to 0 ^{o}C for 30 minutes, S-5 was obtained in 54:46 er (k_{obs} = 3.74±0.04 $\asymp$ 10^{-3} s^{-1}). This directly suggests that racemization is faster than DTR at 0 °C, hence the rapid loss of configurational stability under the reaction conditions. This might also implicate fast ligand exchange at 0 ^{o}C. Clearly, careful control of temperature is necessary to achieve a CDR.

When the above experiment was performed using ligand 10 mol% of 10, the S-5 of 96:4 er (K_{eq} = 24) was obtained after 5 h at –55 °C. Warming to 0 ^{o}C led to an erosion of the er to 53:47 (K_{eq} = 1.1) after 30 min. results are displayed below:

Figure 3.15b. Evolution of er for CDR of 4 in the presence of TMEDA (4.0 equiv) at (a) –55 °C for 3 h, then rapid warming to 0 °C for 30 min

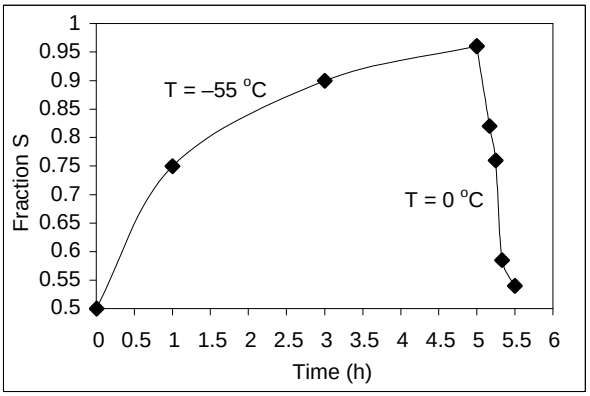
T = –55 °C

Time (h)	er (S:R)
0.0	50:50
1.0	76:24
3.0	90:10
5.0	96:4

T = 0 °C

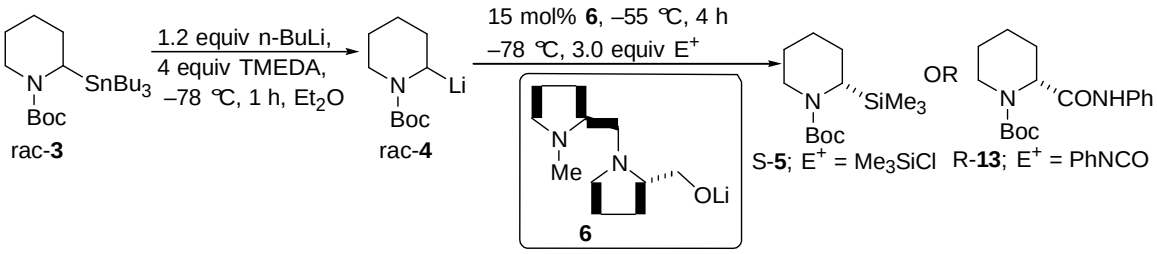
Time (min)	er (S:R)
0.0	96:4
10.0	82:18
15.0	75:25
20.0	60:40
30.0	53:47

Equilibration at –55 °C for 5 h, followed by warming to 0 °C for 30 min.



3.3.6. Variation of Electrophile

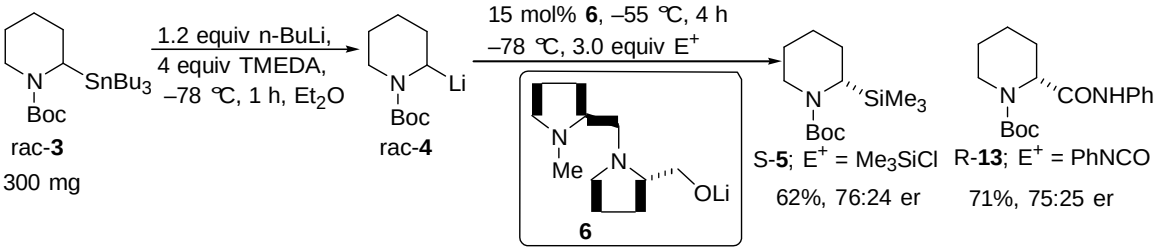
Scheme 3.14. CDR of 4·6 with varying electrophiles at –55 °C



This was followed by generating the racemic organolithium 4 using tin–lithium exchange in Et_2O at –78 °C with n-BuLi and four equivalents of TMEDA, addition of 15 mol% 6 followed by warming to –55 °C for four hours, then cooling to –78 °C and electrophilic quench with excess Me_3SiCl or phenyl isocyanate. The observed enantiomer ratios for S-5 (78:22 er) and R-13 (77:23 er) are comparable. Note that due to change in CIP priority, S-4·6 affords R-13 by retentive substitution at the metal bearing center.

3.3.7. Optimized yields for CDR of N-Boc-2-lithiopiperidine

Scheme 3.15. Optimized yields for CDR of 4 in the presence of 6 and TMEDA



Starting with rac-3 (300 mg, 0.65 mmol, 0.25 M), 4 equiv TMEDA, 15 mol% 6, stirring at −55 ^{o}C for 4 h and electrophilic quench with Me_3SiCl afforded 112 mg of S-5 as a colorless oil in 62% yield and 76:24 er. When the experiment was conducted with four equivalents of TMEDA and the equilibration temperature increased to −45 ^{o}C, S-5 was obtained in 59% yield and 77:23 er after 3 h. Similarly, with 4 equiv TMEDA, 15 mol% 6, stirring at −55 ^{o}C for 4 h and electrophilic quench with phenyl isocyanate afforded R-13 as a white crystalline solid in 71% yield and 75:25 er.

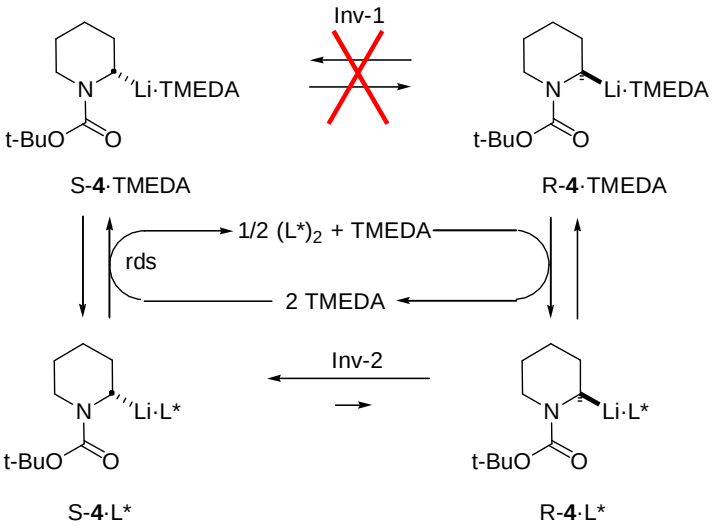
3.3.8. Summary

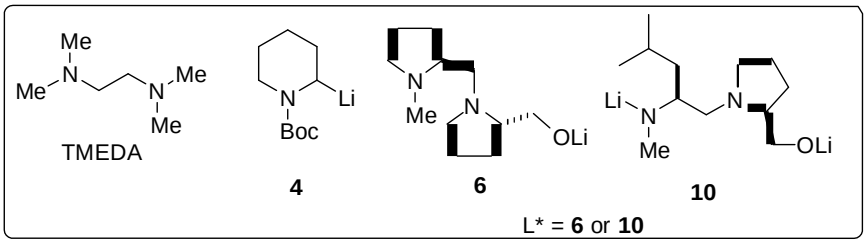
The following mechanistic insights have emerged from these studies:

- The kinetic order for CDR using 15 mol% of 6 is 2nd-order in TMEDA. Therefore, excess TMEDA accelerates the CDR.
- There is an increase in the rate of CDR as [6] increases up to 1:1 molar ratio. The kinetic order for CDR of N-Boc-2-lithiopiperidine 4 is half-order in monolithiated ligand 6, when 4 is in excess of 6, and approximately one-fourth order in dilithiated ligand 10, when 4 is in excess of 10. This implicates deaggregation of both 6_n and 10_8.
- The final er of the stoichiometric DTR of 4·6 or 4·10 and the CDR are the same. Therefore, ligands that afford a larger equilibrium constant between the diastereomeric complexes can enhance a CDR.

- Careful control of temperature is critical to the success of the catalytic dynamic resolution.
- The rate law for the CDR, which converts R-4 to S-4, is: $\frac{d[S\text{-}\mathbf{4}]}{dt} = k_{CDR}[R\text{-}\mathbf{4}][TMEDA]^2[\mathbf{6}]^{0.5}$

Scheme 3.16. Proposed catalytic cycle for CDR of 4·L*





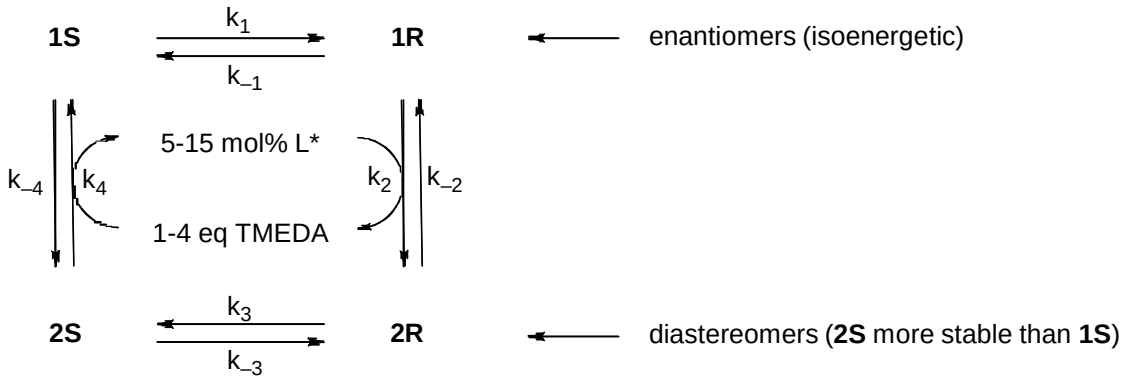
Scheme 3.16 summarizes how a CDR might operate. A co-worker in our lab, William Tyree, has shown that N-Boc-2-lithiopiperidine 4 is either a monomer or a homochiral dimer in its resting state. A joint effort with the Williard group has also revealed that 10 is an octomer in its resting state but the aggregation state of 6 in Et_2O is not known. Both 10 and 6 are drawn as monomers for simplicity. We know that starting from rac-4, there is a buildup of S-4 under the CDR conditions and maintenance of configurational stability for at least 12 hours at –55 °C. Our studies have revealed that TMEDA catalyzes the CDR with a 2nd-order dependence. We have also observed a half-order dependence of the rate of CDR on [6]. The fractional order is

indicative of deaggregation of 6. It is worth noting that alkylation of rac-4·6 under dynamic kinetic conditions at –78 °C with 0.4 equiv Me_3SiCl gives R-5 (72:28 er) indicating that the less stable enantiomer of 4 is more reactive.

Because excess TMEDA beneficially retards racemization, the inversion of monomer ("Inv-1") is not operative at low temperature. TMEDA assists in the deaggregation of chiral ligand 6 or 10 (L* in the scheme), and ligand exchange occurs to give R-4·L*. Dynamic resolution through the bottom horizontal equilibrium denoted as "Inv-2" then occurs. The 2^{nd}-order dependence of the CDR on [TMEDA] is revealing. It indicates that the transition structure contains two TMEDA molecules. It also means that the second ligand exchange which converts S-4·L* to monomeric S-4·TMEDA is rate determining, since the stoichiometry of the transition state would have one 4, ½ L*, and 2 TMEDA molecules, consistent with the rate law.

We have tested the configurational stability of S-4·TMEDA (96:4 er) under the catalytic conditions and found that the curve levels off at the equilibrium value of ligand 6 (77:23 er, S:R). This indicates that the ligand exchange, S-4·TMEDA → S-4·L*, and the "Inv-2" equilibrium, S-4·L* → R-4·L* are both operative under the reaction conditions. The CDR works equally well with PhNCO giving er values similar to those obtained with Me_3SiCl, thus eliminating any kinetic effects arising from the rate of electrophilic quench as well as any counter ion effects.

Consider the following simplistic representation of Scheme 3.16. 1S and 1R represent the two enantiomeric complexes, S-4·TMEDA and R-4·TMEDA respectively. 2S and 2R represent the two diastereomeric complexes, S-4·L* and R-4·L* respectively.



Due to the principle of microscopic reversibility, the above rate constants are related by the following equation:

$$1 = \frac{k_4\ k_3\ k_2}{k_{-4}\ k_{-3}\ k_{-2}}$$

We know that dynamic resolution of 4·10 affords 96:4 er, i.e. $\frac{k_3}{k_{-3}} = 24$

such that $\frac{k_2}{k_{-2}} = \frac{k_{-4}}{24 \asymp k_4}$

With a catalyst loading of 5 mol%, and 95% of the reaction mixture having S configuration (1S + 2S),

- $\frac{k_4}{k_{-4}} > 1$, because [1S] > [2S].

  and

- $\frac{k_4}{k_{-4}} \cong 22$, because ~90% of the 96:4 mixture of 1S and 2S is 1S $\frac{0.96 \asymp 0.90}{.04} = 21.6$

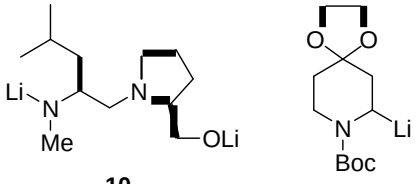
then $\frac{k_2}{k_{-2}} = \frac{1}{518} = 0.0019$, or $\frac{k_{-2}}{k_2} = 518$.

From the above treatment, the principle of microscopic reversibility requires that the k_{-2} reaction is operative, and moreover, that it favors 1R. This represents a paradox, since we

observe a buildup of 1S during the course of the reaction. However, it is worth noting that because both 4 and L* are chiral, S-4·L* and R-4·L* are diastereomeric complexes. It may be possible that only one of the diastereomers is amenable to exchanging L* for TMEDA. The CDR proceeds with largely negative entropies of activation possibly due to multiple pre-equilibria, or a strongly associative pathway. This suggests that there may be other kinetically and spectroscopically invisible intermediates. Simply put, the driving force for the catalytic resolution is not clearly understood at this point.

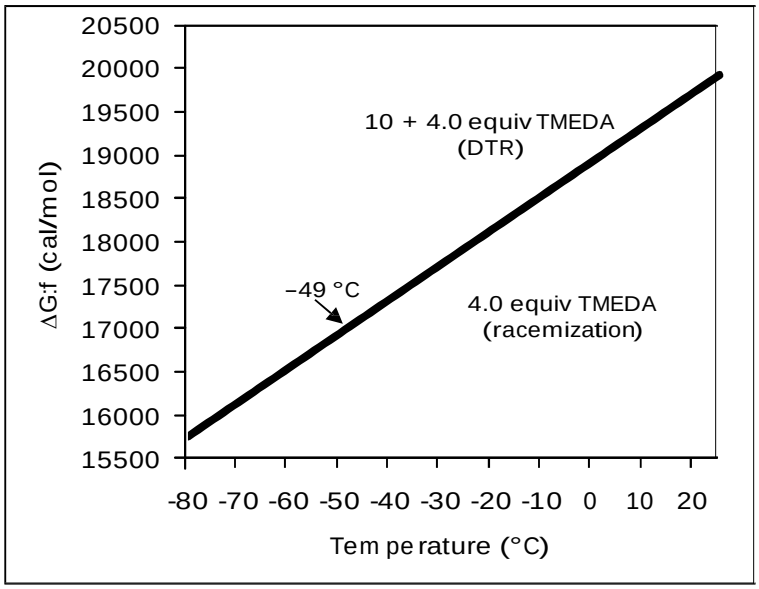
3.4. Limitation(s) of Catalytic Dynamic Resolutions

Figure 3.16. Free energy of activation vs temperature for inversion of 12 in Et_2O



10

12

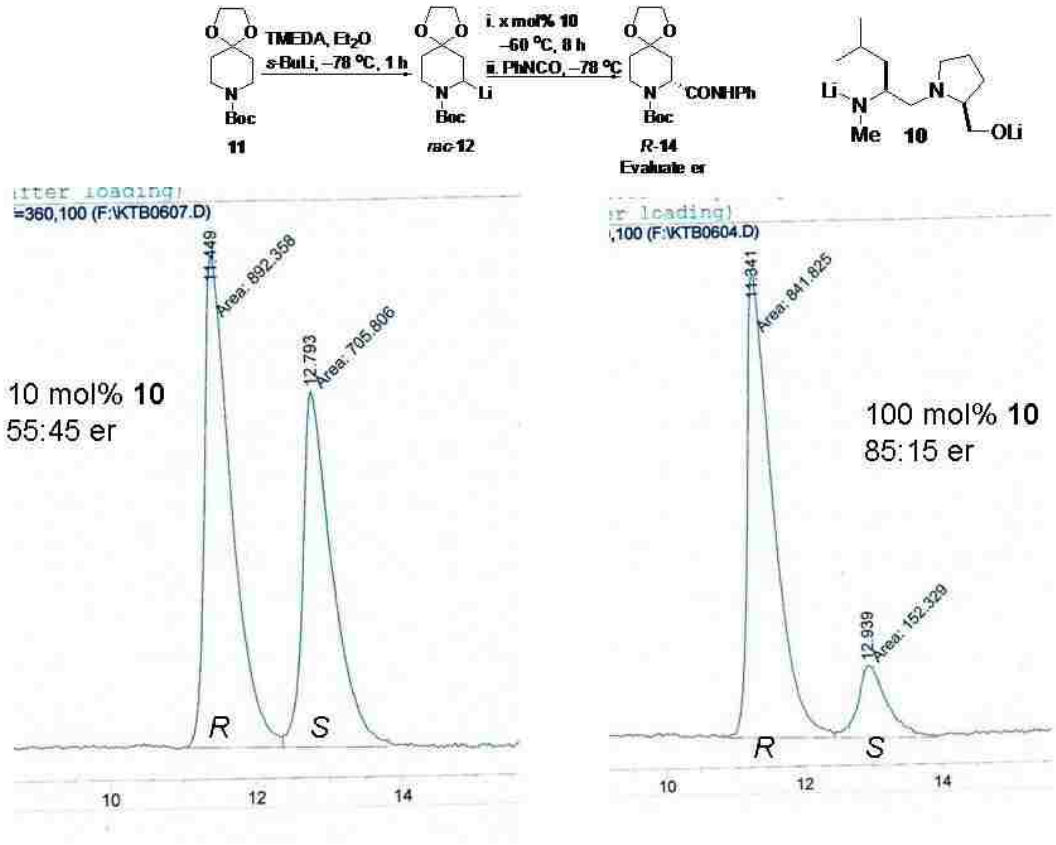


The negative entropy of activation for DTR of lithiated piperidine ketal 12 coordinated to chiral ligand 10, in the presence of TMEDA and the positive entropy of activation for

racemization of 12 in the presence of TMEDA imply that the difference in free energy of activation, $\Delta(\Delta G^{\ddagger})$ between racemization and DTR increases as the temperature is lowered below the "cross-over point". The barrier for DTR of 12·10 in the presence of four equivalents of TMEDA is lower than the barrier for racemization below –49 °C. At –60 °C, the DTR barrier is 16.55 kcal/mol, whereas the racemization barrier is 17.04 kcal/mol. These barriers correspond to half-lives of equilibration of 4.18 h and 6.88 h, respectively. At very low temperatures, DTR is slow because the rate constant decreases with a decrease in temperature. From our activation parameters, we estimate that starting from rac-12, a stoichiometric DTR using 10 and four equivalents of TMEDA would afford S-12 of 98:2 er after 30 h at –60 °C. Knowing that longer reaction times would compromise the chemical stability of the organolithium, we tried the following experiments:

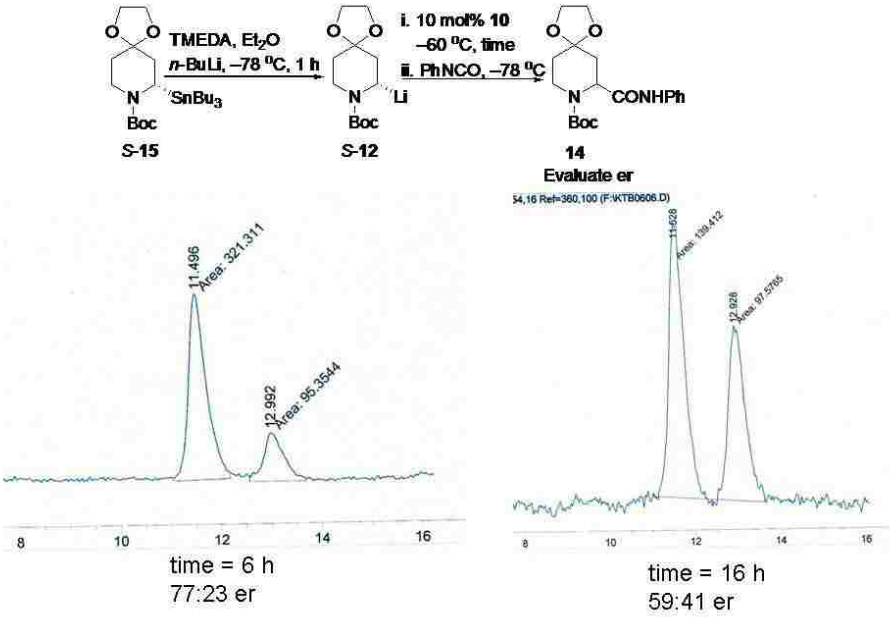
Transmetalation of rac-15 with n-BuLi (1.2 equiv) in the presence of TMEDA (4.0 equiv) at –78 °C for an hour afforded rac-12·TMEDA. Addition of a catalytic amount of 10 (10 mol%) followed by warming to –60 °C for 8 h, then cooling to –78 °C and quenching with phenyl isocyanate gave R-14 in 55:45 er. In a control experiment using a stoichiometric amount of 10, R-14 was obtained in 85:15 er.

Figure 3.17. CSP-SFC traces for reaction of rac-12 with 10 mol% 10 and 4 equiv TMEDA at –60 °C in Et_2O



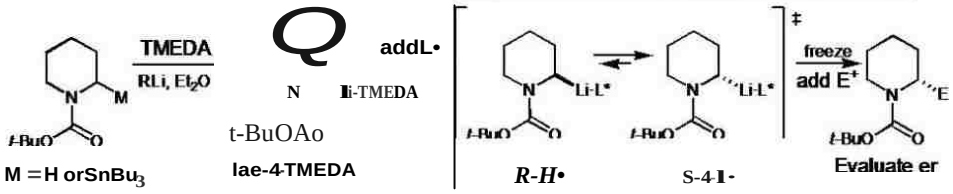
In a separate experiment, transmetalation of S-15 (93:7 er) with n-BuLi (1.2 equiv) in the presence of TMEDA (4.0 equiv) at –78 °C for an hour was accompanied by addition of the chiral ligand 10 (10 mol%), then stirring at –60 °C. After 6 h at this temperature, cooling to –78 °C and quenching with phenyl isocynate revealed a significant loss of er and R-14 was obtained in 77:23 er. When the mixture was stirred for an additional 10 h at –60 °C, R-14 was obtained in 59:41 er.

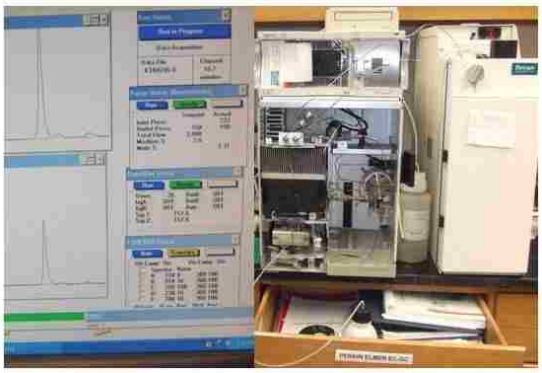
Figure 3.18. CSP-SFC traces for reaction of S-12 with 10 mol% 10 and 4 equiv TMEDA at –60 °C in Et_2O



Crucially, when a parallel experiment was carried out using N-Boc-2-lithiopiperidine, cooling of the resolved mixture and quenching with phenyl isocyanate revealed significant enantioenrichment for both the catalytic and stoichiometric resolutions. With 10 mol% 10, the anilide was obtained in 90:10 er (R:S) after 8 h at –60 °C whereas an er of 95:5 was obtained when a stoichiometric amount of 10 was employed. These results reveal that although 4 and 12 have very similar DTR barriers, the low racemization barrier of 12 in the presence of TMEDA prevents it from being amenable to a catalytic dynamic resolution.

3.5. Experimental Section





CSP-SFC: evaluate er

GC-MS: check chemical purity

Polarimeter:
check optical purity

NMR: check chemical purity

3.5.1. Time Evolution of 4 for CDR in the presence of TMEDA and 6 (15 mol%)

In ten oven-dried septum capped tubes equipped with a stir bar, rac-3 (0.25 M in Et_2O) and TMEDA (1.2 equiv) were treated with n-BuLi (1.2 equiv) at –78 °C for 60 min under nitrogen to effect tin-lithium exchange, affording rac-4·TMEDA. The diaminoalcohol (precursor of 6, 15 mol%) was treated with s-BuLi (20 mol%) at –55 °C for an hour. The preformed alkoxide 6 was added to the flask at –78 °C and the tubes were quickly transferred to a second thermostatted bath at –55 °C. At various time intervals over a 24-h period, a tube was cooled to –78 °C and quenched rapidly with excess Me_3SiCl. After 4 h, MeOH (2 mL) was added. The mixture was warmed to room temperature and HCl (2 M, 1 mL) was added followed by extraction with Et_2O (2 mL). The organic layer was filtered through a plug of Celite and the enantiomer ratio of the silanes was analyzed by CSP-SFC monitoring at 210 nm. Additionally, control experiments with stoichiometric 6 were carried out.

3.5.2. Effect of varying [6] on DR of N-Boc-2-lithiopiperidine 4 in the presence of TMEDA in Et_2O

In eight oven-dried tubes equipped with a stir bar and capped with rubber septa, rac-3 (0.06 M in Et_2O) was treated with n-BuLi (1.2 equiv) and TMEDA (4 equiv) at –78 °C for 1 hour under argon to effect tin-lithium exchange, affording rac-4·TMEDA. The concentration of 6 was varied (0.0 to 100 mol %) and the tubes were quickly transferred to the –55 °C bath. After 4 h at this temperature, the tubes were transferred to the –78 °C bath and quenched rapidly with excess Me_3SiCl. After 4 h, MeOH (2 mL) was added. The mixture was warmed to room temperature and HCl (2 M, 1 mL) was added followed by extraction with Et_2O (2 mL). The organic layer was filtered through a plug of Celite and the enantiomer ratio of the silanes was analyzed by CSP-SFC monitoring at 210 nm.

Note: The above procedure was repeated using ligand 10 at –45 °C for 3 h.

3.5.3. Effect of [TMEDA] on CDR of 4 in the presence of 15 mol% of 6

In eight oven-dried septum capped tubes equipped with a stir bar, rac-3 (0.25 M in Et_2O) and the desired amount of TMEDA (0 to 4.0 equiv) were treated with n-BuLi (1.2 equiv) at –78 °C for 60 min under nitrogen to effect tin-lithium exchange. The diaminoalcohol (precursor of 6, 15 mol%) was treated with s-BuLi (20 mol%) at –55 °C for 10 min. The preformed alkoxide was added to the flask at –78 °C and the tubes were quickly transferred to a second thermostatted bath at –55 °C. At various time intervals, a tube was cooled to –78 °C and quenched rapidly with excess Me_3SiCl. After 4 h, MeOH (2 mL) was added. The mixture was warmed to room temperature and HCl (2 M, 1 mL) was added followed by extraction with Et_2O (2 mL). The organic layer was filtered through a plug of Celite and the enantiomer ratio of the silanes was analyzed by CSP-SFC monitoring at 210 nm. The observed rate constants were determined by nonlinear fits to the zero-order plots.

3.5.4. Time Evolution of S-4 (96:4 er) and R-4 (72:28 er) in the presence of TMEDA (2.0 equiv) and 6 (15 mol%)

In ten oven-dried septum capped tubes equipped with a stir bar, S-3 of 96:4 er (0.25 M in Et_2O) and TMEDA (2.0 equiv) were treated with n-BuLi (1.2 equiv) at –78 °C for 60 min under nitrogen to effect tin-lithium exchange, affording S-4·TMEDA. The diaminoalcohol (precursor of 6, 15 mol%) was treated with s-BuLi (20 mol%) at –55 °C for 10 min. The preformed alkoxide 6 was added to the flask at –78 °C and the tubes were quickly transferred to a second thermostatted bath at –55 °C. At various time intervals over a 36-h period, a tube was cooled to –78 °C and quenched rapidly with excess Me_3SiCl. After 4 h, MeOH (2 mL) was added. The mixture was warmed to room temperature and HCl (2 M, 1 mL) was added followed by

extraction with Et_2O (2 mL). The organic layer was filtered through a plug of Celite and the enantiomer ratio of the silanes was analyzed by CSP-SFC monitoring at 210 nm. The observed rate constants were determined by nonlinear fits to the zero-order plots.

Note: The above procedure was repeated starting from R-3 of 72:28 er.

3.5.5. Control of temperature in the CDR of N-Boc-2-lithiopiperidine

In eight oven-dried septum capped tubes equipped with a stir bar, 1.0 mL of rac-3 (0.06 M in Et_2O) and TMEDA (4.0 equiv) were treated with n-BuLi (1.2 equiv) at –78 °C for 60 min under nitrogen to effect tin-lithium exchange, affording rac-4·TMEDA. The diaminoalcohol (precursor of 6, 15 mol%) was treated with s-BuLi (20 mol%) at –55 °C for an hour. The preformed alkoxide 6 was added to the flask at –78 °C and the tubes were quickly transferred to a second thermostatted bath at –55 °C. At various time intervals, one of four tubes was cooled to –78 °C and quenched rapidly with excess Me_3SiCl. After stirring for 3 h at –55 °C, the remaining four tubes were transferred to a warmer bath thermostatted at 0 ^oC. At various time intervals over a 30-minute period, one of the remaining four tubes was cooled to –78 °C and quenched rapidly with excess Me_3SiCl After 4 h, MeOH (2 mL) was added. The mixture was warmed to room temperature and HCl (2 M, 1 mL) was added followed by extraction with Et_2O (2 mL). The organic layer was filtered through a plug of Celite and the enantiomer ratio of the silanes was analyzed by CSP-SFC monitoring at 210 nm

3.5.6. Optimized yields for CDR of N-Boc-2-lithiopiperidine

In an oven-dried, septum-capped 25 mL round bottom flask equipped with a stir bar, rac-3 (300 mg, 0.65 mmol, 0.25 M) and freshly distilled TMEDA (302 mg, 2.6 mmol, 0.4 mL, 4.0 equiv) were dissolved in freshly distilled Et_2O (2.6 mL) under argon. The solution was cooled to –78 °C and treated with freshly titrated n-BuLi (0.95 M, 0.82 mL, 0.78 mmol 1.2 equiv) and stirred

for 1 hour to effect tin-lithium exchange, affording rac-4· TMEDA. The tin-lithium exchange was monitored by thin layer chromatography to ensure complete transmetalation prior to addition of the chiral ligand. The corresponding diaminoalcohol of 6 (19.2 mg, 0.097 mmol, 0.15 equiv, 0.25 M in Et_2O (0.4 mL) was treated with freshly titrated s-BuLi (0.14 M, 0.83 mL, 0.11 mmol). After complete transmetalation as noted by the disappearance of 3, the preformed alkoxide 6 was then added and the flask was quickly transferred to the –55 °C bath and allowed to stir for 4 h. The mixture was cooled to –78 °C and rapidly quenched with excess Me_3SiCl (0.25 mL, 3.0 equiv). After 4 h, MeOH (10 mL) was added and the mixture was stirred for 5 min. After warming to room temperature, 2 M HCl (10 mL) was added. The layers were separated and the aqueous layer was extracted with Et_2O (3 x 10 mL). The combined organic layers were dried over $MgSO_4$ and evaporated to obtain the crude product as a pale yellow oil. The silanes were purified by silica gel column chromatography eluting with hexane-EtOAc (98:2).

Note 1: The above procedure was repeated with four equivalents of TMEDA at −45 ^{o}C for 3 h.

Note 2: The above procedure was repeated starting with 2 mmol of rac-3, and the electrophile was switched to freshly distilled phenyl isocyanate (0.66 mL, 6.0 mmol, 3.0 equiv). After 2 h, MeOH (10 mL) was added and the mixture was stirred for 5 min. After warming to room temperature, 2 M HCl (20 mL) was added. The layers were separated and the aqueous layer was extracted with Et_2O (3 x 20 mL). The combined organic layers were dried over $MgSO_4$ and evaporated to obtain the crude product as a yellowish solid. The resulting anilide was purified by column chromatography on silica eluting with hexane-EtOAc (90:10).

3.5.7. Determination of the Isolated Yield for Catalytic Dynamic Resolution of 20

In an oven-dried, septum capped 25 mL round bottom flask equipped with a stir bar, rac-19 (200 mg, 0.451 mmol) and freshly distilled 2 (114 mg, 0.541 mmol, 1.2 equiv) were dissolved in

freshly distilled Et_2O (10 mL). The solution was cooled to –5 °C and treated with freshly titrated n-BuLi (1.2 equiv) and stirred for 1 hour to effect tin-lithium exchange, affording rac-20·2. The corresponding diaminoalcohol of (S,R)-6 (13.4 mg, 0.0677 mmol, 0.15 equiv) was treated with freshly titrated s-BuLi (1.2 equiv). After complete transmetalation as noted by the disappearance of 19, the preformed alkoxide (S,R)-6 was then added and the flask was cooled to 0 °C and allowed to equilibrate for one hour. The mixture was cooled to –78 °C and rapidly quenched with excess Me_3SiCl (3.0 equiv). After four hours, 2 M HCl (10 mL) and the contents were transferred into a separatory funnel and further acidified to pH ~ 2. The organic layer highly rich in tetrabutyltin was removed and the aqueous layer was washed with hexane (3 x 20 mL) to further remove any residual Bu_4Sn. The aqueous layer was basified with powdered Na_2CO_3 until pH 10 and extracted with Et_2O (2 x 10 mL) affording all the amines (silane 22, (S,R)-6 and 2) in the organic layer.

Five drops of the concentrated organic layer were placed in a vial, diluted with Et_2O and analyzed for yield on a GC-MS column with 2 as an internal calibration standard. Purification of the crude product by silica gel column chromatography eluting with CH_2Cl_2-MeOH-NH_3(aq) (200:3:1) afforded 48 mg of R-22 as a colorless oil in 48% yield and 72:28 er; data as reported.[3]

3.5.8. Synthesis of R-19

a). Allylic bromination of tetramethylethylene

In an oven-dried, septum capped 100 mL round bottom flask equipped with a stir bar, was added tetramethylethylene (3.4 g, 40 mmol, 1.0 equiv). CCl_4 (25 mL) was added by means of a syringe followed by addition of N-Bromosuccinimide, NBS (7.1 g, 40 mmol, 1.0 equiv). The resulting solution was stirred for 10 minutes at room temperature and benzoyl peroxide (291 mg, 3 mol%) was added and the solution was stirred slowly for 2 h. The mixture was then heated at reflux for

4 h under nitrogen, then cooled to room temperature and filtered to remove any solid residue. The filtrate was concentrated under reduced pressure to obtain the crude product as a liquid. Purification by atmospheric distillation at low temperature (bp 65 ^{o}C at 12 mmHg) afforded 5.85 g of the desired product in 87% yield as a colorless liquid; spectroscopic data as reported.[3]

Caution: The product, 1-bromo-2,3-dimethyl-2-butene is easily lost upon vacuum distillation and any slight increase in temperature leads to rearrangement, followed by undesired elimination to form dimethyl butene.

b). N-Boc-deprotection of N-Boc-2-(tributyl)stannyl pyrrolidine rac-16

To a solution of rac-16 (800 mg, 1.74 mmol, 1.0 equiv) in freshly distilled CH_2Cl_2 (20 mL) was added TMSI (0.88 g, 0.4 mL, 4.36 mmol, 2.5 equiv) dropwise over a 10-minute period under nitrogen. The color change from orange, through yellow to colorless was noted. The mixture was allowed to stir for 2 h at room temperature. Water (5 mL) was added slowly followed by addition of CH_2Cl_2 (40 mL). The layers were separated and the organic layer was then washed with water (2 x 10 mL) and with saturated NaCl (2 x 10 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure to give the crude product as a white solid. The crude product was dissolved in a minimum amount of hot CH_2Cl_2. Freshly distilled hexane (100 mL) was added and the solution was allowed to stand for 5 minutes at room temperature then stored in the freezer overnight prior to gravity filtration. The solid was washed and dried overnight on a high vacuum to afford 780 mg of the hydroiodide salt in 92% yield; data as reported.[3]

c. Synthesis of rac-19

To a solution of (rac)-2-(tributylstannyl) pyrrolidine hydroiodide salt (731 mg, 1.5 mmol, 1.0 equiv) and 2 M $NaOH_{(aq)}$ (5 mL) at –5 °C was added 1-Bromo-2,3-dimethyl-2-butene (245 mg,

1.5 mmol, 1.0 equiv) in CH_2Cl_2 (25 mL) dropwise. After stirring for 2 h at –5 °C, the mixture was washed with saturated Na_2CO_3 (1 x 10 mL) and with brine (1 x 10 mL). The combined organic layer was dried over $MgSO_4$, concentrated in vacuo with NO HEAT to obtain the crude product as a pale yellow oil. Purification of the crude product by flash chromatography on silica eluting with Hexane-EtOAc-EtOH (10:2:1) saturated with $NH_{3(aq)}$ afforded 446 mg of the colorless amine in 67% yield; data as reported.[3]

Note 1. It is important to neutralize the silica gel and minimize time of product on the column. The product was the top spot on TLC plate.

Note 2. The product can also be purified by flash chromatography on basic alumina eluting with Hexane-EtOAc (9:1).

Caution: The product is very sensitive to heat and must be kept at low temperature and under nitrogen at all times.

d). Conversion of rac-19 to R-19 by DTR

In an oven-dried, septum capped 25 mL round bottom flask equipped with a stir bar, rac-19 (200 mg, 0.451 mmol) and freshly distilled TMEDA (62.6 mg, 0.541 mmol, 1.2 equiv) were dissolved in freshly distilled Et_2O (10 mL). The solution was cooled to 0 °C and treated with freshly titrated n-BuLi (0.25 mL, 2.1 M, 1.2 equiv) and stirred for 2 h to effect tin-lithium exchange, affording rac-20·2. The corresponding diaminoalcohol of (S,R)-6 (134 mg, 0.68 mmol, 1.5 equiv) was treated with freshly titrated s-BuLi (0.8 mL, 1.0 M, 1.2 equiv). After complete transmetalation as noted by the disappearance of 19, the preformed alkoxide (S,R)-6 was then added and the flask was cooled to 0 °C and allowed to stir for one hour. The mixture was cooled to –78 °C and rapidly quenched with Bu_3SiCl (0.38 mL, 1.35 mmol, 3.0 equiv). After four hours, 2 M HCl (10 mL) and the contents were transferred into a separatory funnel and further

acidified to pH ~ 2. The organic layer highly rich in tetrabutyltin was removed and the aqueous layer was washed with hexane (3 x 20 mL) to further remove any residual Bu_4Sn. The aqueous layer was basified with powdered Na_2CO_3 until pH 10 and extracted with Et_2O (2 x 10 mL). The organic layers were combined and dried over Na_2SO_4, filtered and concentrated in vacuo with NO HEAT. Purification of the crude product on basic alumina eluting with Hexane-EtOAc (9:1) afforded 82 mg of R-19 as a colorless oil in 41% yield.[3]

3.6. References

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Appendix 5: Time evolution for CDR and stoichiometric DTR of 4 by 6

Time (h)	er (S:R) (15 mol % 6) From rac-3	er (S:R) (15 mol % 6) From R-3 (60:40 er)	er (S:R) (100 mol % 6) From rac-3
0.0	50:50	40:60	50:50
1.0	53:47	43:57	55:45
2.0	56:44	47:53	60:40
3.0	58:42	50:50	64:36
4.0	62:38	52.5:47.5	67:33
5.0	65:35	56:44	72:27
6.0	70:30	58:42	
8.0	75:25	61.5:38.5	75:25
9.0	76:24	63:37	
12.0	76:24	67.5:32.5	77:23
15.0	76:24	70:30	
18.0	76:24		
21.0	77:23		
24.0	77:23		77:23

Appendix 6. Effect of varying [6] or [10] on CDR of 4 with TMEDA (4 equiv) in Et_2O

a) Enantiomer ratios for varying [6] after 4 h at 218 K

equiv 6	Observed er (S:R)	Predicted er at equilibrium for 4·6
0.00	50:50	50.00:50.00
0.05	59:41	51.35:48.65
0.10	70:30	52.70:47.30
0.15	77:23	54.05:45.95
0.20	77:23	55.40:44.60
0.50	77:23	63.50:36.50
0.75	77:23	70.25:19.75
1.00	77:23	77.00:23.00

b) Enantiomer ratios for varying [10] after 3 h at 263 K

equiv 10	Observed er (S:R)	Predicted er at equilibrium for 4·10
0.00	50:50	50.0:50.0
0.05	73:27	52.3:47.7
0.10	94:6	54.6:45.4
0.20	96:4	59.2:40.8
0.50	96:4	73.0:27.0
0.75	96:4	84.5:15.5
1.00	96:4	96.0:4.0

Appendix 7. Enantiomer ratios for resolution of 4 in the presence of 6 (0.15 equiv) varying amounts of TMEDA at –55 °C

a) 4.0 equiv TMEDA

Time (h)	er (S:R)
0	50.50
1	63:37
2.5	75:25
3	77:23
4	77:23

b) 2.0 equiv TMEDA

Time (h)	er (S:R)
0	50:50
1	55:45
2.5	60:40
3	62:38
4	66:34

c) 1.2 equiv TMEDA

Time (h)	er (S:R)
0.0	40:60
1.0	43:57
2.0	47:53
3.0	50:50
4.0	52.5:47.5
5.0	56:44
6.0	58:42
8.0	61.5:38.5
9.0	63:37
12.0	67.5:32.5
15.0	70:30

Appendix 8: Evolution of er in the equilibration of a) S-4 (96:4 er) with 6 (15 mol %) in the presence of TMEDA (2.0 equiv)

Time (h)	er (S:R)
0.0	96:4
2.0	95:5
4.0	92:8
8.0	89:11
12.0	85:15
16.0	83.5:16.5
20.0	80:20
24.0	79:21
28.0	77:23
32.0	77:23

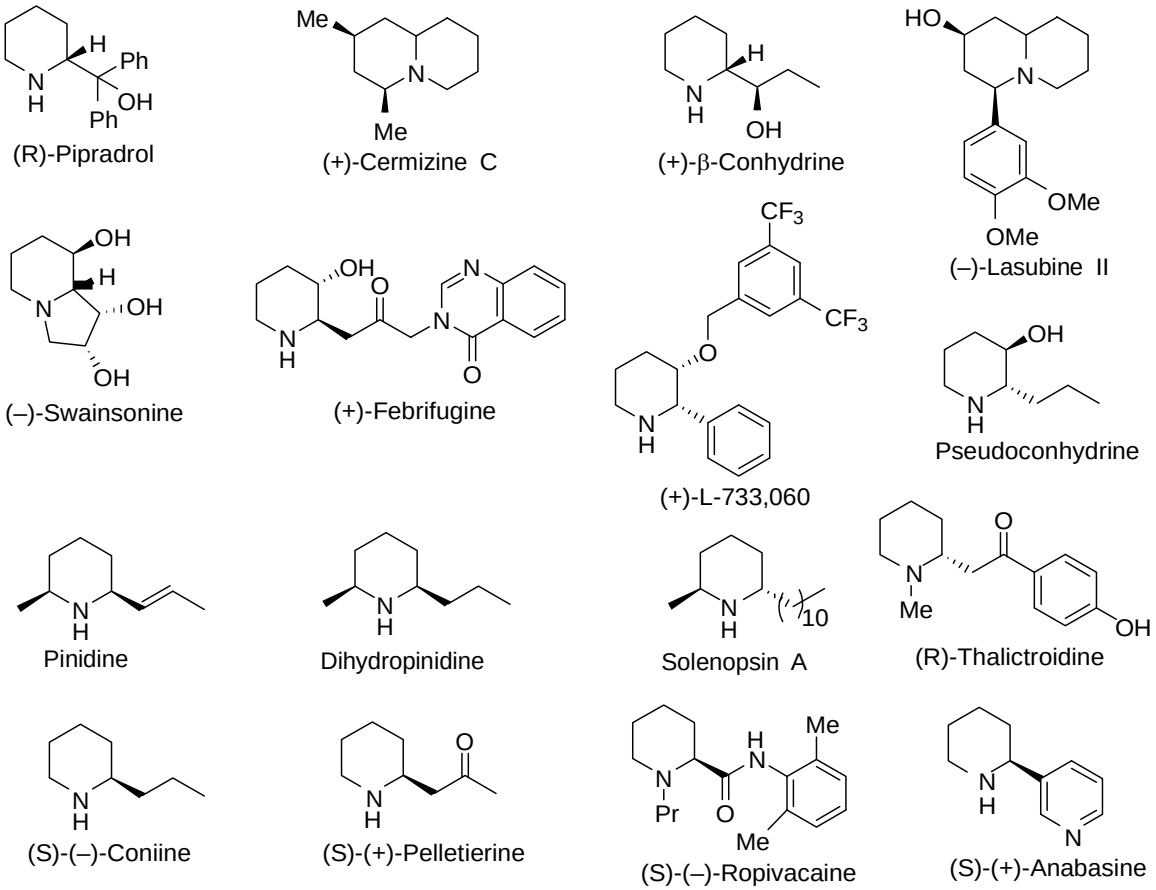
CHAPTER 4

Application of Catalytic Dynamic Resolution of N-Boc-2-lithiopiperidine to the Enantioselective Synthesis of Substituted Piperidines

4.1. Introduction

Optically active piperidines are found in a variety of natural products and some have useful pharmacological properties. In the last two decades, over twelve thousand piperidine derivatives have been utilized in clinical or preclinical studies.[1] Pipradrol is a mild central nervous system stimulant used for counteracting the symptoms of senile dementia and for the treatment of obesity and ADHD.[2] Desoxypipradrol (2-DPMP) acts as a norepinephrine-dopamine reuptake inhibitor.[3] Some piperidine-containing medicinal compounds and alkaloids have the 2,3-substitution pattern. Examples include (+)-febrifugine, an antimalarial agent,[4] (–)-swainsonine, a potential cancer drug,[5] pseudoconhydrine, cassine, and deoxocassine.[6-8] Pinidine, dihydropinidine, and solenopsin A are examples of 2,6-substituted piperidines.[9] Conhydrine is a poisonous oxygenated alkaloid found in hemlock.[10] Anabasine is a pyridine alkaloid found in tree tobacco and used as an insecticide.[11] L-733060 is a drug shown to be an orally active, non-peptide selective antagonist for the NK_1 receptor. It comes from the class of compounds that contain a 3-hydroxypiperidine.[12] Coniine is a poisonous alkaloid found in hemlock and the yellow pitcher plant. It is a neurotoxin known to disrupt the peripheral nervous system. Historically, it is the alkaloid that killed Socrates.[13] Ropivacaine is a drug that has been indicated for local anaesthesia in children over the age of 12 years and in adults. Ropivacaine is often co-administered with fentanyl for epidural analgesia.[14]

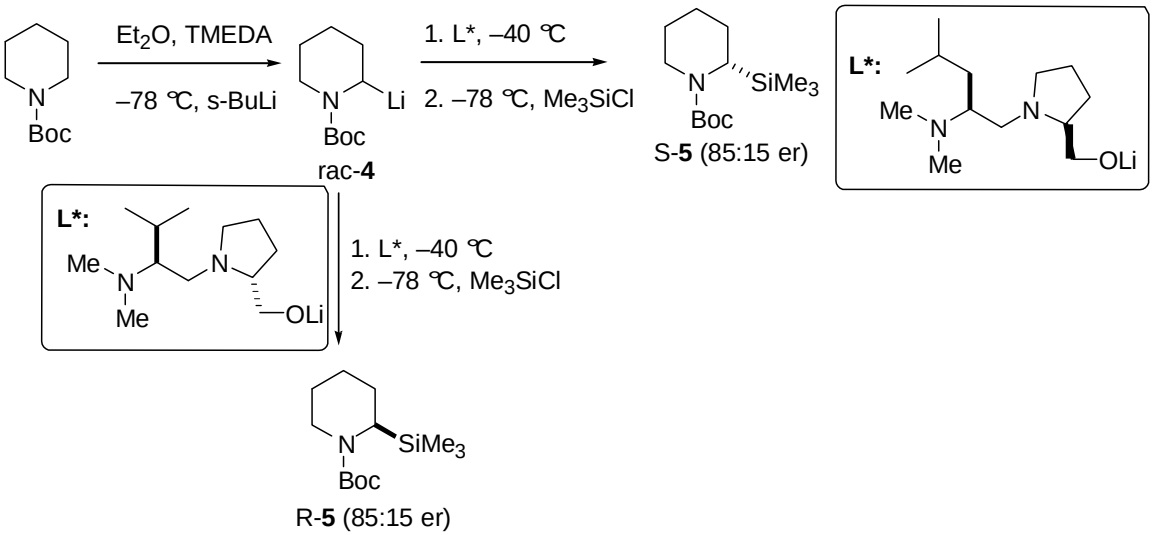
Figure 4.1. Selected piperidine alkaloids and medicinal compounds



In 1989, Beak and coworkers showed that racemic 2-substituted piperidines can be conveniently prepared by deprotonation of N-Boc-piperidine, using s-BuLi and N,N,N',N'-tetramethylethylenediamine (TMEDA) followed by subsequent alkylation of the resulting organolithium.[15] Although the chiral base s-BuLi/(–)-sparteine has been shown to effectively deprotonate N-Boc-pyrrolidine enantioselectively,[16] the same base complex is less effective with N-Boc-piperidine.[17] Recently, using his (+)-sparteine surrogate, O'Brien reported relative success, affording enantiomer ratios as high as 88:12.[18] However, the yields are highly dependent on the electrophile and only the (R)-organolithium can be obtained. An alternative approach to access 2-substituted piperidines is by the use of dynamic resolutions (see Chapters 2

and 3).[19, 20] The Coldham group recently reported that N-Boc-2-lithiopiperidine 4 can be resolved by dynamic thermodynamic resolution (DTR) using a stoichiometric amount of several of his monolithiated diamino alkoxide ligands (Scheme 4.1).[21, 22]

Scheme 4.1. Coldhams' conditions for DTR of N-Boc-2-lithiopiperidine 4.[21]



As noted previously (Chapter 3), a successful catalytic dynamic resolution depends on several factors, including a lower barrier for DTR than for racemization at a given temperature. A plot of $\Delta G^{\ddagger}$ vs. temperature for racemization of 4 in the presence of four equivalents of TMEDA and DTR of 4·10 in the presence of four equivalents of TMEDA revealed that the barrier for DTR is lower than that for racemization below –8 °C (see Chapter 3, Figure 3.10).

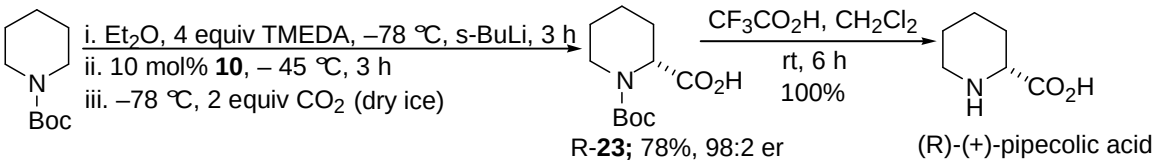
4.2. Results and Discussion

4.2.1. Catalytic Dynamic Resolution (CDR) of N-Boc-2-lithiopiperidine followed by direct trapping with the electrophile[23]

Considering that we are able to resolve N-Boc-2-lithiopiperidine catalytically (see Chapter 3), we investigated a CDR using monolithiated ligands 9 and 10 as illustrated below (Table 4.1). Thus racemic N-Boc-2-lithiopiperidine was generated by deprotonation in Et_2O at –78 °C with s-BuLi/TMEDA for 3 h, followed by addition of 10 mol% of 10, warming to –45 °C for 3 h, then cooling to –78 °C and quenching with the desired electrophile. Electrophilic quench with Bu_3SnCl afforded S-3 in 66% yield and 96:4 er (Table 4.1, entry 1); $[\alpha]_D^{22}$ +41 (c = 2, $CHCl_3$), while CDR using 9 afforded R-3 in 62% yield and 97:3 er (entry 2). The absolute configuration was assigned by comparing the specific rotations to previously reported values; lit.[24] for R-3 (>99:1 er, $[\alpha]_D^{22}$ −42.2 (c = 1.8, $CHCl_3$). Quenching with Me_3SiCl afforded S-5 in 74% yield and 96:4 er (entry 3), $[\alpha]_D^{22}$ +38 (c = 2, $CHCl_3$), lit.[25] for S-5 of 95:5 er, +36.4, c = 1.95, $CHCl_3$). With ligand 9, R-5 was obtained in 70% yield and 98:2 er (entry 4).

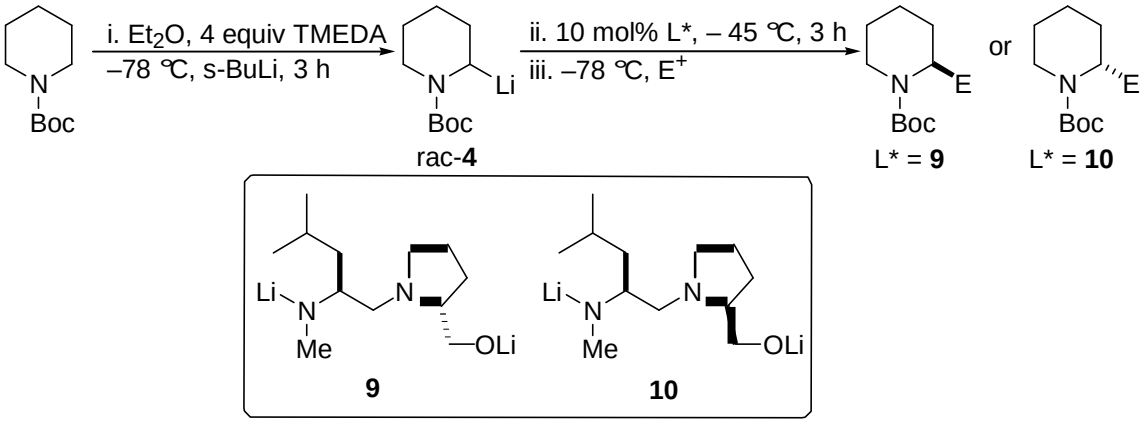
(R)-(+)-pipecolic acid: When CO_2 was used as the electrophile, N-Boc-(R)-(+)-pipecolic acid, R-23, was obtained in 78% yield and 98:2 er (entry 5) using ligand 10. Hydrolysis of the carbamate with trifluoroacetic acid provided (R)-(+)-pipecolic acid in just two steps (Scheme 4.2), $[\alpha]_D^{22}$ +42.0 (c = 1, MeOH). This represents the shortest synthesis of this synthetically useful compound.[26-28] Similarly, (S)-(–)-N-Boc-pipecolic acid was obtained in 81% yield and 97:3 er (entry 6) by CDR using ligand 9; lit.[9] for S-23 of >99:1 er, $[\alpha]_D^{22}$ –45.777 (c = 1.0 MeOH).

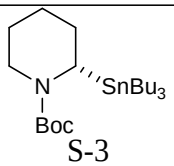
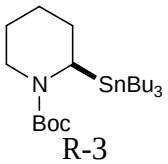
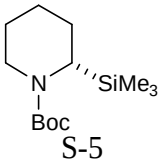
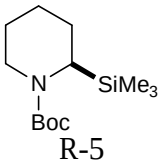
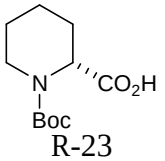
Scheme 4.2. Synthesis of (R)-(+)-pipecolic acid.[26]

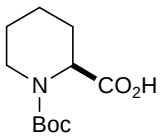
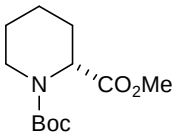
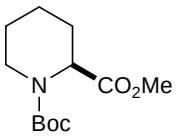
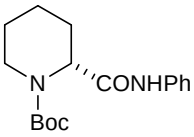
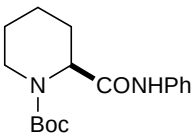
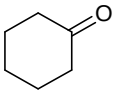
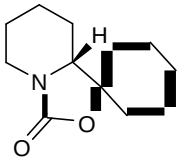
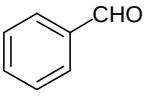
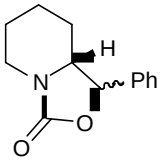
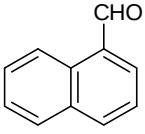
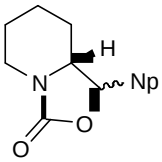
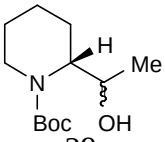
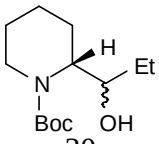


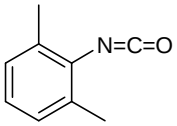
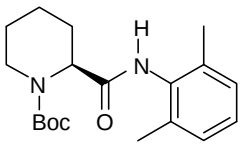
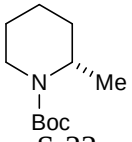
R-**23;** 78%, 98:2 er (R)-(+)-pipecolic acid

Table 4.1. CDR of rac-4 at –45 °C for 3 h in Et_2O using ligand 9 or 10.[23]



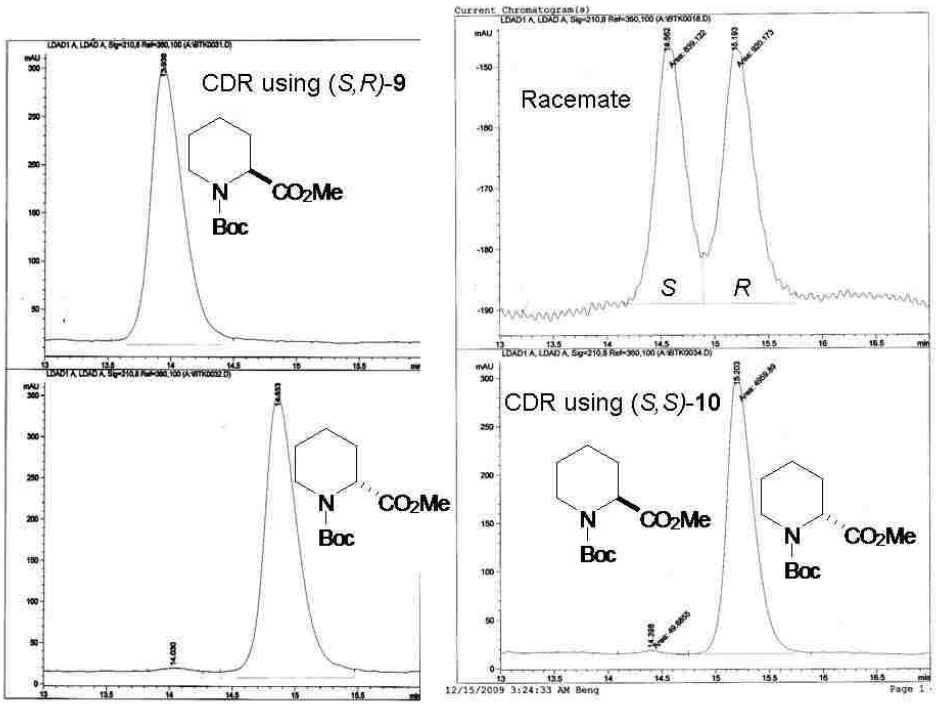
Entry	Ligand	Electrophile	Product	Yield (%)	er (R:S)
1	10	Bu_3SnCl	 S-3	66	4:96
2	9	Bu_3SnCl	 R-3	62	97:3
3	10	Me_3SiCl	 S-5	74	4:96
4	9	Me_3SiCl	 R-5	70	98:2
5	10	CO_2	 R-23	78	98:2

6	9	CO_2	 S-23	81	3:97
7	10	MeOCOCl	 R-24	88	>99:1
8	9	MeOCOCl	 S-24	85	<1:99
9	10	PhNCO	 R-25	68	>99:1
10	9	PhNCO	 S-25	72	<1:99
11	10		 R-26	60	94:6
12	10		 27	74 (62:38 dr) (syn:anti)	>99:1 & 98:2
13	10		 28	66 (82:18 dr) (anti:syn)	94:6 & 93:7
14	10	CH_3CHO	 29	76 (85:15 dr) (anti:syn)	>99:1 for both
15	10	EtCHO	 30	84 (70:30 dr) (anti:syn)	96:4 for both

16	9		 S-31	75	4:96
17	10	MeI	 S-33	62	93:7

CDR using ligand 10 followed by quenching with methyl chloroformate afforded enantiopure methyl pipecolate ester R-24 in 88% yield (entry 7); $[a]_D^{22}$ +45.2 (c = 2, $CHCl_3$), lit[29] for S-24 of 85% ee; $[a]_D^{20}$ −48.1 (c = 1.11, $CHCl_3$) and of 88:12 er; $[a]_D^{20}$ −31.7 (c = 1.0, $CHCl_3$).[30] Similarly, enantiopure S-24 was obtained in 85% yield by CDR using ligand 9. Figure 4.2 shows the CSP-SFC traces for rac-, R-, and S-24.

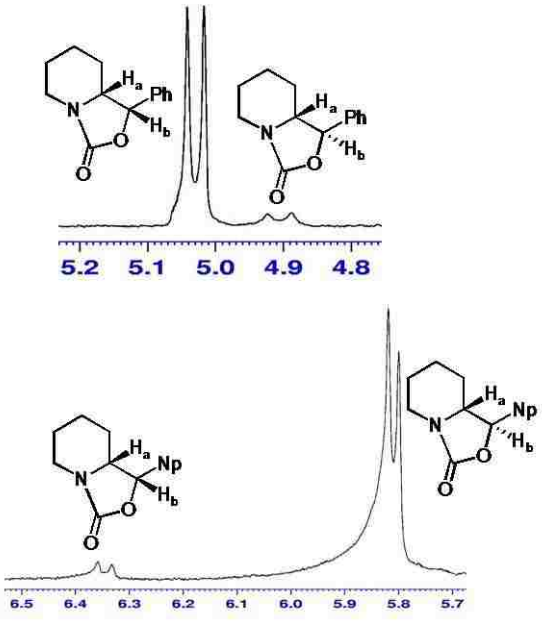
Figure 4.2. CSP-SFC traces for 24



Using phenyl isocyanate as the electrophile, the anilide R-25 was obtained in 68% yield as a single enantiomer (entry 9), $[a]_D^{22}$ +41 (c = 2, $CHCl_3$). Similarly, ligand 9 afforded S-25 in 72% yield and >99:1 er (entry 10).

We also investigated the lithiation-substitution of rac-4 with aldehydes and ketones under CDR conditions. With cyclohexanone, in situ cyclization afforded the oxazolidinone R-26 in 60% yield and 94:6 er (entry 11), $[a]_D^{22}$ –38 (c = 1, $CHCl_3$).[31] Electrophilic quench with benzaldehyde afforded 27 in 74% yield as a mixture of diastereomers, (62:38 dr) in 74% yield (entry 12); $[a]_D^{22}$ –7.7 (c = 1, $CHCl_3$), lit[32] for 27 of 80:20 dr; $[a]_D^{22}$ –2.9 (c = 1.1, $CHCl_3$). DFT calculations at the B3LYP level using 6-311g (d,p) basis set gave results consistent with our assignments. After calculating the ^{1}H NMR spectrum, we found that the chemical shift of the cis diastereomer, cis-H_aH_b, where H_a is the proton at C-2 and H_b is the proton on the carbon bearing the phenyl substituent (see Figure below) is higher than that of the trans diastereomer. Since the doublet of the H_b proton in the major diastereomer is more downfield than that of the minor diastereomer, we inferred that the cis diastereomer is the major isomer. CSP-SFC analysis gave four separate peaks (one for each enantiomer of the diastereomers) and revealed excellent enantioselectivity (major diastereomerer >99:1, minor diastereomer er 98:2).[33] Quenching with 1-naphthaldehyde afforded 28 in 66% yield (entry 13) as a mixture of diastereomers (82:18 dr). An analogous DFT calculation revealed that the chemical shift of the H_b proton of the trans diastereomer is lower than that of the cis diastereomer. The observed ^{1}H NMR spectrum showed that the H_b proton of the major isomer is less deshielded than that of the minor isomer. We inferred that the trans isomer is the major isomer. CSP-SFC analysis of the crude mixture gave four separate peaks having 94:6 er for the major diastereomer and 93:7 er for the minor diastereomer

Figure 4.3. Partial ^{1}H NMR spectra for 27 (top) and 28 (bottom) showing the doublet for the H_b proton for the different diastereomers.



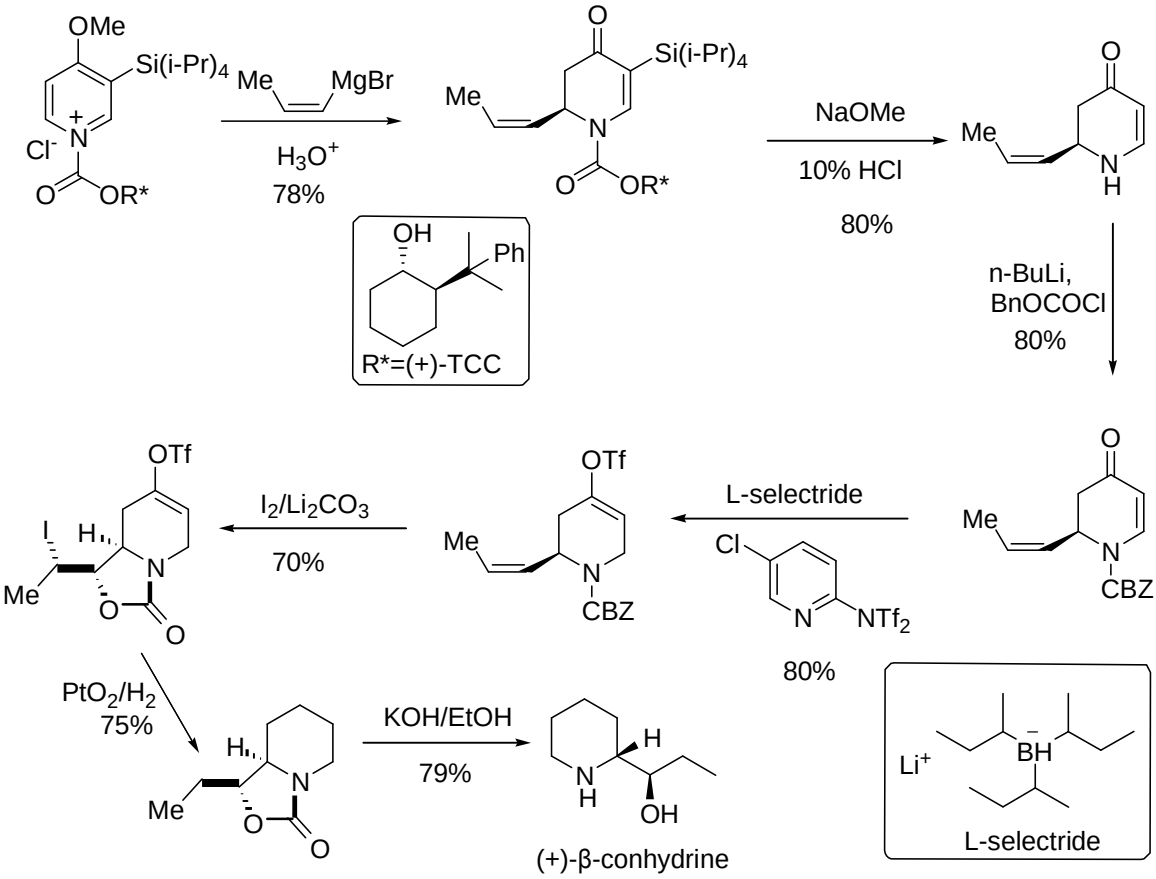
It should be noted that the R-configuration at the lithium bearing center on C-2 was maintained for all three oxazolidinones, 26, 27 and 28.

Electrophilic quench with acetaldehyde provided a convenient way to prepare the enantiopure alcohol 29 in 78% yield as a mixture of diastereomers (85:15 dr, entry 14).

(+)-ℐℐ-conhydrine

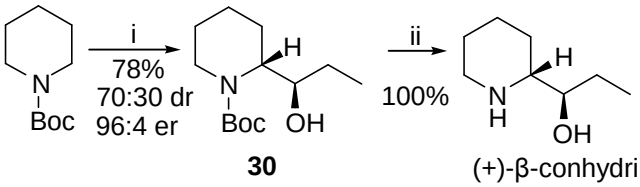
The synthesis of the alkaloid, (+)-�-conhydrine has been accomplished by a variety of research groups.[10, 34-36] In his synthetic route, Comins utilized the highly versatile N-acyl-2,3-dihydro-4-pyridone (Scheme 4.3). Conjugate addition and enolate trapping with his triflating agent was followed by iodolactonization, then concomitant reduction of both the iodide and the vinyltriflate, and base hydrolysis of the lactone provided (+)-�-conhydrine in seven overall steps.[34]

Scheme 4.3. Comins' synthesis of (+)-⊡-conhydrine[34]



Our synthesis of (+)-⊡-conhydrine involves a catalytic dynamic resolution of N-Boc-2-lithiopiperidine. When CDR of rac-4 was accompanied by electrophilic quench with propionaldehyde, the alcohol 30 was obtained in 84% yield as a mixture of diastereomers (70:30 dr (R,S:R,R)), both of which had 96:4 er (entry 15). Separation of the diastereomers by column chromatography and hydrolysis of the carbamate from the major diastereomer afforded (+)-⊡-conhydrine in just two steps, $[a]_D^{22}$ +7.4 (c = 0.9, EtOH); lit[34] $[a]_D^{22}$ +8.3 (c = 0.9, EtOH). The relative configuration of the alkaloid was assigned based on the agreement in the specific rotation with the literature.[34]

Scheme 4.4. Synthesis of (+)-⊡-conhydrine

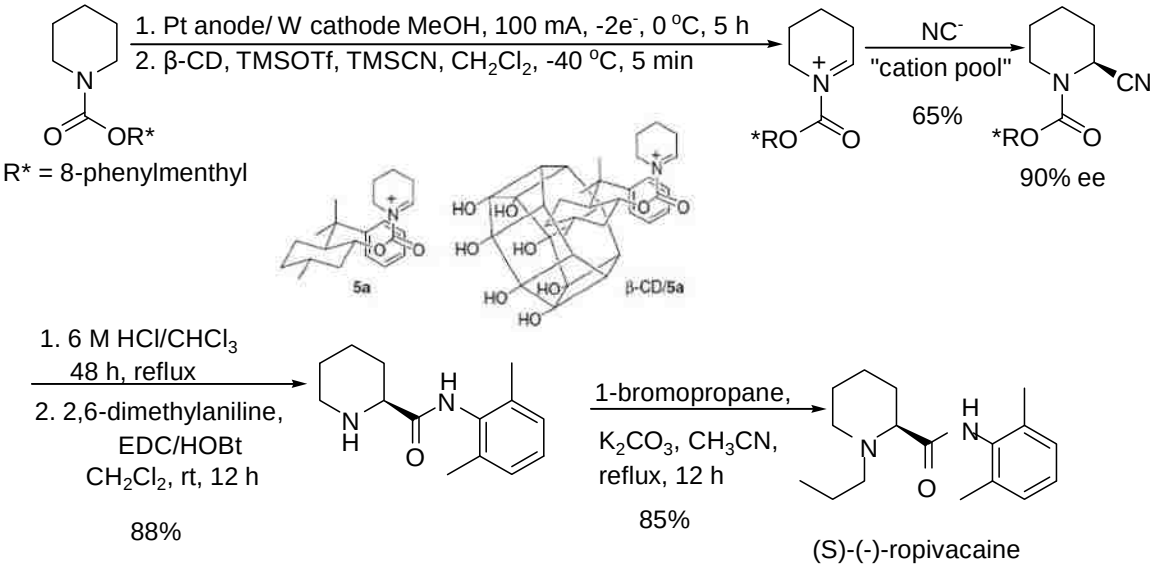


i) s-BuLi (1.2 equiv), Et_2O, TMEDA (4.0 equiv), –78 °C, 3 h, then 10, (10 mol%), –45 °C, 3 h, EtCHO (3.0 equiv), –78 °C, 2 h; ii) CF_3CO_2H, CH_2Cl_2, rt, 6 h.

(S)-(–)-ropivacaine

Ropivacaine is a drug that is often co-administered with fentanyl for epidural analgesia. It has been synthesized by several research groups around the world. However, few asymmetric methods exist and a majority of the procedures involve resolution of racemic mixtures containing the pipecolic moiety. Shankaraiah et al utilized the "cation pool" strategy (Scheme 4.5) whereby ions are accumulated in solution by low temperature electrolysis.[14]

Scheme 4.5. Shankaraiah's synthesis of (S)-(–)-ropivacaine.[14]

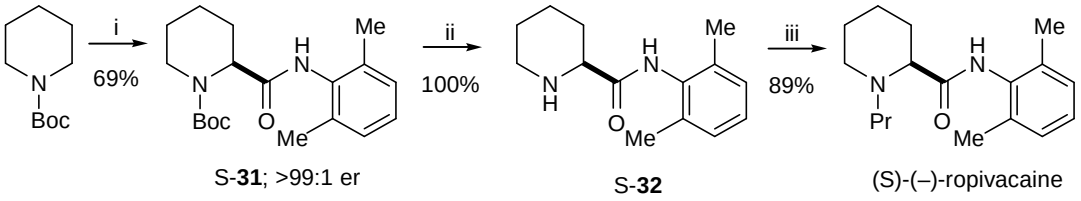


They generated an N-acyliminium ion via an anodic reaction and carried out in situ nucleophilic addition of TMSCN. Acid hydrolysis of the nitrile gave crude pipecolic acid, which was coupled

with 2,6-dimethylaniline under EDC/HOBt conditions to give the anilide. N-Propylation under basic conditions afforded (S)-(–)-ropivacaine in five steps.

Our synthesis of (S)-(–)-ropivacaine involved the CDR of 4 with ligand 9 and electrophilic quench with 2,6-dimethylphenyl isocyanate to give enantiopure (>99:1 er) S-31 in 69% yield (Table 4.1, entry 16), $[a]_D^{22}$ –57 (c = 2, $CHCl_3$). After Boc-deprotection using CF_3CO_2H or $SOCl_2$/MeOH, N-alkylation with 1-bromopropane in the presence of K_2CO_3 yielded (S)-(–)-ropivacaine in three overall steps and 61% overall yield; $[a]_D^{25}$ −80 (c = 2, MeOH), lit. $[a]_D^{25}$ −82 (c = 2, MeOH).[14]

Scheme 4.6. Synthesis of (S)-(–)-ropivacaine.



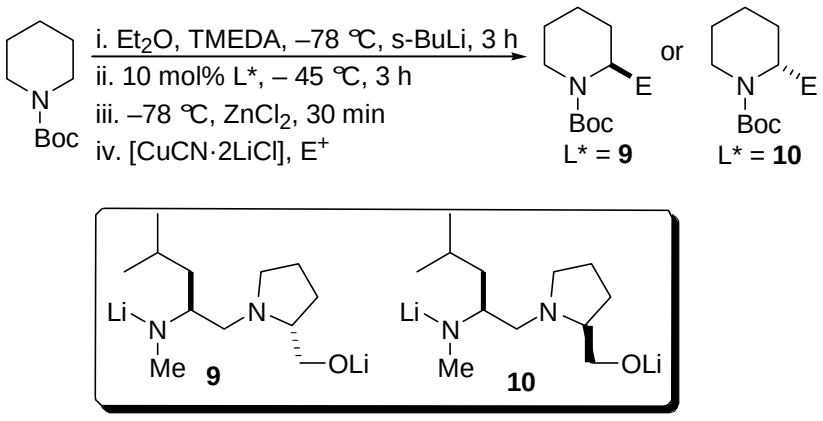
S-**31**; >99:1 er S-**32** (S)-(–)-ropivacaine

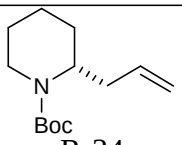
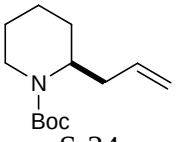
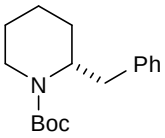
i) s-BuLi (1.2 equiv), Et_2O, TMEDA (4.0 equiv), –78 °C, 3 h, then 9, (10 mol%), –45 °C, 3 h, –78 °C, 2,6-dimethylphenyl isocyanate, 2 h, >99:1 er; ii) CF_3COOH, CH_2Cl_2, rt, 10 h, then NaOH; iii) isopropyl alcohol, 1-bromopropane (3.0 equiv), K_2CO_3 (3.0 equiv), H_2O, 100 ^oC, 6 h. When CDR of 4 was followed by alkylation with methyl iodide, S-33 was obtained in 62% yield and 93:7 er (Table 4.1, entry 17).

4.2.2. Catalytic Dynamic Resolution (CDR) of N-Boc-2-lithiopiperidine followed by Transmetalation and Copper-mediated Coupling: Allylation and benzylation.

The electrophilic bimolecular substitutions discussed above (Table 4.1, entries 1 to 17), are known to proceed via a polar pathway, presumably with retentive substitution at the metal bearing carbon (S_E2ret).[37] However, when S-4 was trapped directly with allyl chloride, R-34 was obtained in low yield (29%) and very low er (57:43). Similarly, with benzyl bromide, R-35 was obtained in nearly racemic form (58:42 er).

Table 4.2. CDR of rac-4 at –45 °C for 3 h using ligand 10 or 9 followed by copper-mediated allylation or benzylation.

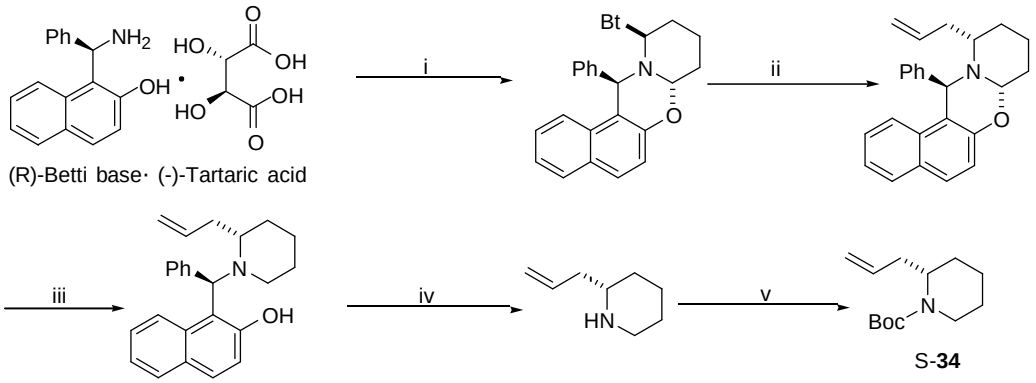


Entry	Ligand	Electrophile	Product	Yield (%)	er (R:S)
1	10	CH_2=$CHCH_2Cl$	 R-34	63	95:5
2	9	CH_2=$CHCH_2Br$	 S-34	59	4:96
3	10	$PhCH_2Br$	 R-35	65	>99:1

These two reactions probably proceeded through a single electron transfer (SET) pathway.[38-40] The enantioselectivity of the allylations was therefore evaluated under copper-mediated conditions, which have been successfully applied in this system,[18] whereby 4 is transmetalated with $ZnCl_2$ and coupled using CuCN·2LiCl. The organocopper intermediate is either RCu(CN)Li or $R_2CuLi·LiCl$.

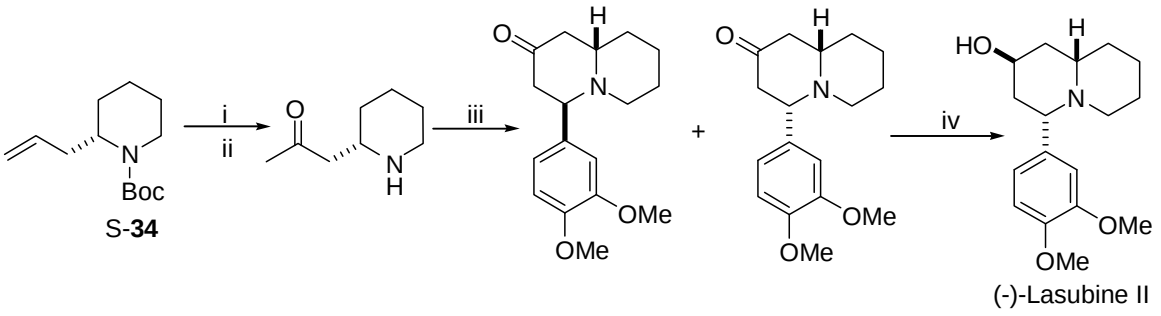
Under these conditions, allyl bromide afforded R-34 with ligand 10 in 63% yield and 95:5 er (Table 4.2, entry 1), $[a]_D^{22}$ +45 (c = 1, $CHCl_3$). When CDR using ligand 9 was employed, S-34 was obtained in 59% yield and 96:4 er (entry 2), lit.[41] for S-34 (>99:1 er, $[a]_D^{25}$ −49.2 (c = 0.9, $CHCl_3$). A similar protocol using ligand 10 and Negishi-type coupling with benzyl bromide gave enantiopure R-35 in 65% yield (entry 3). Hydrolysis of the N-Boc-group affords enantiopure 2-benzylpiperidine, whose racemic form is used as a stimulant drug. It is mostly used as a synthetic intermediate for the synthesis of other drugs. Cheng and coworkers synthesized S-34 starting from glutaraldehyde and showed that S-34 can be readily converted to (+)-cermizine C and to (–)-lasubine II via (S)-(+)-pelletierine.[42]

Scheme 4.7a. Cheng's synthesis of (S)-N-Boc-2-allylpiperidine S-34.[42]



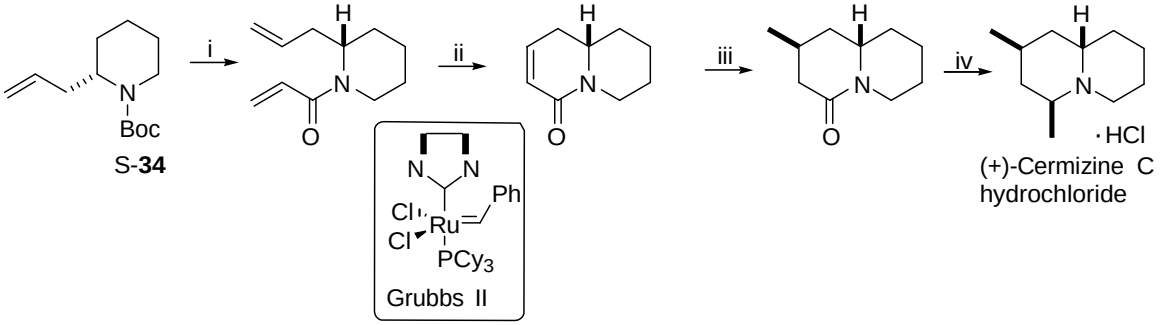
i) $CHO(CH_2)_3CHO$, 1,2,3-benzotriazole (BtH), $K_2CO_{3(aq)}$, CH_2Cl_2, 0 °C, 20 min, 93%; ii) $H_2C{=}CHCH_2TMS$, $BF_3·Et_2O$, CH_2Cl_2, –20 °C to 0 °C, 2 h, 90%; iii) $LiAlH_4$, THF, 0 °C, 30 min; iv) $NaOH_{(aq)}$; v) Boc_2O.

Scheme 4.7b. Cheng's synthesis of (–)-lasubine II.[42]



i) $PdCl_2$, CuCl, O_2, DMF, H_2O, rt, 10 h, 91%; ii) CF_3CO_2H, CH_2Cl_2, rt, 2 h, 99%; iii) 3,4-dimethoxybenzaldehyde, 2 M $NaOH_{(aq)}$, MeOH, 60 ^oC, 70 h, 70%; iv) K-selectride, THF, –78 ^oC, 1 h, 90%.

Scheme 4.7c. Cheng's synthesis of (+)-cermizine C.[42]

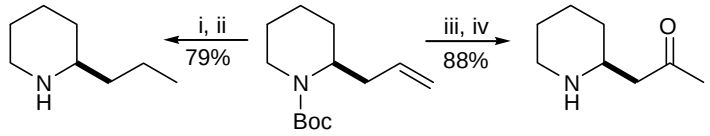


i) a) CF_3CO_2H, CH_2Cl_2, rt, 2 h; b) H_2C=CHCOCl, $NaOH_{(aq)}$, rt, 4 h; ii) Grubbs II, CH_2Cl_2, reflux, 15 min; iii) Me_2CuLi, $BF_3 \cdot Et_2O$, Et_2O, –78 ^oC, 1 h; iv) a) MeMgBr, THF, 65 ^oC, 3 h, (b) $NaBH_3CN$, AcOH, 1 h, (c) saturated HCl in MeOH.

(S)-(–)-Coniine and (S)-(+)-Pelletierine

Hydrogenation of S-34 obtained from CDR using ligand 9 (Table 4.2, entry 2) and hydrolysis of the carbamate afforded the alkaloid (S)-(–)-coniine in three overall steps, $[a]_D^{22}$ −6.7 (c = 1.0, MeOH), lit.[43] $[a]_D^{20}$ −7.3 (c = 1.0, MeOH). Wacker oxidation[44] and deprotection afforded (S)-(+)-pelletierine, $[a]_D^{22}$ +16.8 (c = 0.5, EtOH), lit.[42] $[a]_D^{25}$ +19.4 (c = 0.47, EtOH).

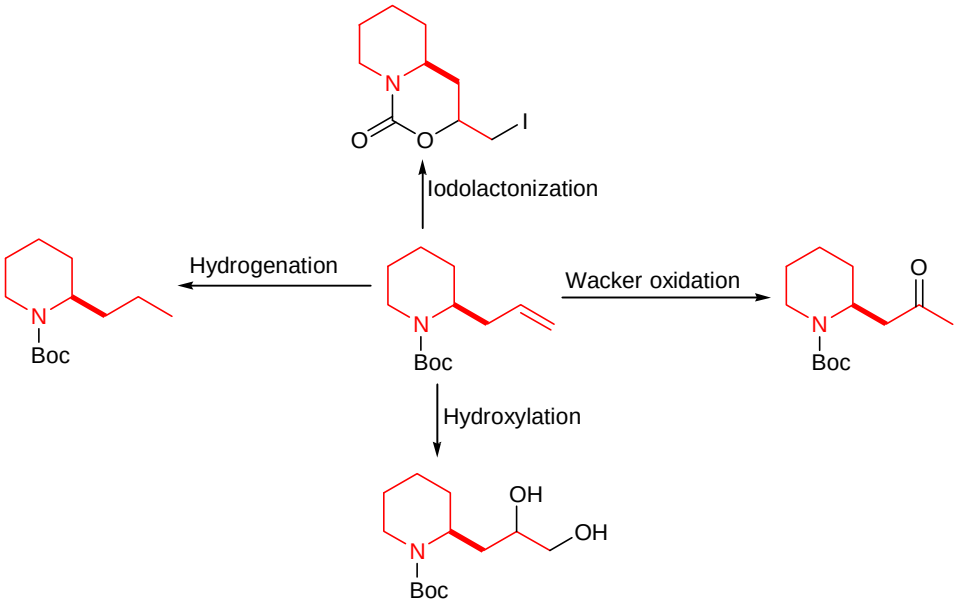
Scheme 4.8. Synthesis of (S)-(–)-coniine and (S)-(+)-pelletierine



(S)-(–)-coniine S-**34**; 96:4 er (S)-(+)-pelletierine

i) $Pd(OH)_2$ (1.0 equiv), H_2 (1 atm), MeOH, rt, 48 h; ii) CF_3CO_2H, CH_2Cl_2, 0 ^oC, 2 h, then NaOH, pH 10; iii) $PdCl_2$ (1.0 equiv), CuCl (10 mol%), O_2, DMF/H_2O (10:1), rt, 10 h; iv) CF_3CO_2H, CH_2Cl_2, 0 ^oC, 2 h, then NaOH.

Figure 4.4. Utility of compound 34 in piperidine alkaloid synthesis

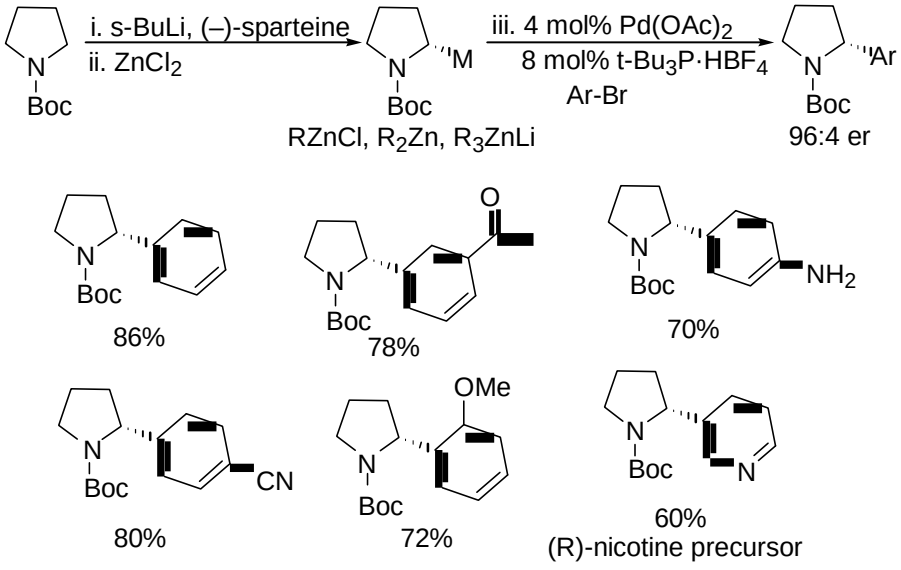


The synthesis of 2-allyl-piperidines has received considerable attention in the last two decades. Asymmetric catalytic methods,[45-48] chiral pool,[49-52] and chiral auxiliary based methods[53-57] have all been utilized. The synthetic utility of compound 34 is illustrated in Figure 4.4. In addition to hydrogenation[45, 54] and Wacker oxidation[44, 52, 58, 59], 34 can undergo hydroxylation[50, 51] and iodolactonization.[44, 52]

4.2.3. Enantioselective Arylation and Vinylation of N-Boc-2-lithiopiperidine[60]

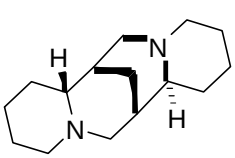
Optically active 2-aryl- and 2-vinyl-piperidines are found in a variety of natural products and some have useful pharmacological properties. Previously, Dieter demonstrated that transmetalation of an organolithium precursor to its organocopper counterpart provides a convenient way to synthesize vinylated products.[61, 62] In 2006, using an asymmetric deprotonation methodology with the chiral base s-BuLi/(–)-sparteine[63, 64] to generate an enantioenriched organolithium, Campos et al accomplished the direct enantioselective synthesis of 2-aryl-pyrrolidines by transmetalation of the enantioenriched N-Boc-2-lithiopyrrolidine to an organozinc species prior to entering into a palladium-catalyzed Negishi coupling with an aryl bromide (Scheme 4.9).[30, 65, 66] The remarkable chemical and configurational stability of the intermediate organozinc compound, even at 60 °C, and the high degree of tolerance for both electron rich and electron deficient aryl halides make this transformation very attractive.

Scheme 4.9. Campos' conditions for enantioselective arylation of N-Boc-pyrrolidine.[65]

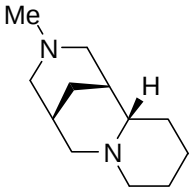


Campos also showed that substoichiometric (35 and 60 mol%) and stoichiometric amounts of $ZnCl_2$ work equally well, suggesting that the structure of the organozinc intermediate is not well defined. R_3ZnLi, R_2Zn and RZnCl are all plausible organozinc intermediates.

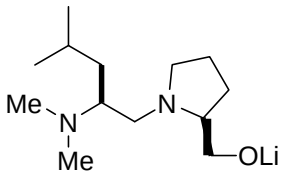
Previous attempts to synthesize enantioenriched 2-aryl-piperidines via Negishi coupling conditions have been less effective. O'Brien recently reported an asymmetric deprotonation of N-Boc-piperidine using s-BuLi complexed with his diamine[30] and direct trapping with 4-bromoveratrole, affording the arylated product in 33% yield and 82:18 er (S:R).[30]



(–)-sparteine



O'Brien's diamine



Coldham's ligand

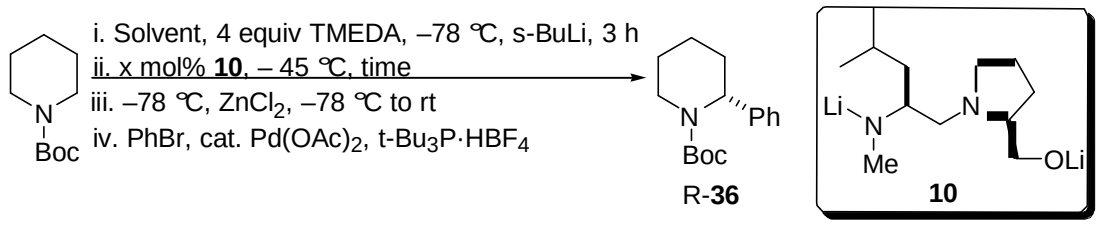
Although the Coldham group successfully synthesized racemic members of this family,[67] their attempt to effect enantioselectivity by dynamic thermodynamic resolution (DTR) using stoichiometric amount of chiral ligand resulted in no arylated products.[22] They reported two examples of enantioenriched 2-aryl-piperidines (er 82:18 (R:S)) obtained indirectly by transmetalation of an enantioenriched stannane to the organolithium under conditions that ensured configurational stability of the latter. As shown in Table 4.2, we also utilized Negishi-type coupling conditions to synthesize enantioenriched 2-allyl and 2-benzyl-piperidines by copper mediated coupling of an organozinc reagent derived from the resolved N-Boc-2-lithiopiperidine 4. During transmetalation of lithium to zinc, then to copper, configurational stability is maintained. Based on Campos' results (Scheme 4.7), we hoped that during transmetalation from zinc to palladium, configurational integrity would be retained.

Considering that we are able to resolve N-Boc-2-lithiopiperidine catalytically, we investigated a CDR in the Negishi arylations and vinylations. The synthetic potential of our methodology is now expanded to the direct enantioselective synthesis of 2-aryl and 2-vinyl-piperidines. Good yields and er's of the Negishi coupling products are obtained with a 5%

catalyst loading. Our method obviates the need for an enantioselective deprotonation or the asymmetric synthesis of a precursor stannane.

The conditions for the CDR of rac-4 were optimized as illustrated in Table 4.3, beginning with the previously optimized conditions.[23] In oven-dried, septum-capped flasks, rac-4 was generated by deprotonation of N-Boc-piperidine in either Et_2O or MTBE at –78 °C with s-BuLi/TMEDA, followed by addition of 10, warming to –45 °C for 3 to 5 h, then cooling to –78 °C. A solution of $ZnCl_2$ in THF was added prior to warming to room temperature and introduction of $Pd(OAc)_2$, t-$Bu_3P{\cdot}HBF_4$ and phenyl bromide sequentially (see Experimental Section below for details).

Table 4.3. Optimization of the enantioselective arylation of N-Boc-2-lithiopiperidine



Entry	mol % 10	Time (h)	Solvent	Yield (%) of 36	er (R:S)
1	10	3	Et_2O	74	90:10
2	10	3	MTBE	65	86:14
3	5	3	Et_2O	70	93:7
4	5	5	Et_2O	68	96:4
5	5	5	MTBE	60	89:11

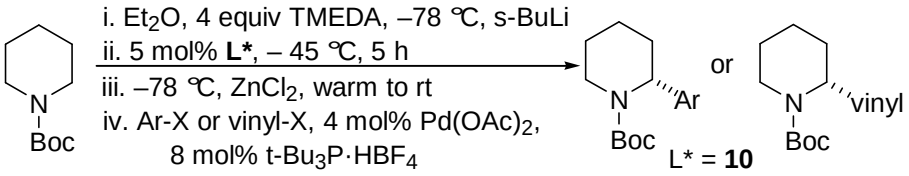
After stirring for 3 h with 10 mol% of 10 in the presence of Et_2O, R-36 was obtained in 74% yield and 90:10 er (Table 4.3, entry 1). With MTBE, R-36 was obtained in 65% yield and 86:14 er (entry 2). After lowering the catalyst loading to 5 mol%, stirring at –45 °C for 3 h in Et_2O improved the er to 93:7 (entry 3). Performing the CDR for an additional 2 h at –45 °C led to a

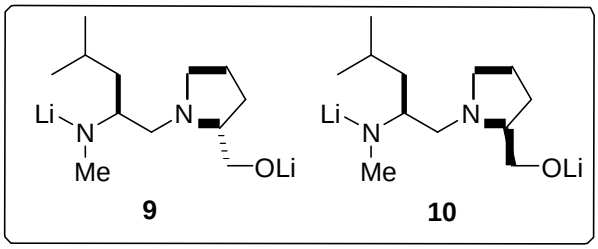
further enhancement in the er of R-36 to 96:4 (entry 4), $[a]_D^{22}$ +76.2 (c = 1, $CHCl_3$), lit[68]. for R-36; $[a]_D^{25}$ +83.7 (c = 0.98, $CHCl_3$). However, with MTBE, the same conditions afforded R-36 in 60% yield and 89:11 er (entry 5).

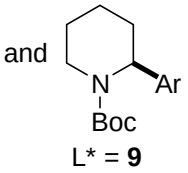
Two important findings emerged from the optimization; (i) the yields and er's are lower in MTBE than in Et_2O, (ii) the er's are higher with lower loading of 10. The yields obtained in these Negishi arylations are remarkably high since the secondary alkyl ligands on palladium would be expected to undergo facile β-hydride elimination. Several other aryl and vinyl halides were evaluated under the optimized CDR conditions, with the results summarized in Table 4.4. In all cases, good yields and high er's were obtained. Quenching with o-bromotoluene afforded R-37 in 63% yield and 92:8 er, $[a]_D^{22}$ +114.2 (c = 1, $CHCl_3$) (entry 1) and S-37 of 6:94 er using ligand 9 (entry 2). Electrophilic quench with 4-bromoveratrole gave R-38 in 75% yield and 97:3 er (entry 3), $[a]_D^{22}$ +106.2 (c = 1.0, $CHCl_3$), lit[30]. for S-38 of 82:18 er ($[a]_D^{20}$ –49.6 (c = 0.275, $CHCl_3$). Quenching with p-tert-butylbromobenzene afforded R-39 in 69% yield and 95:5 er, $[a]_D^{22}$ +104.4 (c = 1, $CHCl_3$) (entry 4) while 2-bromomesitylene gave R-40 in 64% yield and 92:8 er (entry 5), $[a]_D^{22}$ +97.1 (c = 1, $CHCl_3$).

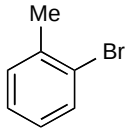
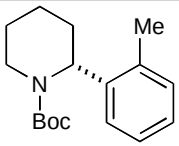
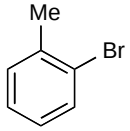
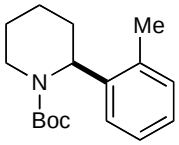
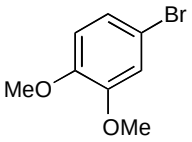
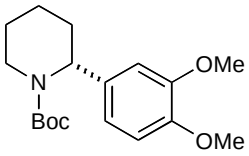
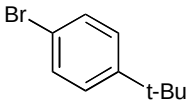
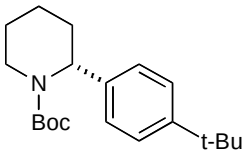
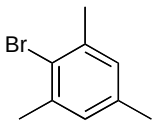
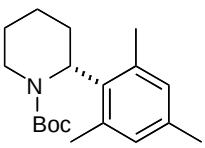
Some electron deficient aryl bromides were evaluated in order to investigate the degree of tolerance of electron-poor heterocycles to aryl coupling. With p-bromoacetophenone, R-41 was obtained in 66% yield and 91:9 er (entry 6), $[a]_D^{22}$ +126.5 (c = 1, $CHCl_3$). Electrophilic quench with 4-bromobenzonitrile gave R-42 in 66% yield and 90:10 er (entry 7), $[a]_D^{22}$ +147.8 (c = 1, $CHCl_3$).

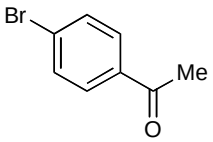
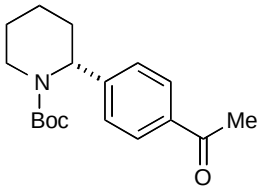
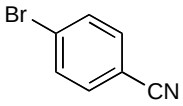
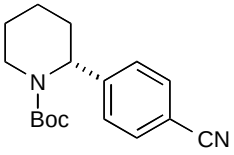
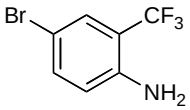
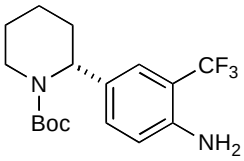
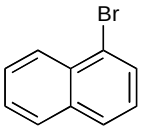
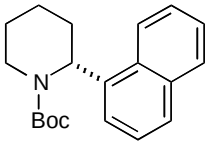
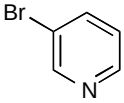
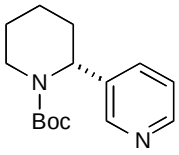
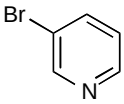
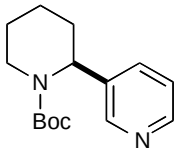
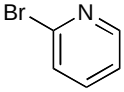
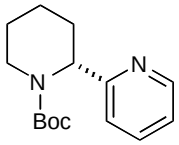
Table 4.4. CDR of rac-4 followed by Negishi arylation or vinylation

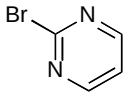
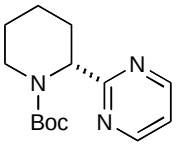
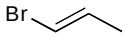
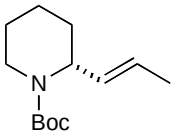
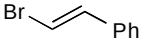
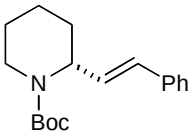






Entry	Electrophile	Product	Yield (%)	er (R:S)
1[a]		 R-37	63	92:8
2[a,b]		 S-37	59	6:94
3[a]		 R-38	75	97:3
4[a]		 R-39	69	95:5
5[a]		 R-40	64	92:8

6[a]		 R-41	60	91:9
7[a,c]		 R-42	66	90:10
8[a]		 R-43	60	93:7
9[e]		 R-44	67	97:3
10[d]		 R-45	46	88:12
11[b,d]		 S-45	51	10:90
12[d]		 R-46	50	93:7

13[d]		 R-47	53	85:15
14[a]		 R-48	63	92:8
15[a,e]		 R-49	66	93:7

a) stirred at rt for 18 h during step (iv), b) CDR using 9; c) the aryl bromide contained a small amount of 2-bromobenzonitrile leading to formation of the ortho cyano structural isomer in 90:10 er; d) stirred at 60 ^{o}C for 22 h during step (iv), e) a small amount of the Z-alkene was obtained as a minor isomer in 92:8 er.

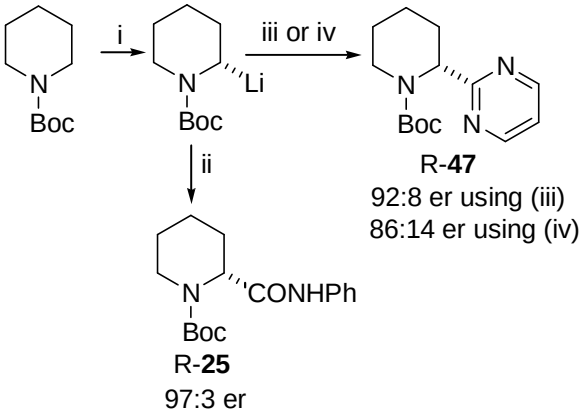
Quenching with 4-bromo-2-trifluoromethyl aniline afforded R-43 in 60% yield 93:7 er (entry 8), $[a]_D^{22}$ +101.6 (c = 1, $CHCl_3$), thus illustrating that this Negishi arylation works even in the presence of an unprotected amine. Electrophilic quench with 1-bromonaphthalene gave R-44 in 67% yield and 97:3 er (entry 9).

When heteroaryl halides were employed, the arylations occurred rather slowly and required mild heating to 60 °C. Quenching with 3-bromopyridine gave R-45 in 46% yield and 88:12 er (entry 10), $[a]_D^{22}$ +88.6 (c = 1, $CHCl_3$). When the CDR was carried out using 9, S-45 was obtained in 51% yield and 90:10 er (entry 11). With 2-bromopyridine, R-46 of 50% yield and 93:7 er was obtained (entry 12), $[a]_D^{22}$ +93.1 (c = 1, $CHCl_3$). Electrophilic quench with 2-bromopyrimidine gave R-47 in 53% yield and 85:15 er (entry 13), $[a]_D^{22}$ +75.6 (c = 1, $CHCl_3$).

Vinylation was also investigated using the same reaction conditions. Thus, quenching with 1-bromo-1-propene afforded R-48 in 63% yield and 92:8 er (entry 14), $[a]_D^{22}$ 10.1 (c = 0.3, $CHCl_3$). With ⍺-bromostyrene, R-49 was obtained in 66% yield and 93:7 er (entry 15), $[a]_D^{22}$ 108.5 (c = 0.3, $CHCl_3$), lit[42] for S-49 ($[a]_D^{25}$ –116.9 (c = 0.3, $CHCl_3$).

We wondered whether the comparatively low er's in the heterocycle arylations (Table 4.4, entries 10-13) were due to slight loss of configurational stability at 60 °C or some unidentified process. Scheme 4.10 shows a control experiment in which the er was monitored at some key stages of the reaction. After performing a CDR at –45 °C for 5 h and then cooling to –78 °C, an aliquot was quenched with phenyl isocyanate. CSP-SFC analysis revealed that the product, R-25 had 97:3 er. After adding $ZnCl_2$ to the remaining mixture, warming to room temperature and introduction of $Pd(OAc)_2$, t-$Bu_3P{\cdot}HBF_4$, and 2-bromopyrimidine, a second aliquot was allowed to stir for two days at room temperature. This aliquot showed that R-47 had 92:8 er. The remaining heterogeneous mixture was heated to 60 °C for 22 h, then cooled. The er from this sample was 86:14. Although the slight loss of er from 97:3 to 92:8 was anticipated, the significant loss of er to 86:14 reveals that the configurational stability with the piperidine system is compromised at 60 °C, in contrast with the pyrrolidines.[65]

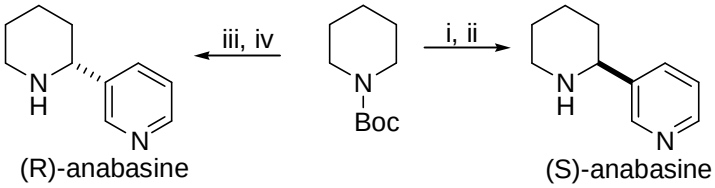
Scheme 4.10. Monitoring of the er during enantioselective arylation



i) s-BuLi (1.2 equiv), Et_2O, TMEDA (4.0 equiv), –78 °C, 3 h, then 10, (5 mol%), –45 °C, 5 h, (ii) –78 °C, PhNCO (3.0 equiv), 1 h, 97:3 er, (iii) –78 °C, $ZnCl_2$ (1.3 equiv), –78 °C to rt, $Pd(OAc)_2$ (4 mol%), t-Bu_3P•HBF_4 (8 mol%), 2-bromopyrimidine (1.3 equiv), 60 ^oC, rt, 48 h, 92:8 er, (iv) –78 °C, $ZnCl_2$ (1.3 equiv), –78 °C to rt, $Pd(OAc)_2$ (4 mol%), t-Bu_3P•HBF_4 (8 mol%), 2-bromopyrimidine (1.3 equiv), 60 ^oC, 22 h, 86:14 er.

Synthesis of anabasine enantiomers: The synthesis of either enantiomer of the tobacco alkaloid anabasine was accomplished as illustrated in Scheme 4.11. CDR of rac-4 using either 9 or 10, transmetalation, and Negishi coupling with 3-bromopyridine afforded S-45 or R-45 respectively. Hydrolysis of the respective carbamates with trifluoroacetic acid afforded (S)- or (R)-anabasine in just two steps.

Scheme 4.11. Preparation of (S)- or (R)-anabasine.[11]



i) s-BuLi (1.2 equiv), Et_2O, TMEDA (4.0 equiv), –78 °C, 3 h, then 9, (5 mol%), –45 °C, 5 h, then –78 °C, $ZnCl_2$ (1.3 equiv in THF), then warm to rt, add $Pd(OAc)_2$ (4 mol%), t-Bu_3P·HBF_4

(8 mol%), 3-bromopyridine (1.3 equiv), warm to 60 ^{o}C, 22 h, 51%, 90:10 er, ii) CF_3CO_2H, CH_2Cl_2, rt, 10 h, then NaOH, 100%, $[a]_D^{22}$ −73.4 (c = 1.0, MeOH), lit.[11] $[a]_D^{20}$ –80 (92% ee; c = 0.91, MeOH), iii) same as (i) but using 10, 46%; 88:12 er, (iv) same as (ii), $[a]_D^{22}$ 70.9 (c = 1.0, MeOH).

4.3. Summary

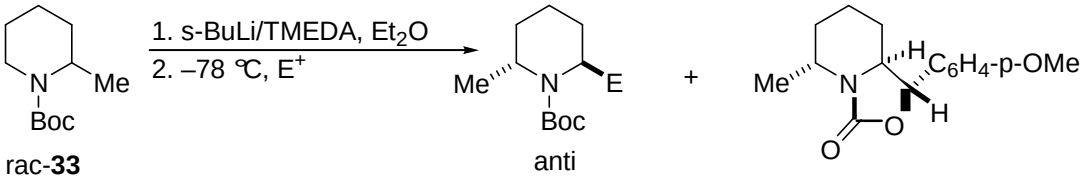
The asymmetric synthesis of 2-substituted piperidines has been accomplished through catalytic dynamic resolution of N-Boc-2-lithiopiperidine followed by one of three different methods; (i) direct electrophilic quench, (ii) transmetalation and copper-mediated allylation or benzylation, and (iii) transmetalation and Negishi arylation or vinylation. Diastereomeric ligands 9 and 10 afford opposite configurations of N-Boc-2-lithiopiperidine with excellent enantioselectivity. Most aryl and vinyl halides produce coupling products of the chiral organozinc intermediate with high enantioselectivity at room temperature. When somewhat elevated temperatures are required, such as with π-deficient heterocycles, some racemization occurs.

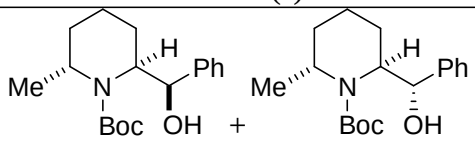
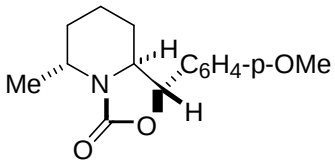
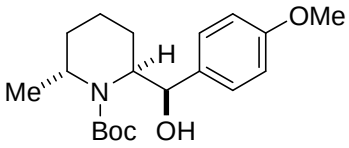
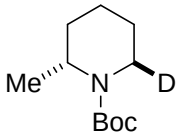
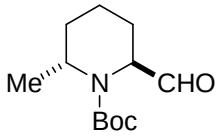
4.4. Synthesis of 2,6-Disubstituted Piperidines

In 1993, Beak carried out the deprotonation of racemic N-Boc-2-methylpiperidine using s-BuLi/TMEDA at C-6. Electrophilic quench of the resulting carbanionic species afforded the trans-2,6-disubstituted piperidines shown in Scheme 4.12. With benzaldehyde, both the syn and anti alcohols were obtained at –78 °C. However, after quenching with para-methoxybenzaldehyde at –78 °C, warming to –20 °C for 30 min led to in situ cyclization of the syn isomer to form the oxazolidinone 51 but the anti isomer was obtained as the alcohol. In a competition experiment between rac-33 and trans-53, the authors showed that lithiation-substitution with excess Me_3SiCl afforded the monosilylated product only from rac-33, with

complete recovery of unreacted trans-53. From this result, the authors concluded that lithiation of rac-33 requires an equatorial hydrogen. The authors also noted that trans-54 can be epimerized to the cis isomer by column chromatrography on silica gel pretreated with triethylamine.[31]

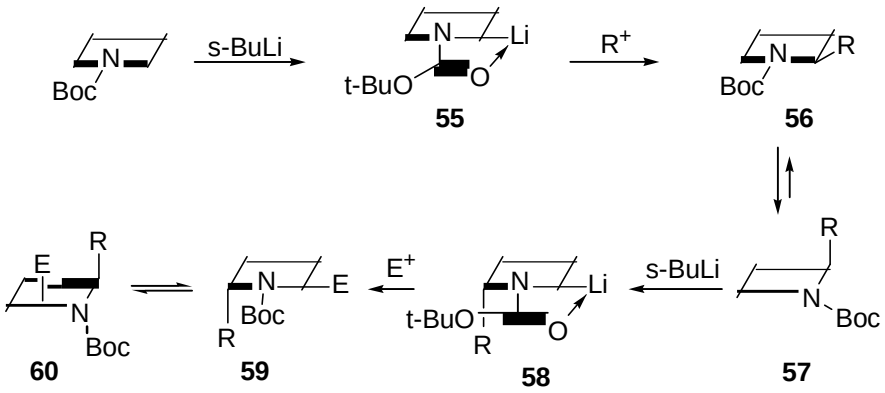
Scheme 4.12. Beak's lithiation-substitution of rac-N-Boc-2-methylpiperidine[31]



Entry	Electrophile	Product(s)	Yield (s) (%)
1	PhCHO	 anti:syn-50	49% (anti) and 47% (syn)
2a	MeO-p-C_6H_4-CHO	 syn-51	41%
2b	MeO-p-C_6H_4-CHO	 anti-52	57%
3	MeOD	 trans-53	90
4	DMF	 trans-54	87

Experimental and theoretical evidence revealed that $A^{1,3}$-strain dictates the diastereoselectivity of the above electrophilic substitutions.[31] Removal of an equatorial hydrogen from a chair-like conformation of N-Boc-piperidine (Figure 4.5) using s-BuLi leads to transition structure 55. The amide n-bond and the p-orbital of the carbanionic center are orthogonal to each other. This arrangement is enforced by the stabilization arising from the chelation of the lithium to the carbonyl oxygen[30] as well as the HOMO-HOMO stereoelectronic repulsion in the axial anion.[69-71] The equatorially lithiated species then undergoes retentive substitution[72, 73] at the lithium-bearing carbon to give 56.

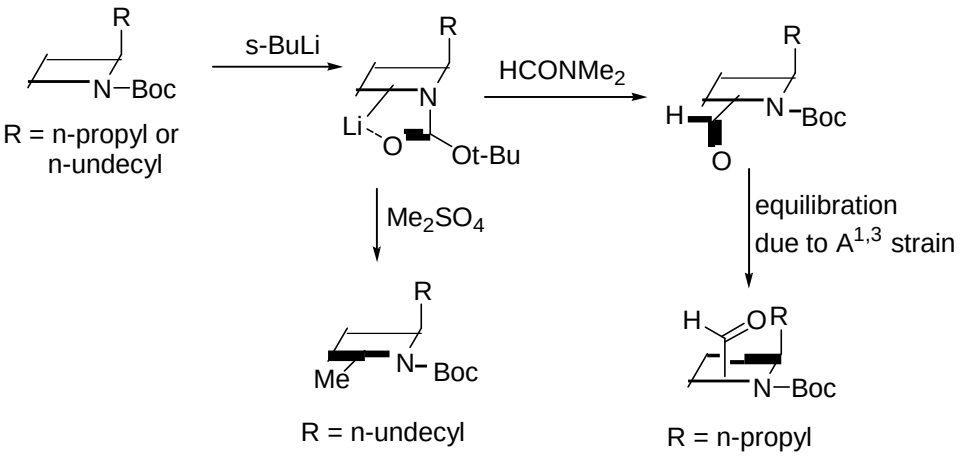
Figure 4.5. Mechanistic hypothesis for the diastereoselective formation of trans-2,6-disubstituted N-Boc-piperidines.[9, 31]



Previous work on 2-piperidides revealed that due to $A^{1,3}$ strain, the axially substituted 2-piperidides are more stable than their corresponding equatorially substituted counterparts.[72, 74] Therefore, compound 56 is likely to undergo conformational equilibration leading to the formation of 57. Removal of the equatorial hydrogen at C-6 during a second lithation would furnish transition structure 58. Subsequent retentive electrophilic quench proceeds through 58 and provides the trans-2,6-disubstituted piperidine. In 2000, Beak showed that, when the second electrophilic quench introduces a carbonyl at C-6, as is the case with DMF, another case of $A^{1,3}$-

strain can provide enough driving force for equilibration in favor of the cis-2,6-substituted piperidine (Figure 4.6).[9]

Figure 4.6. Beak's diastereoselective synthesis of 2,6-disubstituted piperidines.[9]



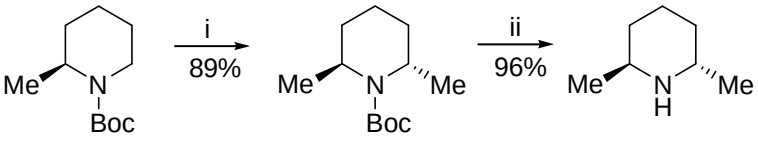
Our approach to enantioenriched 2,6-disubstituted piperidines consists of two steps: (i) catalytic dynamic resolution of N-Boc-2-lithiopiperidine, which furnishes the 2-substituted product; (ii) a second lithiation-substitution to obtain the diastereomeric 2,6-substituted products.

Thus a catalytic dynamic resolution using 5 or 10 mol% of (S,S)-10 was evaluated using the conditions in Table 4.5. After stirring for 3 h at –45 °C, cooling to –78 °C and quenching with precooled methyl iodide afforded S-33 in 62% yield and 93:7 er. Using Me_2SO_4, the yield and enantiomer ratio were improved to 71% and 96:4 (S:R) respectively. Further lithiation of S-33 in the absence of a chiral ligand followed by quenching with several electrophiles provided the diastereomeric products listed in Table 4.5. We monitored the extent of lithiation of S-33 using GC-MS by quenching aliquots with MeOD and checking for deuterium incorporation. After 4 h of lithiation at –78 °C, only ~45% of S-6 was converted to trans-61, in contrast with N-Boc-piperidine[60], which shows complete deprotonation under these conditions. Thus a solution of S-33 was added to a cloudy mixture of s-BuLi/TMEDA/Et_2O at –78 °C. After 30 min, the mixture

was transferred to a second thermosttated bath at –45 °C and stirred for 3 h, prior to cooling to –78 °C and addition of the desired electrophile.

Quenching with Me_2SO_4 provided trans-62 in 89% yield and 96:4 er. Hydrolysis of the carbamate with CF_3CO_2H afforded (S,S)-63, corresponding to the relative configuration of (+)-lupeditine (Scheme 2).

Scheme 4.13. Preparation of trans-(+)-lupetidine

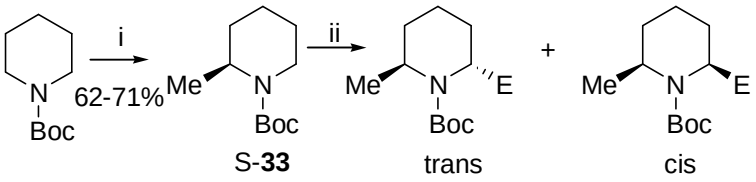


S-**33** (96:4 er) trans-**62** trans-(+)-Lupetidine

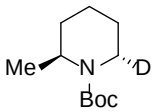
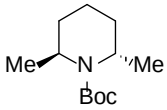
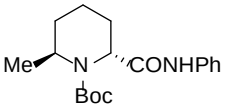
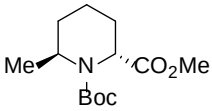
i) s-BuLi (1.2 equiv), Et_2O, TMEDA (4.0 equiv), –78 °C, 30 min, then –45 °C, 3 h, –78 °C, Me_2SO_4 (1.5 equiv), –78 °C to rt, 18 h, 89%, 96:4 er, ii) CF_3CO_2H, CH_2Cl_2, 5 h, then 2 M NaOH (aq), 96%.

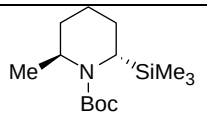
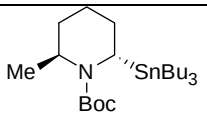
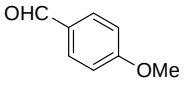
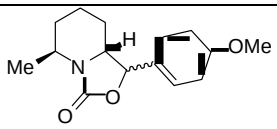
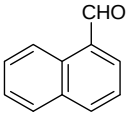
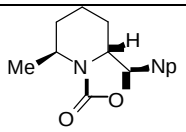
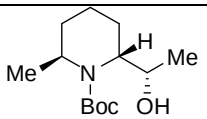
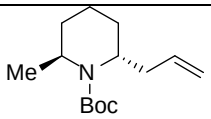
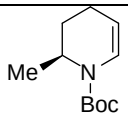
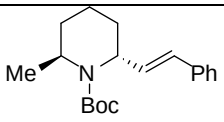
With phenyl isocyanate, the anilide 64 was obtained in 75:25 dr and 93:7 er (entry 3). DFT calculations at the B3LYP level using the 6-311g (d,p) basis set confirmed that trans-64 is more stable than cis-64. Methyl chloroformate yielded 65 in 85:15 dr with no loss of er (entry 4). DFT calculations also confirmed that trans-65 is more stable than cis-65. Me_3SiCl afforded trans-66 as the only diastereomer in 75% yield and 96:4 er (entry 7). When Bu_3SiCl was employed, the trans isomer of the stannane 67 was obtained in 67% yield with no loss of er (entry 6).

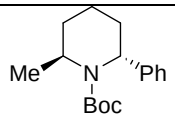
Table 4.5. Lithiation-substitution of (S)-2-methyl-N-Boc-piperidine prepared by CDR of N-Boc-2-lithiopiperidine.



i) s-BuLi (1.2 equiv), Et_2O, TMEDA (4.0 equiv), –78 °C, 3 h, (S,S)-2, (10 mol%), –45 °C, 3 h, –78 °C, 62% and 93:7 er using MeI (3.0 equiv), 71% and 96:4 er using Me_2SO_4, ii) s-BuLi (1.2 equiv), Et_2O, TMEDA (4.0 equiv), –78 °C, 30 min, then –45 °C, 3 h, –78 °C, precooled E^+ (1.5 equiv).

Entry	Electrophile	Product	Yield (%)	er (S:R)
1[a]	MeOD	 61	nd	96:4
2[a]	Me_2SO_4	 62	89%	96:4 (>99:1)[b]
3[a]	PhNCO	 64	73 75:25 dr	93:7 & 92:8
4[a]	MeOCOCl	 65	81 85:15 dr	93:7 for both

5[a]	Me_3SiCl	 66	75 >99:1 dr	96:4
6[a]	Bu_3SnCl	 67	67 >99:1 dr	96:4
7[c]		 68	82 67:33 dr	96:4
8[a,c]		 69	69 95:5 dr	93:7
9[a]	MeCHO	 70	73 84:16 dr	93:7 for both (>99:1)[b]
10[d]	CH_2=$CHCH_2Br$	 71	57 76:24 dr	96:4 (>99:1)[b]
11[e]	I_2 in THF	 S-74	79	96:4 (>99:1)[b]
12[f]	PhCH=CHBr		61	96:4 for both

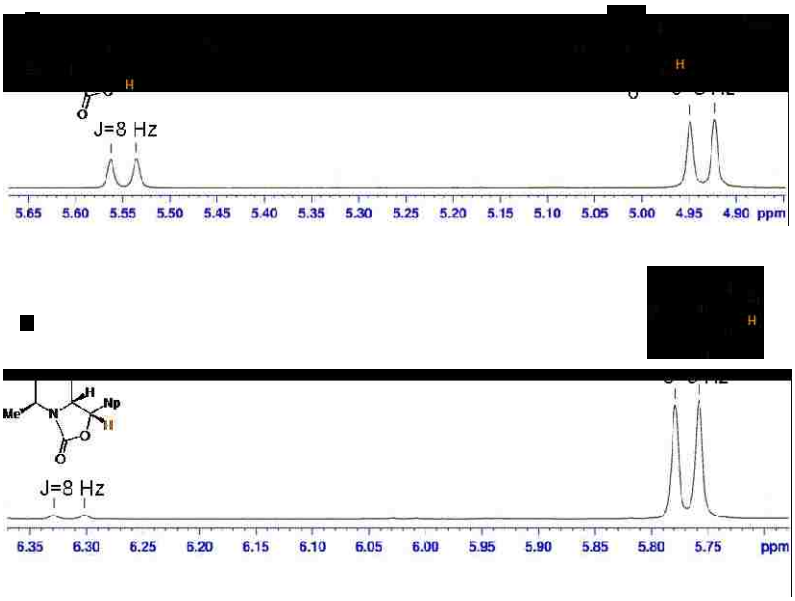
		75	89:11 dr	
13[f]	PhBr	 76	73 87:13 dr	96:4

a. direct electrophilic quench of the organolithium species, b) 10 mg scale reaction in which the equilibration at –45 °C was in the presence on 1 equiv (S,S)-10, c) MeOH added after warming to room temperature, d) via copper-mediated coupling conditions, e) via $ZnCl_2$, f) via palladium-mediated coupling conditions.

Lithiation-substitution with aldehydes was also investigated. After quenching with para-methoxybenzaldehyde and warming to room temperature, MeOH was added. Under these conditions, in situ cyclization of the initially formed piperidinols gave an inseparable mixture of two diastereomeric oxazolidinones 68 in 82% yield, 67:33 dr (syn:anti) and 96:4 er for both diastereomers (entry 7). Base hydrolysis of the oxazolidinones provided the unprotected piperidinols separable by column chromatography. NOESY experiments performed on the major diastereomer confirmed that it was indeed the syn isomer. It is worth noting that after quenching lithiated rac-33 with para-methoxybenzaldehyde and using different workup conditions (warming to –20 ^{o}C for 30 min), Beak reported that only the syn diastereomer cyclized to the corresponding oxazolidinone[75]. Quenching with 1-naphthaldehyde afforded 69 as two diastereomeric oxazolidinones in 69% yield and 95:5 dr (see Figure 4.7). DFT calculations of the ^{1}H NMR spectrum revealed that the chemical shift of the syn diastereomer is higher than that of the anti diastereomer. The observed ^{1}H NMR spectrum showed that the oxazolidinone proton of the major isomer is less deshielded than that of the minor isomer. From these data, we

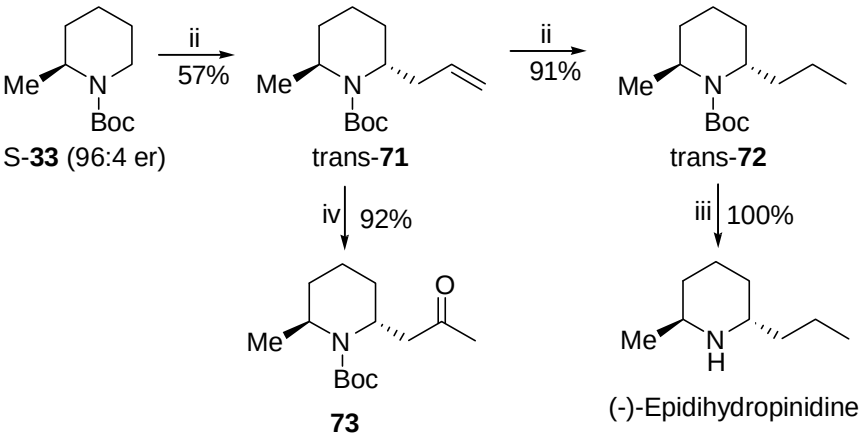
inferred that the anti isomer is the major diastereomer. When S-33 of 93:7 er was lithiated and quenched with acetaldehyde, the alcohol 70 was obtained in 73% yield as a mixture of three diastereomers in 84:16 dr with no loss in er (entry 9). In small scale reactions, enantiopure S-33 was lithiated at –45 °C in the presence of a stoichiometric amount of (S,S)-10. Under these conditions enantiopure 70 was obtained.

Figure 4.7. Partial ^{1}H NMR spectra showing the doublet of the oxazolidinone proton formed from the reaction of lithiated S-33 with (A) 4-methoxybenzaldehyde, (B) 1-naphthaldehyde.



Under copper-mediated coupling conditions,[22, 23, 25, 43] quenching with allyl bromide afforded 71 in 57% yield, 76:24 dr (trans:cis), and 96:4 er (entry 10). Hydrogenation of trans-71 yielded trans-72, which was deprotected to give (–)-epidihydropinidine in just three steps starting from S-33.[76] Starting from (R)-N-Boc-2-piperidine ethanol, Passarella et al synthesized (2R,6S)-71 in five steps and used it to prepare both enantiomers of epidihydropinine.[76] Highly regioselective Wacker oxidation[42] of trans-17 afforded the pelletierine derivative 73 in 92% yield, which is the protected form of the alkaloid (–)-epipinidinone.

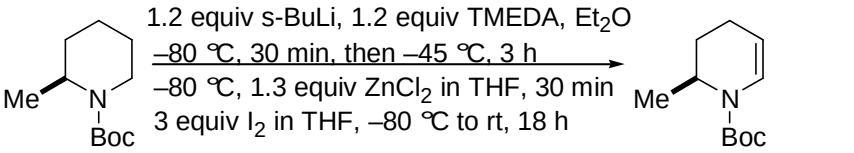
Scheme 4.14. Preparation of (–)-epidihydropinidine[76-81] and trans-73



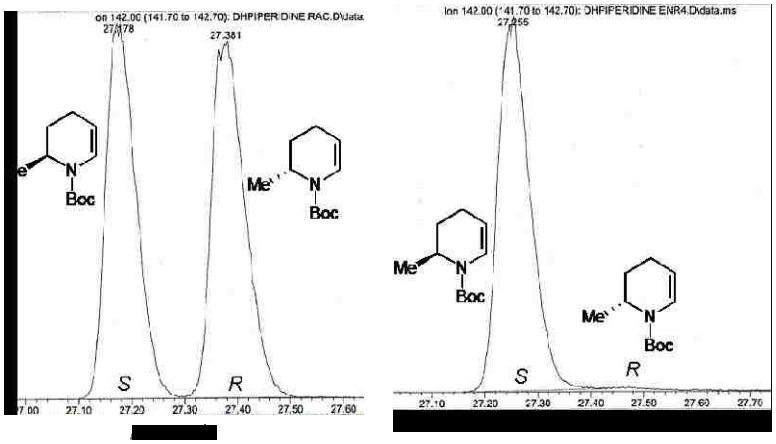
i) s-BuLi (1.2 equiv), Et_2O, TMEDA (4.0 equiv), –78 °C, 30 min, then –45 °C, 3 h, –78 °C, $ZnCl_2$ (1.3 equiv in THF), 30 min, CuCN·2LiCl (in THF), 30 min, allyl bromide (1.5 equiv), 10 h, then MeOH, warm to rt, 57%, 76:24 dr, 96:4 er, separate diastereomers, , ii) $Pd(OH)_2$ (1.0 equiv), H_2 (1 atm), MeOH, rt, 48 h, 91%, iii) CF_3CO_2H, CH_2Cl_2, 5 h, then 2 M NaOH (aq), 100%, iv) $PdCl_2$ (10 mol%), CuCl (1 equiv), O_2, DMF/H_2O (10:1), rt, 18 h, 92%.

Adamo and coworkers have reported a synthesis of (–)-epidihydropinidine whereby enantiopure S-33 (obtained in 44% yield from a classical resolution using (S)-mandelic acid) is lithiated and alkylated with propyl iodide).[77] In our hands, direct alkylation of lithiated 33 using 1-bromopropane proved to be problematic. We detected significant amounts of the enamide S-74 (entry 11) and reformed S-33, with both byproducts showing partial racemization from er 96:4 to 80:20 (S:R). As noted previously, such byproducts are formed via a single electron transfer (SET).[82-84] An efficient synthesis of S-74 involved transmetalation of lithiated S-33 of 96:4 er to the organozinc counterpart using $ZnCl_2$, and quenching with a solution of iodine in THF. Under these conditions S-74 was obtained in 79% yield with no loss of er (entry 11, Scheme 4.15).

Scheme 4.15. Synthesis of (S)-6-methyltetrahydropyridine 74



S-**33**; ≥96:4 er S-**74**; 79%**,** ≥96:4 er



Electrophilic quench with β-bromostyrene under our previously reported palladium-catalyzed coupling conditions[60] afforded 75 in 61% yield, 89:11 dr (trans:cis), and 96:4 er for both diastereomers (entry 12). Substituted vinyl piperidines such as 21 serve as important intermediates for the enantio- and diastereoselective synthesis of fused bicyclic lactams. Palladium-catalyzed arylation of lithiated S-33 using bromobenzene afforded the 2,6-disubstituted piperidine 76 in 73% yield, 92:8 dr (trans:cis), and 95:5 er (entry 13). Knochel and coworkers recently demonstrated that when the diastereoselective arylation of rac-33 is carried out using a 1:1 mixture of $Pd(dba)_2$:RuPhos in place of a 1:2 mixture of $Pd(OAc)_2$:t-$Bu_3P \cdot HBF_4$, the cis-2-methyl-5-phenyl piperidine is formed by a 1,2-palladium migration. With piperidines in a single chair conformation, these authors observed >95:5 dr for arylations at the 2-position.[85]

In summary, the asymmetric synthesis of optically active 2,6-disubstituted piperidines has been accomplished through catalytic dynamic resolution of N-Boc-2-lithiopiperidine and electropilic quench with methyl iodide or dimethylsulfate followed by a second-lithiation

substitution in the absence of a ligand. The method has been exemplified through the synthesis of lupetidine and epidihydropinidine. In all cases, calculations showed that the trans-2,6-disubstituted piperidine is more stable than the cis-2,6-adduct.

4.5. Experimental Section

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 9 and 10 were purified by Kugelrohr distillation. Solutions of $ZnCl_2$ (1 M in Et_2O or THF) were obtained from commercial sources. Solid $ZnCl_2$, CuCN, LiCl were flame-dried under vacuum 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.[86] 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 $KMnO_4$ staining. For all enantiomer ratio (er) analyses, authentic racemic compounds were used to establish the method of separation of the enantiomers. The reaction temperatures were 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, ^{1}H, ^{13}C, DEPT-135, COSY 45, HMQC, HMBC, NOESY NMR spectra were acquired using $CDCl_3$ as solvent at ambient temperature. Chemical shifts are quoted in parts per million, referenced to residual $CHCl_3$ at 7.27 ppm. DFT calculations were performed on the B3LYP level using the 6-311g (d,p) basis set.

4.5.2 General Procedure A: Catalytic Dynamic Resolution (CDR) of 2-lithio-N-Boc-piperidine followed by direct trapping with the electrophile.

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-4·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 diamino alcohol, precursor of 10 (10 mol%) in Et_2O was treated with freshly titrated s-BuLi (20 mol%). After complete deprotonation of N-Boc-piperidine as noted by GC-MS, the preformed alkoxide 10 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.

4.5.3. General Procedure B: Catalytic Dynamic Resolution (CDR) of 2-lithio-N-Boc-piperidine by deprotonation followed by Negishi type-coupling (Allylation)

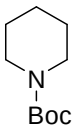
In an oven-dried, septum-capped 25 mL round bottom flask equipped with a stir bar, N-Boc-piperidine (1.0 equiv) and freshly distilled TMEDA (4.0 equiv) were dissolved in freshly distilled Et_2O under argon. The solution was cooled to –78 °C and s-BuLi (1.2 equiv) was added slowly by means of a syringe over a ten minute period. The mixture was stirred for 3 h to effect deprotonation, affording rac-4·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 diamino alcohol precursor of 10 (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 10 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.

4.5.4. General Procedure C: Catalytic Dynamic Resolution (CDR) of 2-lithio-N-Boc-piperidine followed by Transmetalation and Negishi Cross Coupling (Arylation and Vinylation)

In an oven-dried, septum-capped 25 mL round bottom flask equipped with a stir bar, freshly distilled N-Boc-piperidine (2 mmol, 1.0 equiv) and freshly distilled TMEDA (8 mmol, 4.0 equiv) were dissolved in freshly distilled Et_2O under argon. The solution was cooled to –78 °C and s-BuLi (2.4 mmol, 1.2 equiv) was added slowly by means of a syringe, down the side of the flask, over a ten minute period. The mixture was stirred for 3 h to effect deprotonation, affording rac-4·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 freshly distilled diamino alcohol, precursor of 10 (0.1 mmol, 5 mol%) in Et_2O was treated with s-BuLi (10 mol%). After complete deprotonation of N-Boc-piperidine as noted by MS, the preformed alkoxide 10 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 –78 °C and a solution of $ZnCl_2$ (2.6 mmol in 2.6 mL THF, 1.0 M, 1.3 equiv), was added slowly over a ten minute period and the mixture was stirred for 30 minutes followed by warming to room temperature. After 30 minutes, $Pd(OAc)_2$ (0.08 mmol, 4 mol%), t-Bu_3P·HBF_4 (0.16 mmol, 8 mol%) and the aryl bromide, for example bromobenzene (2.6 mmol, 1.3 equiv) were added sequentially. After stirring for 18 h at room temperature, NH_4OH (10 mL, 10% aqueous solution) was added dropwise and the mixture was stirred for 30 minutes. The resulting slurry was filtered through Celite and rinsed with 10 mL Et_2O. The filtrate was washed with 1 M $HCl_{(aq)}$ (20 mL), then with water (2 x 10 mL), dried over Na_2SO_4 and evaporated under reduced pressure to obtain the crude

product. Purification by silica gel column chromatography was accompanied by er determination.

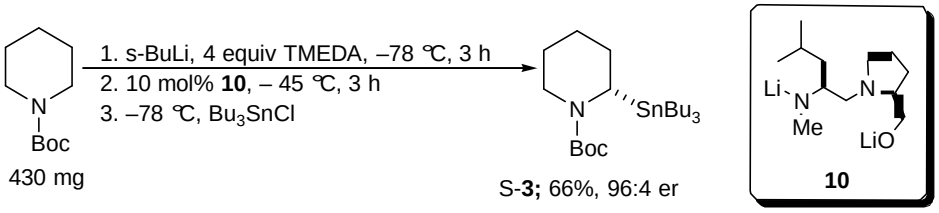
N-Boc-piperidine



To a flask containing piperidine (10.0 g, 133 mmol, 1.0 equiv), di-tert-butyl dicarbonate (14.9 g, 127 mmol, 0.95 equiv) in CH_2Cl_2 (100 mL) was added slowly by means of a dropping funnel at 0 ^oC. The mixture was stirred for 3 h, then washed with saturated NaCl (3 x 50 mL) and with H_2O (2 x 50 mL). The combined organic layers were dried with anhydrous $MgSO_4$, filtered and evaporated to give 23.6 g of N-Boc-piperidine as a colorless oil in 96% yield, data as reported.[31]

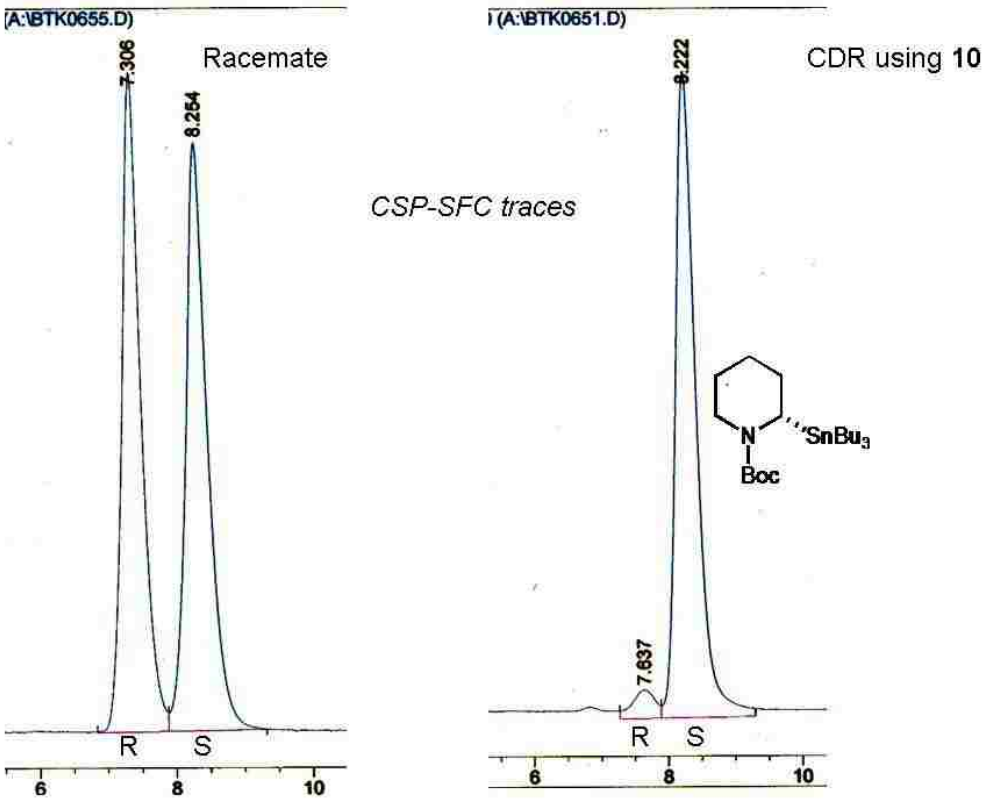
Lithiation-Substitution of N-Boc-2-lithiopiperidine

1. Electrophilic quench with tributyltin chloride: Synthesis of S-3[24]



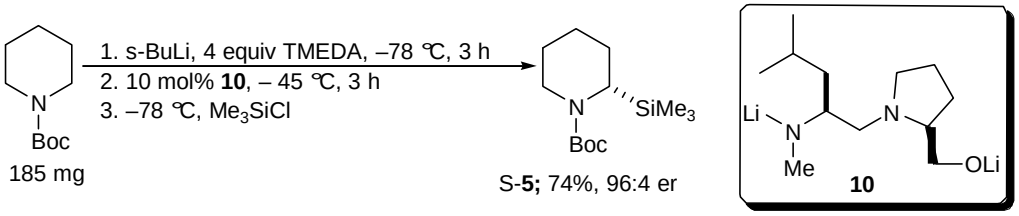
Using General Procedure A, N-Boc-piperidine (0.43 g, 2.35 mmol), TMEDA (1.4 mL, 9.24 mmol, 4.0 equiv) in 10 mL Et_2O, the alcohol precursor of 10 (50.5 mg, 0.24 mmol, 10 mol%.) in 1.0 mL Et_2O, Bu_3SnCl (0.75 mL, 2.8 mmol, 1.2 equiv) for 4 h, gave the crude product as a pale yellow oil. Purification by silica gel chromatography eluting with hexane-EtOAc (99:1) afforded 735 mg of S-3 as a colorless oil in 66% yield and 96:4 er, data as reported.[24] $[\alpha]_D^{22}$ +41 (c = 2, $CHCl_3$), lit. for S-3 (80:20 er, +28, c = 1.0, $CHCl_3$) and for R-3 (>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:

Whelk-O-1, flow Rate = 1.0 mL/min, polarity modifier = 1.2% methanol; outlet pressure = 150 psi, oven temperature = 35 °C, R-3 elutes after 7.5 minutes and S-3 elutes after 8.3 minutes.



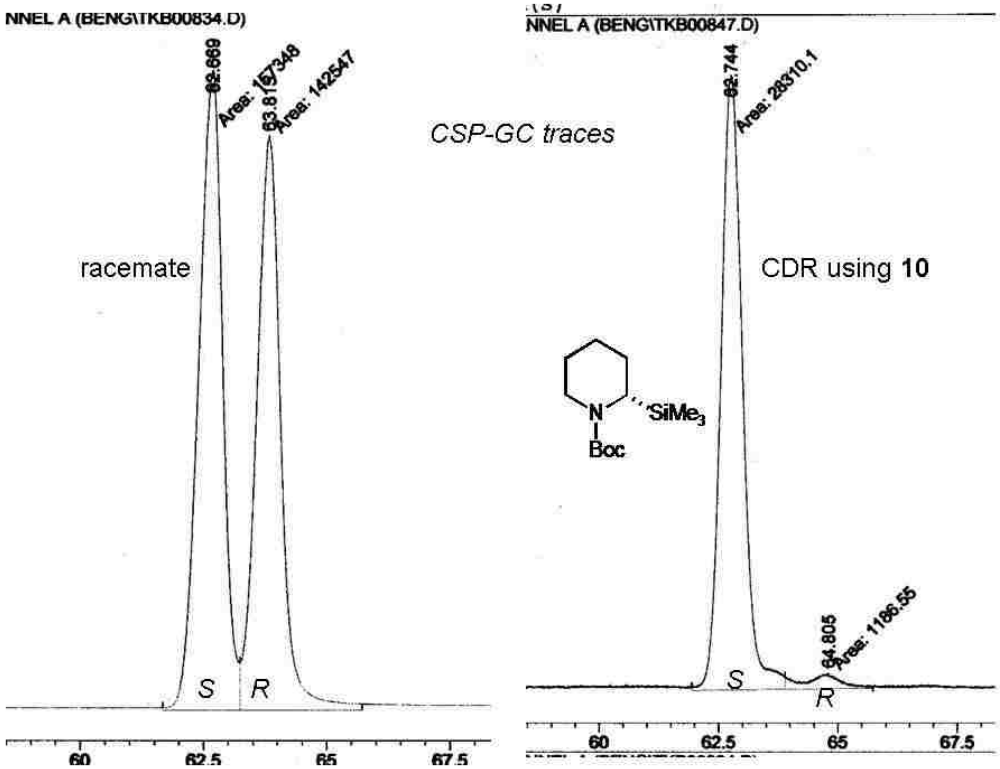
Note: R-3 (97:3 er) was prepared in 62% yield, in the same way as S-3 using 9 as the chiral ligand, L*. $[a]_D^{22}$ −38.5 (c = 2, $CHCl_3$), lit.[24] for R-3 (>99:1 er, $[a]_D^{22}$ −42.2 (c = 1.8, $CHCl_3$).

2. Electrophilic quench with trimethylsilyl chloride: Synthesis of S-5.[25]



Using General Procedure A, N-Boc-piperidine (185 mg, 1.0 mmol), TMEDA (0.6 mL, 4 mmol, 4.0 equiv) in 10 mL Et_2O, the alcohol precursor of 10 (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.

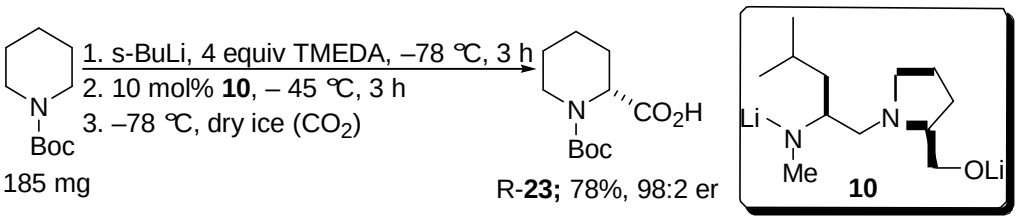
Purification by silica gel chromatography eluting with hexane-EtOAc (98:2) afforded 188 mg of S-5 as a colorless oil in 74% yield (96:4 er), data as reported.[25]. $[a]_D^{22}$ +38 (c = 2, $CHCl_3$), lit. for S-5 of 95:5 er, +36.4, c = 1.95, $CHCl_3$). Evaluation of the enantiomer ratio was performed 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-5 elutes after ~62.5 min and R-5 elutes after ~64.5 min.



Alternatively, the enantiomers were resolved by CSP-SFC under the following conditions: Column: Regis Technologies Pirkle Whelk-O-1, flow rate = 1.0 mL/min, polarity modifier = 1.0% EtOH; outlet pressure = 150 psi, oven temperature = 35 °C, hold time = 3.0 min. R-5 elutes after 9.97 min and S-5 elutes after 10.5 min.

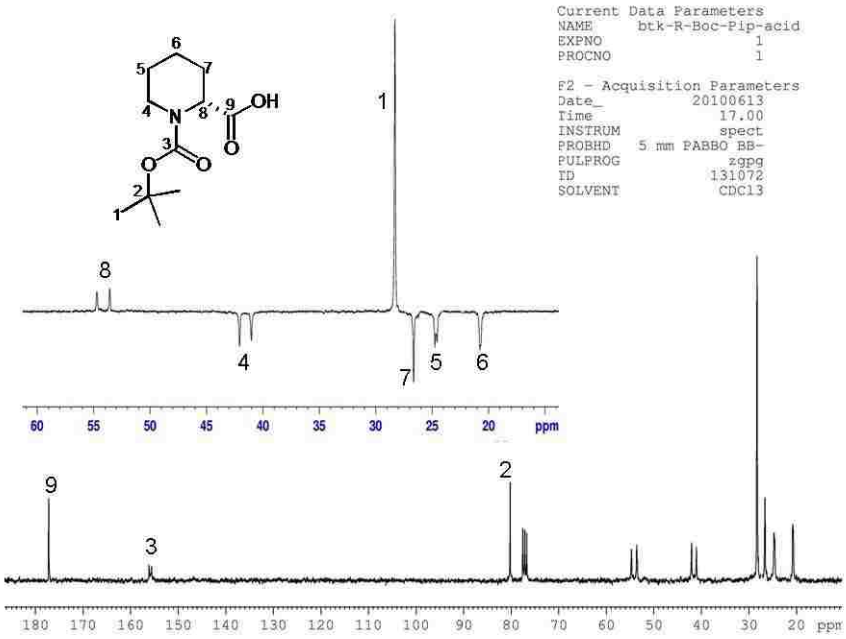
Note: R-5 (98:2 er) was prepared in 70% yield, in the same way as S-5 using ligand 9.

3. Electrophilic quench with carbon dioxide: Synthesis of N-Boc-(R)-(+)-pipecolic acid (R-23).[9]

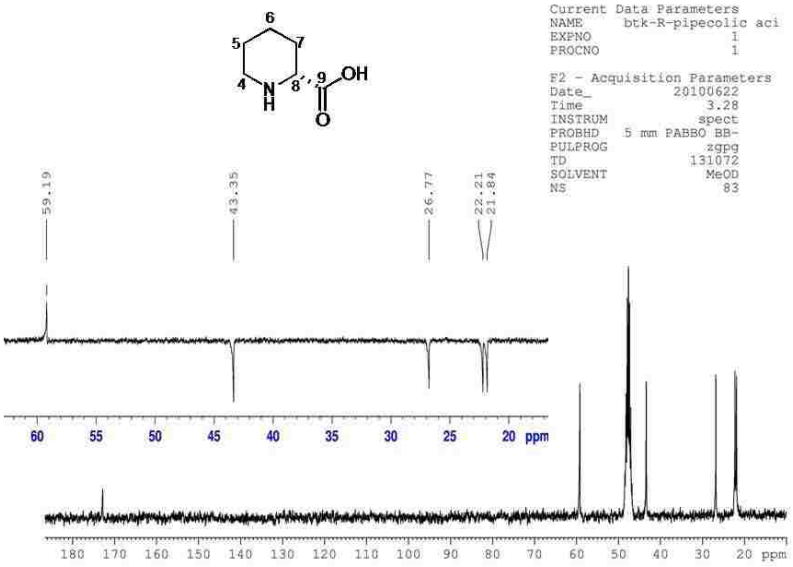


Using General Procedure A, N-Boc-piperidine (185 mg, 1.0 mmol), TMEDA (0.6 mL, 4 mmol, 4.0 equiv) in 10 mL Et_2O, the alcohol precursor of 10 (21.4 mg, 10 mol%) in 1.0 mL Et_2O were stirred for 3 h at −45 ^oC. The solution was cooled to –78 °C and quenched by bubbling dry ice (88 mg, 2 mmol, 2.0 equiv) into the reaction mixture 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-23 as a colorless oil in 78% yield and 98:2 er, data as reported.[9] $[a]_D^{22}$ +42.0 (c = 1, MeOH), {lit for S-23 of >99:1 er $[a]_D^{22}$ –45.777 (c = 1.0 MeOH). ^1H NMR (300 MHz, $CDCl_3$, rotamers) o = 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) o = 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-23 to its corresponding methyl ester, R-24.

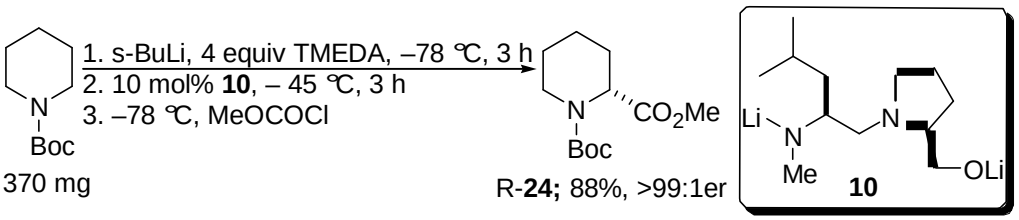
Note: S-23 (97:3 er) was prepared in 81% yield, in the same way as R-23 using ligand 9.



(R)-(+)-pipecolic acid



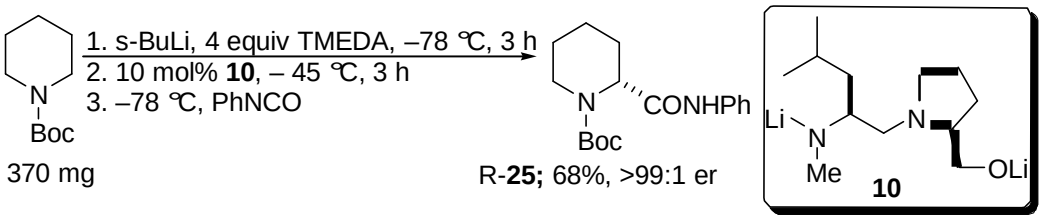
4. Electrophilic quench with methyl chloroformate: Synthesis of (R)-N-Boc-piperidine-2-carboxylic acid methyl ester R-24.[29]



Using General Procedure A, N-Boc-piperidine (370 mg, 2.0 mmol), TMEDA (1.2 mL, 8.0 mmol, 4.0 equiv) in 10 mL Et_2O, the alcohol precursor of 10 (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-24 as a colorless oil in 88% yield, 98:2 er. $[a]_D^{22}$ +45.2 (c = 2, $CHCl_3$), lit[29] for S-24 of 85% ee); $[a]_D^{20}$ −48.1 (c = 1.11, $CHCl_3$) and of 88:12 er; $[a]_D^{20}$ −31.7 (c = 1.0, $CHCl_3$).[30.] ^{1}H NMR (300 MHz, $CDCl_3$) o = 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, $CDCl_3$) o = 170.5 (C=O), o = 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: Pirkle Whelk-O-1, flow rate = 1.0 mL/min, polarity modifier = 1.2% MeOH, outlet pressure = 150 psi, oven temperature = 35 ^{o}C. R-24 elutes after S-24 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 ^{o}C, final temperature = 150 ^{o}C, hold time = 5 min, rate = 0.5 ^{o}C/min. S-24 elutes before R-24 after ca 55 minutes (see Figure 4.2)

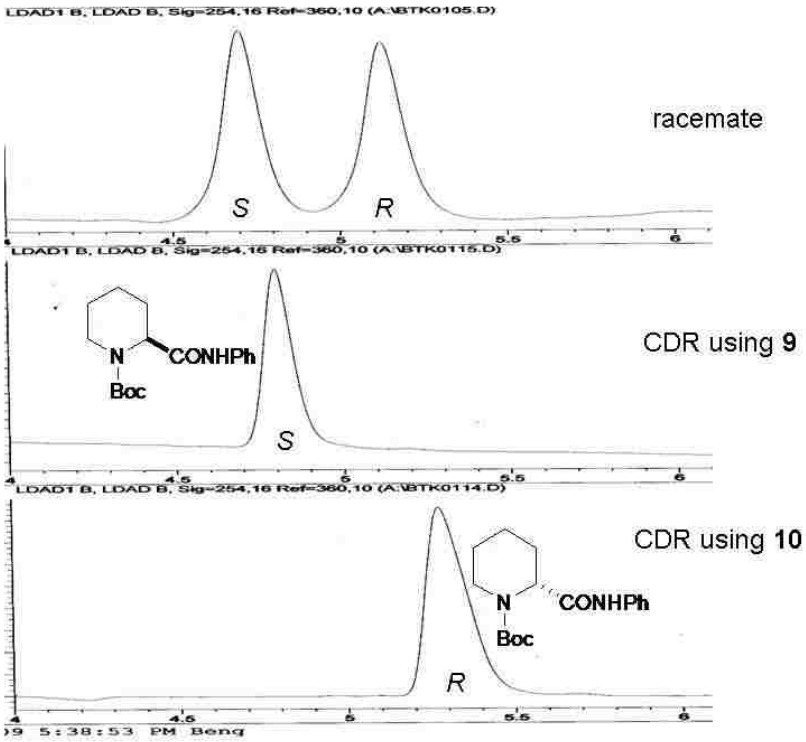
Note: S-24 (>99:1 er) was prepared in 85% yield, in the same way as R-24 using ligand 9.

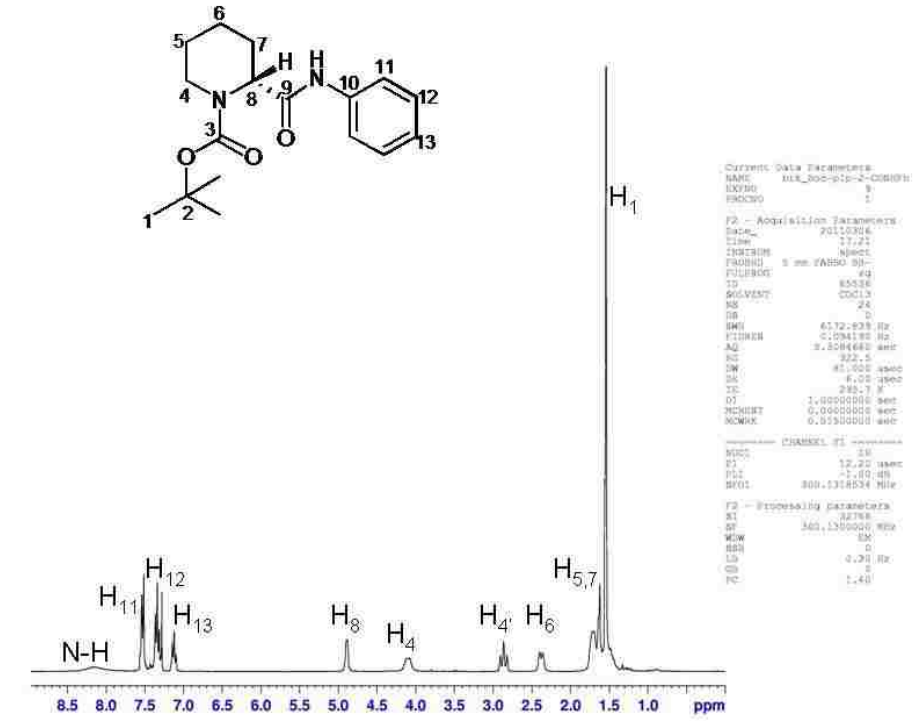
5. Electrophilic quench with phenyl isocyanate: Synthesis of (R)-N-Boc-piperidine-2-carboxylic acid phenyl amide R-25

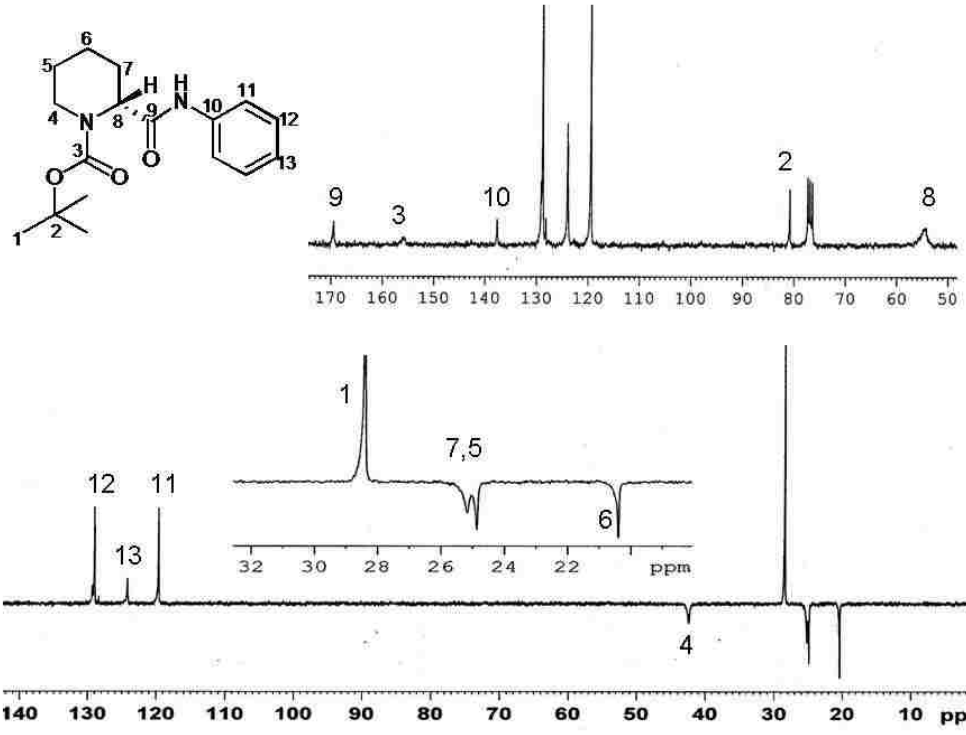


Using General Procedure A, N-Boc-piperidine (370 mg, 2.0 mmol), TMEDA (1.2 mL, 8.0 mmol, 4.0 equiv) in 10 mL Et_2O, the alcohol precursor of 10 (43.0 mg, 0.2 mmol, 10 mol%) in 1.0 mL Et_2O, phenyl isocyanate (0.66 mL, 6.0 mmol, 3.0 equiv) for 2 h prior to addition of 2 mL MeOH, gave the crude product as a yellowish solid. Purification by silica gel chromatography eluting with hexane-EtOAc (90:10) afforded 414 mg of R-25 as a white crystalline solid in 68% yield and 98:2 er. $[a]_D^{22}$ +41 (c = 2, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) o = 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, $CDCl_3$) o = 170.5 (C=O), o = 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: Pirkle Whelk-O-1, Flow Rate = 3.0 mL/min, Polarity Modifier = 3.0% EtOH, Outlet Pressure = 150 psi, Oven Temperature = 35 ^{o}C, S-25 elutes after 4.8 minutes and R-25 elutes after 5.3 minutes. Alternatively, the er was determined using a different column as follows: Column: Daicel Chiralcel OD-H; Flow Rate = 3.5 mL/min, Polarity Modifier = 5.0% EtOH, S-25 elutes after 2.2 minutes and R-25 elutes after 3.5 minutes.

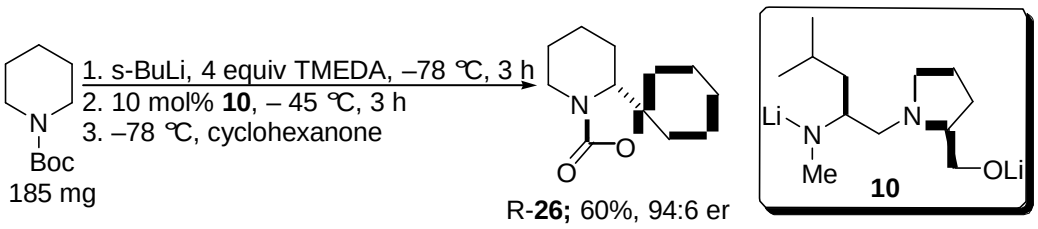
Note: Enantiopure S-25 was prepared in 72% yield by CDR using ligand 9.




H1
H5,7
H12
H11
H13
H8
H4
H4'
H6
N-H
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm

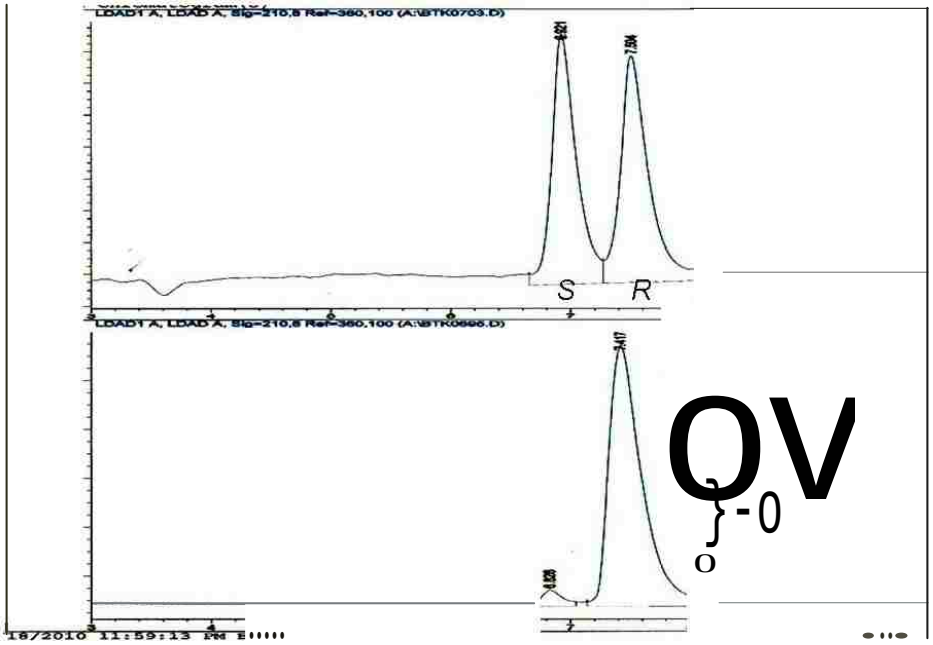

9
3
10
2
8
170 160 150 140 130 120 110 100 90 80 70 60 50
1
7,5
6
12
11
13
4
32 30 28 26 24 22 ppm
140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

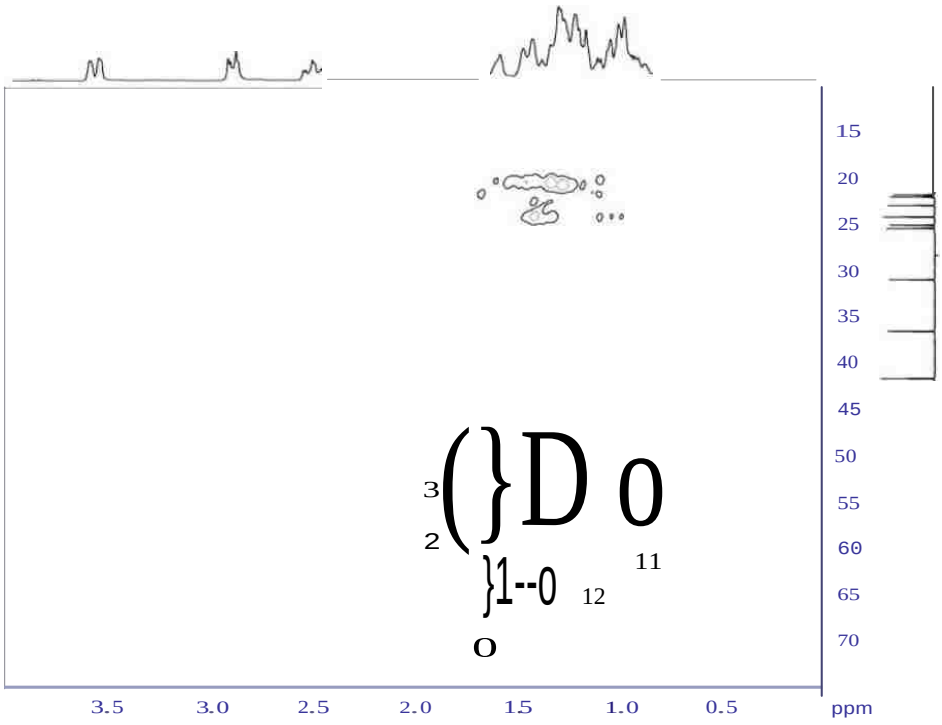
6. Electrophilic quench with cyclohexanone: Synthesis of the oxazolidinone R-26.[31]



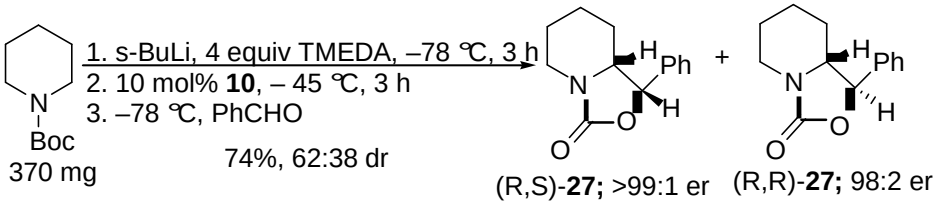
Using General Procedure A, N-Boc-piperidine (185 mg, 1.0 mmol), TMEDA (0.6 mL, 4.0 mmol, 4.0 equiv) in 10 mL Et_2O, the alcohol precursor of 10 (21.4 mg, 0.1 mmol, 10 mol%) in 1.0 mL Et_2O, cyclohexanone (294 mg, 3.0 mmol, 3.0 equiv) for 2 h, warming to room temperature and addition of MeOH (2 mL), gave 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 ^{o}C, $[a]_D^{22}$ –38 (c = 1, $CHCl_3$). The spectroscopic data was in accordance with the literature.[31] ^{13}C NMR (75.5 MHz, $CDCl_3$) o = 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; Flow Rate = 3.0 mL/min, Polarity Modifier = 3.0% EtOH, R-26 elutes after 6.85 minutes and S-26 elutes after 7.45 minutes.

CSP-SFC

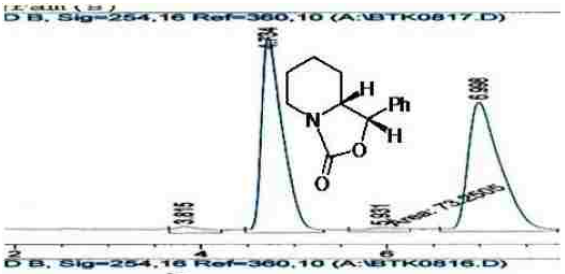




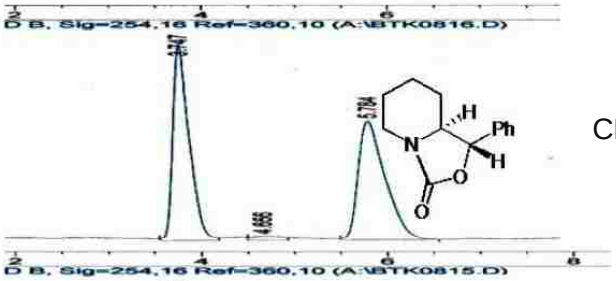
7. Electrophilic quench with Benzaldehyde: Synthesis of the oxazolidinone 27.[23]



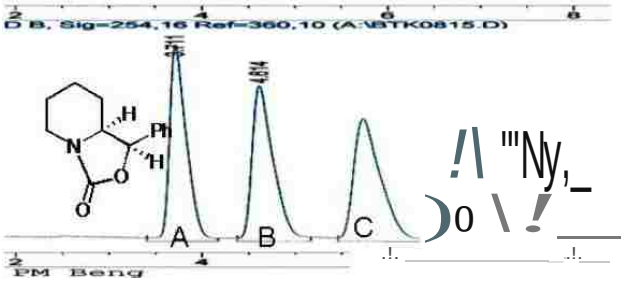
Using General Procedure A, N-Boc-piperidine (370 mg, 2.0 mmol), TMEDA (1.2 mL, 8.0 mmol, 4.0 equiv) in 10 mL Et_2O, the alcohol precursor of 10 (43 mg, 0.2 mmol, 10 mol%) in 10 mL Et_2O, freshly distilled benzaldehyde (640 mg, 6 mmol, 3.0 equiv) for 2 h, warming to room temperature and addition of MeOH gave the crude product as a pale yellow oil. Purification by silica gel chromatography eluting with hexane-EtOAc (60:40) afforded 321 mg of 27, as a mixture of diastereomers (dr ~62:38) in 74% yield; major diastereomerer >99:1, minor diastereomer er 98:2. The spectroscopic data was in accordance with the literature. $[a]_D^{22}$ –7.7 (c = 1, $CHCl_3$), lit[32] for 27 of 80:20 dr; $[a]_D^{22}$ –2.9 (c = 1.1, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) o = 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) o = 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, Flow Rate = 3.0 mL/min, Polarity Modifier = 3.0% EtOH.



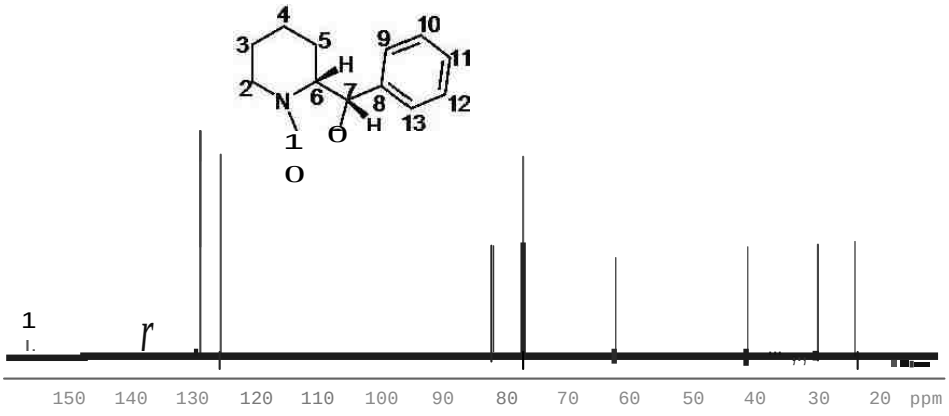
CDR using (S,S)-10

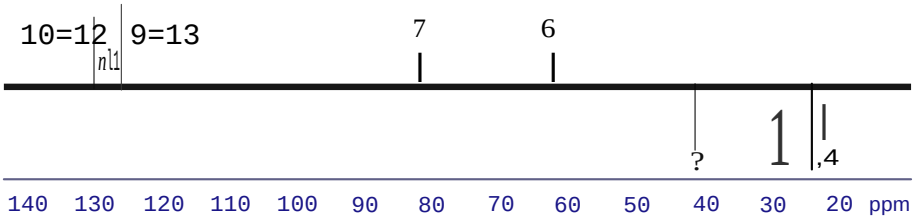


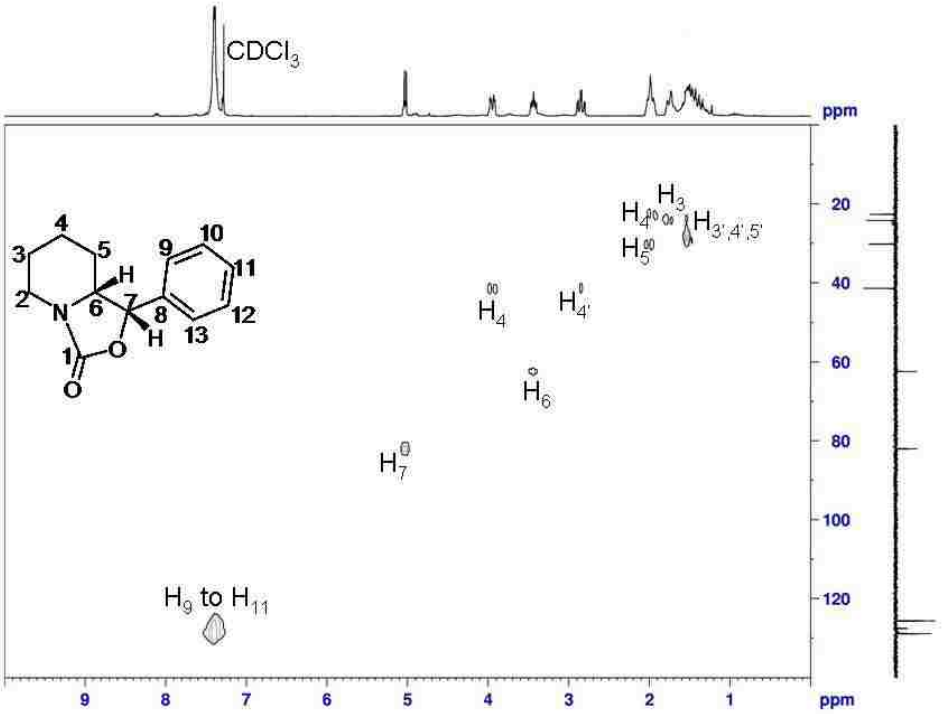
CDR using (S,R)-9



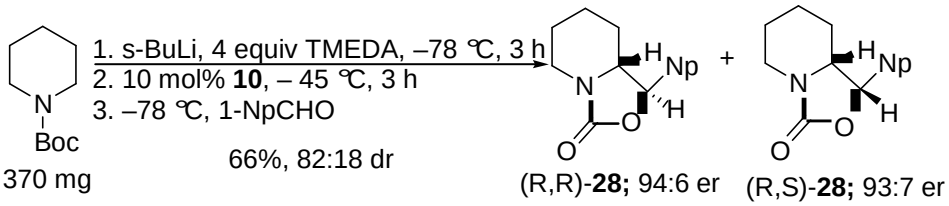
Racemate



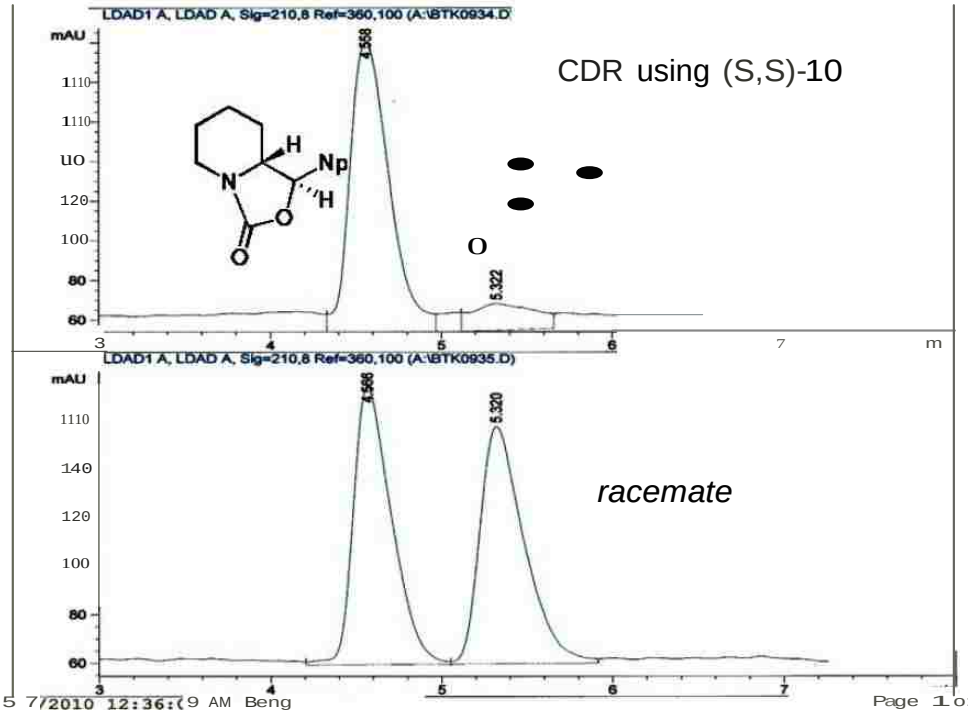


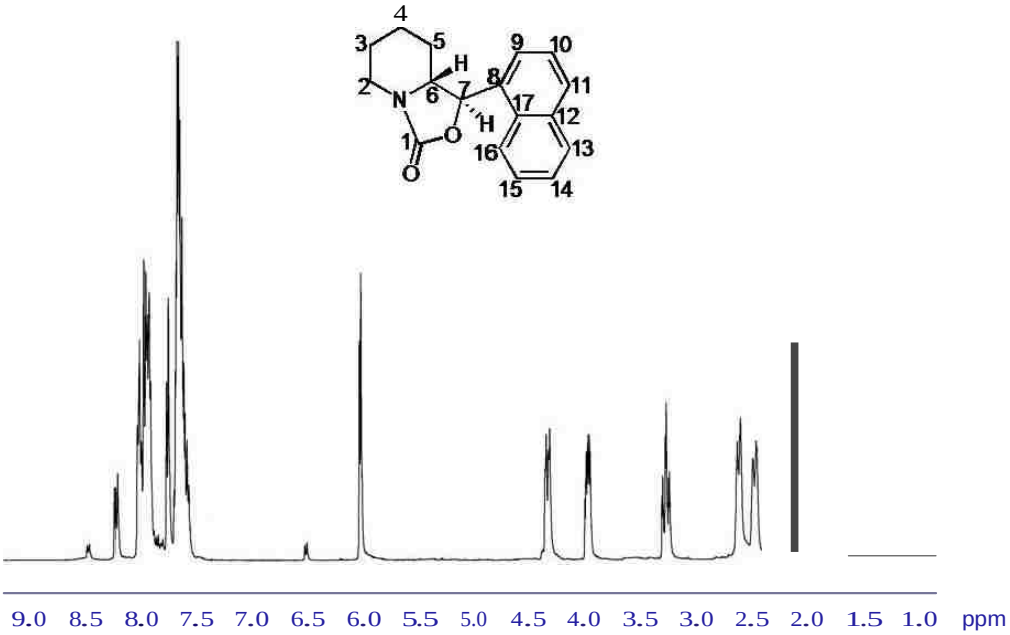


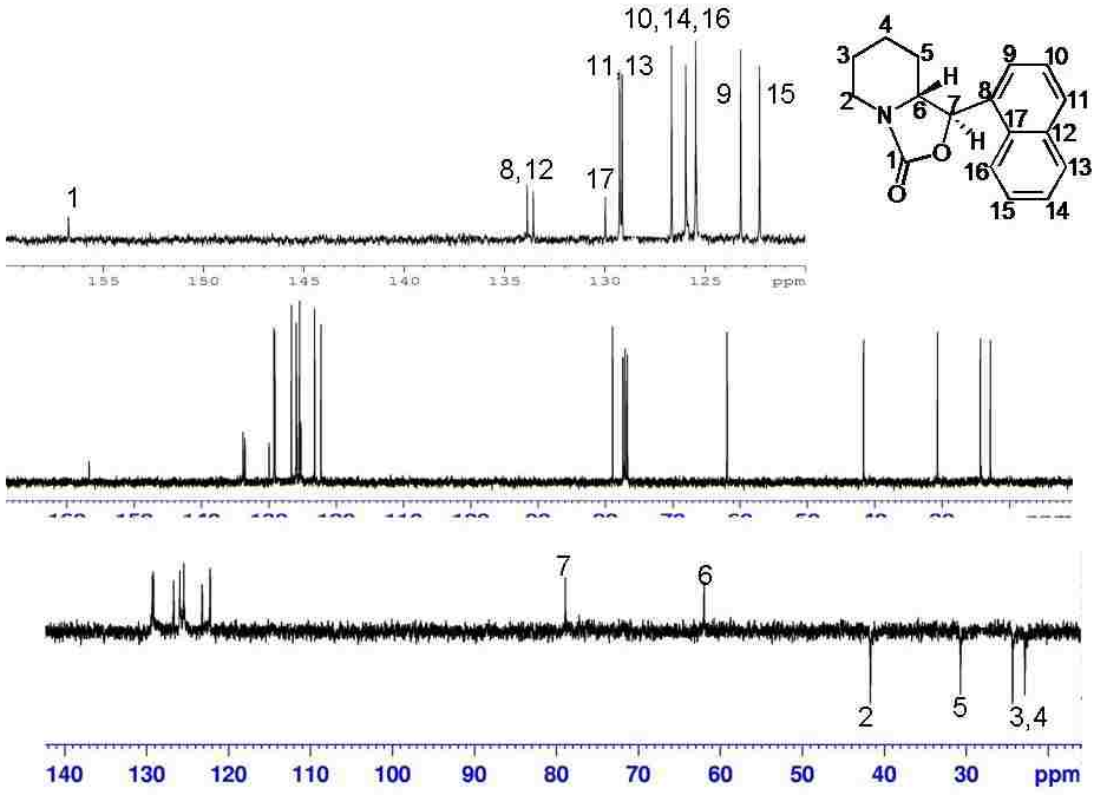
8. Electrophilic quench with 1-naphthaldehyde: Synthesis of the oxazolidinone 28.[23]



Using General Procedure A, N-Boc-piperidine (370 mg, 2.0 mmol), TMEDA (1.2 mL, 8.0 mmol, 4.0 equiv) in 10 mL Et_2O, the alcohol precursor of 10 (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 28 as a mixture of diastereomers (82:18 dr) in 66% yield; 94:6 er for the major diastereomer, 93:7 er for the minor diastereomer.


LDAD1 A, LDAD A, Sig=210,8 Ref=360,100 (A:\BTK0934.D
mAU
5.358
5.322
CDR using (S,S)-10
H
Np
N
H
O
O
LDAD1 A, LDAD A, Sig=210,8 Ref=360,100 (A:\BTK0935.D)
mAU
5.358
5.320
racemate
5 7/2010 12:36:(9 AM Beng
Page 1o:


4
3
5
H
9
10
2
N
6
7
8
11
17
12
1
O
H
16
13
O
15
14
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm


10,14,16
11,13
9
15
8,12
17
1
155
150
145
140
135
130
125
ppm
7
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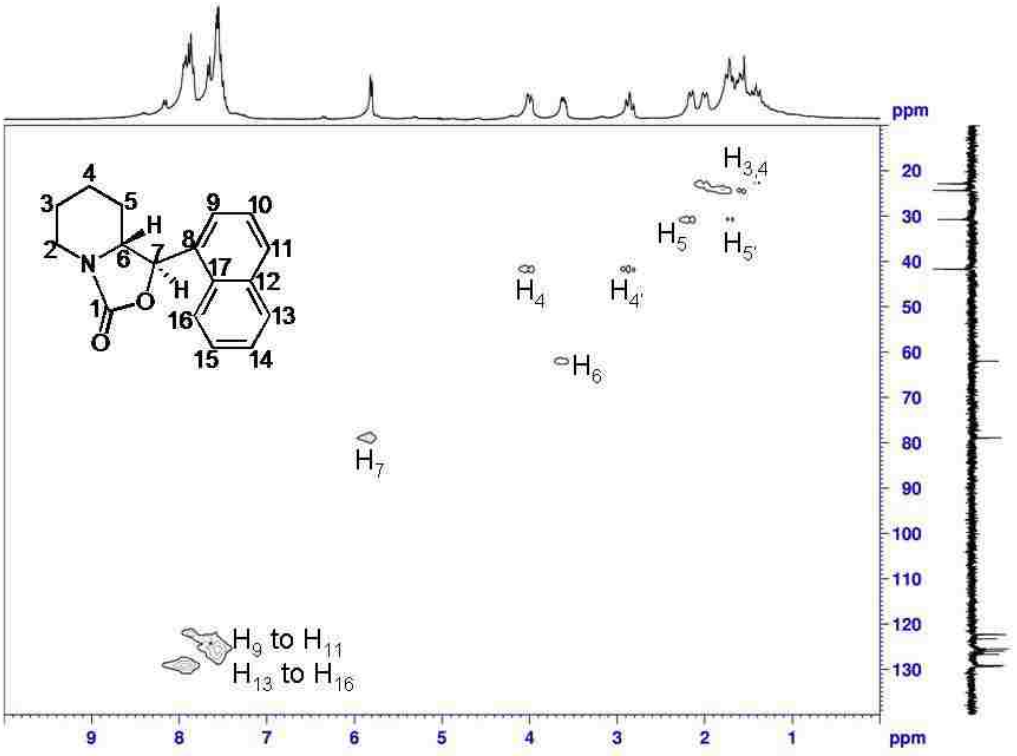
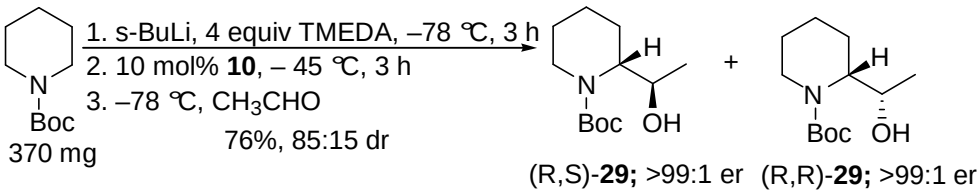
110
100
90
80
70
60
50
40
30
ppm


ppm
H3,4
H5
H5'
H4
H4'
H6
H7
H9 to H11
H13 to H16
20
30
40
50
60
70
80
90
100
110
120
130
9
8
7
6
5
4
3
2
1
ppm

9. Electrophilic quench with acetaldehyde: Synthesis of alcohol 29



(R,S)-**29;** >99:1 er (R,R)-**29;** >99:1 er

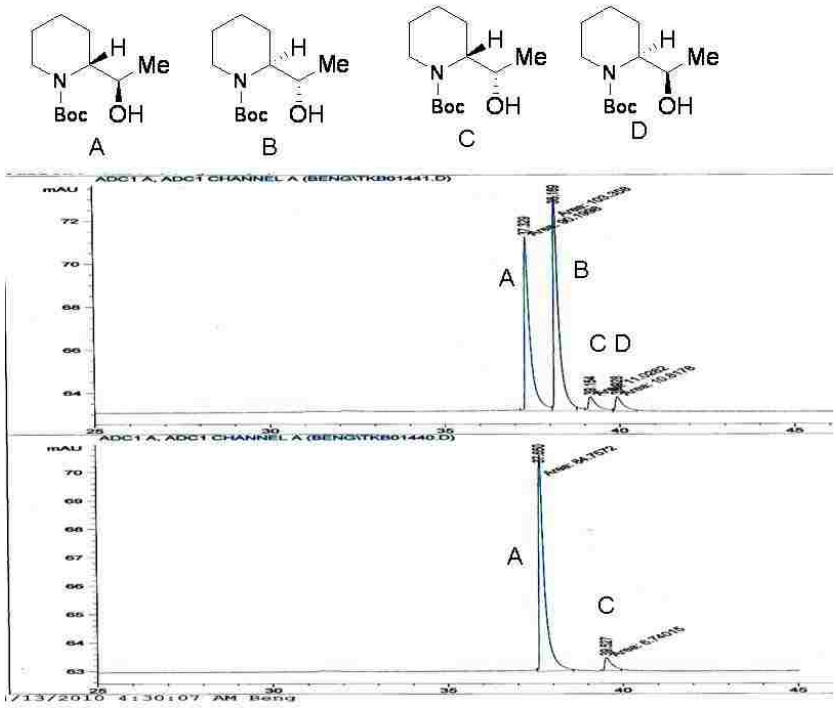
Using General Procedure A, N-Boc-piperidine (370 mg, 2.0 mmol), TMEDA (1.2 mL, 8.0 mmol, 4.0 equiv) in 10 mL Et_2O, the alcohol precursor of 10 (43.0 mg, 0.2 mmol, 10 mol%) in 1.0 mL Et_2O, acetaldehyde (264 mg, 0.33 mL, 6 mmol, 3.0 equiv) for 2 h, 2 mL MeOH gave the crude product as a pale yellow oil. 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 dr, >99:1 er for both). ^{1}H NMR (300 MHz, $CDCl_3$) o =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, $CDCl_3$) o = 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).

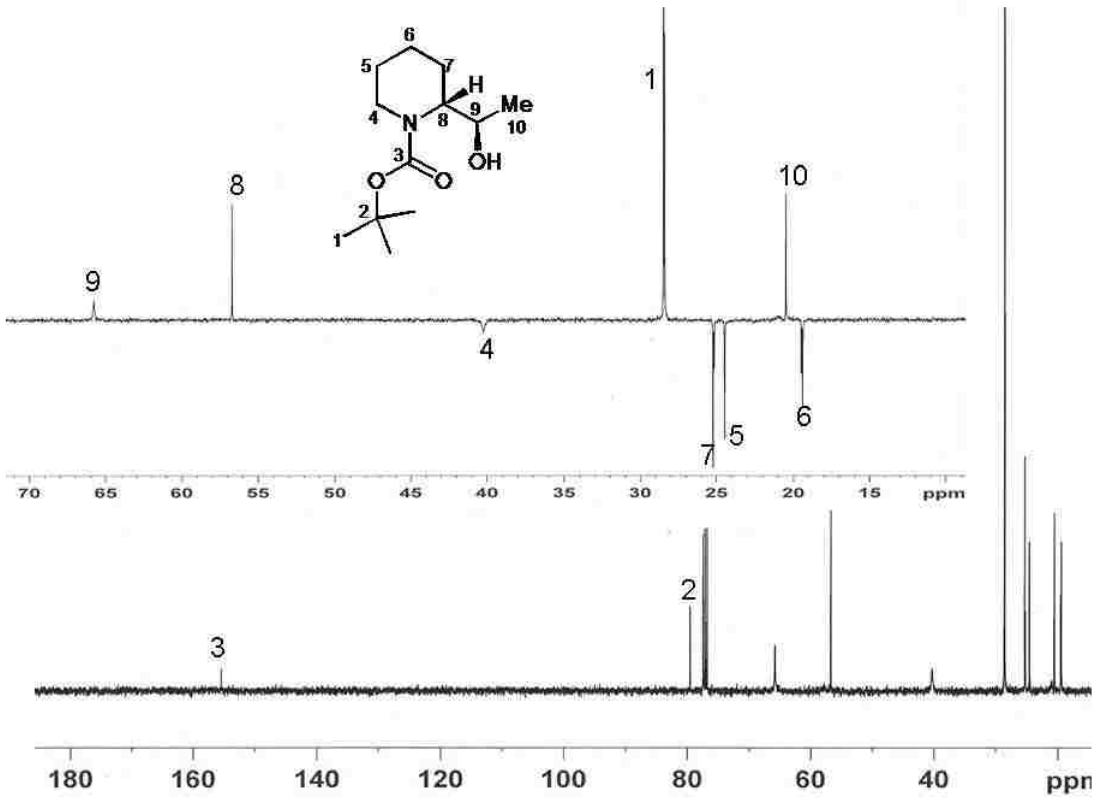
Minor diastereomer:

^{13}C NMR (100.6 MHz, $CDCl_3$) o = 155.3 (C=O), 79.9 (C), 65.8 (CH), 56.7 (CH), 40.2 (CH_2), 28.5 (CH_3), 25.8 (CH_2), 25.1 (CH_2), 20.9 (CH_3) and 19.5 (CH_2).

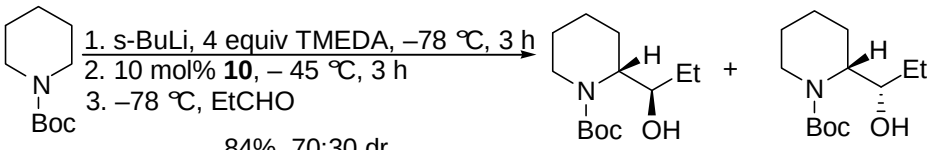
The enantiomers were resolved by CSP GC {β-cyclodextrin-permethylated 120 fused silica capillary column [30 m × 0.25 mm i.d., 20% permethylated β-cyclodextrin in SPB-35 poly(35% diphenyl/65% dimethyl)siloxane, Pressure = 100 kPa, Initial temperature = 150 ^{o}C, Final temperature = 200 ^{o}C, Hold time = 2 min, Rate = 1.0 ^{o}C/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 ^{o}C. 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.





9. Electrophilic quench with propionaldehyde: Synthesis of N-Boc-(+)-⁄⁄-conhydrine[34]



(R,S)-**30;** 96:4 er (R,R)-**30;** 96:4 er

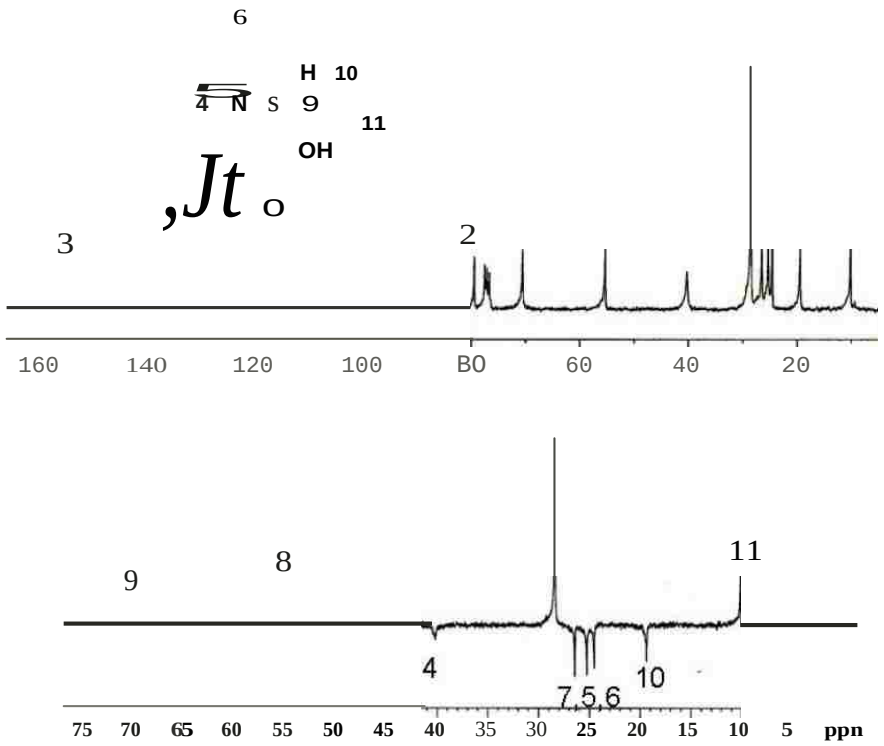
Using General Procedure A, N-Boc-piperidine (370 mg, 2.0 mmol), TMEDA (1.2 mL, 8.0 mmol, 4.0 equiv) in 10 mL Et_2O, the alcohol precursor of 10 (43.0 mg, 0.2 mmol, 10 mol%) in 1.0 mL Et_2O, propionaldehyde (348 mg, 6 mmol, 3.0 equiv) for 2 h, 2 mL MeOH gave the crude product as a pale yellow oil. Purification 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 and 96:4 er for both diastereomers. The major diastereomer, N-Boc-(+)-⁄-conhydrine was isolated in 61% yield $[a]_D^{22}$ +24.3 (c = 1, $CHCl_3$), {lit[32] for N-Boc-(+)-⁄-conhydrine of

84:16 er $[a]_D^{22}$ +17.8 (c = 1.1, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) o =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, $CDCl_3$) o = 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), 19.5 (CH_2) and 10.1 (CH_3).

Minor diastereomer:

^{13}C NMR (75.5 MHz, $CDCl_3$) o = 155.2 (C=O), 79.2 (C), 70.1 (CH), 55.1 (CH), 40.0 (CH_2), 28.3 (CH_3), 26.4 (CH_2), 25.6 (CH_2), 25.1 (CH_2), 19.3 (CH_2) and 9.4 (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.


6
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4 N S 9
11
OH
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3
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8
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7.5.6
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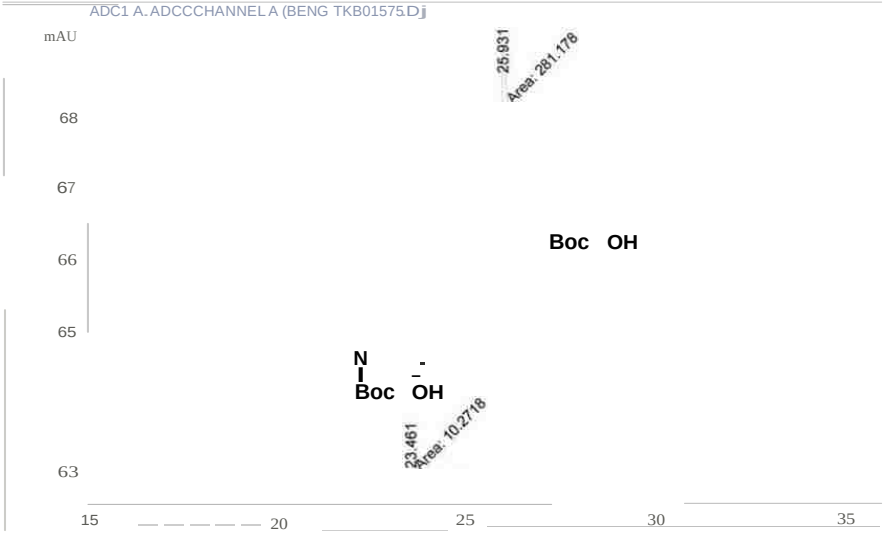
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66
65
63
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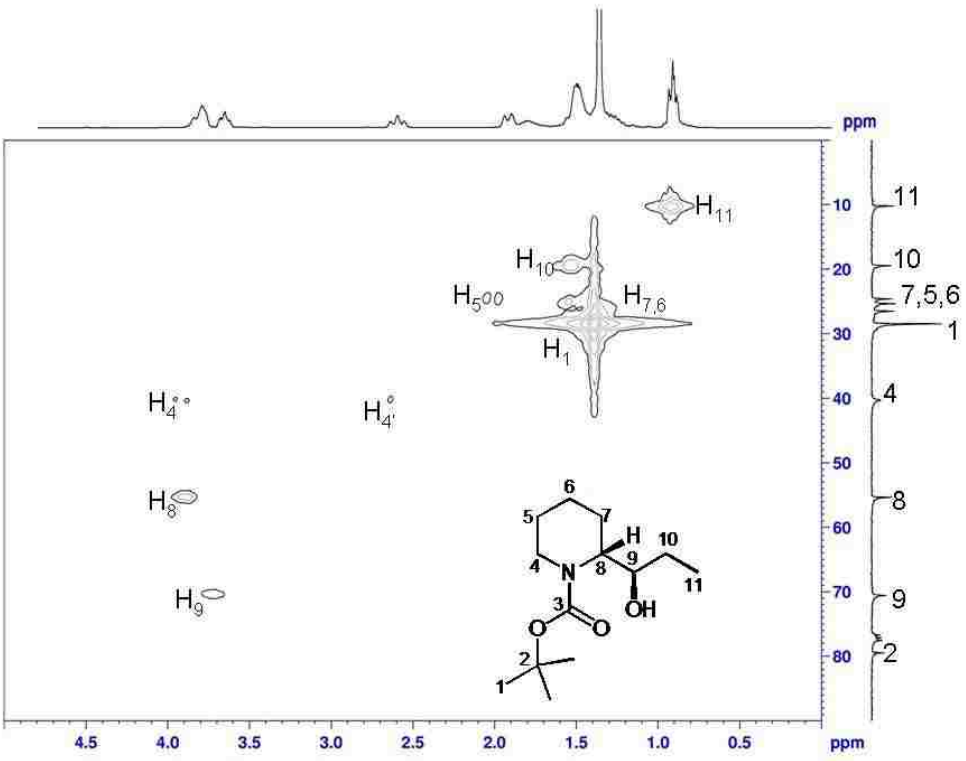
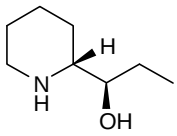
15 20 25 30 35



Hydrolysis of N-Boc-(+)-JJ-conhydrine 18: Synthesis of (+)-JJ-conhydrine

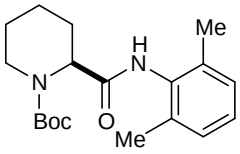


(+)-β-conhydrine

To N-Boc-(+)-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 (+)-conhydrine in 100% yield. $[a]_D^{22}$ +7.4 (c = 0.9, EtOH); lit[34] $[a]_D^{22}$ +8.3 (c = 0.9, EtOH). ^{1}H NMR (300 MHz, $CDCl_3$) o: 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,

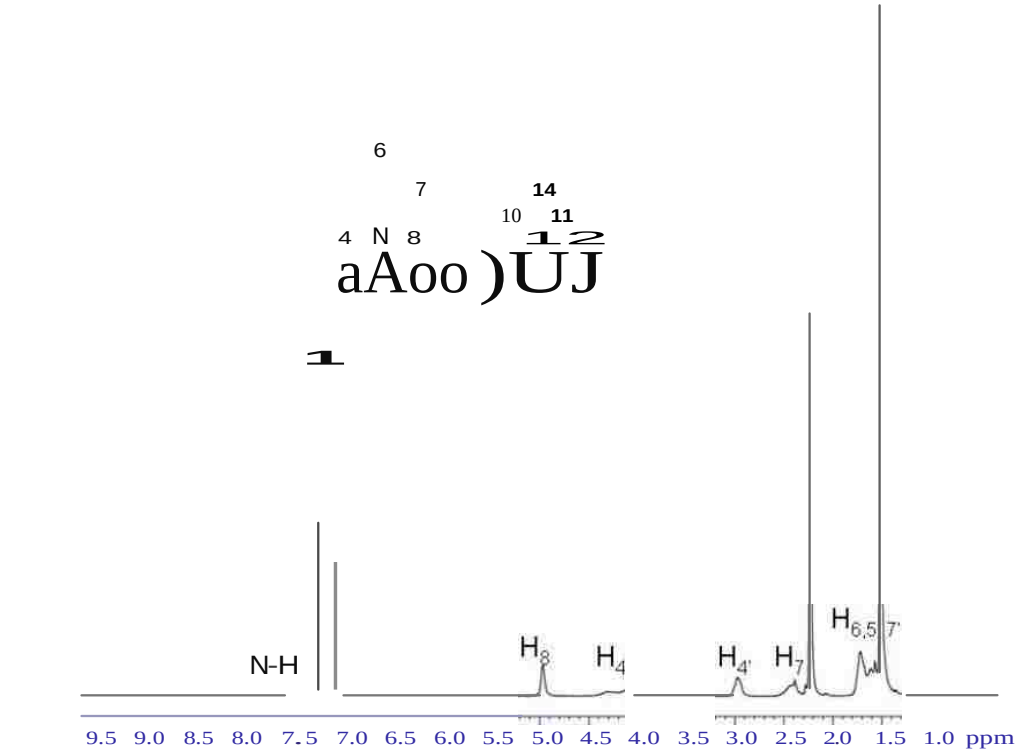
CH), 1.65-1.52 (2H, m, CH_2), 1.51-1.19 (5H, m, CH and 2 × CH_2), 0.96 (3H, t, CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$) o = 74.8 (CH), 60.3 (CH), 46.5 (CH_2), 26.3 (CH_2), 25.7 (CH_2), 25.1 (CH_2), 24.3 (CH_2) and 10.7 (CH_3).

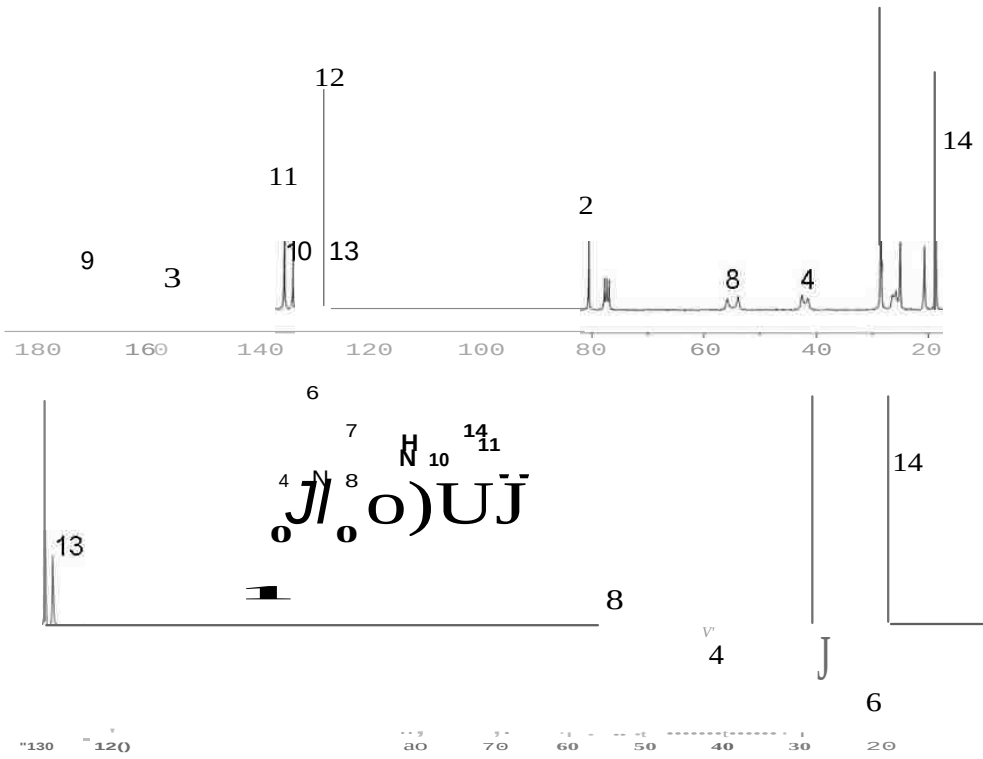
10. Synthesis of (S)-N-Boc-piperidine-2-carboxylic acid 2,6-dimethylphenyl amide: S-31



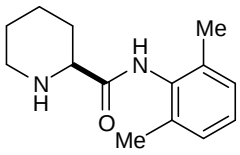
S-**31**

Using General Procedure A, 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), the alcohol 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-31 in 69% yield and >99:1 er. $[a]_D^{22}$ –57 (c = 2, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) o = 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, $CDCl_3$) o = 172.0 (C=O), o = 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: Pirkle Whelk-O-1, Flow Rate: 3.0 mL/min, Polarity Modifier %: 3.2% EtOH, Outlet Pressure = 150 psi, Oven Temperature = 35 ^{o}C, S-31 elutes before R-31.


N-H
H8
H4
H4'
H7
H6,5
7'
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm


12
11
14
2
9
3
10
13
8
4
180 160 140 120 100 80 60 40 20

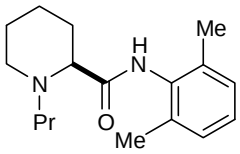
(S)-piperidine-2-carboxylic acid 2,6-dimethylphenyl amide S-32



S-**32**

To S-31 (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-32 as a white solid in 100% yield. $[a]_D^{22}$ 33 (c = 2, HCl 1 M), mp 127–129 ^oC; lit. $[a]_D^{25}$ 35 (c = 2, HCl 1 M).[14]

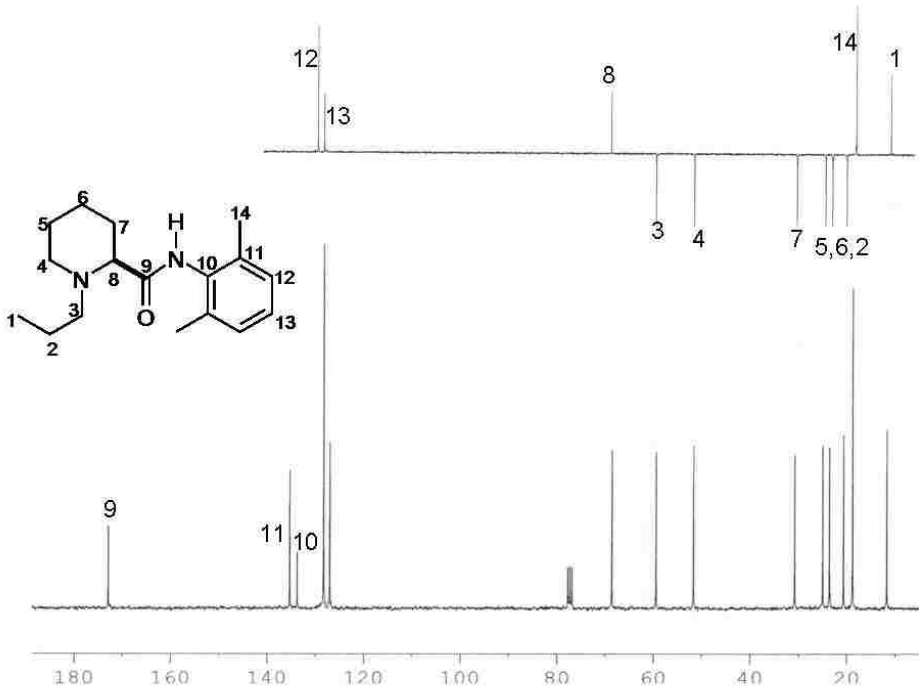
(S)-N-propylpiperidine-2-carboxylic acid 2,6-dimethylphenyl amide: (S)-(-)-Ropivacaine



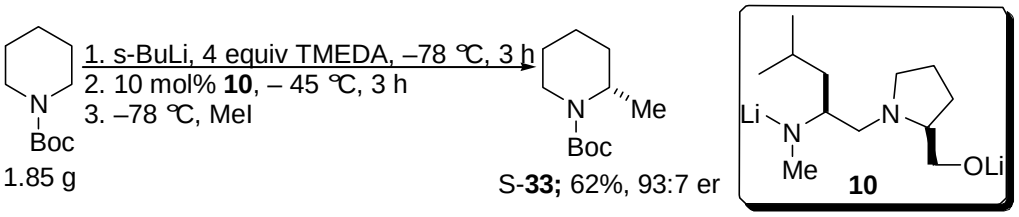
(S)-(–)-ropivacaine

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)-32 (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 °C afforded the crude product. Recrystallization of the crude product from toluene afforded 58.5 mg of (S)-(-)-ropivacaine in 89% yield. $[a]_D^{25}$ −80 (c = 2, MeOH), mp 145 – 147 °C; lit. values are as follows: mp 144–146 °C, $[a]_D^{25}$ −82 (c = 2, MeOH).[14] ^{1}H NMR (300 MHz, $CDCl_3$), 0 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, $CDCl_3$), 0 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).



11. Electrophilic quench with methyl iodide: Synthesis of (S)-N-Boc-2-methylpiperidine

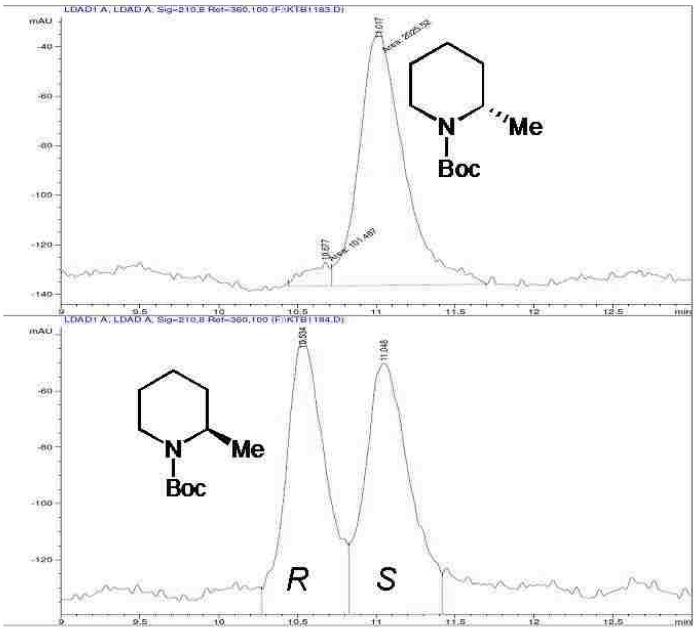


Using General Procedure A, N-Boc-piperidine (1.85 g, 10.0 mmol), TMEDA (6.0 mL, 40 mmol, 4.0 equiv) in 100 mL Et_2O, the alcohol precursor of 10 (215 mg, 1.0 mmol, 10 mol%) in 20 mL Et_2O, methyl iodide (1.85 mL, 30 mmol, 3.0 equiv) for 2 h, gave the crude product as an oil. Purification by silica gel chromatography eluting with hexane-EtOAc (99:1) afforded 1.51 g of S-33 as a colorless oil in 62% yield, 93:7 er, data as reported. $[a]_D^{22}$ +39.5 (c = 1, $CHCl_3$), lit[87]. for R-33 (100:0 er, −46.4, c = 0.83, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) o = 4.63−4.10 (1H, br, NCH), 3.87 (1H, dd, NCH), 2.76 (1H, td, NCH), 1.70−1.20 (6H, m, 3 x CH_2), 1.41 (9H, s, t-Bu), 1.07 (3H, d, CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$) o = 155.1 (C=O), 79.0 (C), 46.1 (CH), 38.7 (CH_2), 30.1 (CH_2), 28.5 (3 x CH_3), 25.7 (CH_2), 18.7 (CH_2), 15.7 (CH_3). The er was determined by CSP-SFC as follows: Column: Pirkle Whelk-O-1, Flow Rate = 1.0 mL/min, Polarity Modifier = 1.0% EtOH. R-33 elutes after 10.5 min and S-33 elutes after 11.0 min.

Note 1. A slight improvement of the er to 96:4 er was observed when Me_2SO_4 was used as the electrophile.

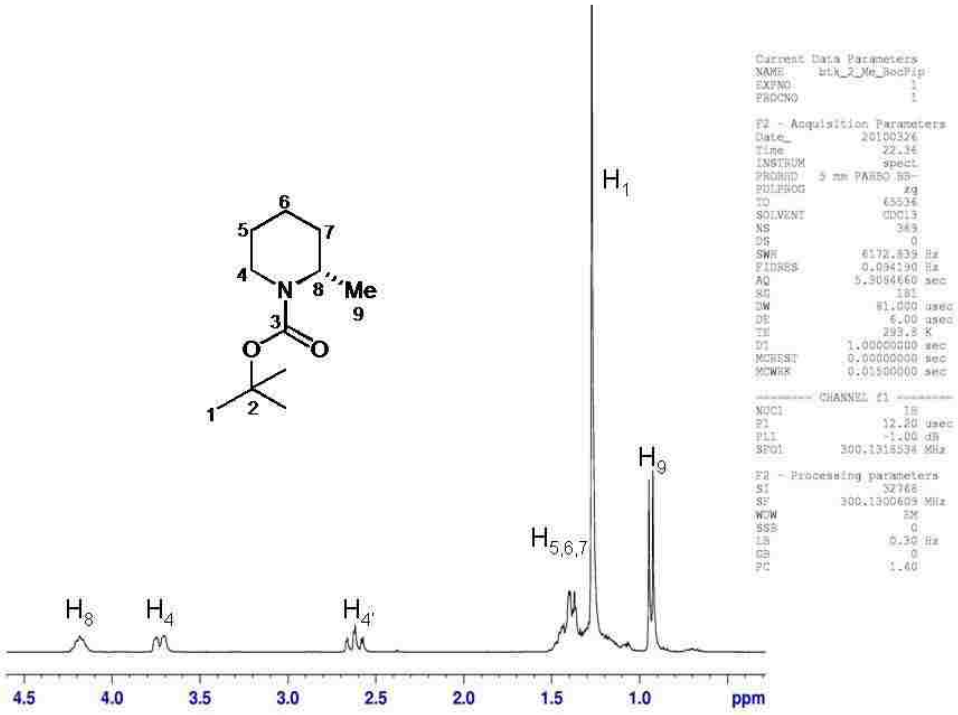
Note 2: On one occasion, enantiopure S-6 was obtained but typical er's ranged from 93:7 to 96:4 (S:R)

CSP-SFC traces



From CDR

racemate

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PROCNO                  1

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PULPROG               zg
TD                 65536
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FIDRES           0.094190 Hz
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RG                   181
DW                81.000 usec
DE                 6.00 usec
TE                293.3 K
D1             1.00000000 sec
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MCWRK          0.01500000 sec

-------- CHANNEL f1 --------
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PL1                 -1.00 dB
SFO1         300.1318534 MHz

F2 - Processing parameters
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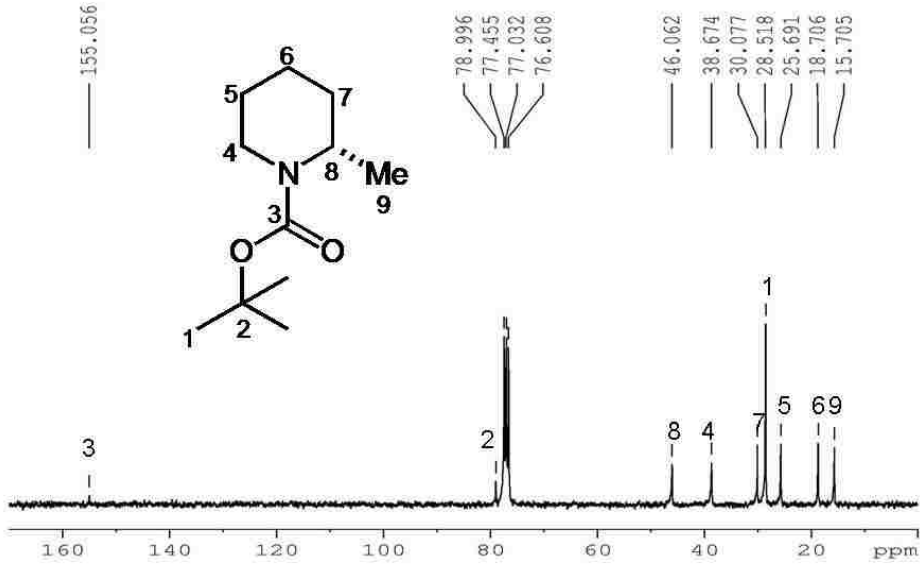
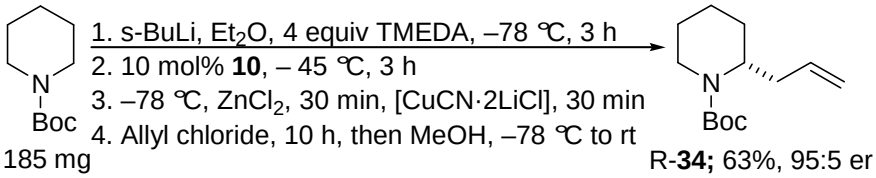
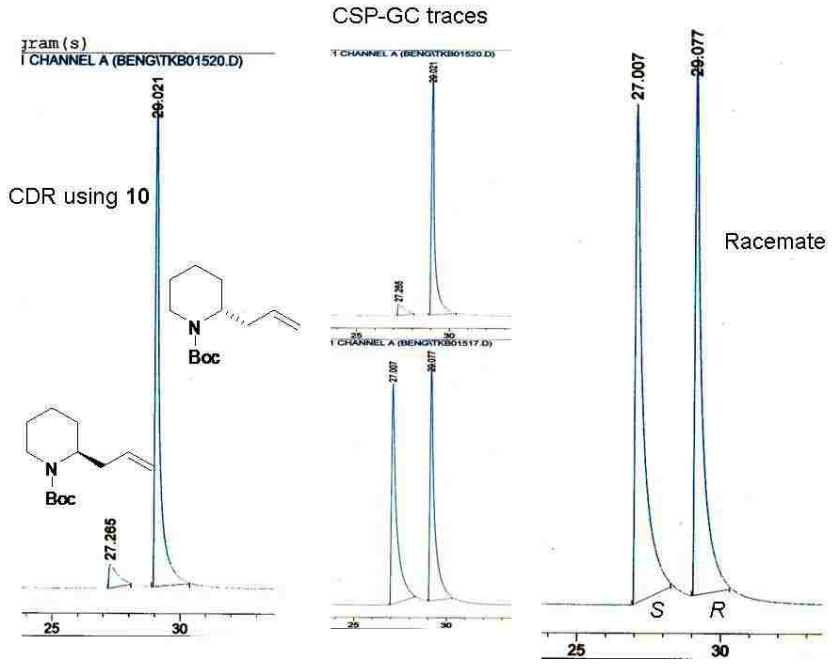


12. Electrophilic quench with allyl chloride: Synthesis of (R)-tert-Butyl-2-allylpiperidine-1-carboxylate R-34.[42]

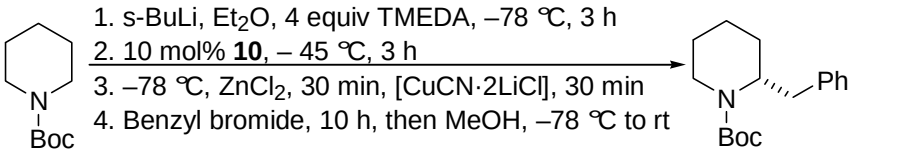


Using General Procedure B, N-Boc-piperidine (185 mg, 1.0 mmol, 0.25 M), TMEDA (586 mg, 4.0 mmol, 0.62 mL, 4.0 equiv), Et_2O (4 mL), s-BuLi (1.2 mL, 1.0 M, 1.2 mmol, 1.2 equiv), the alcohol precursor of 10 (21.4 mg, 0.1 mmol, 10 mol%, in 0.40 mL Et_2O pretreated with freshly titrated s-BuLi), $ZnCl_2$ (180 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-34 as a colorless oil in 63% yield and 95:5 er, data as reported.[42] $[a]_D^{22}$

+45 (c = 1, $CHCl_3$), lit[41]. for S-34 (>99:1 er, $[a]_D^{25}$ −49.2 (c = 0.9, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) o = 5.72 (1H, ddt, $CH=CH_2$), 5.10 to 4.87 (2H, m, $CH=CH_2$), 4.25 (1H, br t, NCH), 3.94 (1H, br d, NCH), 2.85 to 2.63 (1H, m, CH), 2.45 to 2.10 (2H, m, CH_2), 1.65 to 1.46 (6H, m, 3 x CH_2), 1.42 (9H, s, t-Bu); ^{13}C NMR (100 MHz, $CDCl_3$) o = 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: Pirkle Whelk-O-1, Flow Rate = 1.0 mL/min, Polarity Modifier = 1.2 % MeOH, Outlet Pressure = 150 psi, Oven Temperature = 35 °C. S-34 elutes before R-34 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 °C, Final temperature = 150 °C, Hold time = 2 min, Rate = 1.0 °C/min. S-34 after ~27 min and R-34 elutes after ~ 29 min.



12. Electrophilic quench with benzyl bromide: Synthesis of (R)-N-Boc-2-benzylpiperidine R-35

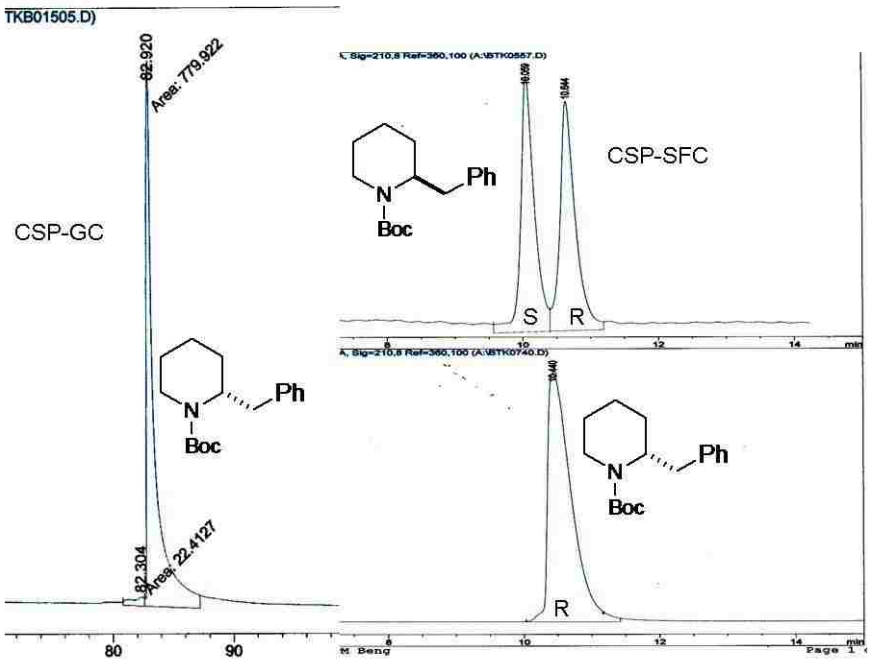


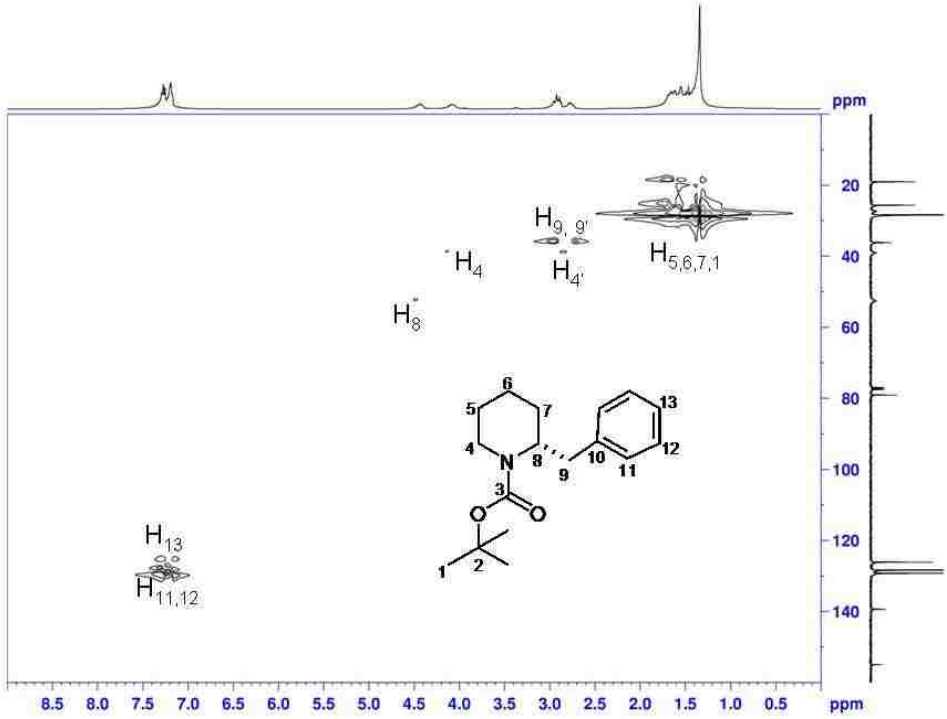
185 mg

R-**35;** 65%, >99:1 er

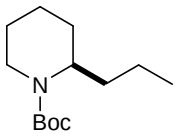
Using General Procedure B, N-Boc-piperidine (185 mg, 1.0 mmol, 0.25 M), TMEDA (586 mg, 4.0 mmol, 0.62 mL, 4.0 equiv) in Et_2O (4 mL), s-BuLi (1.2 equiv), the alcohol precursor of 10 (21.4 mg, 0.1 mmol, 10 mol%, 0.25 M in 0.40 mL Et_2O), $ZnCl_2$ (180 mg, 1.3 mmol, 1.3 equiv) in THF (2 mL), CuCN·2LiCl [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-35 as a colorless oil in 65% yield and >99:1 er. ^1H NMR (300 MHz, $CDCl_3$) o = 7.52 to 6.72 (5H, m, Ar-H), 4.45 (1H, m, br, NCH), 4.15 (1H, br m, NCH), 3.2 to 2.7 (3H, m, NCH + benzylic CH_2), 2.0 to 1.1 (15H, m, 3 x CH_2 and t-Bu); ^{13}C NMR (75.6 MHz, $CDCl_3$) o = 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-35 elutes after 82 min and R-35 elutes after 83 min. Alternatively, the enantiomers were resolved by CSP-SFC under the following conditions: Column: Pirkle Whelk-O-1, Flow Rate = 1.0

mL/min, Polarity Modifier = 1.2% MeOH, Outlet Pressure = 150 psi, Oven Temperature = 35 ^{o}C. S-35 elutes before R-35 after ca 11 minutes.

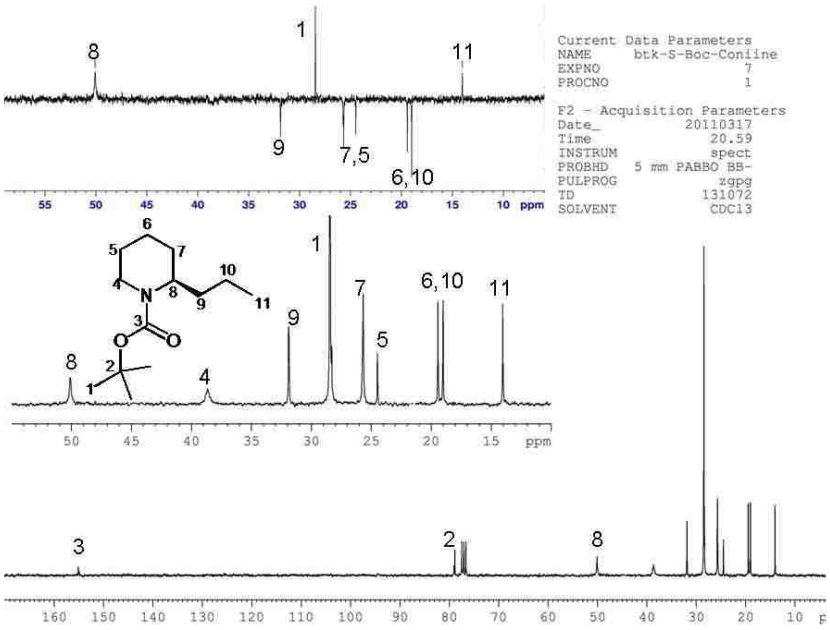




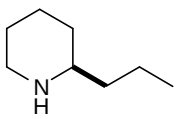
Synthesis of tert-Butyl 2-N-Propylpiperidine-1-carboxylate (N-Boc-(S)-(-)-coniine)



$Pd(OH)_2$ (123 mg, 0.88 mmol, 40 mol%) was added to a solution of S-34 (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.[88]



(S)-(-)-Coniine

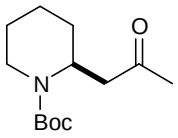


(S)-(–)-coniine

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

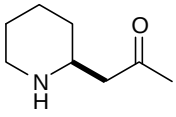
concentrated in vacuo to obtain the salt. The salt was basified to pH 10 – 12 with 20% $NaOH_{(aq)}$. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 5 mL). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure to give 158 mg of (S)-(-)-coniine in 100% yield. $[a]_D^{22}$ −6.7 (c = 1.0, MeOH), lit.[43] $[a]_D^{20}$ −7.3 (c = 1.0, MeOH). All other spectroscopic data as reported.[9]

Synthesis of N-Boc-(S)-(+)-Pelletierine



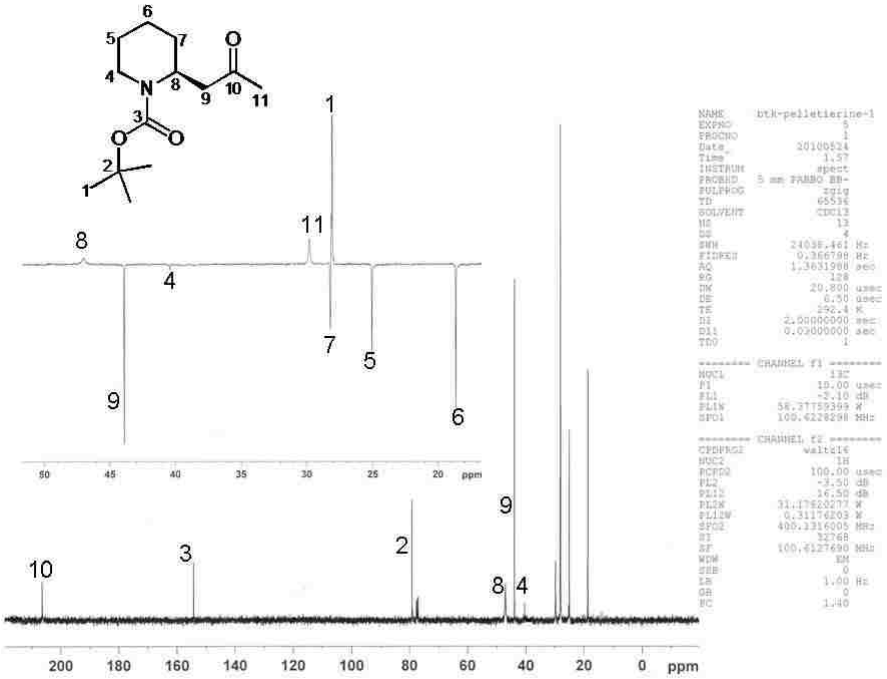
CuCl (220 mg, 2.2 mmol, 1 equiv) and $PdCl_2$ (40 mg, 0.22 mmol, 10 mol%) were dissolved in 3 mL of DMF/H_2O (10:1) and the resulting suspension was stirred for 1 h at room temperature under an O_2.atmosphere. A solution of S-34 (96:4 er; prepared by CDR using ligand 9) (500 mg, 2.2 mmol, 1.0 equiv) 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-34 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.[42] $[a]_D^{22}$ −11 (c = 0.2, $CHCl_3$), lit.[42] $[a]_D^{25}$ −12.7 (c = 0.22, $CHCl_3$).

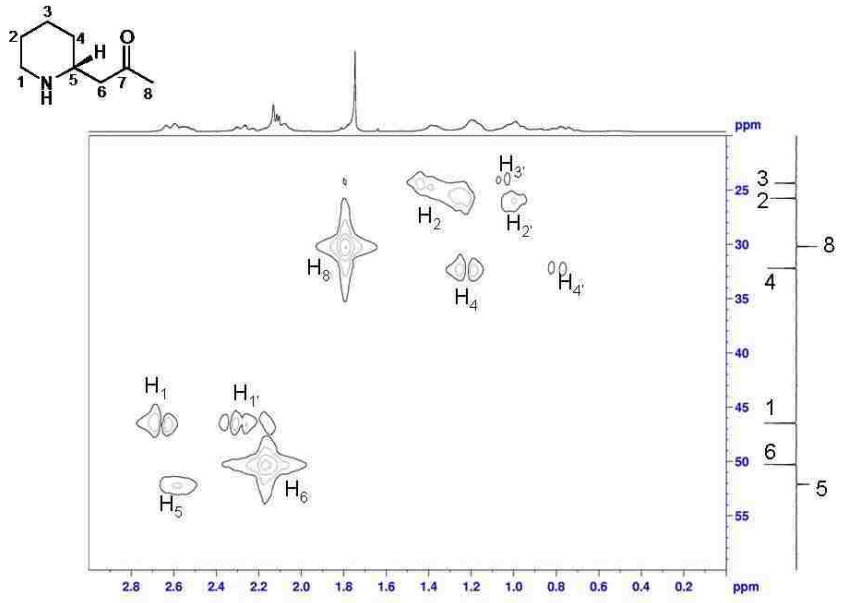
(S)-(+)-pelletierine



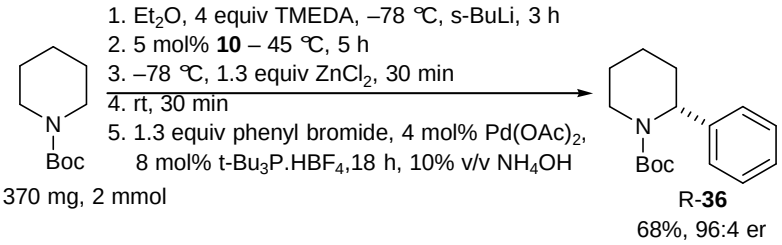
(S)-(+)-pelletierine

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 ^oC. 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. $[a]_D^{22}$ +16.8 (c = 0.5, EtOH), lit.[42] $[a]_D^{25}$ +19.4 (c = 0.47, EtOH).

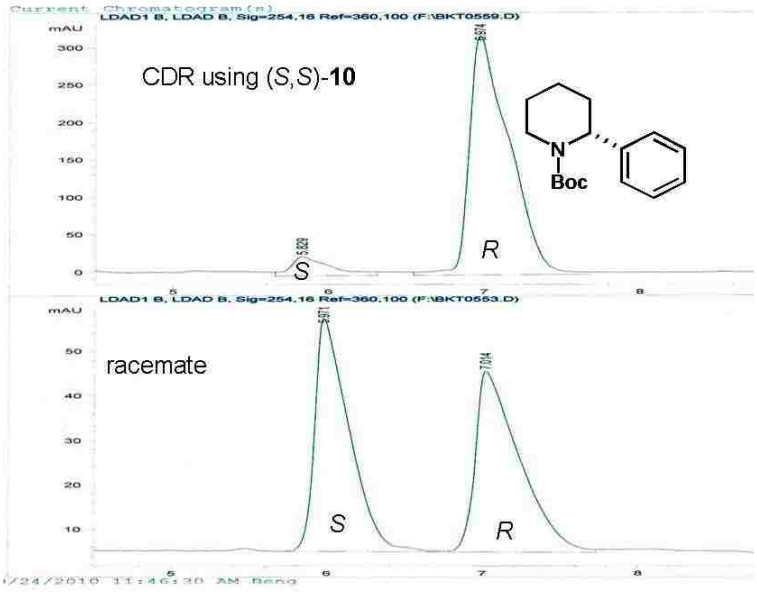




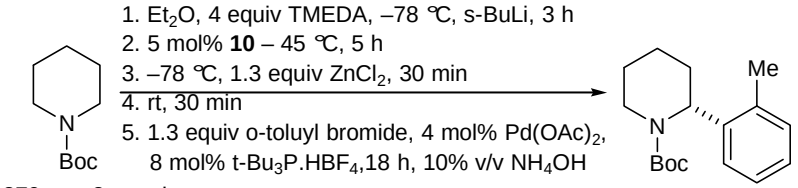
13. Electrophilic quench with phenyl bromide: Synthesis of R-36



Using General Procedure C, N-Boc-piperidine (370 mg, 2.0 mmol), TMEDA (1.2 mL, 8.0 mmol, 4.0 equiv), Et_2O (10 mL), s-BuLi (2.4 mL, 1.0 M, 2.4 mmol, 1.2 equiv), the alcohol precursor of 10 (21.4 mg, 0.1 mmol, 5 mol%, in 0.40 mL Et_2O pretreated with freshly titrated s-BuLi), $ZnCl_2$ (355 mg, 2.6 mmol, 1.3 equiv) in THF (2 mL), phenyl bromide (0.30 mL, 2.6 mmol, 1.3 equiv), $Pd(OAc)_2$ (20 mg, 0.08 mmol, 4 mol%) and t-$Bu_3P{\cdot}HBF_4$ (46 mg, 0.16 mmol, 8 mol%) gave the crude product as an oil. Purification by silica gel column chromatography eluting with hexane-EtOAc (94:6) afforded 355 mg of the pure product as an oil in 68% yield and 96:4 er; spectroscopic data as reported.[67, 68] $[a]_D^{22}$ +76.2 (c = 1, $CHCl_3$), lit[68]. for R-36; $[a]_D^{25}$ +83.7 (c = 0.98, $CHCl_3$).



14. Electrophilic quench with o-toluyl bromide: Synthesis of R-37



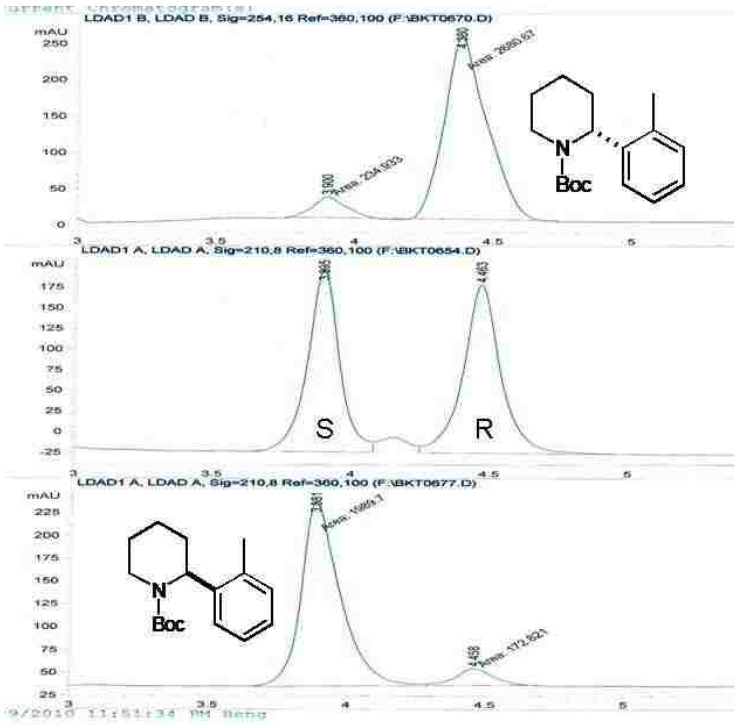
370 mg, 2 mmol

R-**37**
63%, 92:8 er

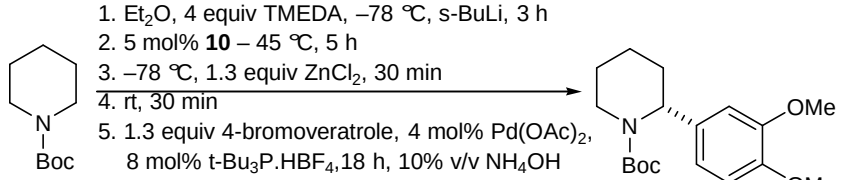
Using General Procedure C, N-Boc-piperidine (370 mg, 2.0 mmol), TMEDA (1.2 mL, 8.0 mmol, 4.0 equiv), Et_2O (10 mL), s-BuLi (2.4 mL, 1.0 M, 2.4 mmol, 1.2 equiv), the alcohol precursor of 10 (21.4 mg, 0.1 mmol, 5 mol%, in 0.40 mL Et_2O pretreated with freshly titrated s-BuLi), $ZnCl_2$ (355 mg, 2.6 mmol,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

Outlet Pressure = 150 psi, Oven Temperature = 35 °C. The minor enantiomer elutes after ~3.9 min and the major enantiomer elutes after ~4.5 min. ^{1}H NMR (300 MHz, $CDCl_3$) 0 7.23-7.07 (m, 4H), 5.15 (br, s, 1H), 4.08-3.95 (m, 1H), 3.3 (m, 1H), 2.23 (s, 3H), 2.22 (m, 1H), 1.94-1.51(m, 5H), 1.42 (s, 9H); ^{13}C NMR (75.5 MHz, $CDCl_3$) 0 155.0, 142.5, 134.5, 130.5, 126.6, 125.4, 125.1, 79.4, 52.5, 41.2, 28.8, 28.4, 25.8, 19.3, 18.2.

CSP-SFC



15. Electrophilic quench with 4-bromoveratrole: Synthesis of R-38

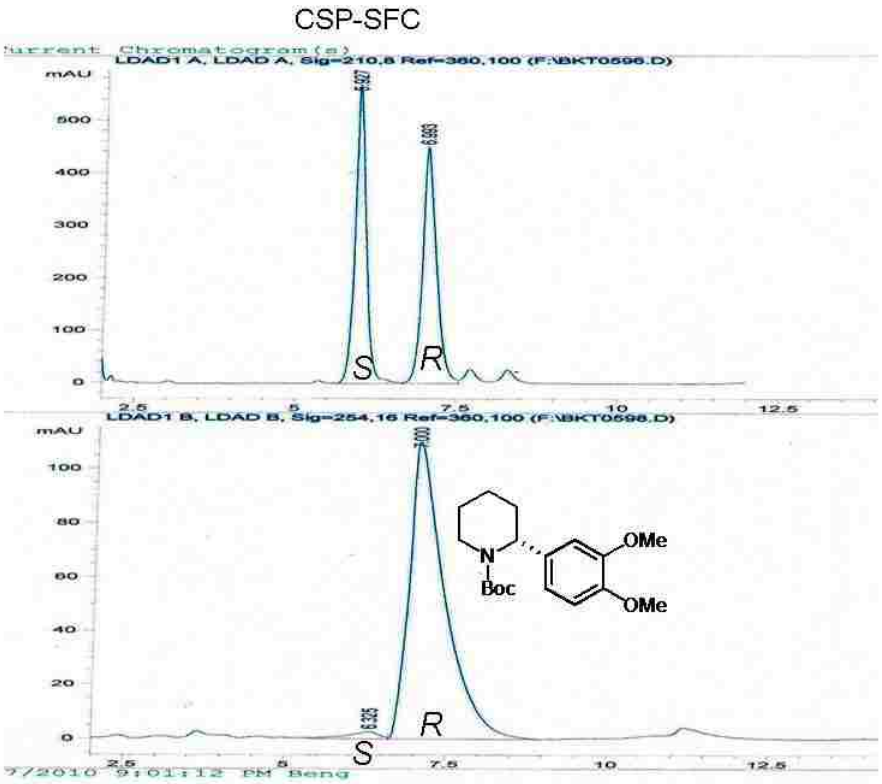


370 mg, 2 mmol

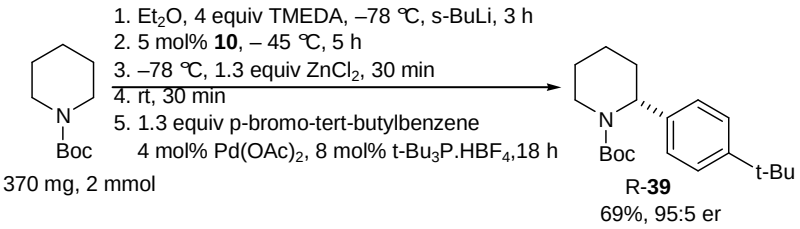
R-**38**
73%, 97:3 er

Using General Procedure C, N-Boc-piperidine (370 mg, 2.0 mmol), TMEDA (1.2 mL, 8.0 mmol, 4.0 equiv), Et_2O (10 mL), s-BuLi (2.4 mL, 1.0 M, 2.4 mmol, 1.2 equiv), the alcohol

precursor of 10 (21.4 mg, 0.1 mmol, 5 mol%, in 0.40 mL Et_2O pretreated with freshly titrated s-BuLi), $ZnCl_2$ (355 mg, 2.6 mmol, 1.3 equiv) in THF (2 mL), 4-bromoveratrole (0.38 mL, 2.6 mmol, 1.3 equiv), $Pd(OAc)_2$ (20 mg, 0.08 mmol, 4 mol%) and t-$Bu_3P{\cdot}HBF_4$ (46 mg, 0.16 mmol, 8 mol%) gave the crude product as an oil. Purification by silica gel column chromatography eluting with hexane-EtOAc (85:15) afforded 482 mg of the pure product as an oil in 75% yield and 97:3 er; spectroscopic data as reported.[30] $[a]_D^{22}$ +106.2 (c = 1.0, $CHCl_3$), lit[30]. for S-38 of 82:18 er ($[a]_D^{20}$ –49.6 (c = 0.275, $CHCl_3$). The er was determined by CSP-SFC as follows: Column: Pirkle-Whelk-O-1, Flow Rate: 3.0 mL/min, Polarity Modifier %: 3.0% EtOH, Outlet Pressure = 150 psi, Oven Temperature = 35 ^oC. The minor enantiomer elutes after ~6.2 min and the major enantiomer elutes after ~7.2 min. ^1H NMR (300 MHz, $CDCl_3$) 0 6.85-6.70 (m, 3H), 5.35 (br, s, 1H), 4.08-3.99 (m, 1H), 3.88 (s, 3H), 3.86 (s, 3H), 2.65 (m, 1H), 2.33-2.22 (m, 1H), 1.94-1.81 (m, 1H), 1.66-1.52 (m, 4H), 1.48 (s, 9H); ^{13}C NMR (75.5 MHz, $CDCl_3$) 0 155.6, 149.1, 147.5, 132.8, 118.6, 111.0, 109.9, 79.5, 55.83, 55.77, 52.7, 40.0, 28.4, 27.9, 25.5, 19.4.



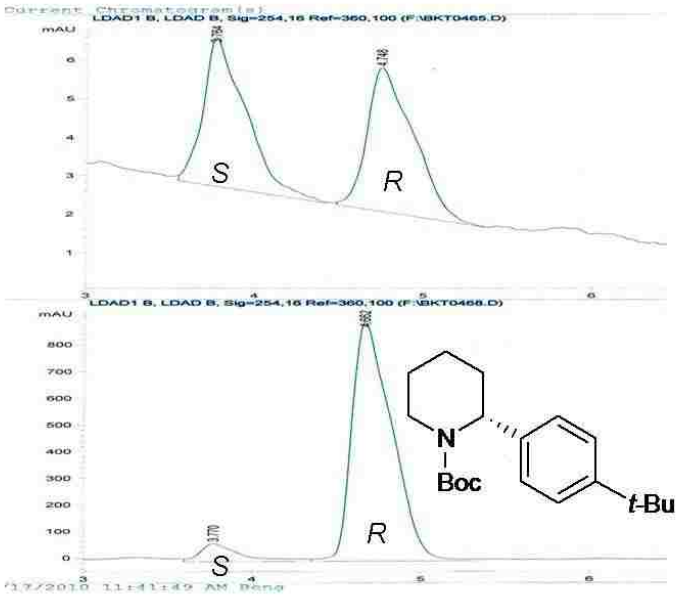
16. Electrophilic quench with p-bromo-tert-butylbenzene: Synthesis of R-39

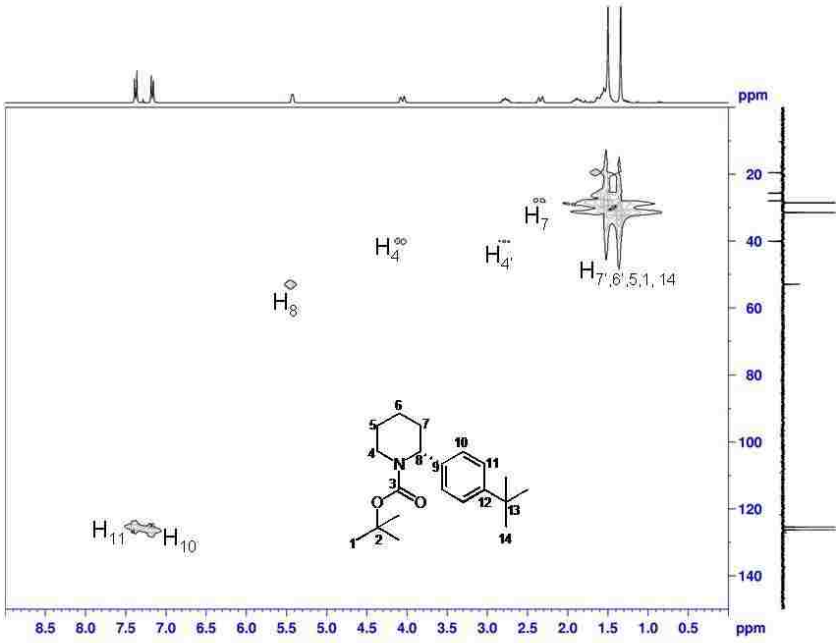


Using General Procedure C, N-Boc-piperidine (370 mg, 2.0 mmol), TMEDA (1.2 mL, 8.0 mmol, 4.0 equiv), Et_2O (10 mL), s-BuLi (2.4 mL, 1.0 M, 2.4 mmol, 1.2 equiv), the alcohol precursor of 10 (21.4 mg, 0.1 mmol, 5 mol%, in 0.40 mL Et_2O pretreated with freshly titrated s-BuLi), $ZnCl_2$ (355 mg, 2.6 mmol, 1.3 equiv) in THF (2 mL), p-bromo-tert-butylbenzene (0.43 mL, 2.6 mmol, 1.3 equiv), $Pd(OAc)_2$ (20 mg, 0.08 mmol, 4 mol%) and t-$Bu_3P{\cdot}HBF_4$ (46 mg, 0.16 mmol, 8 mol%) gave the crude product as an oil. Purification by silica gel column chromatography eluting with hexane-EtOAc (99:1) afforded 437 mg of the pure product as an oil

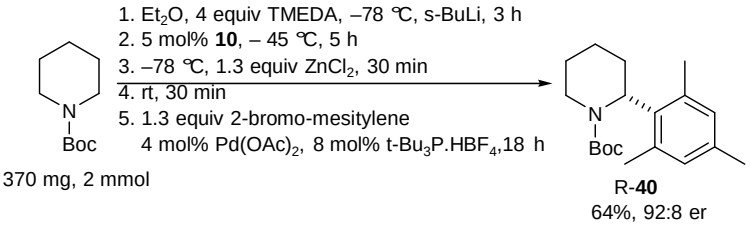
in 69% yield and 95:5 er; $[a]_D^{22}$ +104.4 (c = 1, $CHCl_3$). The er was determined by CSP-SFC as follows: Column: Daicel Chiralcel OD-H, Flow Rate = 2.0 mL/min, Polarity Modifier = 3.0% EtOH. The minor enantiomer elutes after ~3.8 min and the major enantiomer elutes after ~4.7 min. ^{1}H NMR (300 MHz, $CDCl_3$) 0 7.4-7.3 (d, 2H), .7.2-7.1 (d, 2H), 5.4 (br, s, 1H), 4.1-3.98 (m, 1H), 2.85-2.7 (m, 1H), 2.34-2.25 (m, 1H), 1.92-1.57 (m, 5H) 1.48 (s, 9H), 1.25 (s, 9H); ^{13}C NMR (75.5 MHz, $CDCl_3$) 0 155.6, 149.1, 137.1, 126.2, 125.4, 79.4, 52.9, 40.0, 34.3, 31.4, 28.5, 27.9, 25.6, 19.5.

CSP-SFC





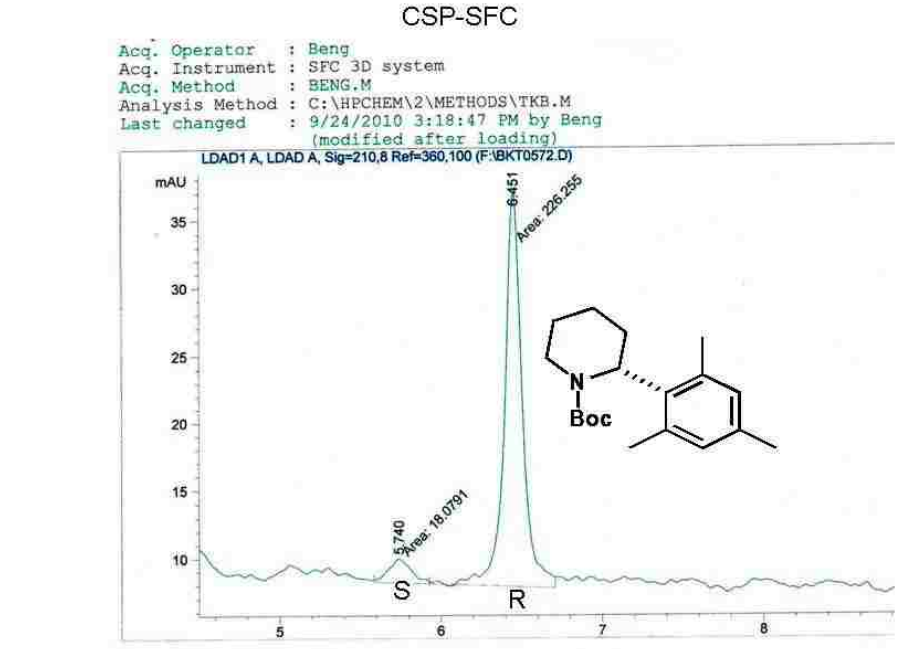
17. Electrophilic quench with 2-bromomesitylene: Synthesis of R-40

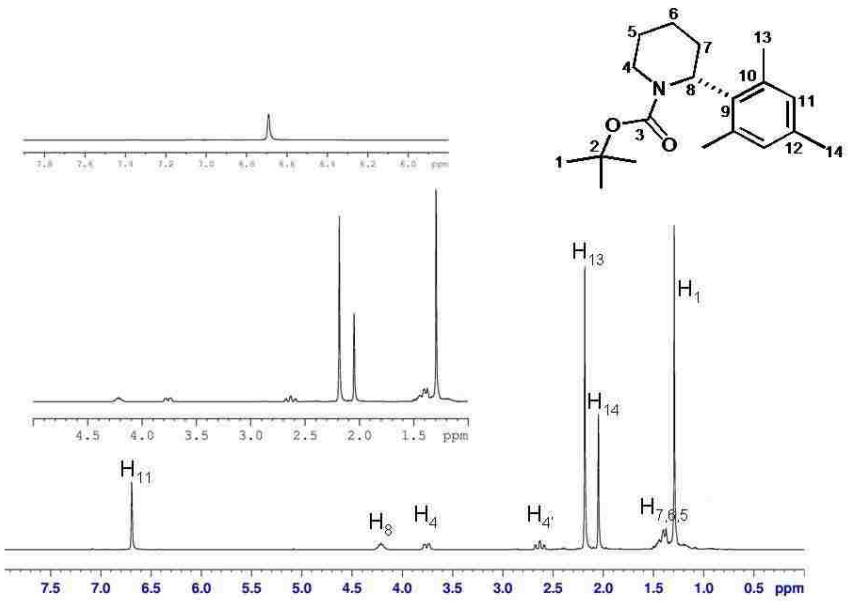


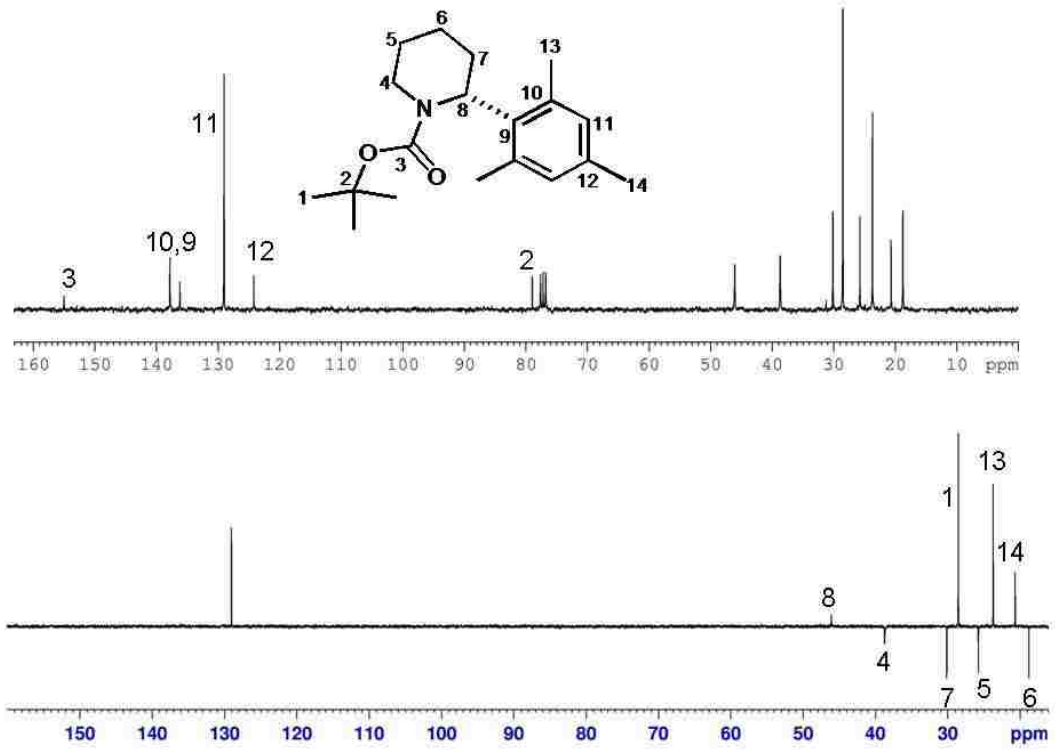
R-**40**
64%, 92:8 er

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

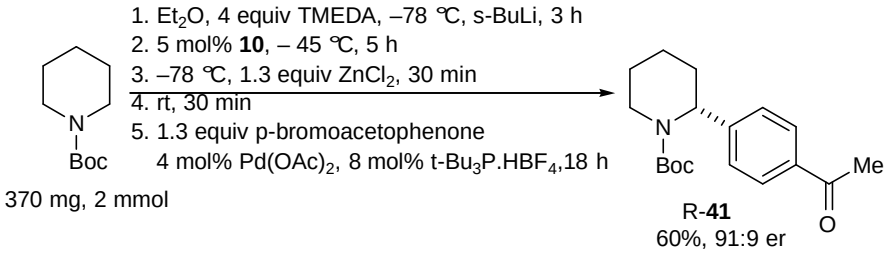
Pressure = 150 psi, Oven Temperature = 35 ^{o}C. The minor enantiomer elutes after ~5.7 min and the major enantiomer elutes after ~6.5 min.





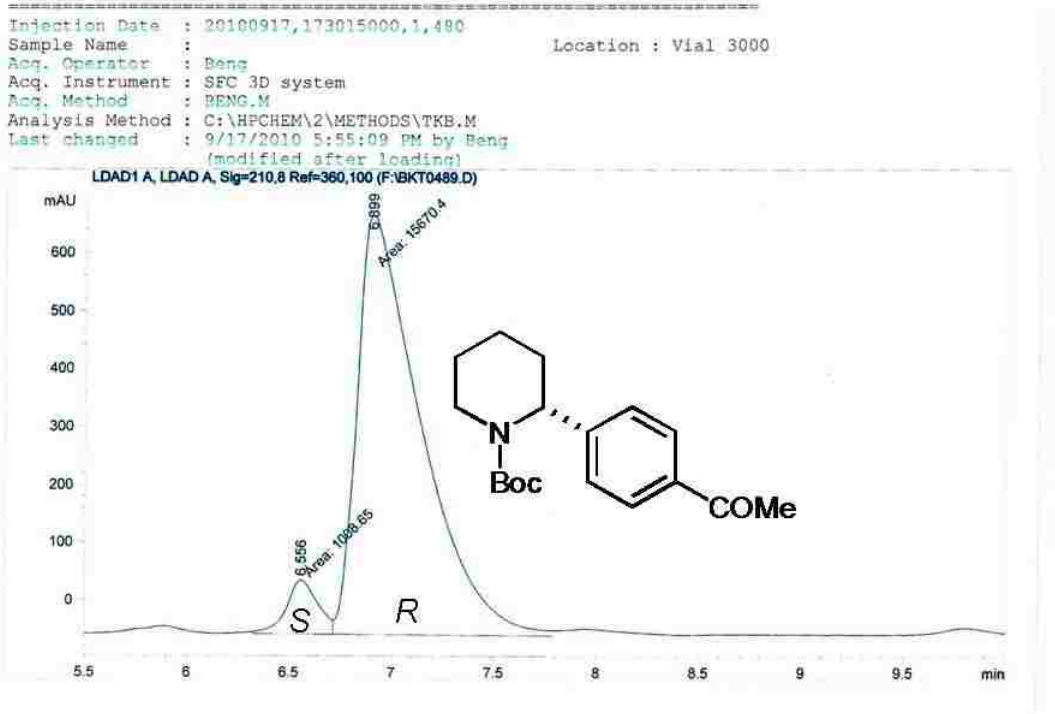


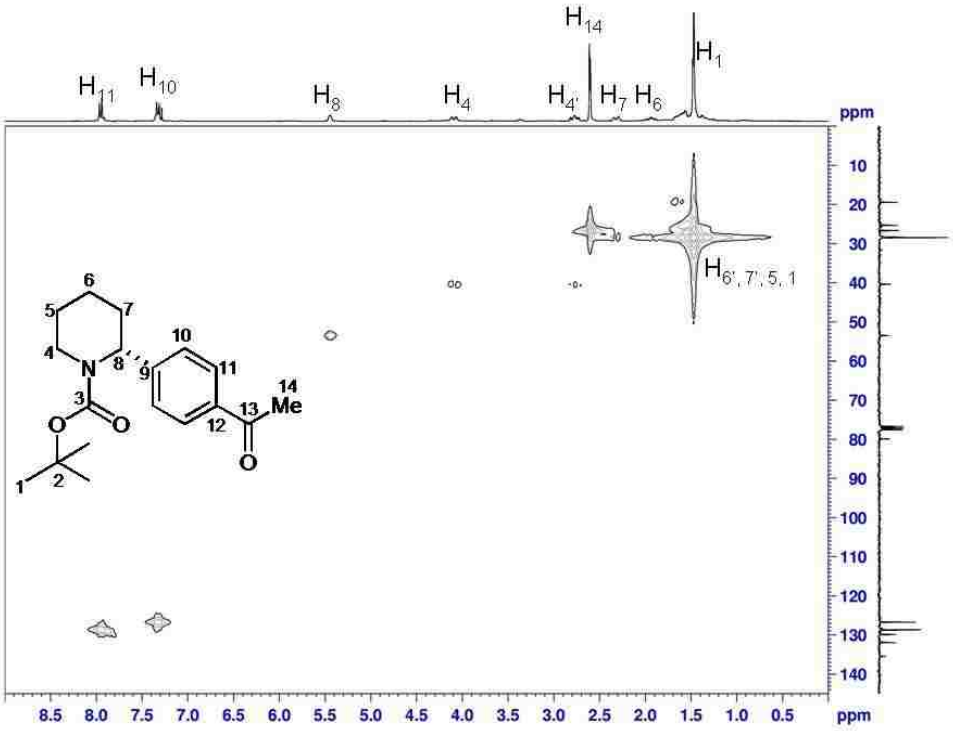
18. Electrophilic quench with p-bromoacetophenone: Synthesis of R-41



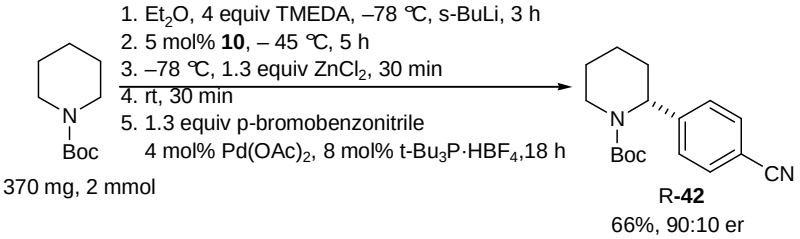
Using General Procedure C, N-Boc-piperidine (370 mg, 2.0 mmol), TMEDA (1.2 mL, 8.0 mmol, 4.0 equiv), Et_2O (10 mL), s-BuLi (2.4 mL, 1.0 M, 2.4 mmol, 1.2 equiv), the alcohol precursor of 10 (21.4 mg, 0.1 mmol, 5 mol%, in 0.40 mL Et_2O pretreated with freshly titrated s-BuLi), $ZnCl_2$ (355 mg, 2.6 mmol, 1.3 equiv) in THF (2 mL), 4-bromoacetophenone (517 mg, 2.6 mmol, 1.3 equiv), $Pd(OAc)_2$ (20 mg, 0.08 mmol, 4 mol%) and t-$Bu_3P{\cdot}HBF_4$ (46 mg, 0.16 mmol, 8 mol%) gave the crude product as an oil. Purification by silica gel column chromatography eluting with hexane-EtOAc (80:20) afforded 364 mg of the pure product as an oil in 60% yield

and 91:9 er; $[a]_D^{22}$ +126.5 (c = 1, $CHCl_3$). The er was determined by CSP-SFC as follows: Column: Pirkle-Whelk-O-1, Flow Rate: 3.0 mL/min, Polarity Modifier %: 3.0% EtOH, Outlet Pressure = 150 psi, Oven Temperature = 35 ^oC. The minor enantiomer elutes after ~6.5 min and the major enantiomer elutes after ~7.0 min. ^1H NMR (300 MHz, $CDCl_3$) 0 7.95-7.90 (d, 2H), .7.83-7.78 (d, 2H), 5.45 (br, s, 1H), 4.15-4.08 (m, 1H), 2.82-2.71 (m, 1H), 2.60 (s, 3H); 2.32-2.27 (m, 1H), 1.92-1.57 (m, 5H) 1.48 (s, 9H), ^{13}C NMR (75.5 MHz, $CDCl_3$) 0 197.5, 155.6, 146.5, 135.4, 128.7, 126.7, 79.9, 53.4, 40.3, 28.4, 28.3, 26.6, 25.2, 19.4.



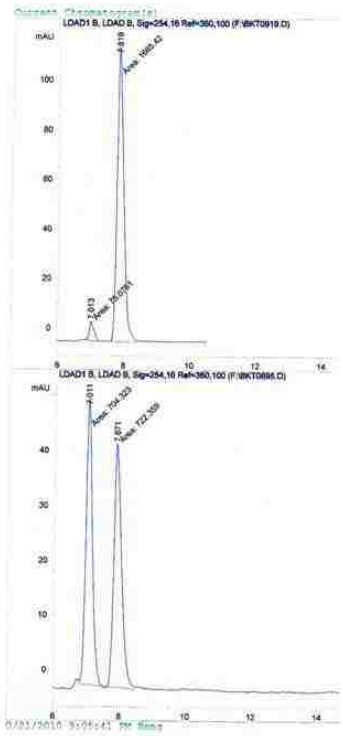


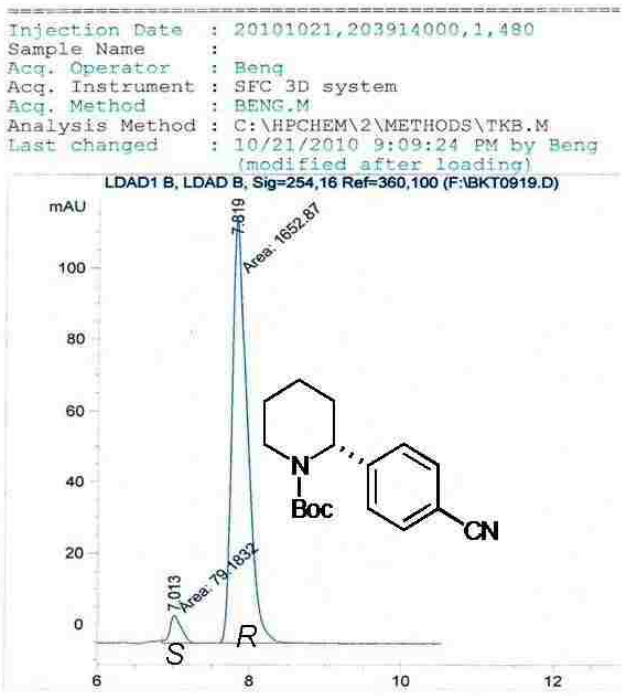
19. Electrophilic quench with p-bromobenzonitrile: Synthesis of R-42

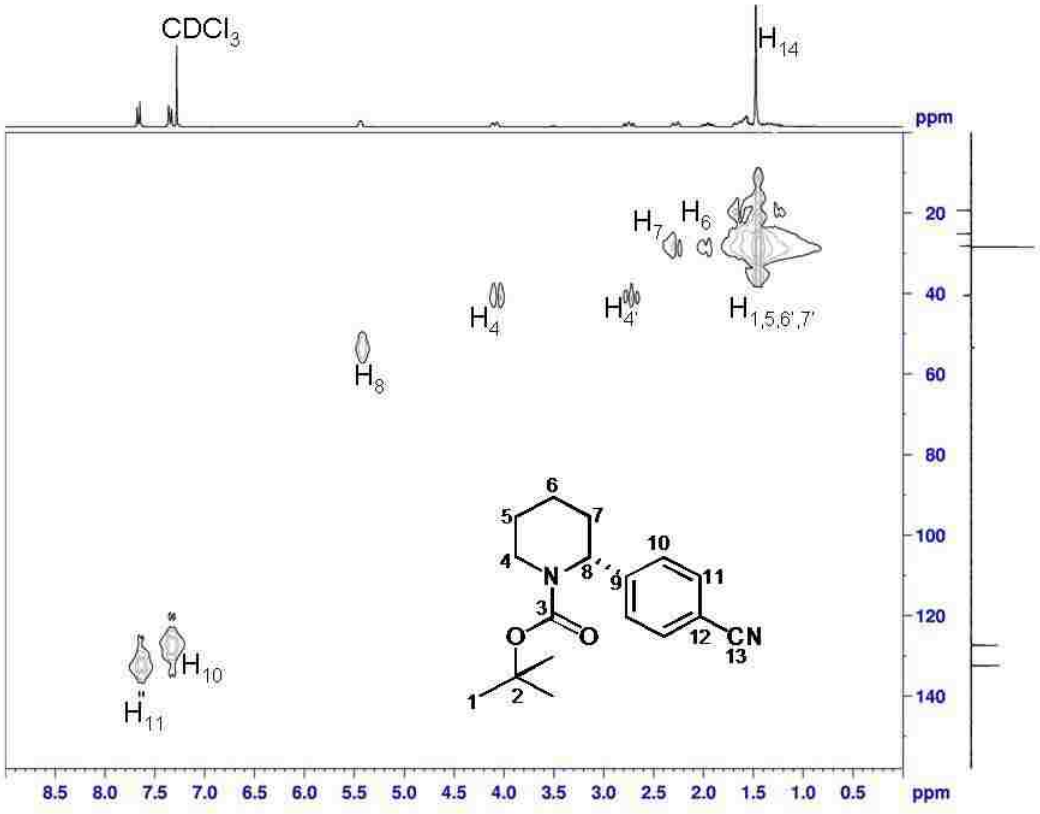


Using General Procedure C, N-Boc-piperidine (370 mg, 2.0 mmol), TMEDA (1.2 mL, 8.0 mmol, 4.0 equiv), Et_2O (10 mL), s-BuLi (2.4 mL, 1.0 M, 2.4 mmol, 1.2 equiv), the alcohol precursor of 10 (21.4 mg, 0.1 mmol, 5 mol%, in 0.40 mL Et_2O pretreated with freshly titrated s-BuLi), $ZnCl_2$ (355 mg, 2.6 mmol, 1.3 equiv) in THF (2 mL), 4-bromobenzonitrile (471 mg, 2.6 mmol, 1.3 equiv), $Pd(OAc)_2$ (20 mg, 0.08 mmol, 4 mol%) and t-$Bu_3P{\cdot}HBF_4$ (46 mg, 0.16 mmol, 8 mol%) gave the crude product as an oil. Purification by silica gel column chromatography eluting with hexane-EtOAc (90:10) afforded 378 mg of the pure product as an oil in 66% yield and 90:10 er; , $[a]_D^{22}$ +147.8 (c = 1, $CHCl_3$). The er was determined by CSP-SFC as follows:

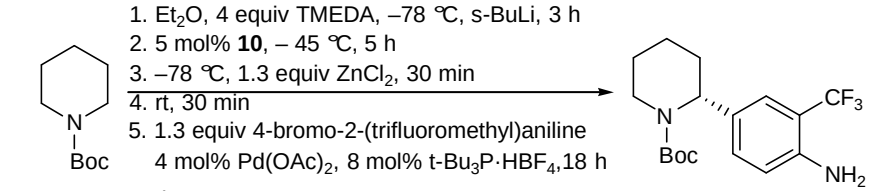
Column: Pirkle-Whelk-O-1, Flow Rate: 2.0 mL/min, Polarity Modifier %: 2.0% EtOH, Outlet Pressure = 150 psi, Oven Temperature = 35 ^{o}C. The minor enantiomer elutes after ~7.0 min and the major enantiomer elutes after ~7.8 min. ^{1}H NMR (300 MHz, $CDCl_3$) 0 7.60 (d, 2H), .7.30 (d, 2H), 5.25 (br, s, 1H), 3.87 (m, 1H), 2.55-2.48 (m, 1H), 2.10-2.05 (m, 1H), 1.92-1.57 (m, 5H) 1.48 (s, 9H), ^{13}C NMR (75.5 MHz, $CDCl_3$) 0 155.4, 146.6, 132.4, 127.3, 118.9 110.3, 80.0, 53.4, 40.4, 28.4, 28.1, 25.1, 19.3.







20. Electrophilic quench with 4-bromo-2-trifluoromethyl aniline: Synthesis of R-43



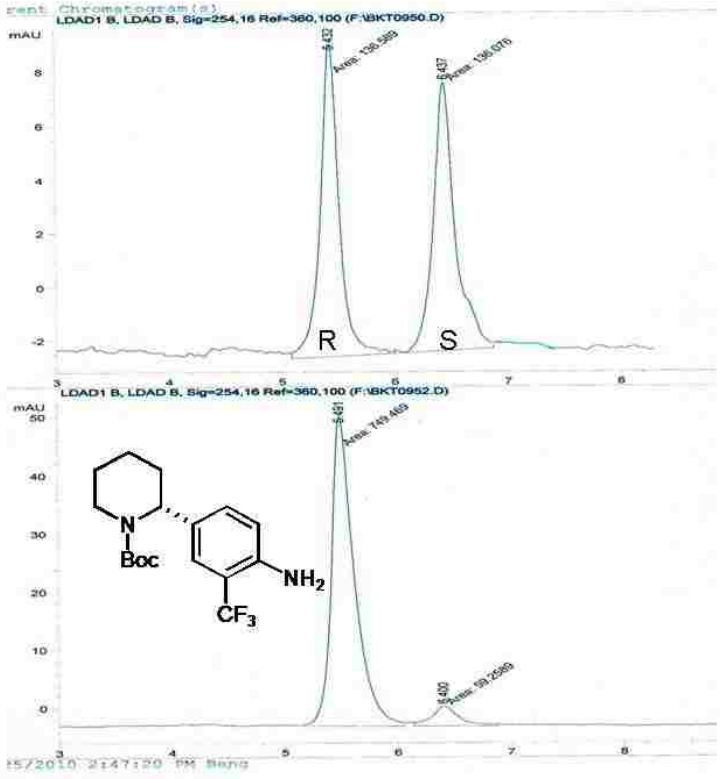
370 mg, 2 mmol

R-**43**

60%, 93:7 er

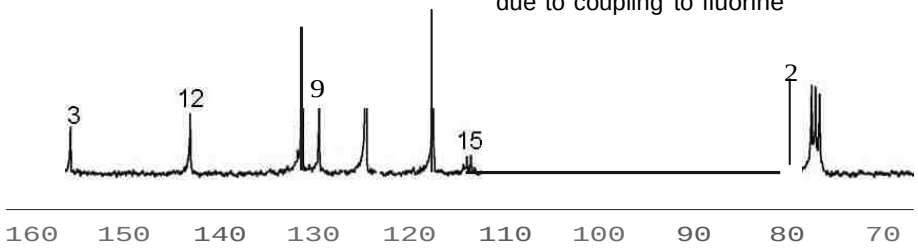
Using General Procedure C, N-Boc-piperidine (370 mg, 2.0 mmol), TMEDA (1.2 mL, 8.0 mmol, 4.0 equiv), Et_2O (10 mL), s-BuLi (2.4 mL, 1.0 M, 2.4 mmol, 1.2 equiv), the alcohol precursor of 10 (21.4 mg, 0.1 mmol, 5 mol%, in 0.40 mL Et_2O pretreated with freshly titrated s-BuLi), $ZnCl_2$ (355 mg, 2.6 mmol, 1.3 equiv) in THF (2 mL), 4-bromo-2-trifluoromethylaniline (621 mg, 2.6 mmol, 1.3 equiv), $Pd(OAc)_2$ (20 mg, 0.08 mmol, 4 mol%) and t-$Bu_3P{\cdot}HBF_4$ (46 mg, 0.16 mmol, 8 mol%) gave the crude product as an oil. Purification by silica gel column

chromatography eluting with hexane-EtOAc (90:10) afforded 413 mg of the pure product as an oil in 60% yield and 93:7 er; , $[a]_D^{22}$ +101.6 (c = 1, $CHCl_3$). The er was determined by CSP-SFC as follows: Column: Pirkle-Whelk-O-1, Flow Rate: 2.5 mL/min, Polarity Modifier %: 2.5% EtOH, Outlet Pressure = 150 psi, Oven Temperature = 35 ^oC. The major enantiomer elutes after ~5.4 min and the minor enantiomer elutes after ~6.4 min. ^1H NMR (300 MHz, $CDCl_3$) 0 7.25 (s, 1H), 7.15 (d, 1H), 6.75 (d, 1H), 5.35 (br, s, 1H), 4.15 (br, s, 2H), 4.08-3.99 (m, 1H), 2.68 (m, 1H), 2.28-2.22 (m, 1H), 1.91-1.78 (m, 1H), 1.66-1.52 (m, 4H), 1.48 (s, 9H); ^{13}C NMR (75.5 MHz, $CDCl_3$) 0 155.6, 143.0, 131.2, 129.4, 124.5, 117.6, 114.2, 79.7, 52.3, 39.9, 28.4, 27.7, 25.4, 19.3.



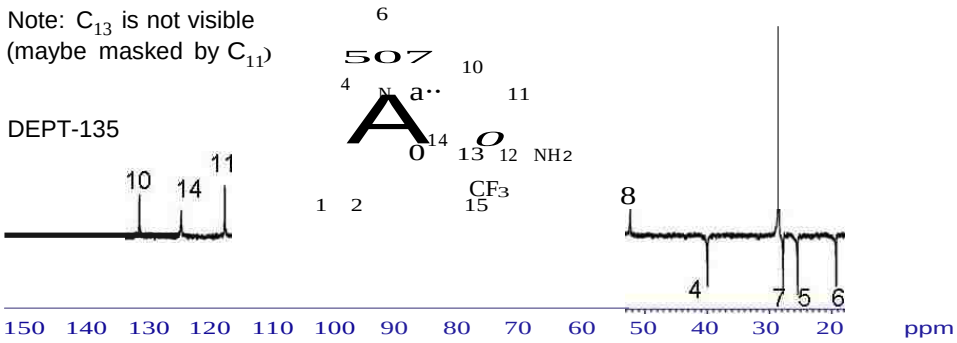
13C NMR (Partial)

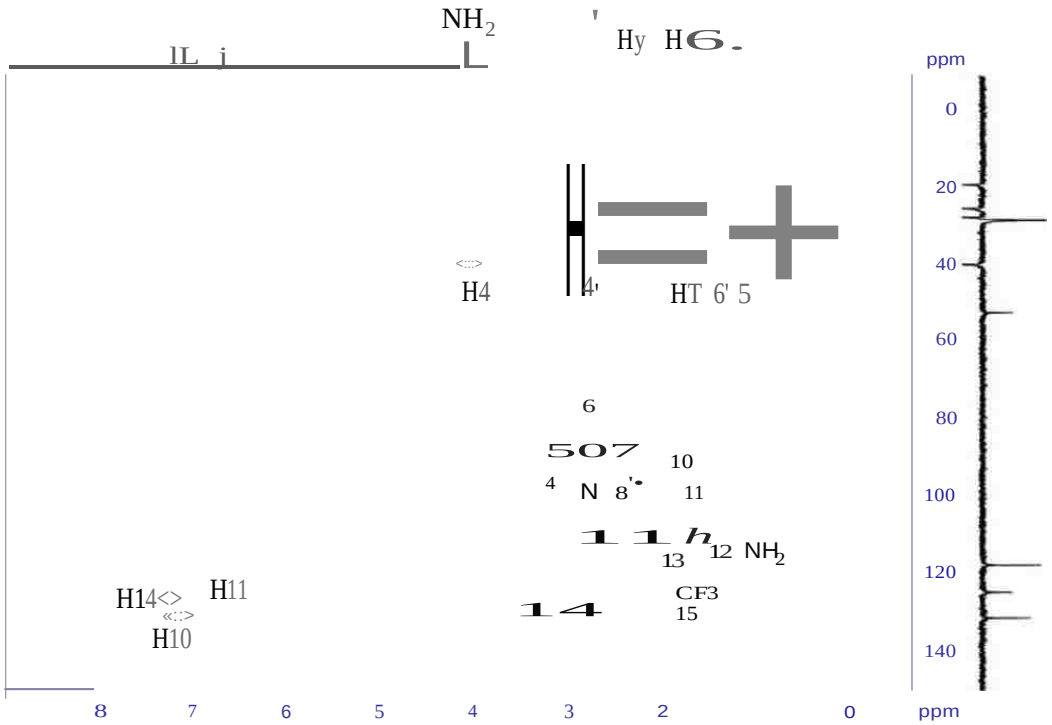
Note: C_{15} is a quartet due to coupling to fluorine



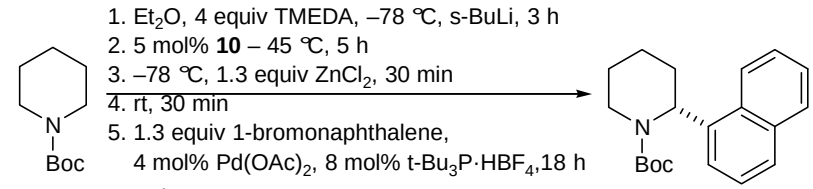
Note: C_{13} is not visible (maybe masked by C_{11})

DEPT-135

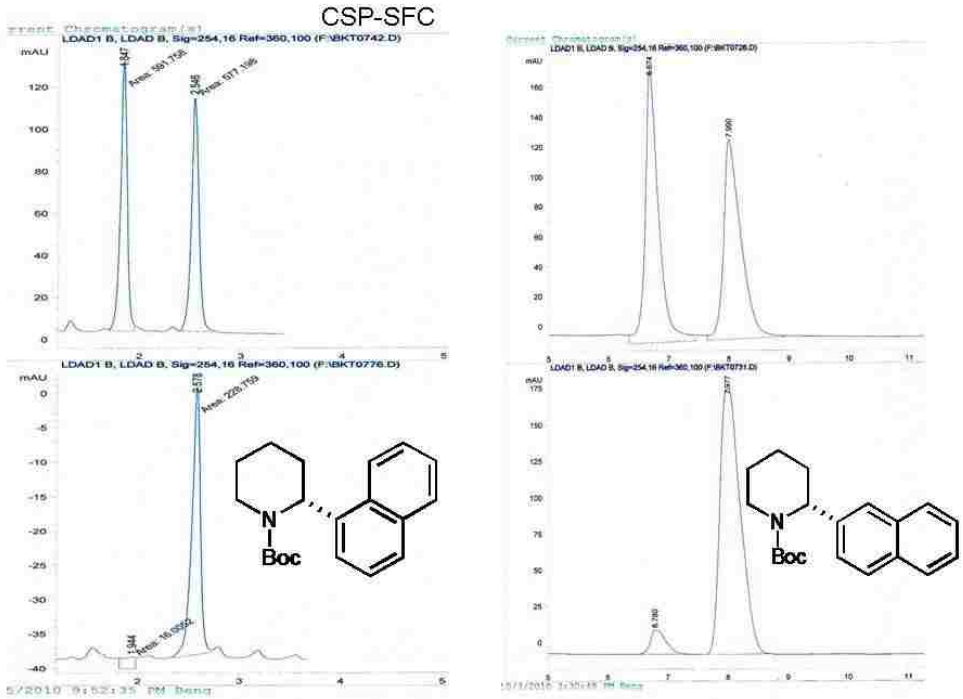




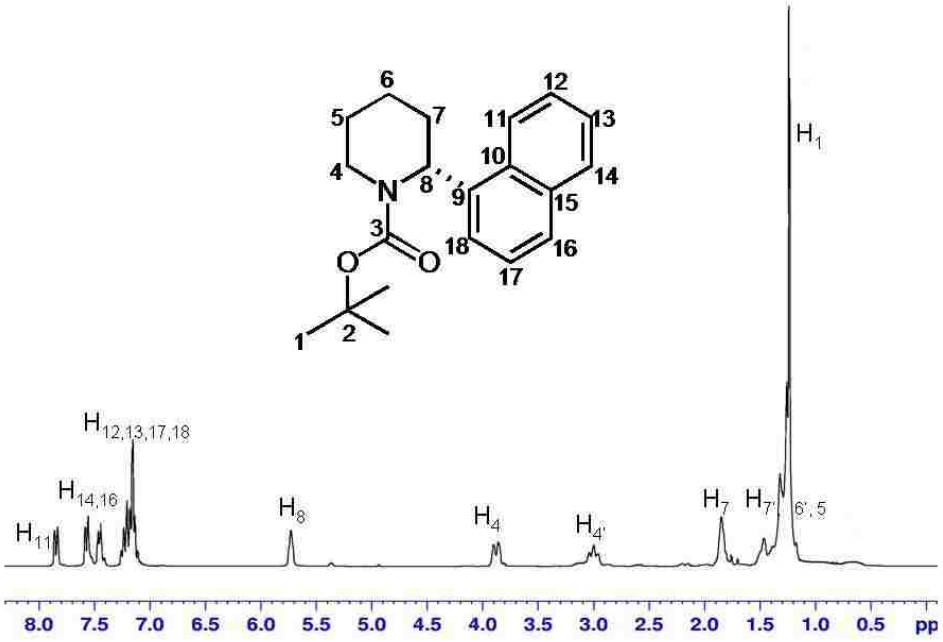
21. Electrophilic quench with 1-Bromonaphthalene: Synthesis of R-44

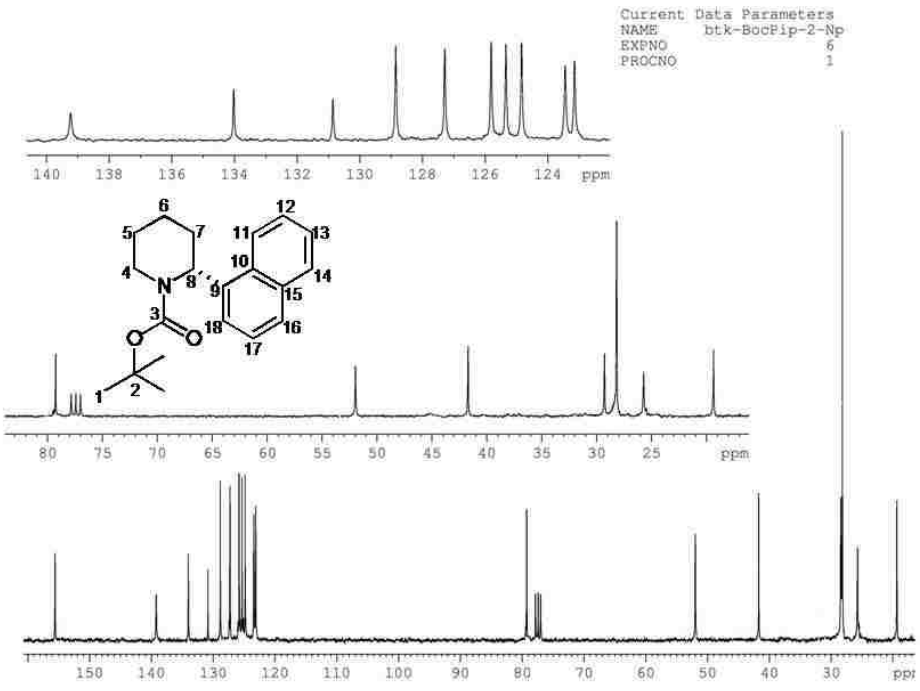


Using General Procedure C, N-Boc-piperidine (370 mg, 2.0 mmol), TMEDA (1.2 mL, 8.0 mmol, 4.0 equiv), Et_2O (10 mL), s-BuLi (2.4 mL, 1.0 M, 2.4 mmol, 1.2 equiv), the alcohol precursor of 10 (21.4 mg, 0.1 mmol, 5 mol%, in 0.40 mL Et_2O pretreated with freshly titrated s-BuLi), $ZnCl_2$ (355 mg, 2.6 mmol,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

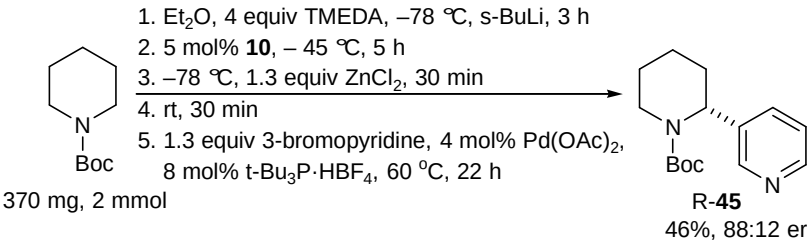


Note: During the synthesis of R-44, the aryl bromide contained small amounts of 2-bromonaphthalene, as such R-44b was prepared in 95:5 er (see SFC trace above). The er was determined by CSP-SFC as follows: Column: Regis Technologies Pirkle-Whelk-O-1, Flow Rate: 2.0 mL/min, Polarity Modifier %: 3.0% EtOH, Outlet Pressure = 150 psi, Oven Temperature = 35 ^{o}C. The minor enantiomer elutes after ~6.7 min and the major enantiomer elutes after ~8.0 min.


H1
H12,13,17,18
H14,16
H11
H8
H4
H4'
H7
H7'
6',5
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 pp

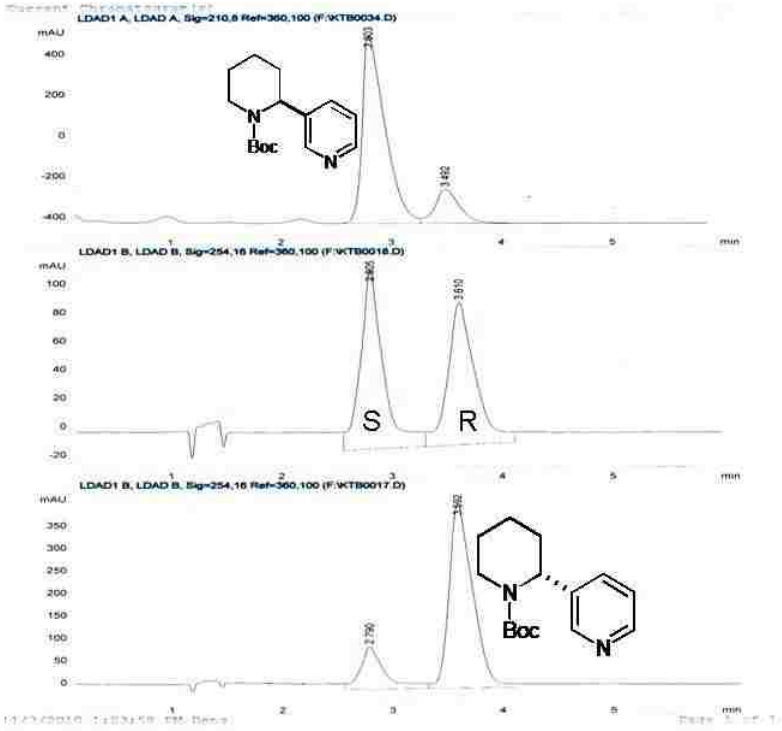

Current Data Parameters
NAME btk-BocPip-2-Np
EXPNO 6
PROCNO 1
140 138 136 134 132 130 128 126 124 ppm
80 75 70 65 60 55 50 45 40 35 30 25 ppm
150 140 130 120 110 100 90 80 70 60 50 40 30 ppm

22. Electrophilic quench with 3-Bromopyridine: Synthesis of R-45

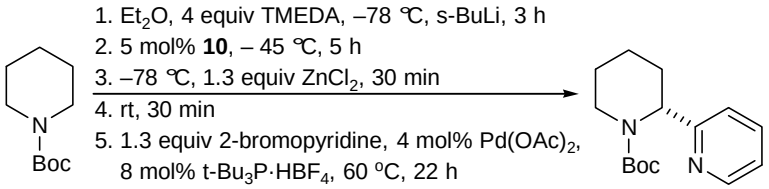


Using General Procedure C, N-Boc-piperidine (370 mg, 2.0 mmol), TMEDA (1.2 mL, 8.0 mmol, 4.0 equiv), Et_2O (10 mL), s-BuLi (2.4 mL, 1.0 M, 2.4 mmol, 1.2 equiv), the alcohol precursor of 10 (21.4 mg, 0.1 mmol, 5 mol%, in 0.40 mL Et_2O pretreated with freshly titrated s-BuLi), $ZnCl_2$ (355 mg, 2.6 mmol, 1.3 equiv) in THF (2 mL), 3-bromopyridine (0.25 mL, 2.6 mmol, 1.3 equiv), $Pd(OAc)_2$ (20 mg, 0.08 mmol, 4 mol%) and t-$Bu_3P{\cdot}HBF_4$ (46 mg, 0.16 mmol, 8 mol%), heating at 60 ^oC for 22 h gave the crude product as an oil. Purification by silica gel column chromatography eluting with hexane-EtOAc (70:30) afforded 241 mg of the pure product as an oil in 46% yield and 88:12 er, $[a]_D^{22}$ +88.6 (c = 1, $CHCl_3$) spectroscopic data as reported.[89] ^1H NMR (300 MHz, $CDCl_3$) o = 8.51 (br, s, 2H), 7.54 (t, 1H), 7.32–7.21 (m, 1H), 5.47 (br, s, 1H), 4.1 (d, 1H), 2.87–2.68 (m, 1H), 2.29 (d, 1H), 1.99–1.87 (m, 1H), 1.71–1.33 (m, 13H); ^{13}C NMR (75.5 MHz, $CDCl_3$) o = 155.7, 148.3, 147.0, 136.4, 134.9, 123.9, 80.1, 47.1, 40.6, 28.8, 28.2, 25.7, 19.7

CSP-SFC



23. Electrophilic quench with 2-Bromopyridine: Synthesis of R-46

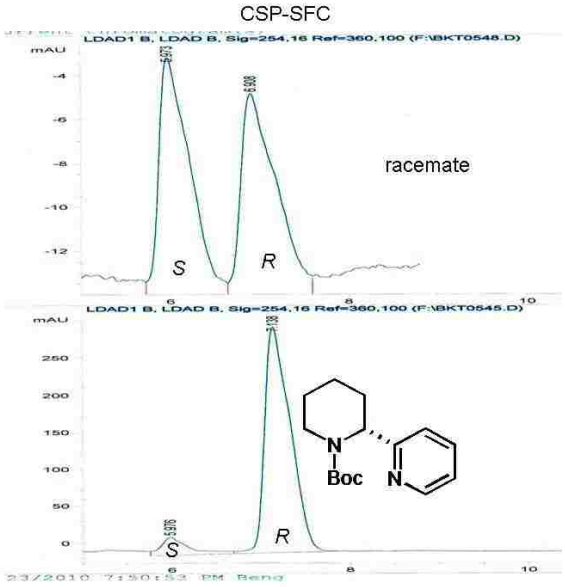


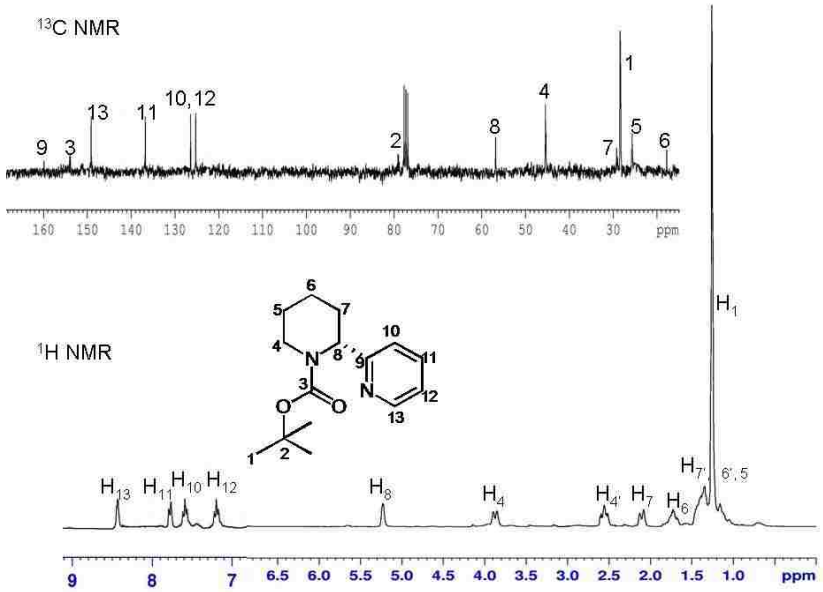
370 mg, 2 mmol

R-**46**
50%, 93:7 er

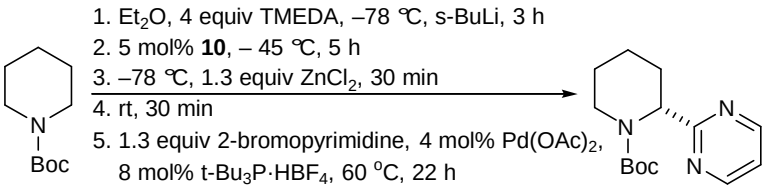
Using General Procedure C, N-Boc-piperidine (370 mg, 2.0 mmol), TMEDA (1.2 mL, 8.0 mmol, 4.0 equiv), Et_2O (10 mL), s-BuLi (2.4 mL, 1.0 M, 2.4 mmol, 1.2 equiv), the alcohol precursor of 10 (21.4 mg, 0.1 mmol, 5 mol%, in 0.40 mL Et_2O pretreated with freshly titrated s-BuLi), $ZnCl_2$ (355 mg, 2.6 mmol, 1.3 equiv) in THF (2 mL), 2-bromopyridine (0.25 mL, 2.6 mmol, 1.3 equiv), $Pd(OAc)_2$ (20 mg, 0.08 mmol, 4 mol%) and t-$Bu_3P{\cdot}HBF_4$ (46 mg, 0.16 mmol, 8 mol%), heating at 60 ^oC for 22 h gave the crude product as an oil. Purification by silica gel

column chromatography eluting with Hexane-EtOAc (70:30) afforded 262 mg of the pure product as an oil in 50% yield and 93:7 er; $[a]_D^{22}$ +93.1 (c = 1, $CHCl_3$) The er was determined by CSP-SFC as follows: Column: Daicel Chiralcel OD-H, Flow Rate = 2.0 mL/min, Polarity Modifier = 2.0% EtOH. The minor enantiomer elutes after ~6 min and the major enantiomer elutes after 7 min.





24. Electrophilic quench with 2-Bromopyrimidine: Synthesis of R-47

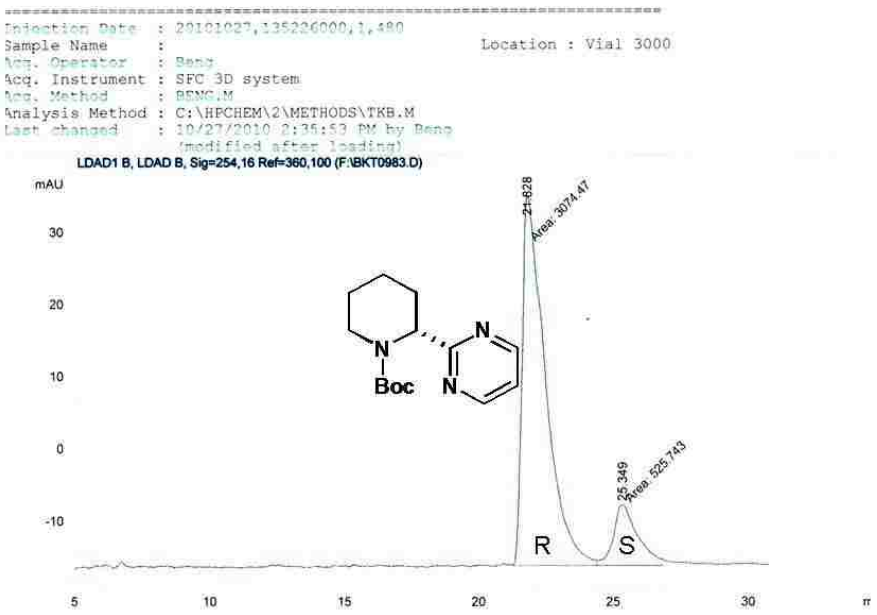


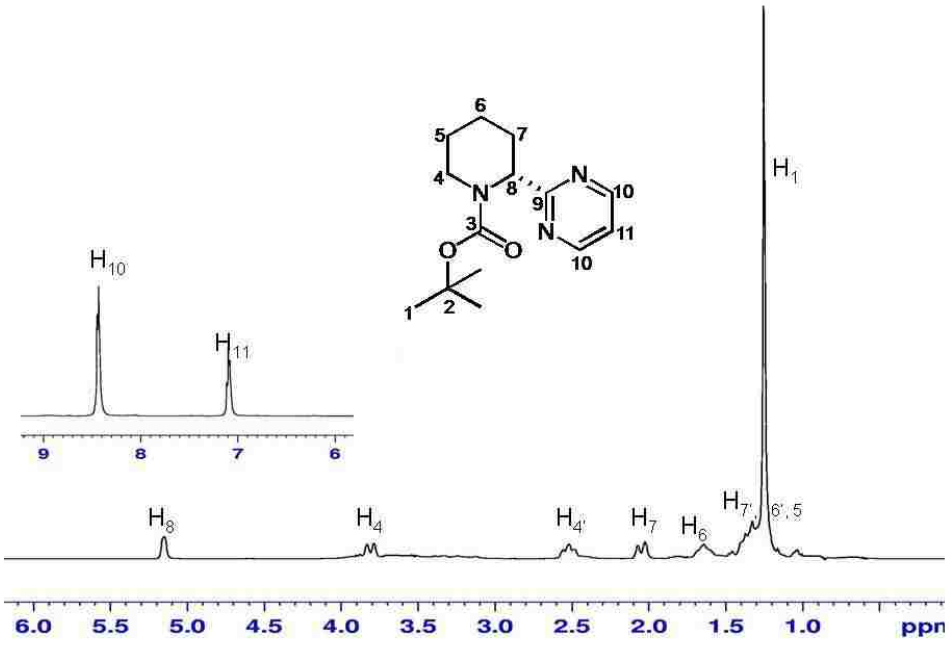
370 mg, 2 mmol

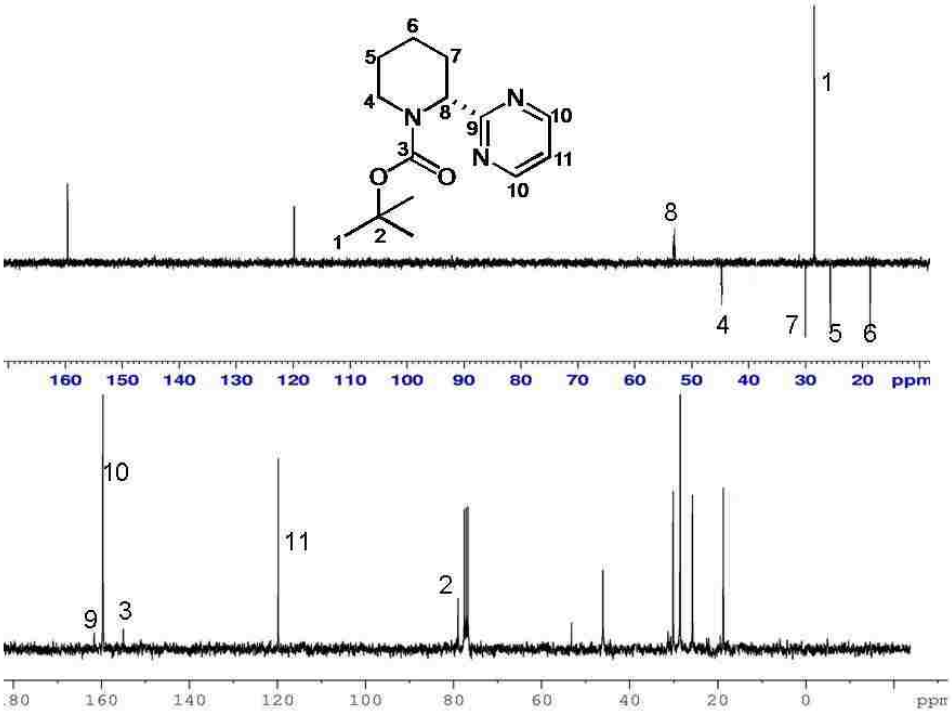
R-**47**
53%, 85:15 er

Using General Procedure C, N-Boc-piperidine (370 mg, 2.0 mmol), TMEDA (1.2 mL, 8.0 mmol, 4.0 equiv), Et_2O (10 mL), s-BuLi (2.4 mL, 1.0 M, 2.4 mmol, 1.2 equiv), the alcohol precursor of 10 (21.4 mg, 0.1 mmol, 5 mol%, in 0.40 mL Et_2O pretreated with freshly titrated s-BuLi), $ZnCl_2$ (355 mg, 2.6 mmol, 1.3 equiv) in THF (2 mL), 2-bromopyrimidine (413 mg, 2.6 mmol, 1.3 equiv), $Pd(OAc)_2$ (20 mg, 0.08 mmol, 4 mol%) and t-$Bu_3P{\cdot}HBF_4$ (46 mg, 0.16 mmol, 8 mol%), heating at 60 ^oC for 22 h gave the crude product as an oil. Purification by silica gel column chromatography eluting with Hexane-EtOAc (60:40) afforded 278 mg of the pure product as an oil in 53% yield and 85:15 er; $[a]_D^{22}$ +75.6 (c = 1, $CHCl_3$). The er was determined by CSP-SFC as follows: Column: Pirkle-Whelk-O-1, Flow Rate: 1.0 mL/min, Polarity Modifier %: 1.0% EtOH, Outlet Pressure = 150 psi, Oven Temperature = 35 ^oC. The major enantiomer elutes after ~21.8 min and the minor enantiomer elutes after ~25.3 min.

CSP-SFC


Injection Date : 20101027,135226000,1,480
Sample Name :
Location : Vial 3000
Acq. Operator : Beng
Acq. Instrument : SFC 3D system
Acq. Method : BENG.M
Analysis Method : C:\HPCHEM\2\METHODS\TKB.M
Last changed : 10/27/2010 2:35:53 PM by Beng
(modified after loading)
LDAD1 B, LDAD B, Sig=254,16 Ref=360,100 (F:\BKT0983.D)
mAU
21.628
Area: 3074.47
25.349
Area: 525.743
Boc
R
S
min


H10
H11
H8
H4
H4'
H7
H6
H7'
6',5
H1
ppm

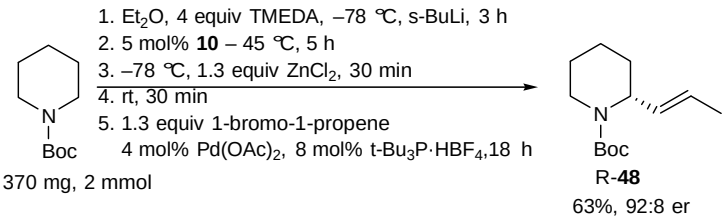


Synthesis of (S)-anabasine

To N-Boc-(S)-(-)-anabasine of 90:10 er (150 mg, 0.58 mol) dissolved in CH_2Cl_2 (3.0 mL), was added CF_3CO_2H (0.25 mL) under argon at room temperature. The mixture was stirred for 10 h at this temperature and concentrated in vacuo to obtain the salt. The salt was basified to pH 10 – 12 with 20% $NaOH_{(aq)}$. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 5 mL). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure to give 92 mg of (S)-(-)-anabasine in 100% yield. $[a]_D^{22}$ −73.4 (c = 1.0, MeOH), lit.[11] $[a]_D^{20}$ −80 (c = 0.91, MeOH); all other spectroscopic data as reported.[11] ^{1}H NMR (300 MHz, $CDCl_3$) o = 8.57 (1H, s), 8.47 (1H, d), 7.77 (1H, d), 7.32–7.15 (1H, m), 3.62 (1H, d), 3.19 (1H, d), 2.79 (1H, t), 2.12–1.42 (6H, m); ^{13}C NMR (75.5 MHz, $CDCl_3$) o = 148.6, 140.6, 134.2, 123.5, 59.8, 47.6, 34.8, 25.7, 25.2.

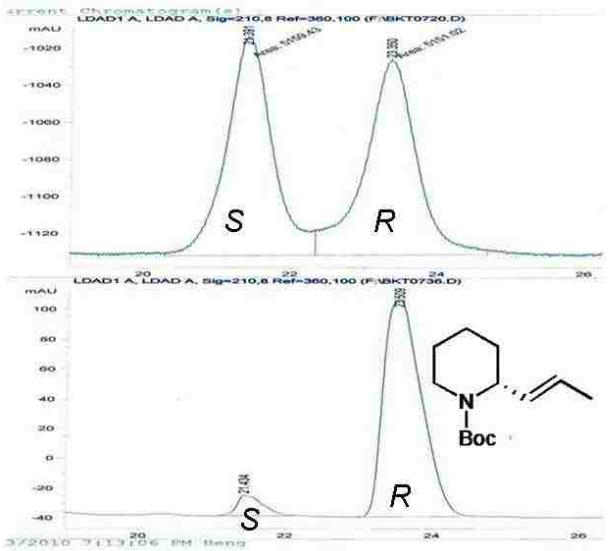
Note: (R)-(+)-anabasine was synthesized in the same was as the S-enantiomer; $[a]_D^{22}$ −70.9 (c = 1.0, MeOH)

25. Electrophilic quench with 1-bromo-1-propene: Synthesis of R-48



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

CSP-SFC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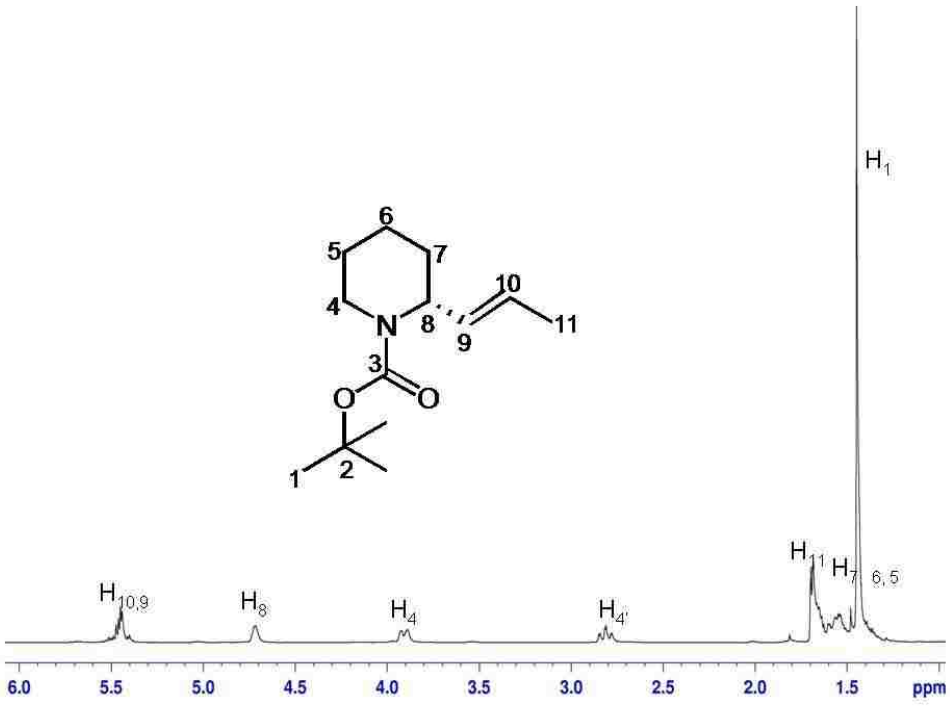
S
R
LDAD1 A, LDAD A, Sig=210,8 Ref=360,100 (F:\BKT0736.D)
mAU
N
Boc
S
R


H1
H11
H7
6, 5
H10,9
H8
H4
H4'
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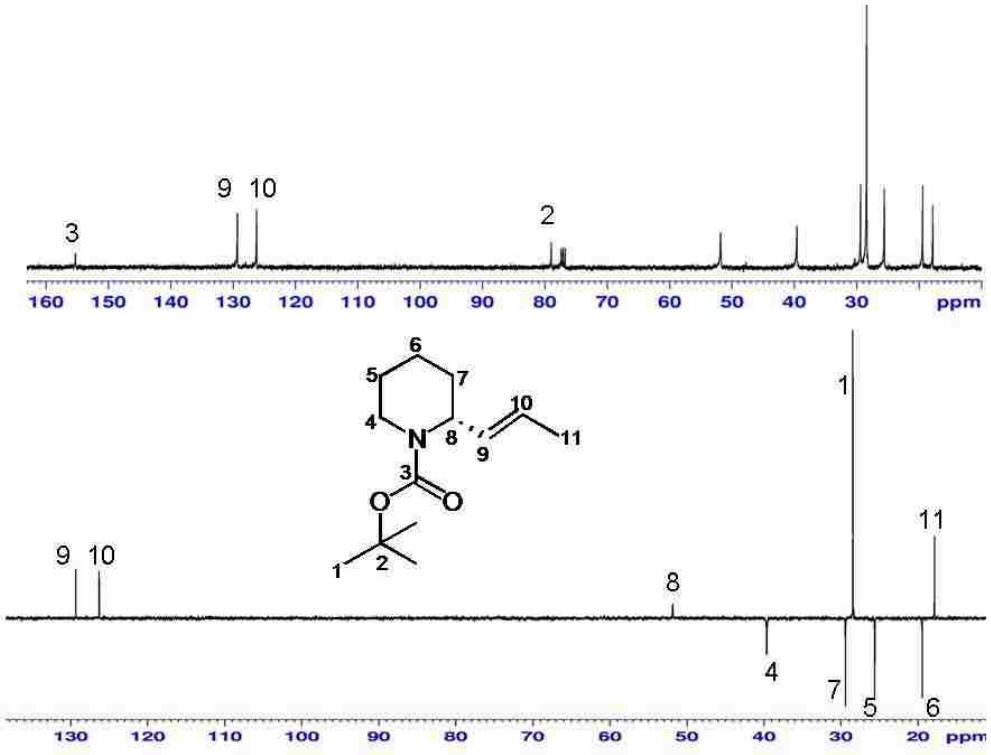
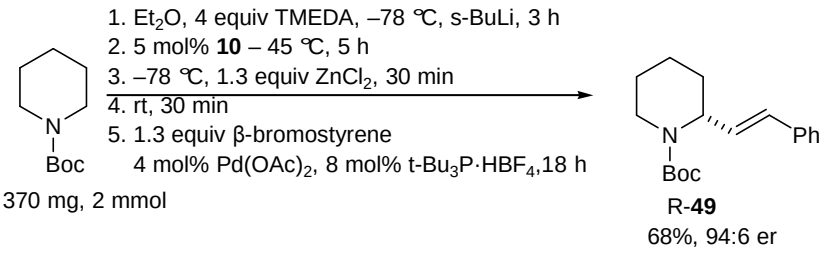
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
ppm



26. Electrophilic quench with ℬ-bromostyrene: Synthesis of R-49

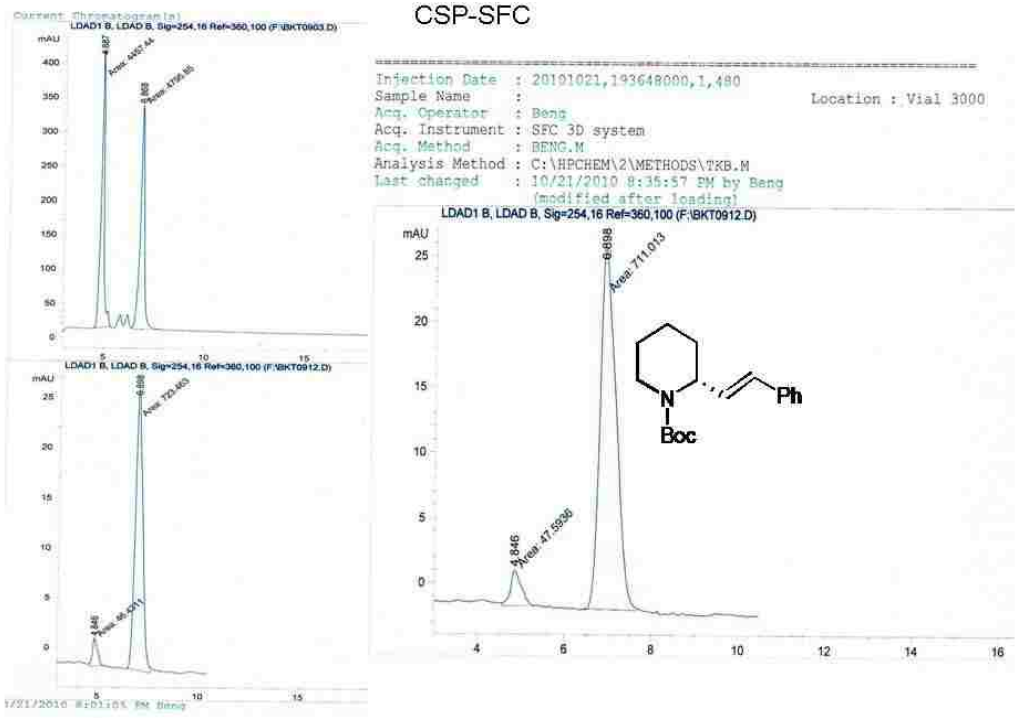


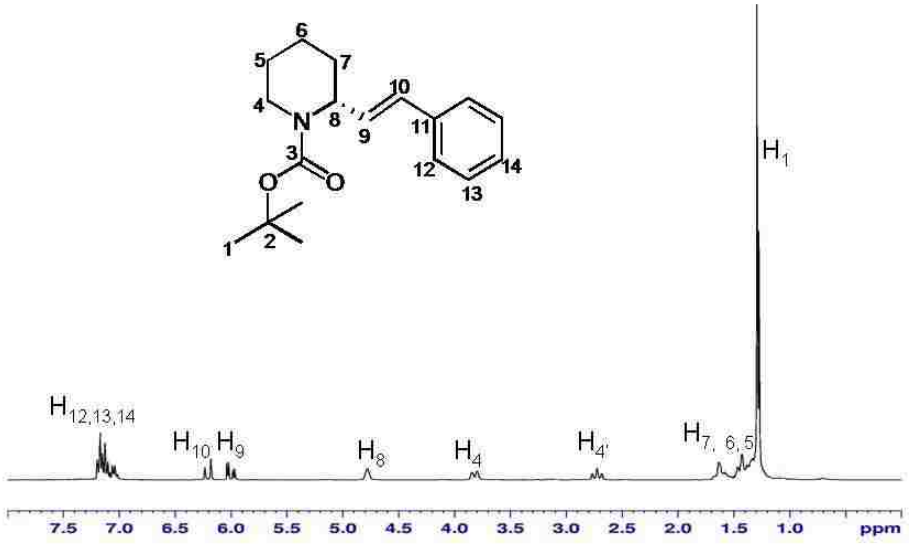
R-**49**

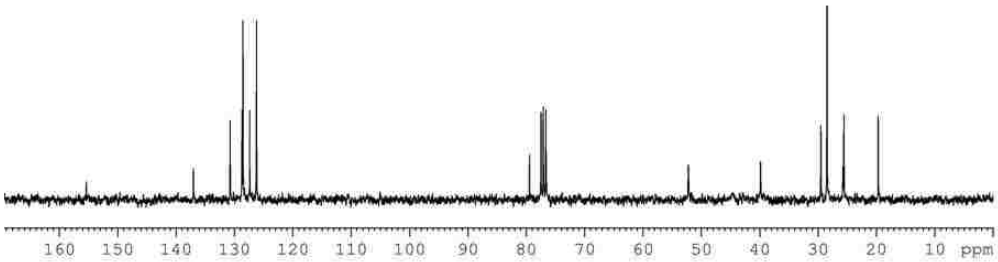
68%, 94:6 er

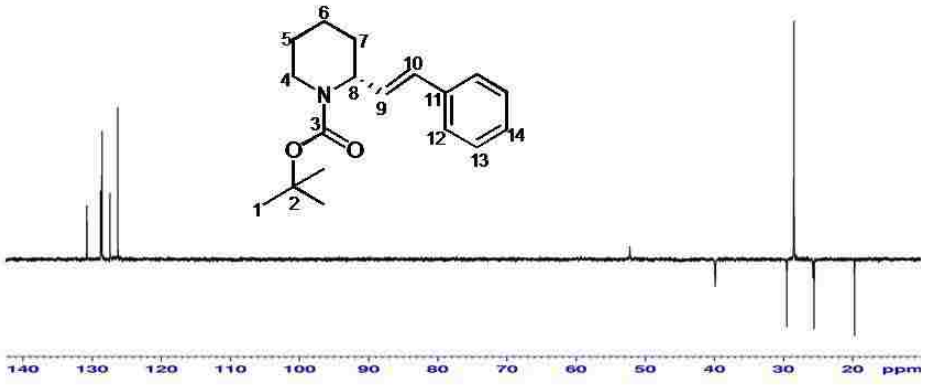
Using General Procedure C, N-Boc-piperidine (370 mg, 2.0 mmol), TMEDA (1.2 mL, 8.0 mmol, 4.0 equiv), Et_2O (10 mL), s-BuLi (2.4 mL, 1.0 M, 2.4 mmol, 1.2 equiv), the alcohol precursor of 10 (21.4 mg, 0.1 mmol, 5 mol%, in 0.40 mL Et_2O pretreated with freshly titrated s-BuLi), $ZnCl_2$ (355 mg, 2.6 mmol, 1.3 equiv) in THF (2 mL), ℬ-bromostyrene (476 mg, 0.35 mL, 2.6 mmol, 1.3 equiv), $Pd(OAc)_2$ (20 mg, 0.08 mmol, 4 mol%) and t-$Bu_3P{\cdot}HBF_4$ (46 mg, 0.16 mmol, 8 mol%) gave the crude product as an oil. Purification by silica gel column chromatography eluting with Hexane-EtOAc (98:2) afforded 390 mg of the pure product as an

oil in 68% yield and 94:6 er; spectroscopic data as reported.[42] $[\alpha]_D^{22}$ 108.5 (c = 0.3, $CHCl_3$), lit[42] for S-49 ($[\alpha]_D^{25}$ –116.9 (c = 0.3, $CHCl_3$). The er was determined by CSP-SFC as follows: Column: Pirkle-Whelk-O-1, Flow Rate: 2.0 mL/min, Polarity Modifier %: 2.0% EtOH, Outlet Pressure = 150 psi, Oven Temperature = 35 °C. The minor enantiomer elutes after ~4.8 min and the major enantiomer elutes after ~6.9 min. ^{1}H NMR: δ 7.38-7.15 (m, 5H), 6.39 (dd, 1H), 6.18 (dd, 1H), 4.95 (br, s, 1H), 3.98 (d, br, 1H), 2.95-2.88 (m, 1H), 1.82-1.52 (m, 6H), 1.46 (s, 9H); ^{13}C NMR (75.5 MHz): δ 155.5, 137.0, 130.7, 128.7, 128.5 (2C), 127.3, 126.2 (2C), 79.4, 52.2, 39.8, 29.5, 28.4 (3C), 25.5, 19.6.

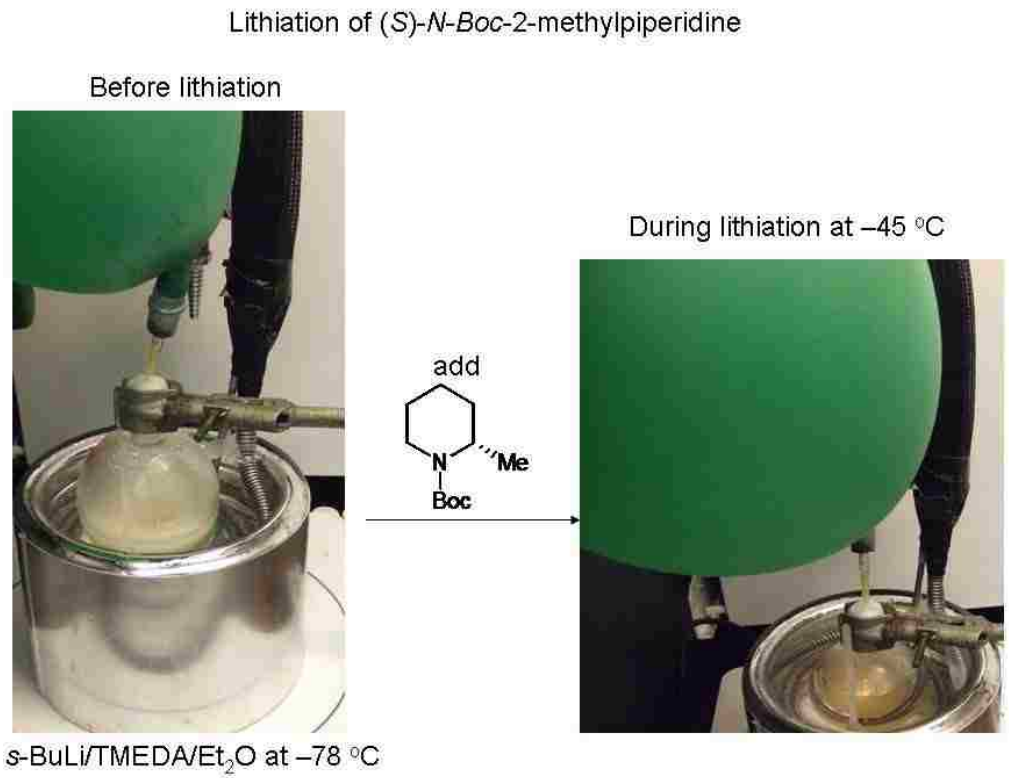



6
5
7
4
N
8
10
9
11
3
12
14
O
O
13
1
2
H1
H12,13,14
H10
H9
H8
H4
H4'
H7, 6,5
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm


160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


6
5
7
4
N
8
10
9
11
3
12
14
O
O
13
1
2
140 130 120 110 100 90 80 70 60 50 40 30 20 ppm

27. General Procedure D: Lithiation-Substitution of (S)-N-Boc-2-methylpiperidine

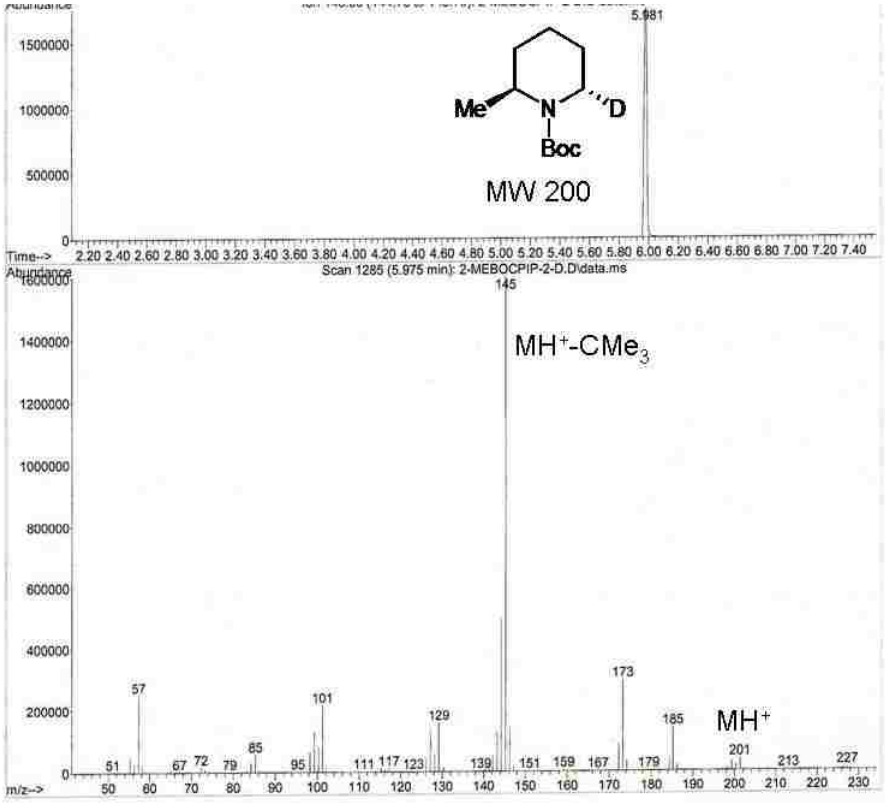


To an oven-dried, septum-capped round bottom flask equipped with a stir bar, was added freshly distilled TMEDA (4.0 equiv) and Et_2O under argon. The solution was cooled to –78 °C and a solution of s-BuLi in cyclohexane (1.2 equiv) was added. A solution of (S)-2-methyl-N-Boc-piperidine S-33 (1.0 equiv) in Et_2O was added to the flask containing the TMEDA/s-BuLi mixture. After 30 min at this temperature, the mixture was warmed to –45 °C and allowed to stir for 3 h. After cooling to –78 °C, the mixture was quenched with the electrophile (~1.1 to 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 flash chromatography on silica was accompanied by er and dr determination.

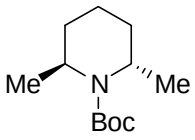
Note 1: In some cases, MeOH was added after warming to room temperature.

27.1. Monitoring the extent of deprotonation of S-33: Quenching with MeOD

To an oven-dried, septum-capped 50 mL round bottom flask equipped with a stir bar, was added freshly distilled TMEDA (4.0 equiv) and Et_2O under argon. The solution was cooled to –78 °C and a solution of s-BuLi in cyclohexane (1.2 equiv) was added. A solution of (S)-2-methyl-N-Boc-piperidine S-33 (1.0 equiv) in Et_2O was precooled to –78 °C. After 5 min, the precooled solution of S-33 was added to the flask containing the TMEDA/s-BuLi mixture. After 30 min at this temperature, the mixture was warmed to –45 °C. CH_3OD (0.1 mL), stored over molecular sieves, was placed in an oven-dried vial and the vial was capped rapidly. At various time intervals (every 30 min), an aliquot (ca 0.1 mL) of the deprotonating mixture was drawn using a syringe equipped with an oven-dried needle, and rapidly placed in the vial containing the CH_3OD. The mixture was diluted with freshly distilled Et_2O (ca 1 mL). The ethereal layer was filtered through Celite. The sample was placed in a GC vial and analyzed by GC-MS for deuterium incorporation using chemical ionization. When the deprotonation is complete, there is a noticeable shift of the protonated molecular ion peak from m/z 200 for N-Boc-2-methylpiperidine to m/z 201 for trans-N-Boc-2-deutero-6-methylpiperidine 61.



27.2. Electrophilic quench with dimethyl sulfate: Synthesis of trans-N-Boc-(+)-lupetidine

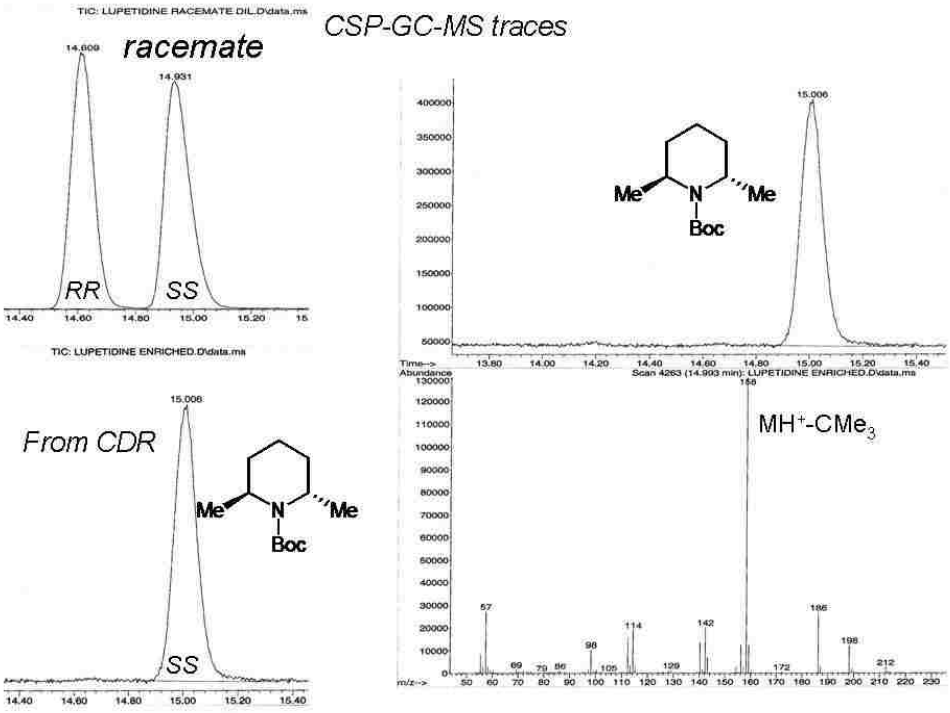


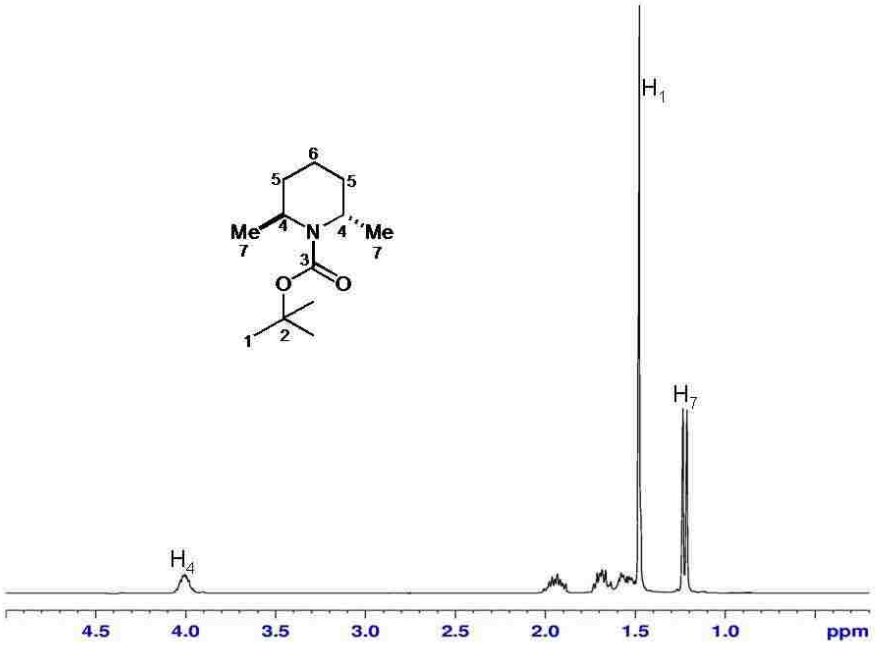
trans-**62**

Using General Procedure D, S-33 of 96:4 er (398 mg, 2.0 mmol), TMEDA (1.2 mL, 8.0 mmol, 4.0 equiv), Et_2O (10 mL), s-BuLi (2.4 mL, 2.4 mmol, 1.0 M, 1.2 equiv), Me_2SO_4 (0.29 mL, 3.0 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 (98:2) afforded 381 mg of trans-62 as a colorless liquid in 89% yield and 96:4 er, all other spectroscopic data as reported.[6] $[a]_D^{22}$ +53.6 (c = 1.25, MeOH), lit[6]. for enantiopure trans-62, +59 (c = 1.25, MeOH). The enantiomer ratio was evaluated by CSP-GC-MS, 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, initial temperature = 120 ^{o}C, final temperature = 200 ^{o}C, hold time = 5 min, rate = 1 ^{o}C/min. The minor enantiomer elutes after 14.6 min and the major enantiomer elutes after 14.9 min.

Note: On one occasion, enantiopure trans-62 was obtained (see CSP-GC trace below) but typical er's ranged from 93:7 to 96:4 (S:R).




H1
H7
H4
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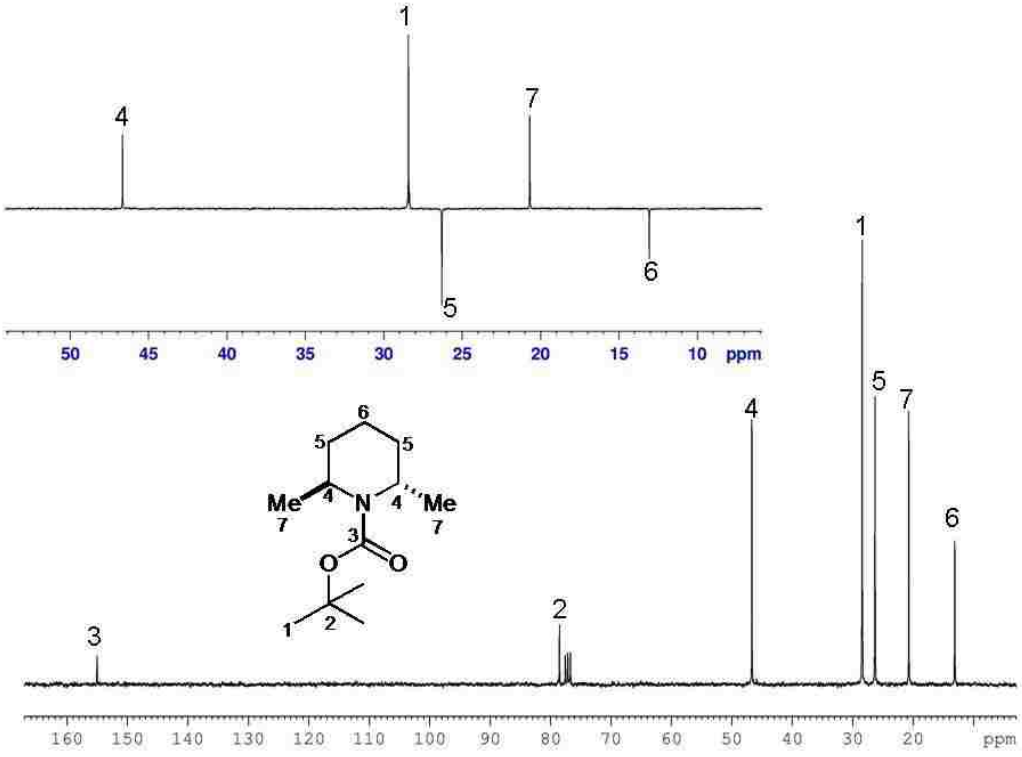
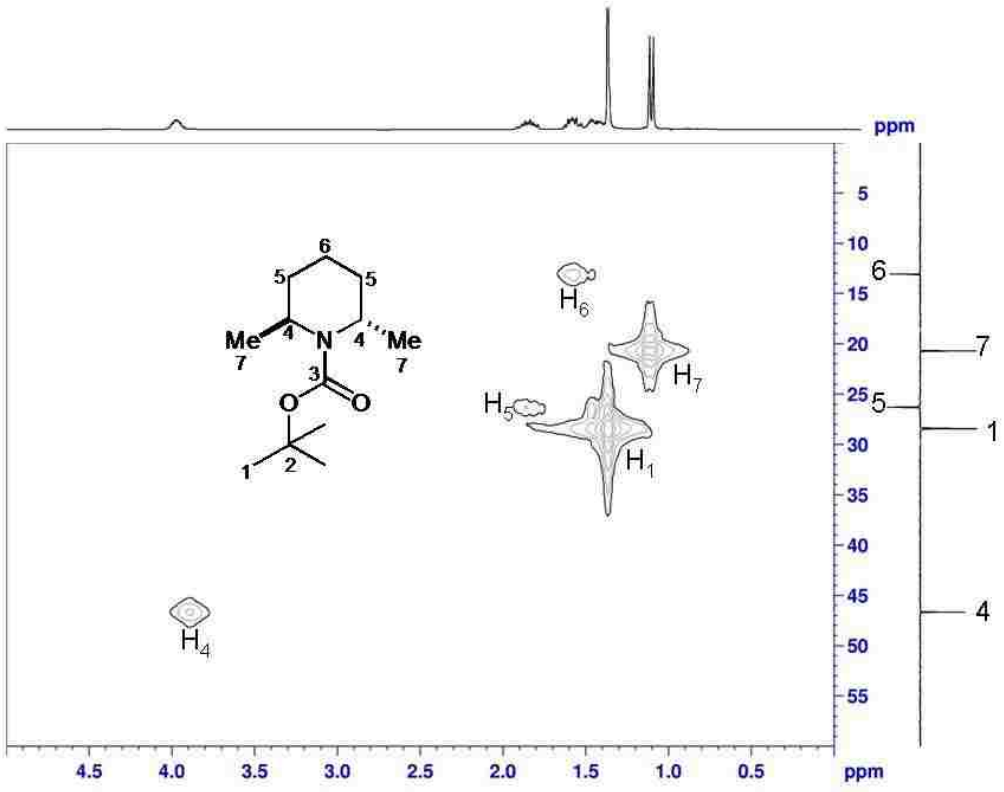
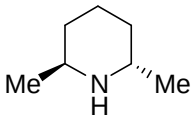
3.5
3.0
2.5
2.0
1.5
1.0
ppm


1
4
7
5
6
50
45
40
35
30
25
20
15
10
ppm
1
5
7
4
6
2
3
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm



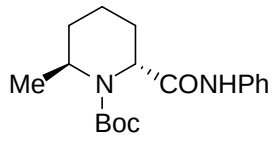
N-Boc-deprotection: Synthesis of trans-63



trans-**63**

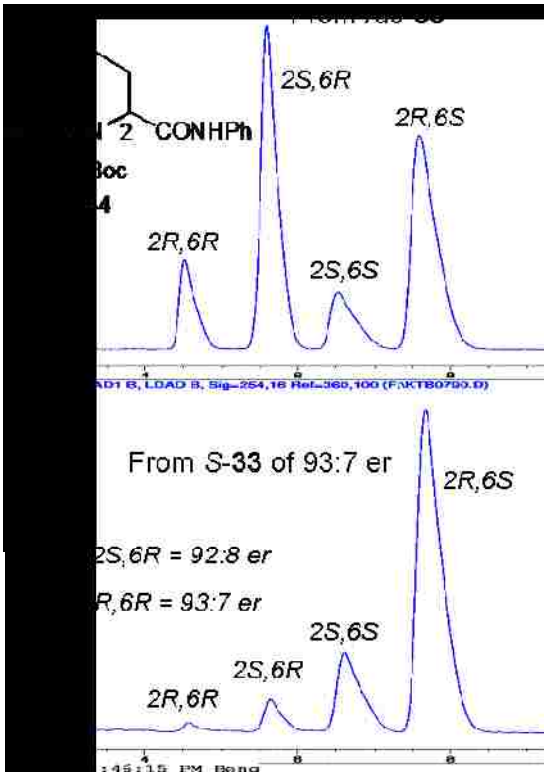
To trans-62 (214 mg, 1.0 mmol) dissolved in CH_2Cl_2 (5.0 mL), was added CF_3CO_2H (1.5 mL) under argon at 0 ^oC. The mixture was stirred for 5 h at this temperature and concentrated in vacuo to obtain the salt. The salt was basified to pH 10 – 12 with 20% $NaOH_{(aq)}$. The layers were separated and 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 109 mg of trans-(+)-lupetidine in 96% yield, $[a]_D^{22}$ +10.3 (c = 0.50, EtOH), lit[6]. $[a]_D$ +12.5 (c = 0.5, EtOH).

27.3. Electrophilic quench with phenyl isocyanate: Synthesis of 64

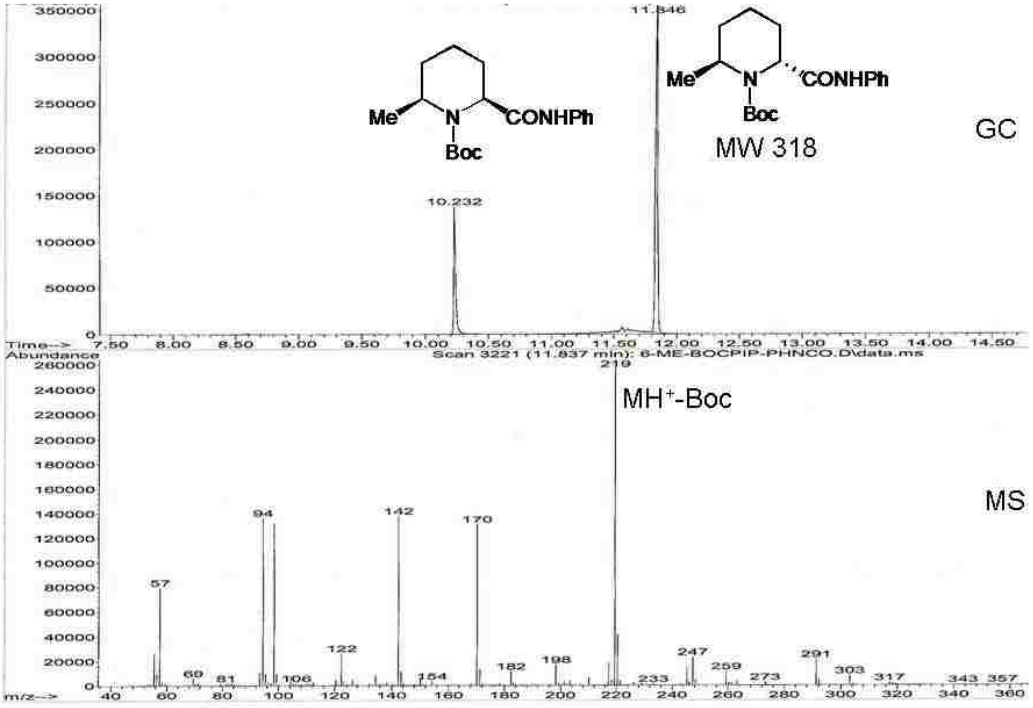


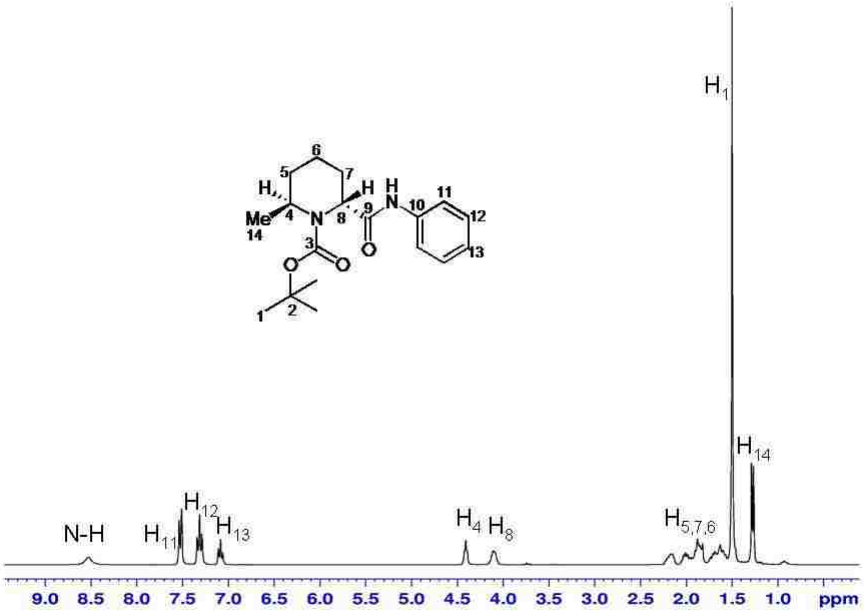
trans-**64**

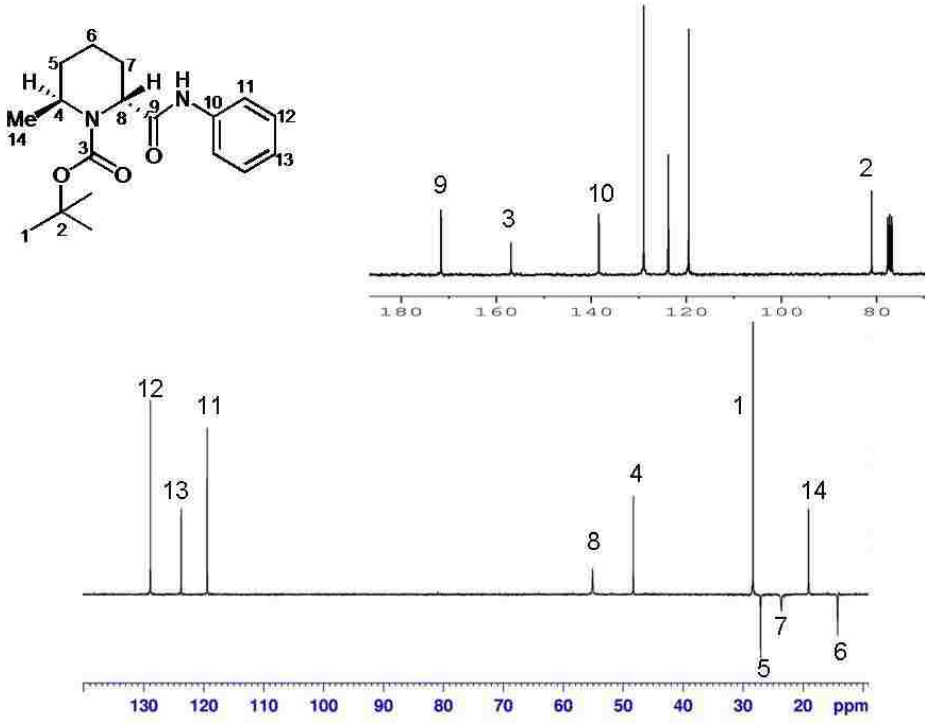
Using General Procedure D, S-33 of 93:7 er (398 mg, 2.0 mmol), TMEDA (1.2 mL, 8.0 mmol, 4.0 equiv), Et_2O (10 mL), s-BuLi (2.4 mL, 2.4 mmol, 1.0 M, 1.2 equiv), precooled phenyl isocyanate (0.33 mL in 1.0 mL Et_2O, 3.0 mmol, 1.5 equiv) for 2 h prior to addition of 2 mL MeOH, gave the crude product as a yellowish solid. Purification by silica gel chromatography eluting with hexane-EtOAc (90:10) afforded 464 mg of 64 as a white solid in 73% yield, 75:25 dr and 93:7 & 92:8 er for the trans and cis diastereomers respectively. Data for the trans-isomer; ^{1}H NMR (300 MHz, $CDCl_3$) o = 8.4 (1H, s, CONH), 7.33–6.85 (5H, m, Ph), 4.19 (1H, br, NCH), 3.91 (1H, br, NCH), 1.95–1.41 (15H, m), 1.29 (3H, d, CH_3) ^{13}C NMR (75.5 MHz, $CDCl_3$) o = 172.3 (C=O), o = 156.9 (C=O), 138.3 (C), 129.0 (CH), 123.8 (CH), 119.5 (CH), 81.0 (C), 55.1 (CH), 48.4 (CH), 28.4 (CH_3), 27.1 (CH_2), 23.5 (CH_2), 19.1 (CH_3) and 14.2 (CH_2). The enantiomer ratio of the crude mixture was evaluated by CSP-SFC, monitoring at 210 or 254 nm, by comparison with an authentic racemic sample, under the following column conditions: Column: Daicel Chiralcel OD-H, Flow Rate = 2.0 mL/min, Polarity Modifier = 5.0% EtOH. For trans-64, the minor enantiomer elutes after 5.6 min and the major elutes after 7.6 min. For cis-64, the minor enantiomer elutes after 4.5 min and the major elutes after 6.6 min.

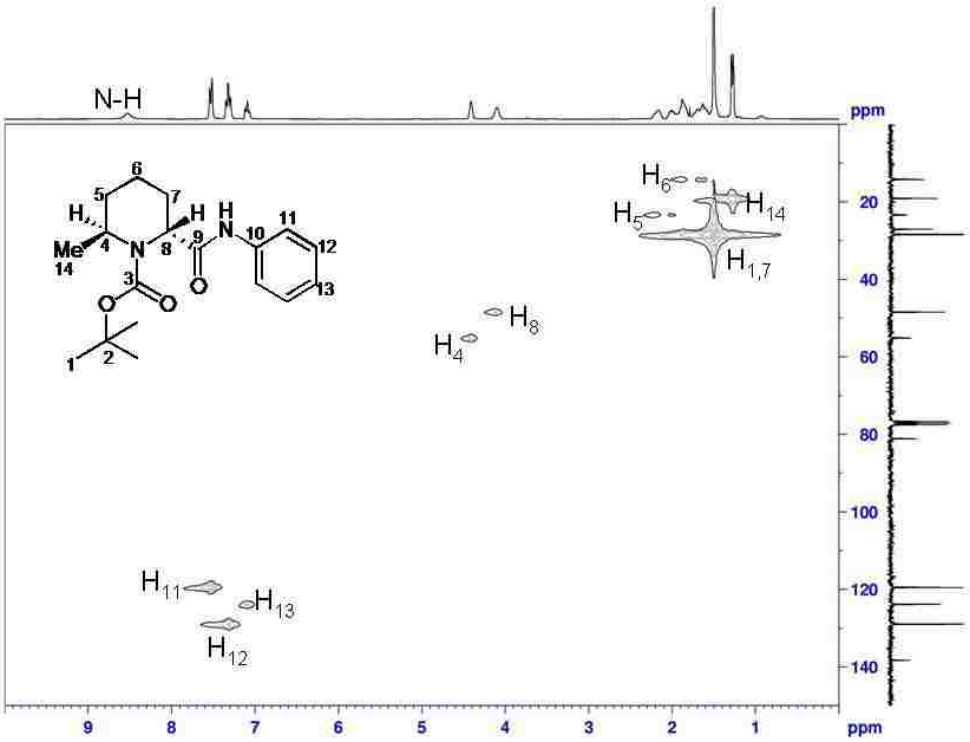


GC-MS of crude diastereomeric mixture

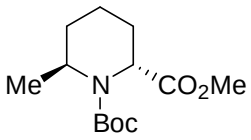



H1
H14
H12
N-H
H11
H13
H4 H8
H5,7,6
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm


9
3
10
2
180 160 140 120 100 80
12
11
13
1
4
14
8
7
6
5
130 120 110 100 90 80 70 60 50 40 30 20 ppm



27.4. Electrophilic quench with methyl chloroformate: Synthesis of 65

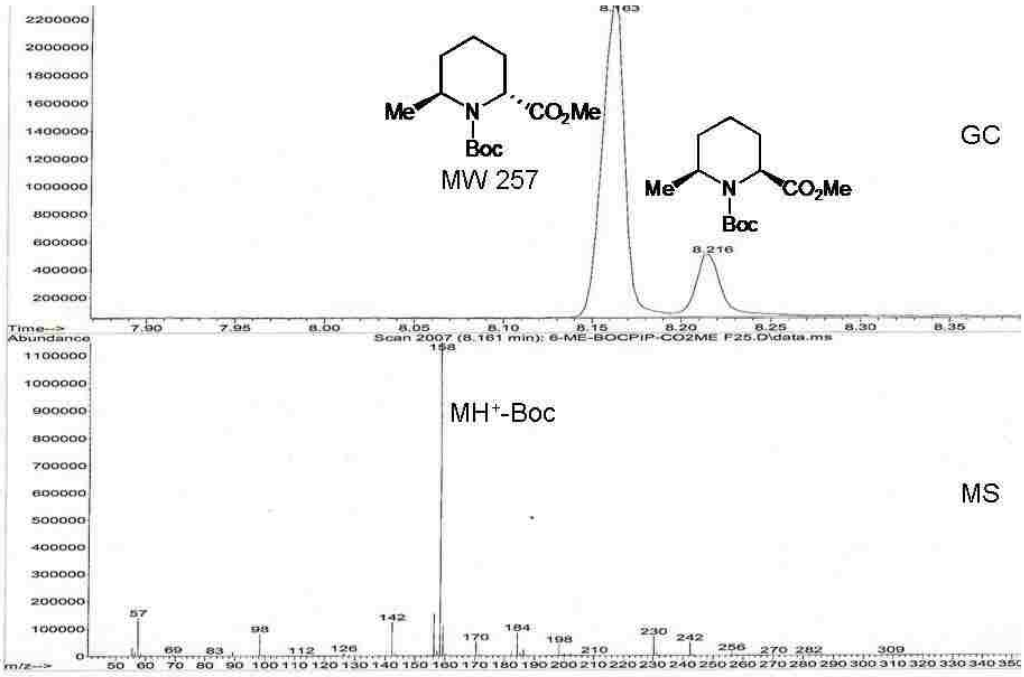


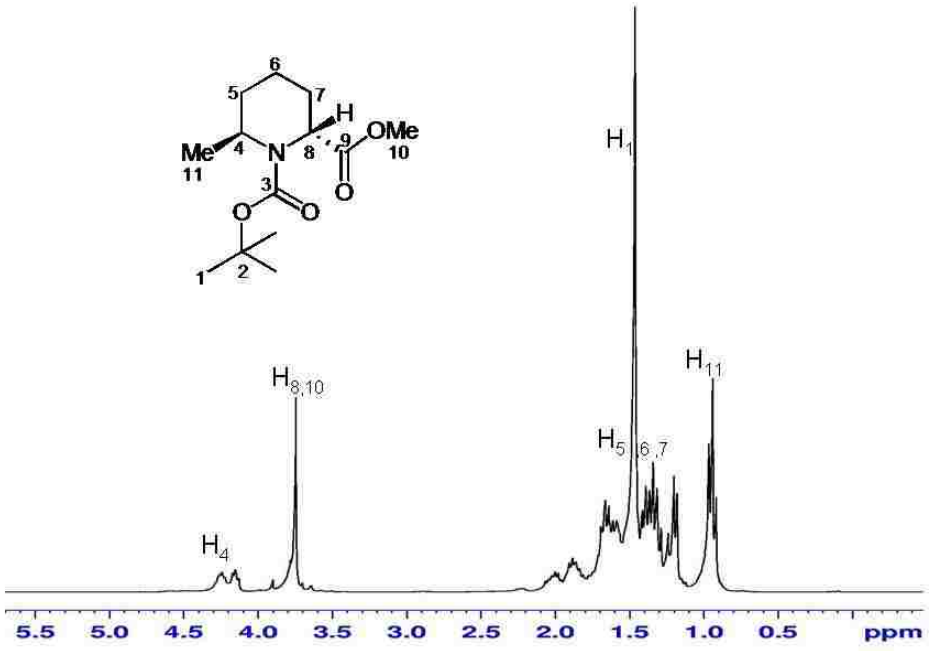
trans-**65**

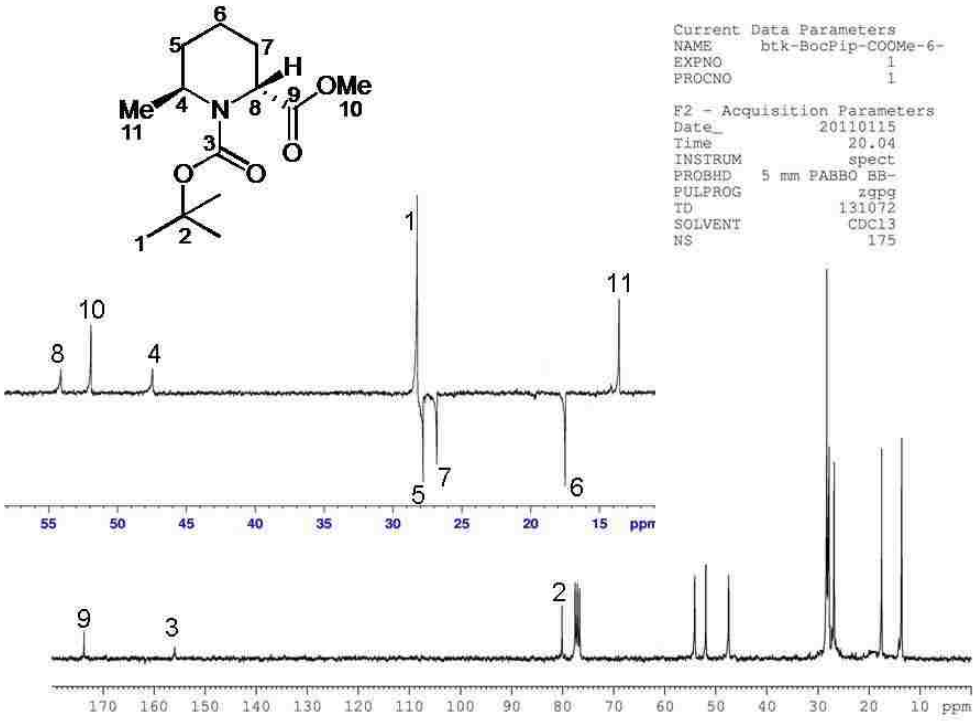
Using General Procedure D, S-33 of 96:4 er (398 mg, 2.0 mmol), TMEDA (1.2 mL, 8.0 mmol, 4.0 equiv), Et_2O (10 mL), s-BuLi (2.4 mL, 2.4 mmol, 1.0 M, 1.2 equiv), precooled methyl chloroformate (0.23 mL in 0.5 mL Et_2O, 3.0 mmol, 1.5 equiv) for 2 h prior to addition of 2 mL MeOH, gave the crude product as an oil. Purification by silica gel chromatography eluting with hexane-EtOAc (95:5) afforded 416 mg of 65 in 81% yield, 85:15 dr (trans:cis) and 93:7 er for both diastereomers. Data for the trans-isomer; ^{1}H NMR (300 MHz, $CDCl_3$) o = 4.25–4.05 (2H, m, NCH), 3.65 (3H, s, OCH_3), 1.91–0.92 (15H, m), 0.75 (3H, d, CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$) o = 174.5 (C=O), o = 156.3 (C=O), 80.2 (C), 54.1 (CH), 52.2 (CH_3), 47.2 (CH), 28.5

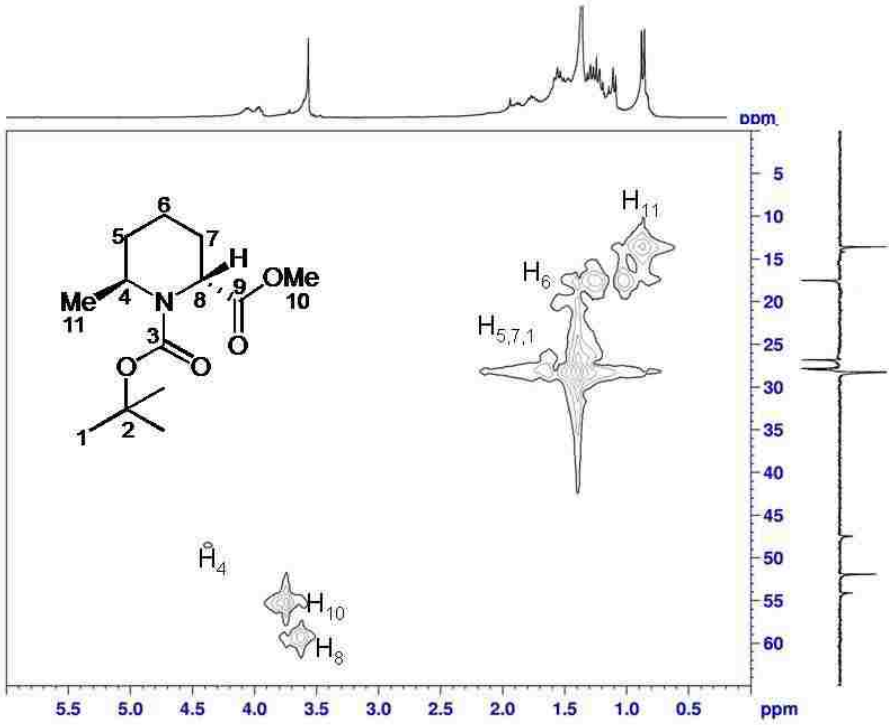
(CH_3), 28.0 (CH_2), 26.8 (CH_2), 17.5 (CH_2) and 13.4 (CH_3). The enantiomer ratio of the major diastereomer was evaluated by CSP-GC-MS, on a β-cyclodextrin-permethylated 120 fused silica capillary column [30 m × 0.25 mm i.d., 20% permethylated β-cyclodextrin in SPB-35 poly(35% diphenyl/65% dimethyl)siloxane, initial temperature = 100 ^{o}C, final temperature = 200 ^{o}C, hold time = 10 min, rate = 5 ^{o}C/min. The minor enantiomer elutes after 26.8 min and the major enantiomer elutes after 26.9 min.

GC-MS of crude diastereomeric mixture

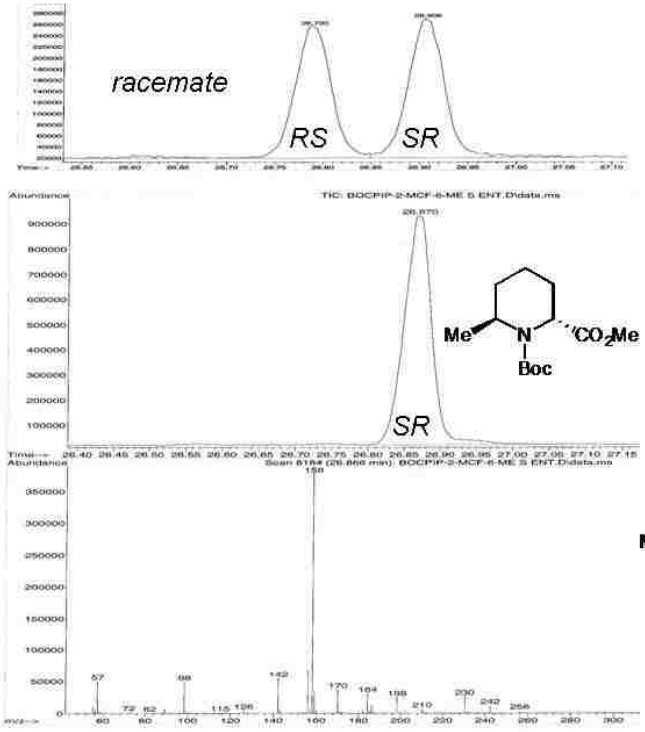



H1
H8,10
H11
H5,6,7
H4
5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm

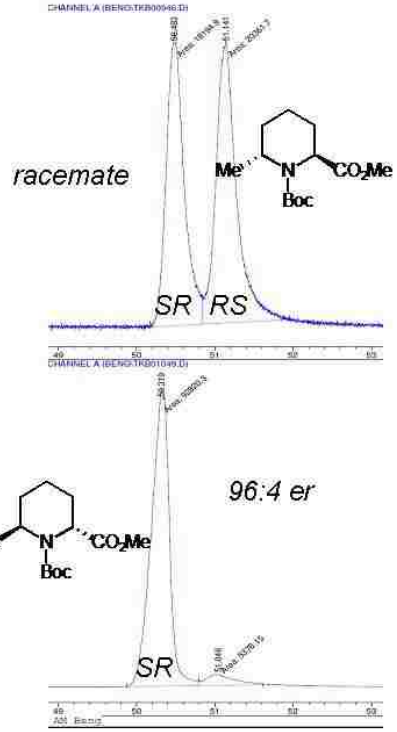

Current Data Parameters
NAME btk-BocPip-COOMe-6-
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20110115
Time 20.04
INSTRUM spect
PROBHD 5 mm PABBO BB-
PULPROG zgpg
TD 131072
SOLVENT CDCl3
NS 175
1
11
10
8
4
5
7
6
2
9
3
55 50 45 40 35 30 25 20 15 ppm
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm



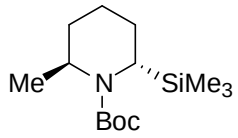
CSP-GC-MS traces



CSP-GC traces

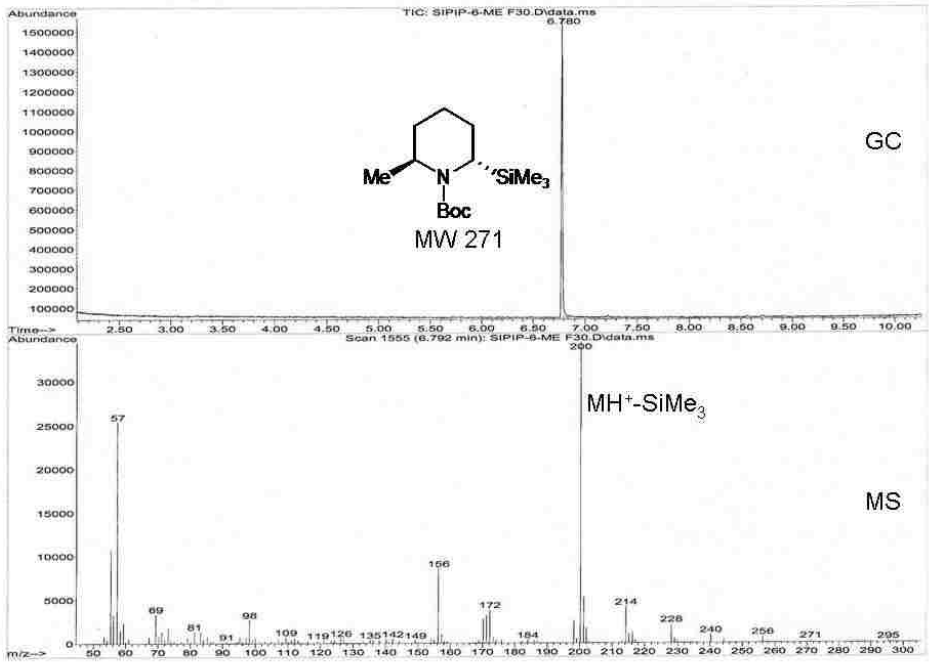


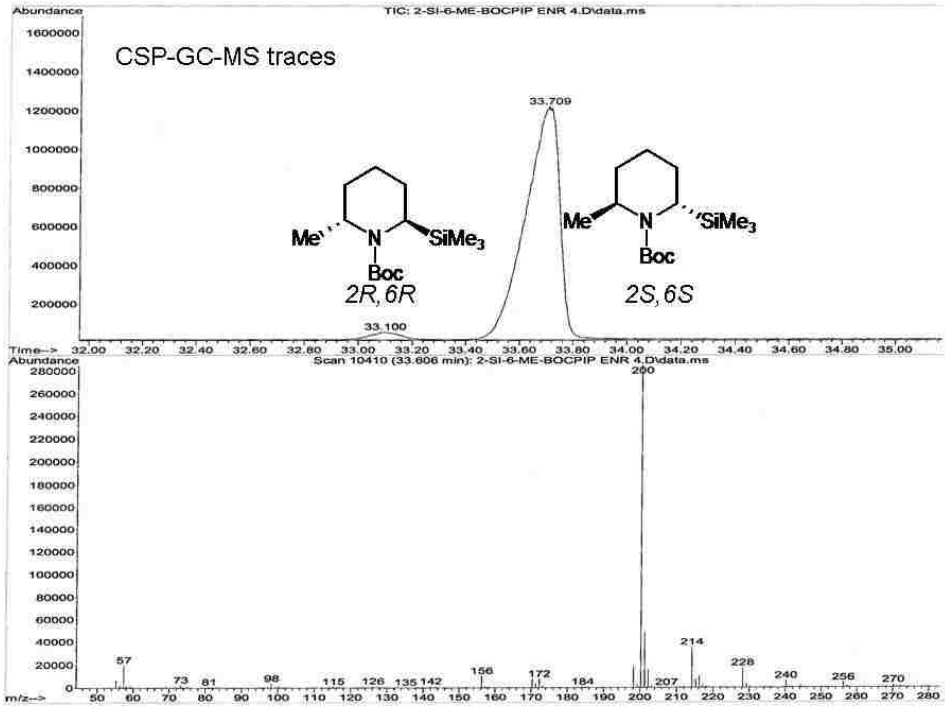
27.5. Electrophilic quench with TMSCl: Synthesis of 66

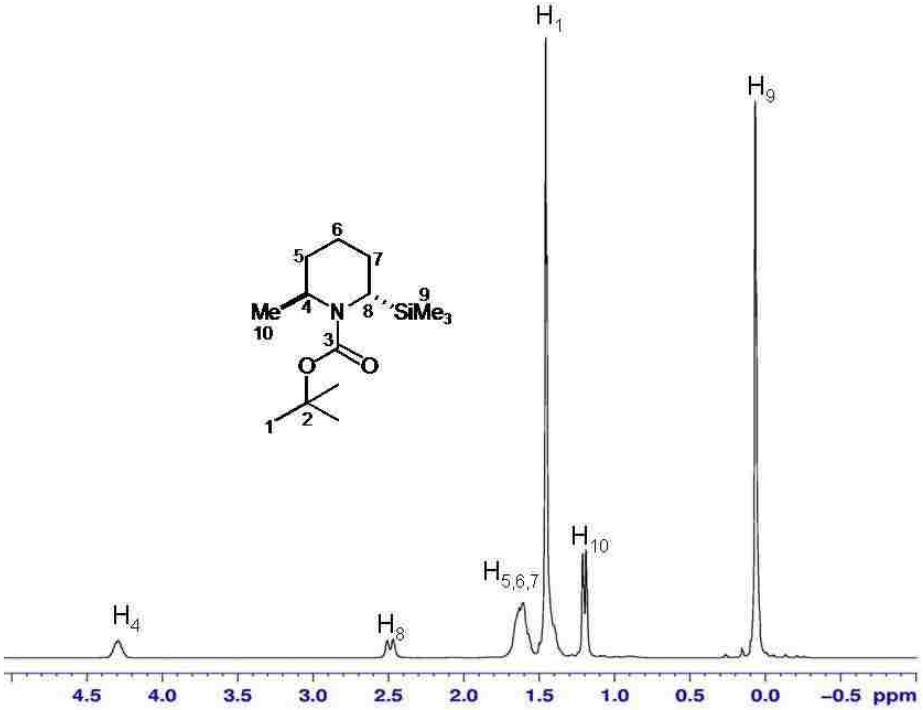


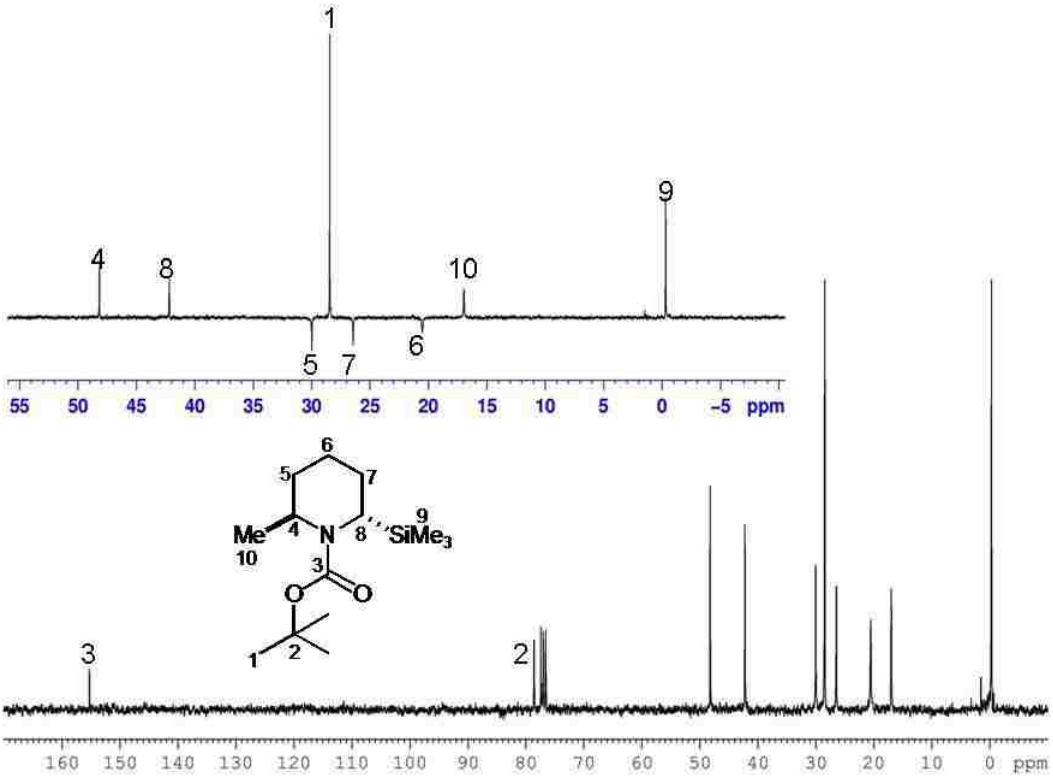
trans-**66**

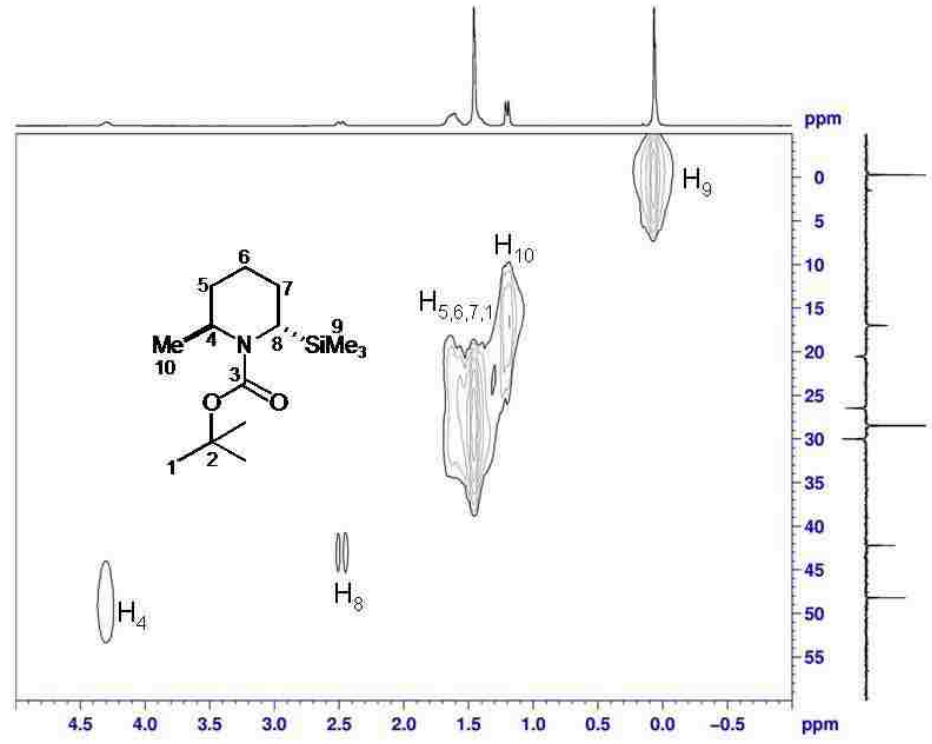
Using General Procedure D, S-33 of 96:4 er (199 mg, 1.0 mmol), TMEDA (0.6 mL, 4.0 mmol, 4.0 equiv), Et_2O (10 mL), s-BuLi (1.2 mL, 1.2 mmol, 1.0 M, 1.2 equiv), Me_3SiCl (144 mg, 1.2 mmol, 1.2 equiv) for 4 h prior to addition of 2 mL MeOH, gave the crude product as an oil. Purification by silica gel chromatography eluting with hexane-EtOAc (98:2) afforded 203 mg of trans-66 in 75% yield, as a single diastereomer in 96:4 er. ^{1}H NMR (300 MHz, $CDCl_3$) o = 4.4–4.2 (1H, m, NCH), 2.5 (1H, m, NCH), 1.8–1.5 (6H, m), 1.4 (9H, s, CH_3), 1.2 (3H, d, CH_3) 0.05 (9H, s, CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$) o = 155.3, 78.6 (C), 48.2 (CH), 42.2 (CH), 30.0 (CH_2), 28.5 (CH_3), 26.5 (CH_2), 20.5 (CH_2), 17.0 (CH_3), and -0.3 (CH_3). The er was evaluated by CSP-GC-MS 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, initial temperature = 90 ^{o}C, final temperature = 120 ^{o}C, hold time = 5 min, rate = 1 ^{o}C/min.

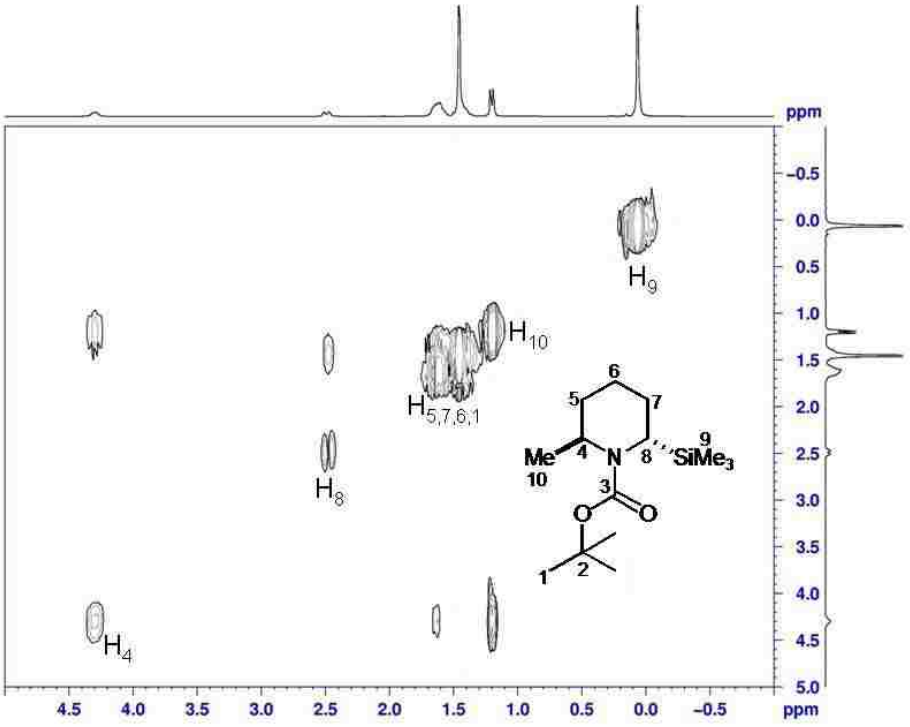

TIC: SIPIP-6-ME F30.D\data.ms
6.780
Me
N
SiMe3
Boc
MW 271
GC
Scan 1555 (6.792 min): SIPIP-6-ME F30.D\data.ms
200
MH+-SiMe3
MS


TIC: 2-SI-6-ME-BOCPIP ENR 4.D\data.ms
CSP-GC-MS traces
33.709
33.100
Me
N
SiMe3
Boc
2R,6R
2S,6S
Scan 10410 (33.606 min): 2-SI-6-ME-BOCPIP ENR 4.D\data.ms
200

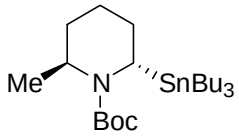

H1
H9
H10
H5,6,7
H4
H8
4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 −0.5 ppm


1
9
4
8
10
5
7
6
55 50 45 40 35 30 25 20 15 10 5 0 −5 ppm
3
2
160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm


H9
H10
H5,6,7,1
H8
H4
Me
10
SiMe3
ppm

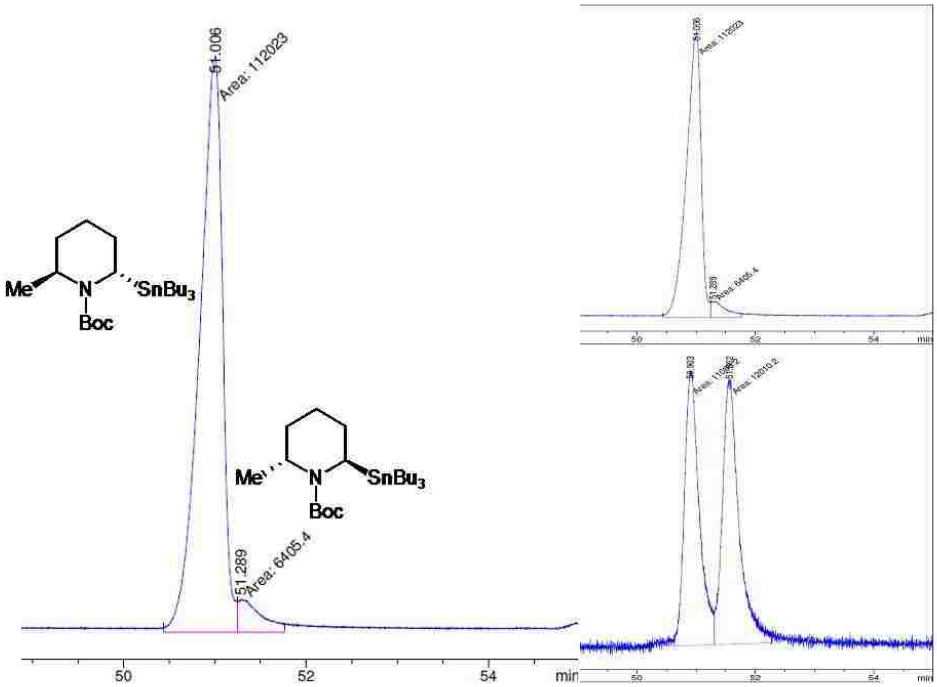

H9
H10
H5,7,6,1
H8
H4
Me
10
SiMe3
ppm

27.6. Electrophilic quench with tributylstannyl chloride: Synthesis of 67

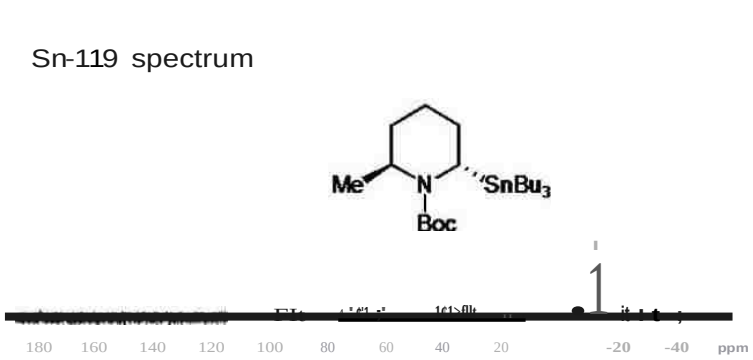


trans-**67**

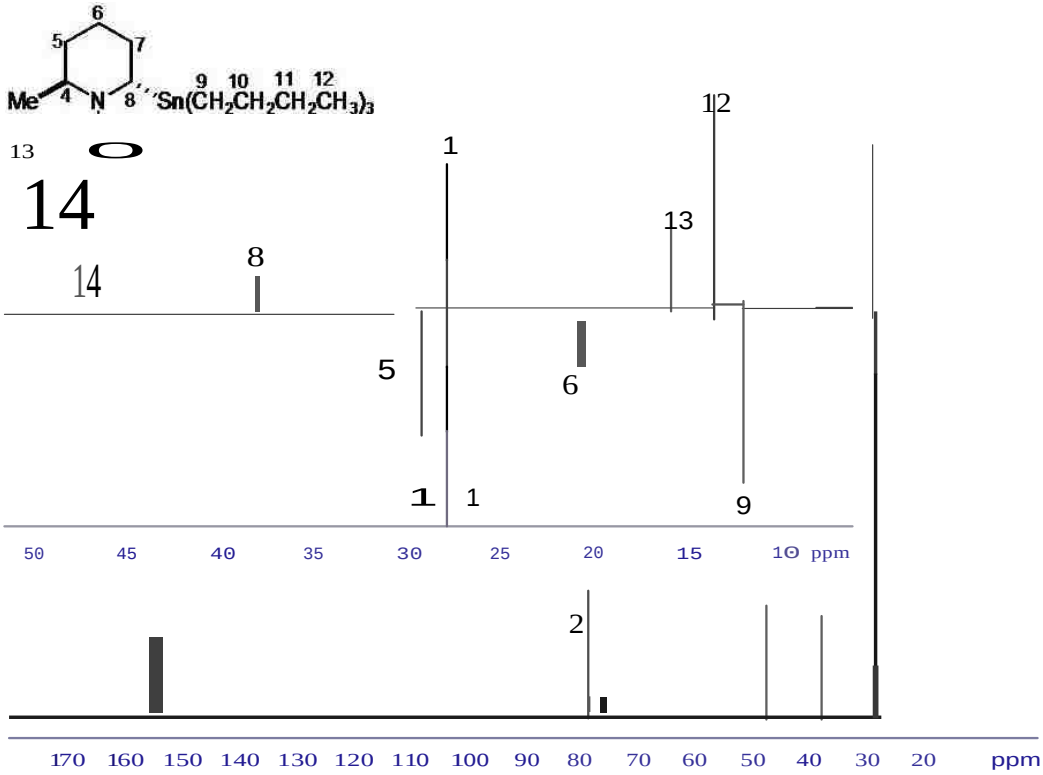
Using General Procedure D, S-33 of 96:4 er (199 mg, 1.0 mmol), TMEDA (0.6 mL, 4.0 mmol, 4.0 equiv), Et_2O (10 mL), s-BuLi (1.2 mL, 1.2 mmol, 1.0 M, 1.2 equiv), precooled Bu_3SnCl (0.32 mL in 0.5 mL Et_2O, 1.2 mmol, 1.2 equiv) for 4 h prior to addition of 2 mL MeOH, gave the crude product as an oil. Purification by silica gel chromatography eluting with hexane-EtOAc (99:1) afforded 323 mg of trans-67 in 67% yield, as a single diastereomer in 96:4 er. ^{13}C NMR o = 156.5, 78.8 (C), 47.7 (CH), 38.3 (CH), 30.7 (CH_2), 30.5 (CH_2), 29.3 (CH_2), 28.3 (CH_3), 27.6 (CH_2), 21.4 (CH_2), 16.0 (CH_3), 13.7 (CH_3), and 12.2 (CH_2). The enantiomers were resolved by CSP-SFC under the following conditions: Column: Pirkle Whelk-O-1, Flow Rate = 1.0 mL/min, Polarity Modifier = 1.0% EtOH, Outlet Pressure = 150 psi, Oven Temperature = 35 ^oC.

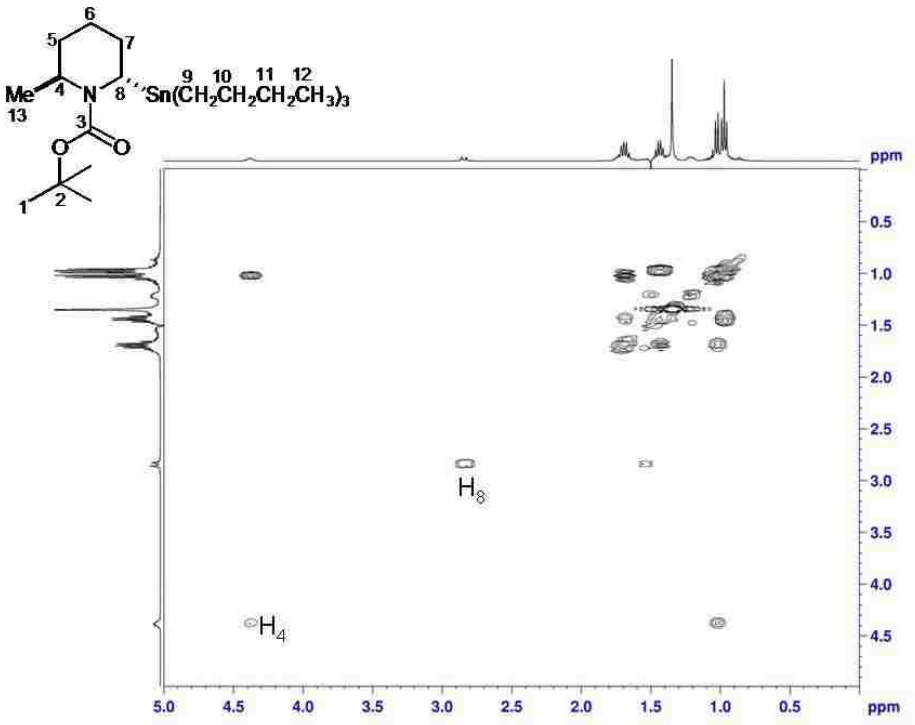


Sn-119 spectrum

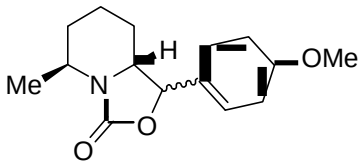


1H NMR spectrum



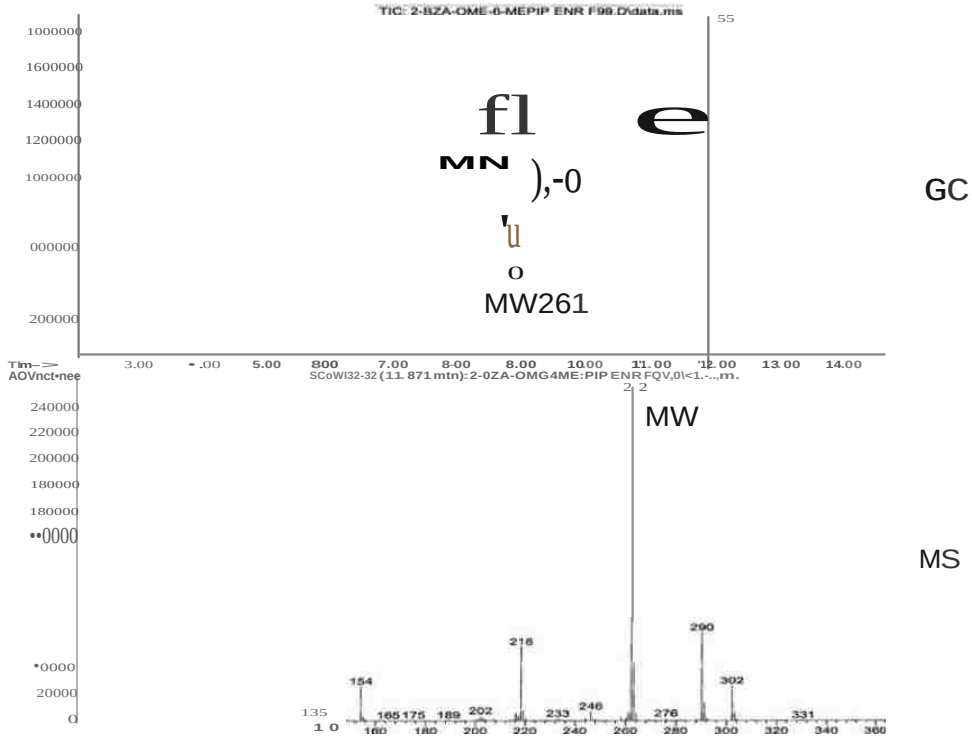


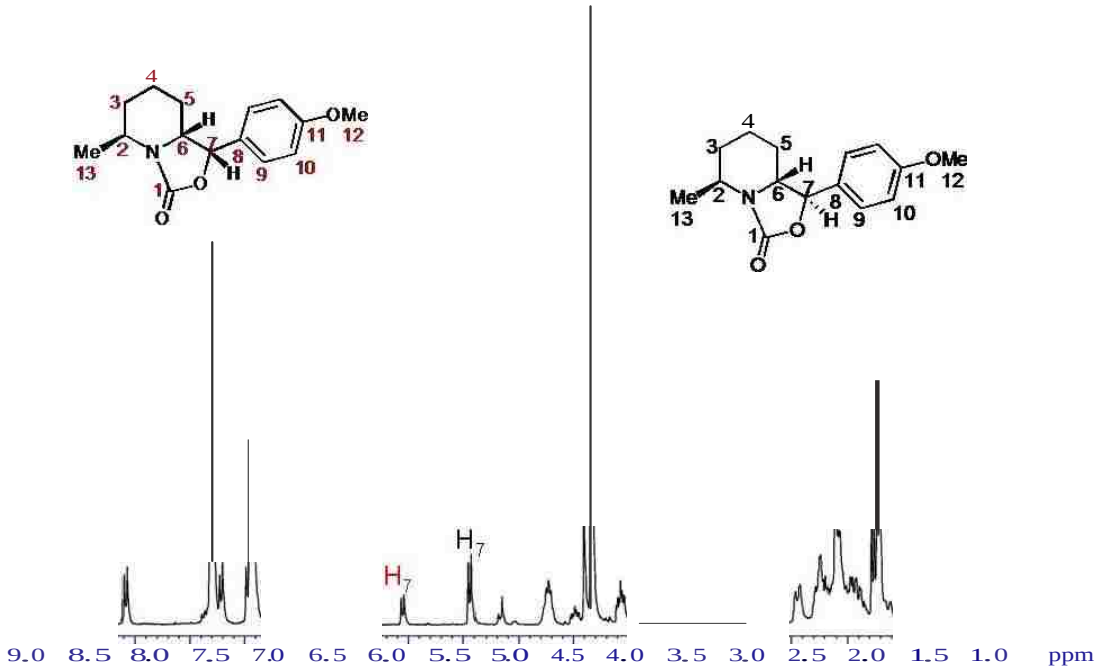
27.7. Electrophilic quench with 4-methoxybenzaldehyde: Synthesis of 68

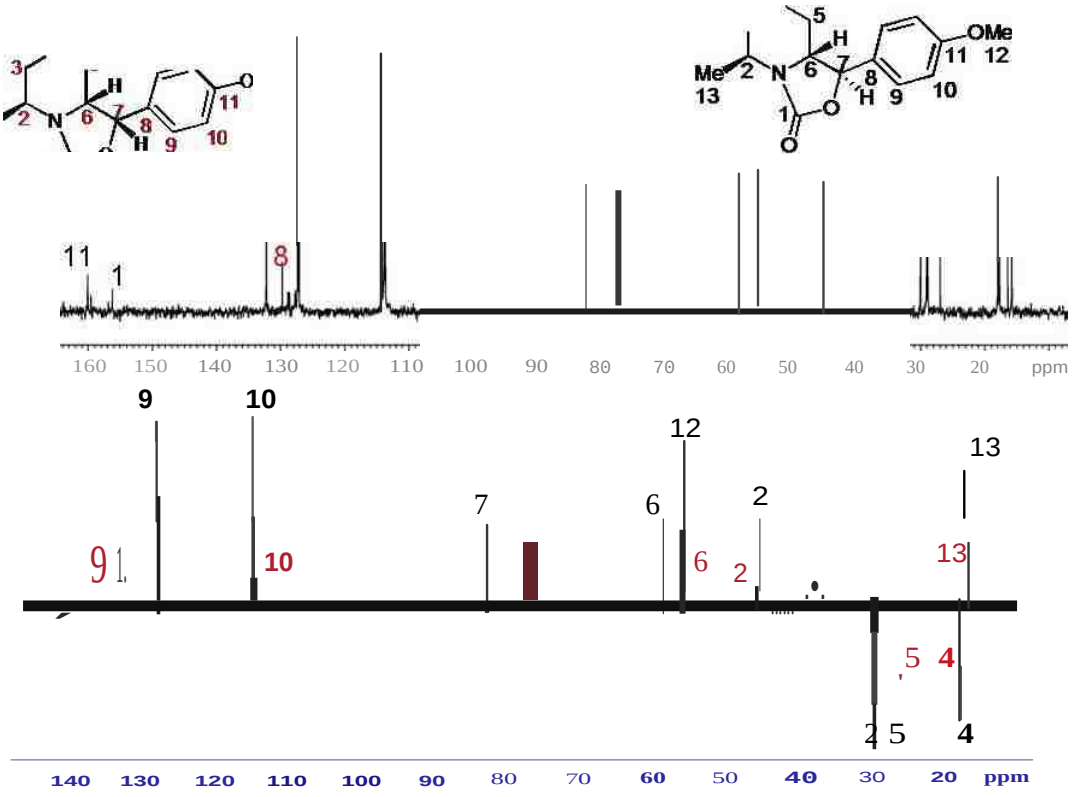


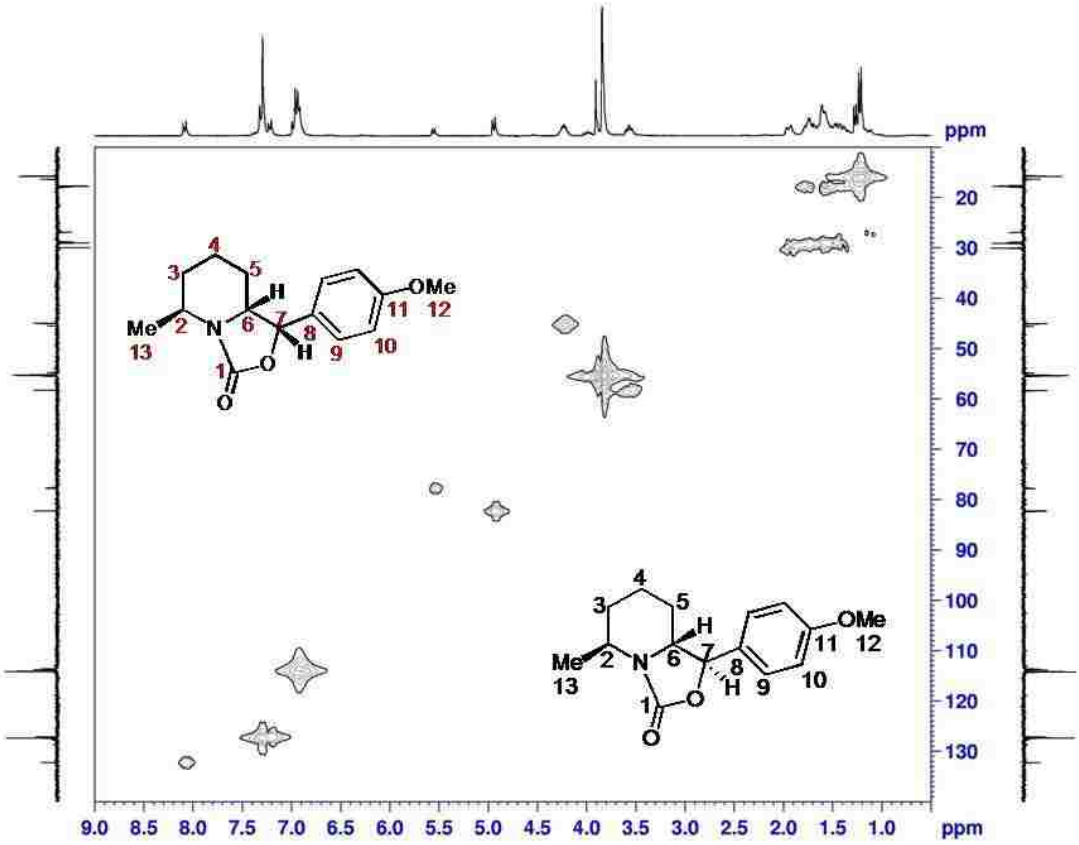
68

Using General Procedure D, S-33 of 96:4 er (398 mg, 2.0 mmol), TMEDA (1.2 mL, 8.0 mmol, 4.0 equiv), Et_2O (10 mL), s-BuLi (2.4 mL, 2.4 mmol, 1.0 M, 1.2 equiv), 4-methoxybenzaldehyde (0.37 mL, 3.0 mmol, 1.5 equiv) for 2 h prior to warming to room temperature and addition of 2 mL MeOH, gave the crude product as a pale yellow oil. Purification by silica gel chromatography eluting with hexane-EtOAc (60:40) afforded 430 mg of 68 in 82% yield, >99:1 dr (syn:anti), 96:4 er for both diastereomers.

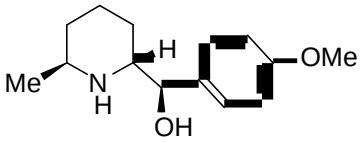

TIC: 2-BZA-OME-6-MEPIP ENR F99.Ddata.ms
MW261
GC
MW
MS


Me
OMe
H7
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm


11
1
8
160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm
9
10
12
13
7
6
2
5
4
140 130 120 110 100 90 80 70 60 50 40 30 20 ppm



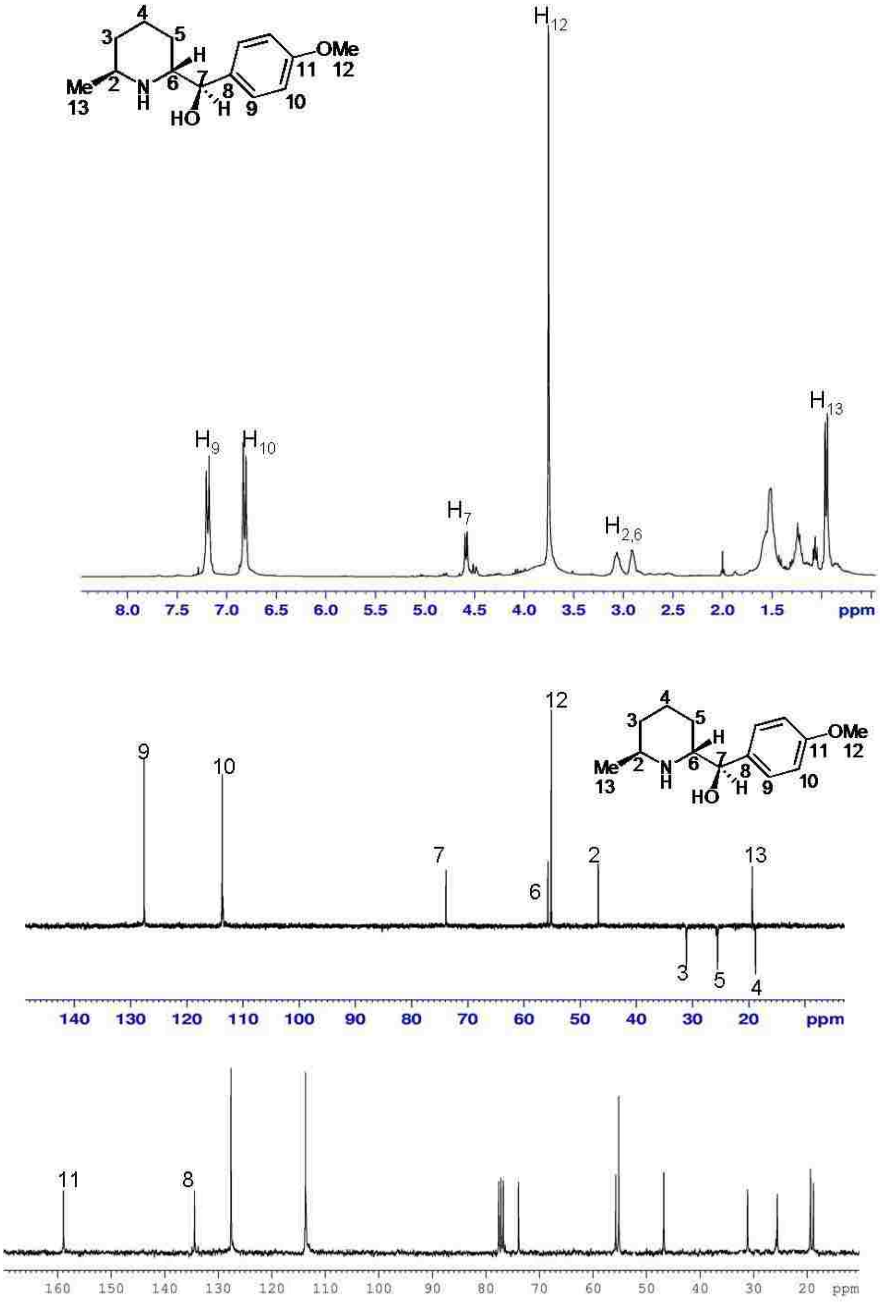
Base Hydrolysis of 68

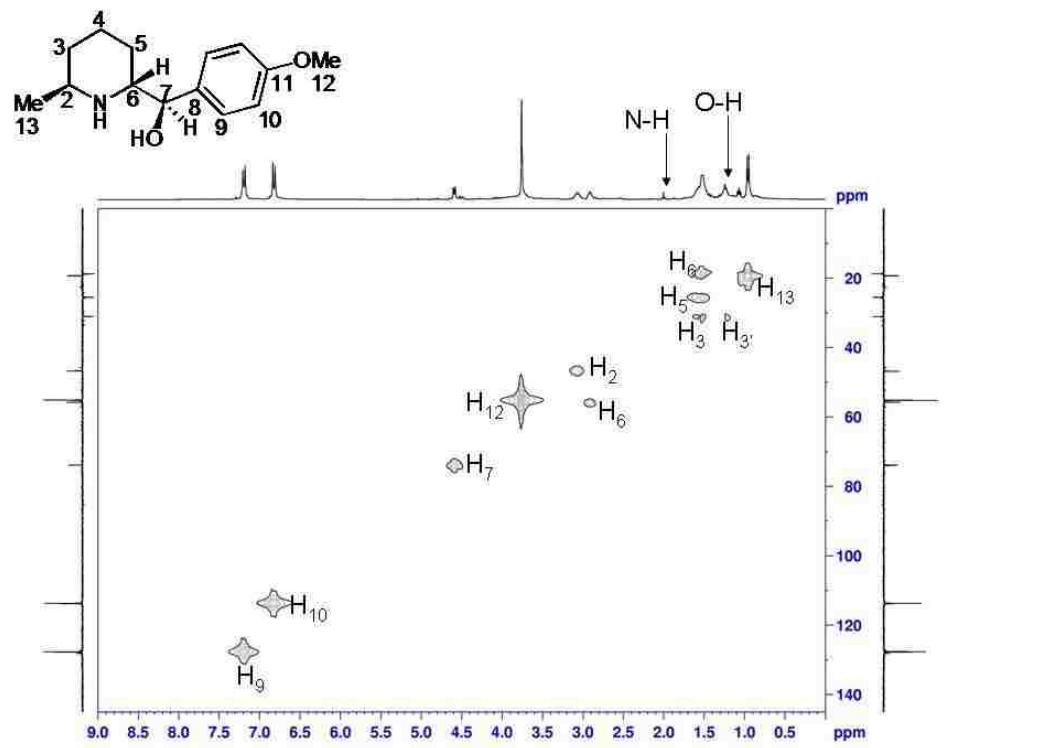


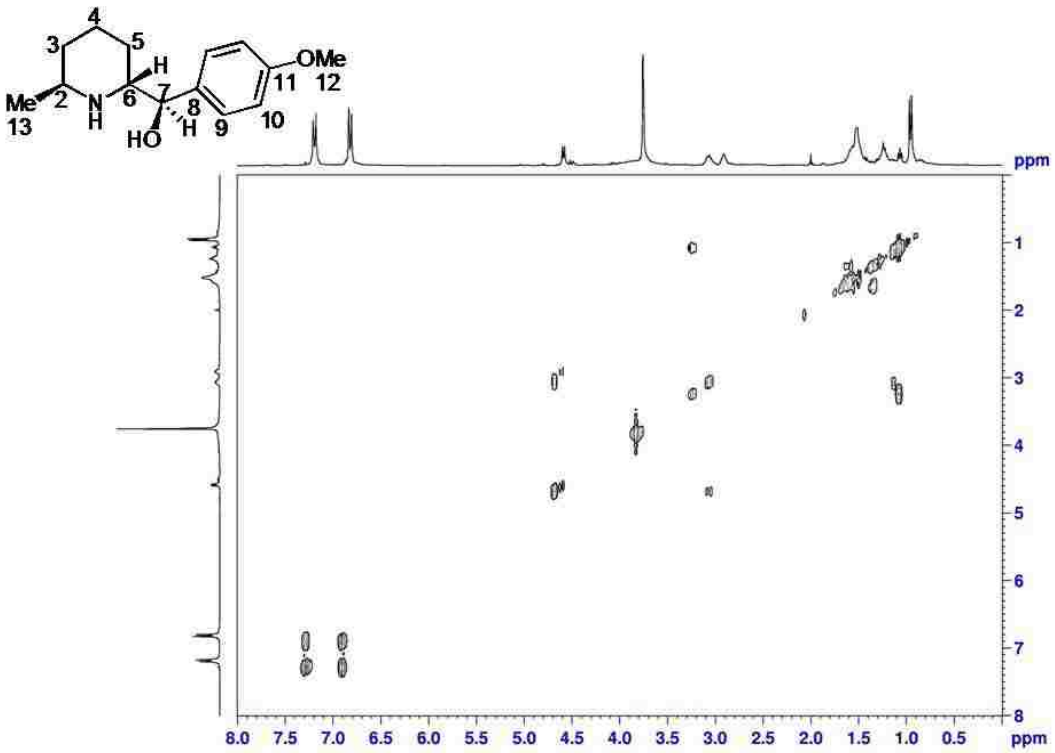
To 68 (261 mg, 1.0 mmol) was added solid NaOH (160 mg, 4 mmol, 4 equiv) and absolute ethanol (5 mL). The resulting suspension was heated at reflux. After 2 h, the mixture was concentrated in vacuo and the orange residue was dissolved in H_2O (5.0 mL). Et_2O (10 mL) was added and the layers were separated. The aqueous layer was extracted with Et_2O (3 x 10 mL). The combined organic layers were dried over K_2CO_3 and concentrated under reduced pressure to give the crude product. Purification by silica gel chromatography eluting with MeOH-CH_2Cl_2-NH_3(aq) (10:5:1) afforded 219 mg of the unprotected piperidinol in 93% yield. ^{13}C NMR (75.5

MHz, $CDCl_3$) o = 158.9 (C), 134.5 (C), 127.6 (CH), 113.6 (CH), 73.9 (CH), 55.8 (CH), 55.2 (CH_3), 46.8 (CH), 31.1 (CH_2), 25.6 (CH_2), 19.4 (CH_3), and 18.8 (CH_2).

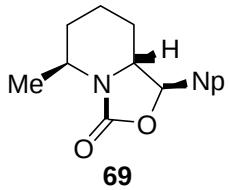
Note: The product is easily oxidized; as such it should be stored under nitrogen in the freezer.




4
3
5
H
OMe
11
12
Me
2
N
H
6
7
8
H
9
10
13
HO
N-H
O-H
ppm
H6'
H13
H5
H3
H3'
H2
H12
H6
H7
H10
H9
20
40
60
80
100
120
140
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
ppm

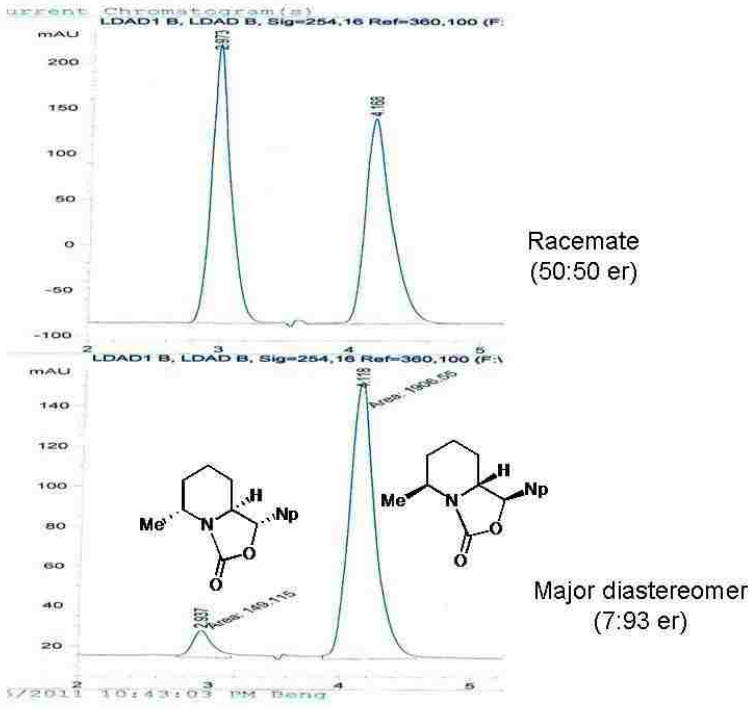

4
3
5
H
OMe
11
12
Me
2
N
H
6
7
8
H
9
10
13
HO
ppm
1
2
3
4
5
6
7
8
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
ppm

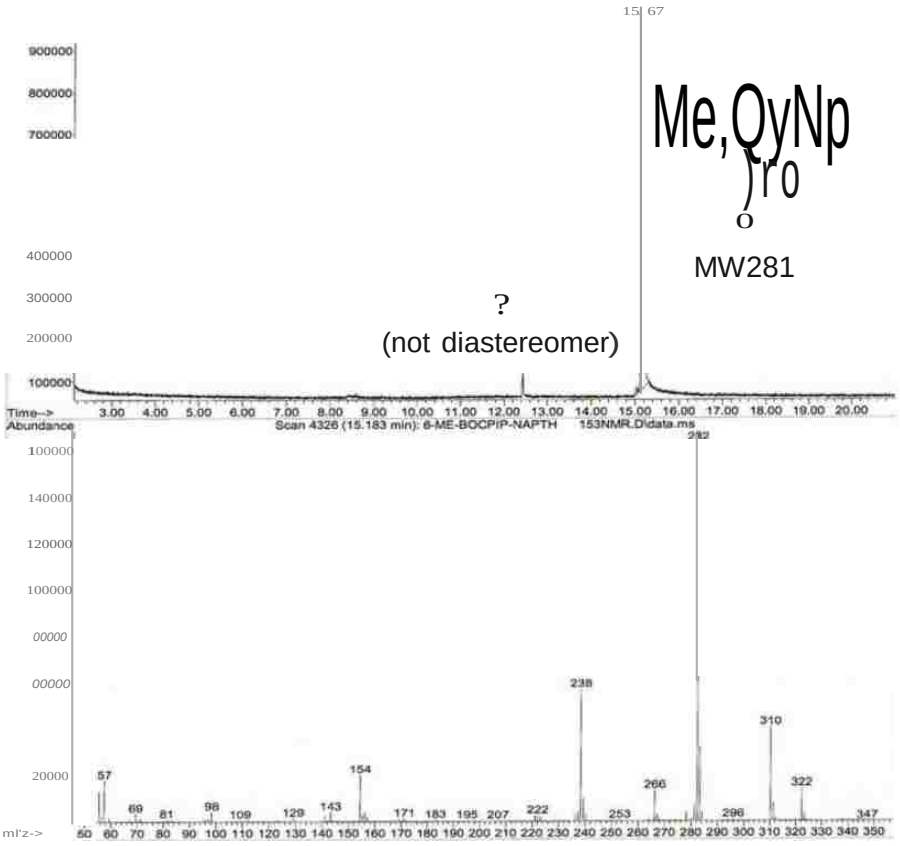
27.8. Electrophilic quench with 1-naphthaldehyde: Synthesis of 69

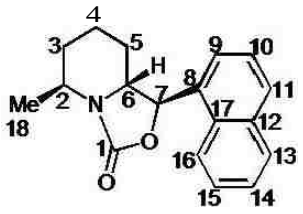


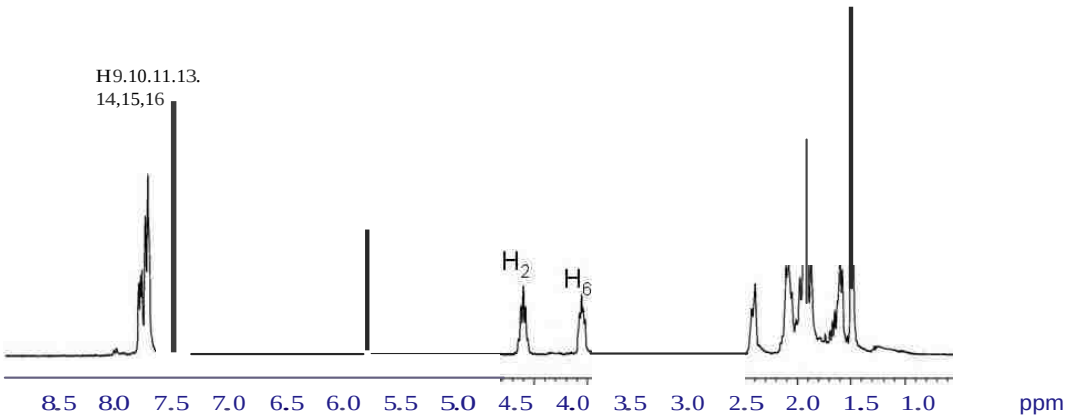
69

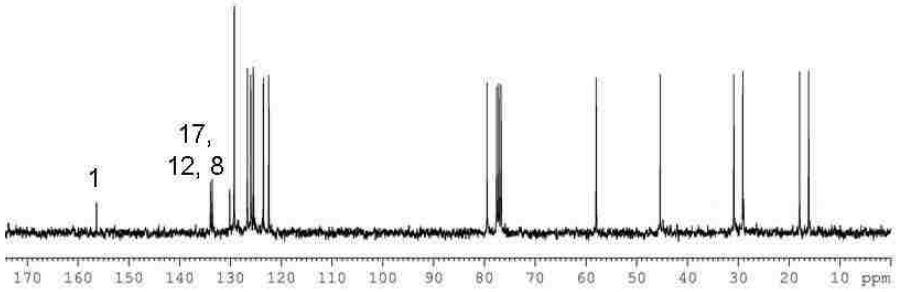
Using General Procedure D, S-33 of 93:7 er (398 mg, 2.0 mmol), TMEDA (1.2 mL, 8.0 mmol, 4.0 equiv), Et_2O (10 mL), s-BuLi (2.4 mL, 2.4 mmol, 1.0 M, 1.2 equiv), 1-naphthaldehyde (0.40 mL, 3.0 mmol, 1.5 equiv) for 2 h prior to warming to room temperature and addition of 2 mL MeOH, gave the crude product as a pale yellow oil. Purification by silica gel chromatography eluting with hexane-EtOAc (60:40) afforded 388 mg of 69 in 69% yield, >99:1 dr (syn:anti), 93:7 er for the major diastereomer. ^{13}C NMR (75.5 MHz, $CDCl_3$) o = 156.3 (C=O), 133.8 (C), 133.5 (C), 131.1 (C), 129.2 (CH), 126.7 (CH), 125.9 (CH), 125.4 (CH), 123.5 (CH), 122.5 (CH) 121.9 (CH), 79.4 (C), 57.8 (CH), 45.3 (CH), 30.7 (CH_2), 29.0 (CH_2), 17.8 (CH_2), 16.0 (CH_3).

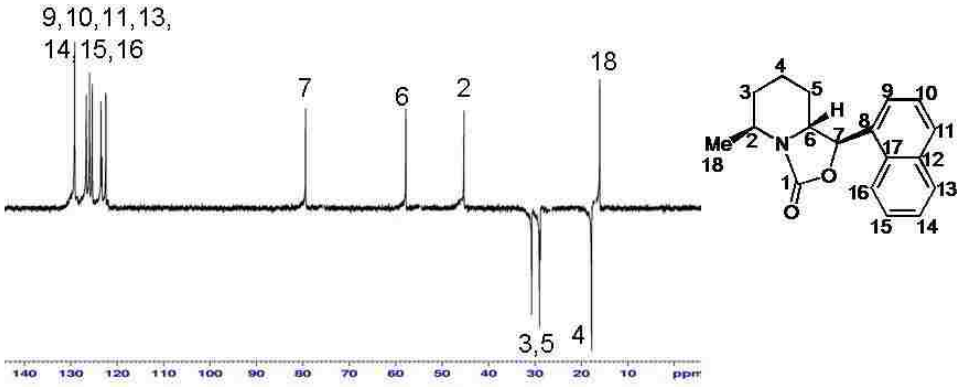



15.67
Me,QyNp
O
MW281
GC
?
(not diastereomer)
Time-->
Abundance
Scan 4326 (15.183 min): 8-ME-BOCPIP-NAPTH 153NMR.D\data.ms
MS
m/z-->


4
3
5
H
9
10
8
Me
2
N
6
7
11
17
12
18
1
O
16
13
O
15
14

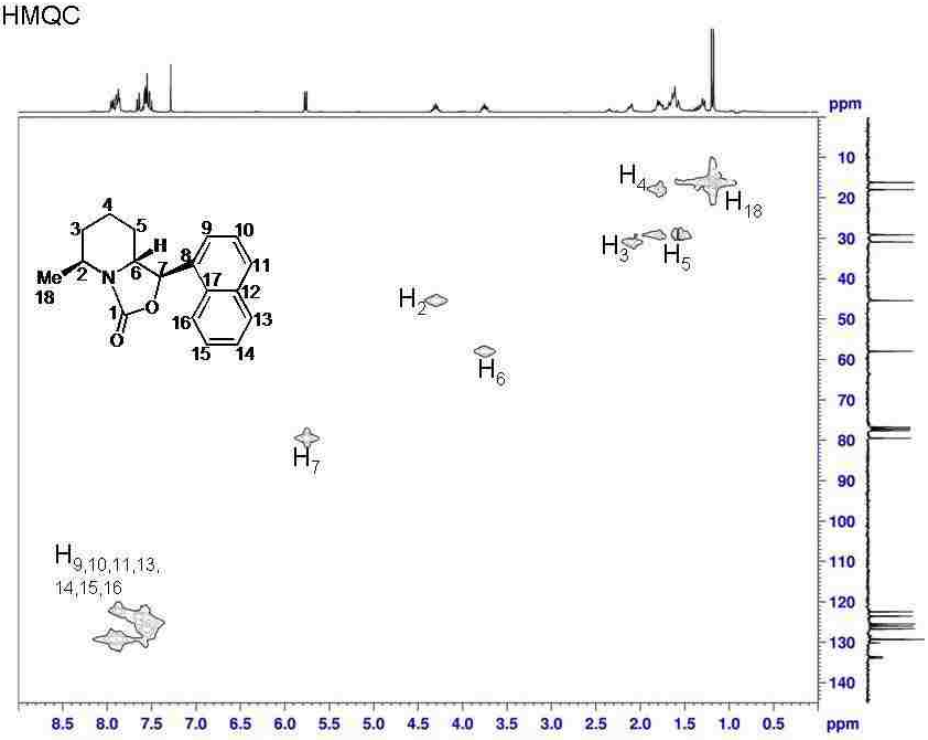

H9.10.11.13.
14,15,16
H2
H6
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0
ppm

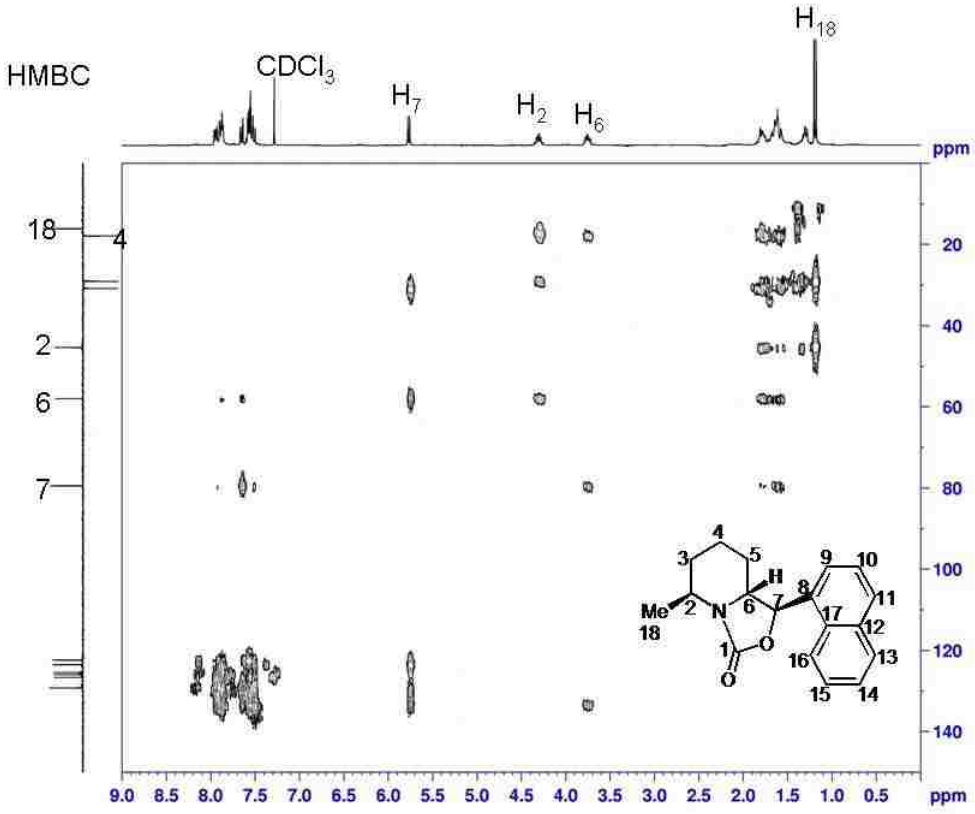

1
17,
12, 8
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


9,10,11,13,
14,15,16
7
6
2
18
3,5
4
140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

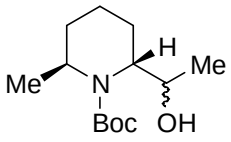
4
3
5
9
10
H
8
Me
2
N
6
7
11
17
18
1
O
12
16
13
O
15
14

HMQC


ppm
H4
H18
H3
H5
H2
H6
H7
H9,10,11,13,
14,15,16
10
20
30
40
50
60
70
80
90
100
110
120
130
140
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
ppm



27.9. Electrophilic quench with acetaldehyde: Synthesis of 70

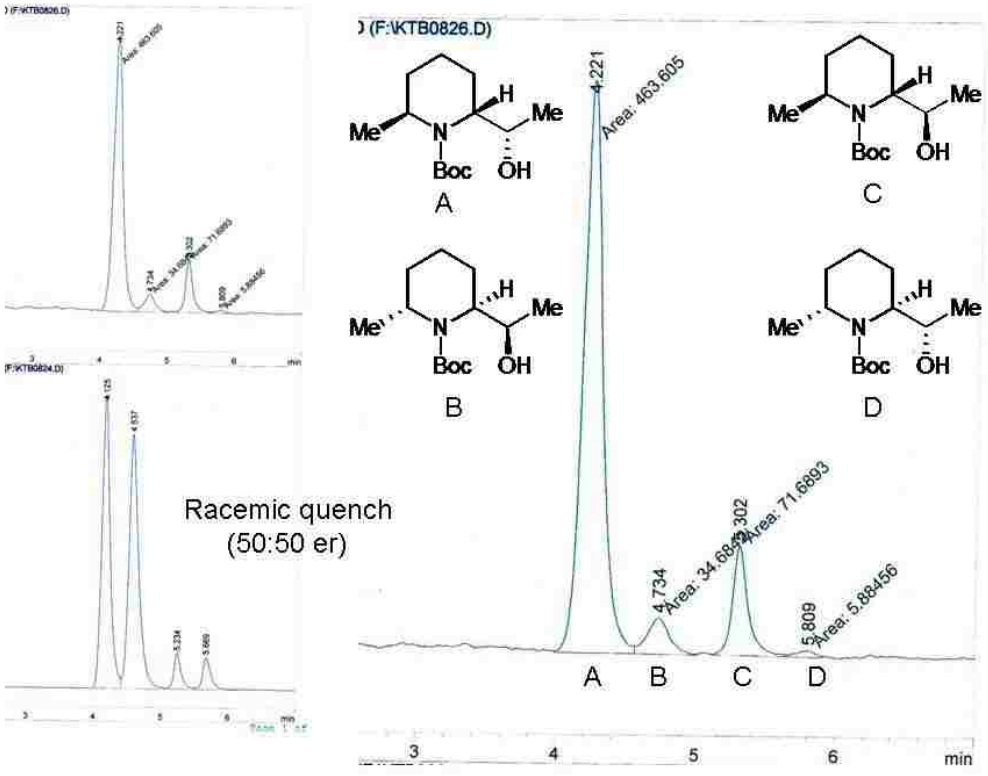


70

Using General Procedure D, S-33 of 93:7 er (398 mg, 2.0 mmol), TMEDA (1.2 mL, 8.0 mmol, 4.0 equiv), Et_2O (10 mL), s-BuLi (2.4 mL, 2.4 mmol, 1.0 M, 1.2 equiv), acetaldehyde (0.16 mL, 3.0 mmol, 1.5 equiv) for 2 h prior to addition of 2 mL MeOH, gave the crude product as a pale yellow oil. Purification by silica gel chromatography eluting with hexane-EtOAc (60:40) afforded 354 mg of 70 in 73% yield, 84:16 dr (anti:syn), 93:7 er for both diastereomers.

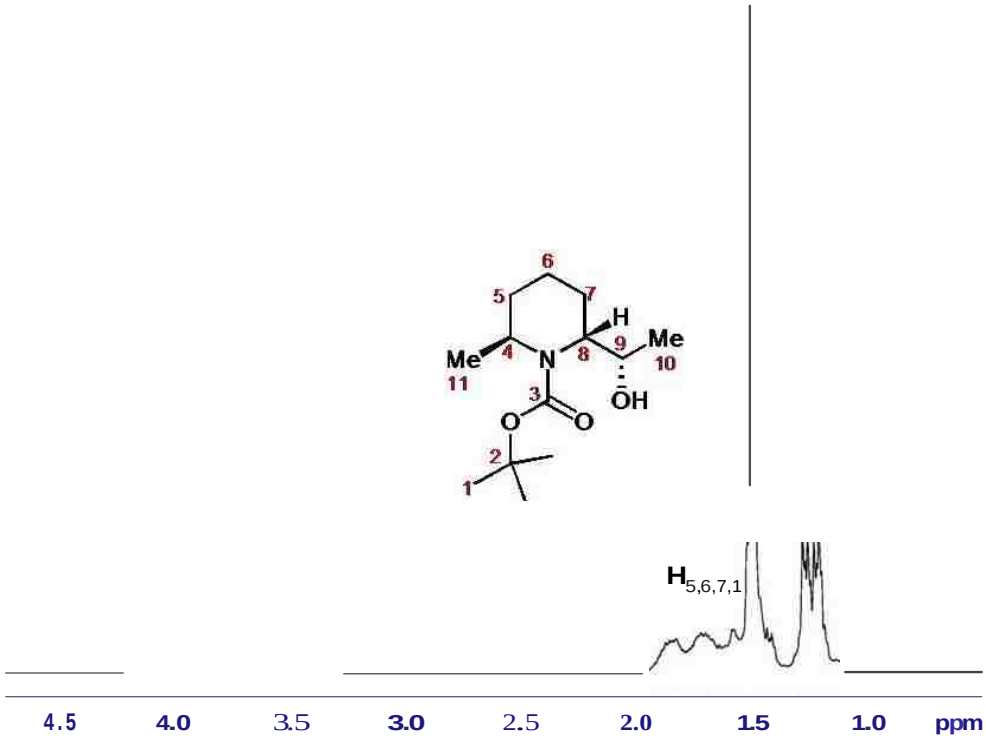
Data for the anti isomer; ^{13}C NMR (75.5 MHz, $CDCl_3$) o = 155.8 (C=O), 79.3 (C), 68.0 (CH), 57.8 (CH), 49.1 (CH), 28.5 (CH_2), 28.1 (CH_3), 22.7 (CH_2), 20.2 (CH_3), 18.1 (CH_3) and 17.2 (CH_2).

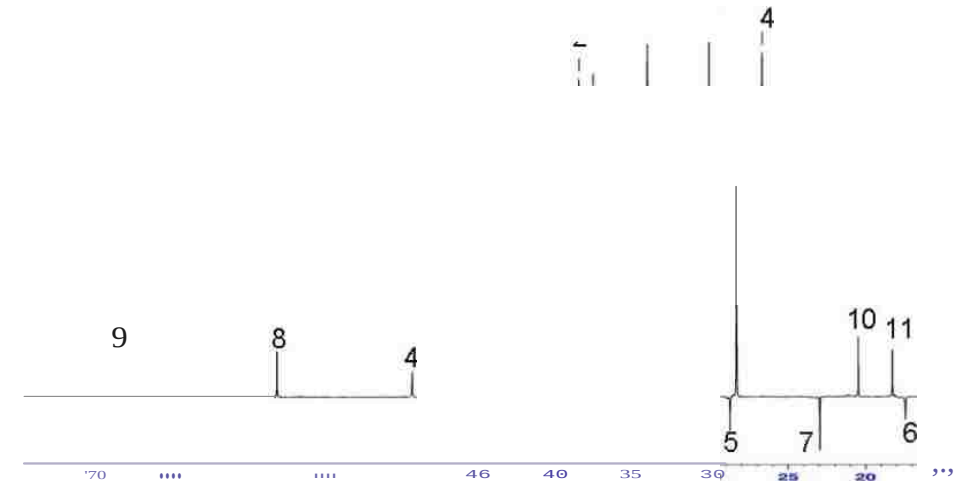
Data for the syn isomer; ^{13}C NMR (75.5 MHz, $CDCl_3$) o = 157.8 (C=O), 80.2 (C), 70.7 (CH), 58.3 (CH), 48.4 (CH), 28.5 (CH_3), 27.0 (CH_2), 23.4 (CH_2), 21.7 (CH_3), 19.8 (CH_3) and 14.8 (CH_2). The enantiomers were resolved by CSP-SFC under the following conditions: Column: Daicel Chiralcel OD-H, Flow Rate: 2.0 mL/min, Polarity Modifier%: 1.0% EtOH, Outlet Pressure = 150 psi, Oven Temperature = 35 ^{o}C. For the anti isomer, the major enantiomer elutes after 4.2 minutes and minor enantiomer elutes after 4.7 minutes. For the syn isomer, the major enantiomer elutes after 5.3 minutes and minor enantiomer elutes after 5.8 minutes.

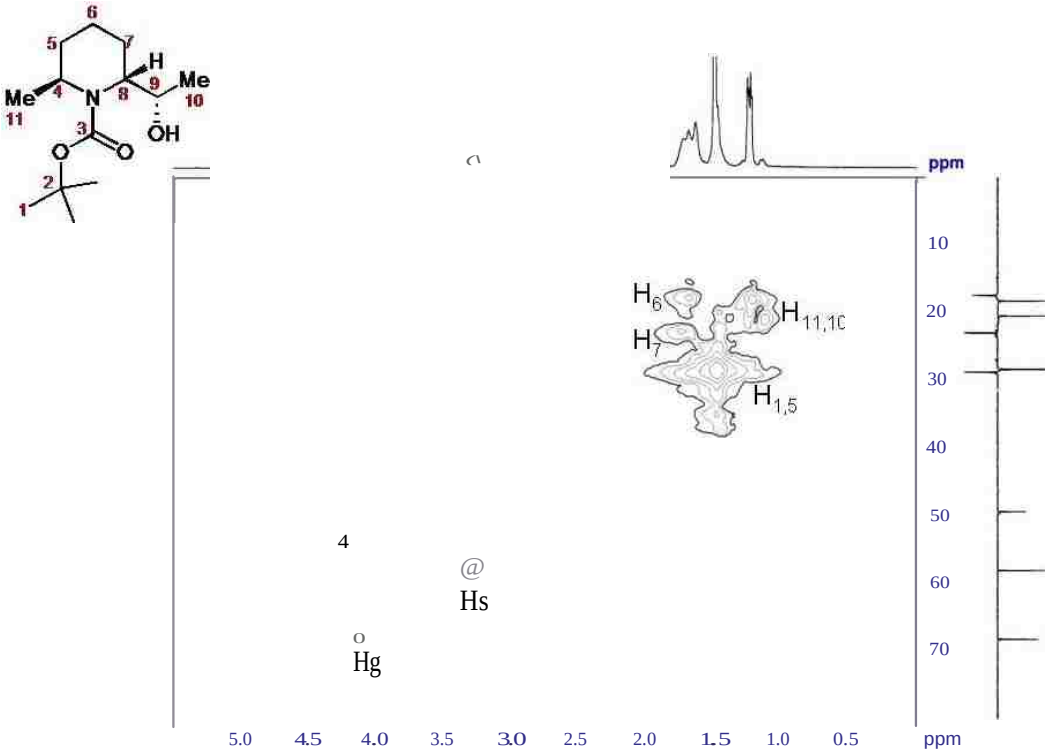


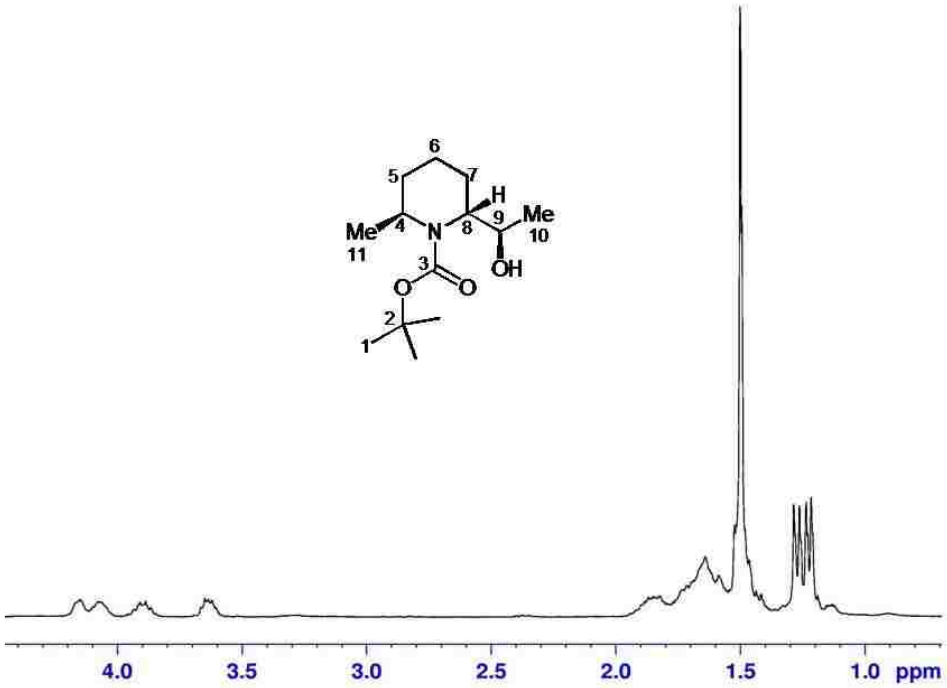
Alternatively, the er was evaluated by CSP-GC-MS on a β-cyclodextrin-permethylated 120 fused silica capillary column [30 m × 0.25 mm i.d., 20% permethylated β-cyclodextrin in SPB-35 poly(35% diphenyl/65% dimethyl)siloxane, initial temperature = 120 ^{o}C, final temperature = 200 ^{o}C, hold time = 5 min, rate = 1 ^{o}C/min. For the second diastereomer, the major enantiomer elutes

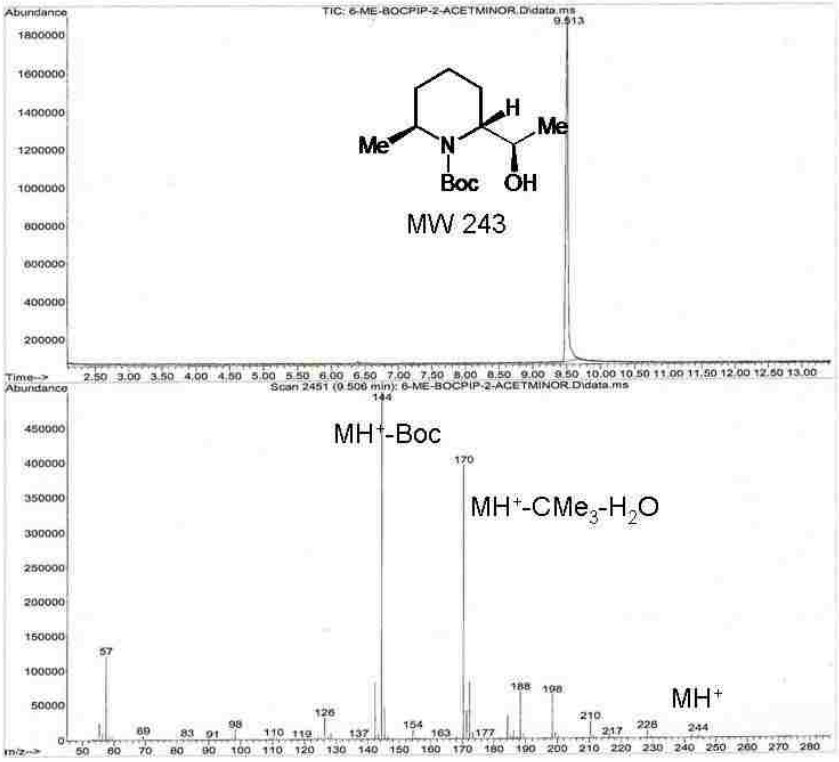
after 38.4 mmor enantiomer elutes after 39.2 mm. For the third diastereomer, the maJor enantiomer elutes after 44.2 min and the minor enantiomer elutes after 44.7 min.




4
9
8
4
10
11
5
7
6
46
40
35
30
25
20

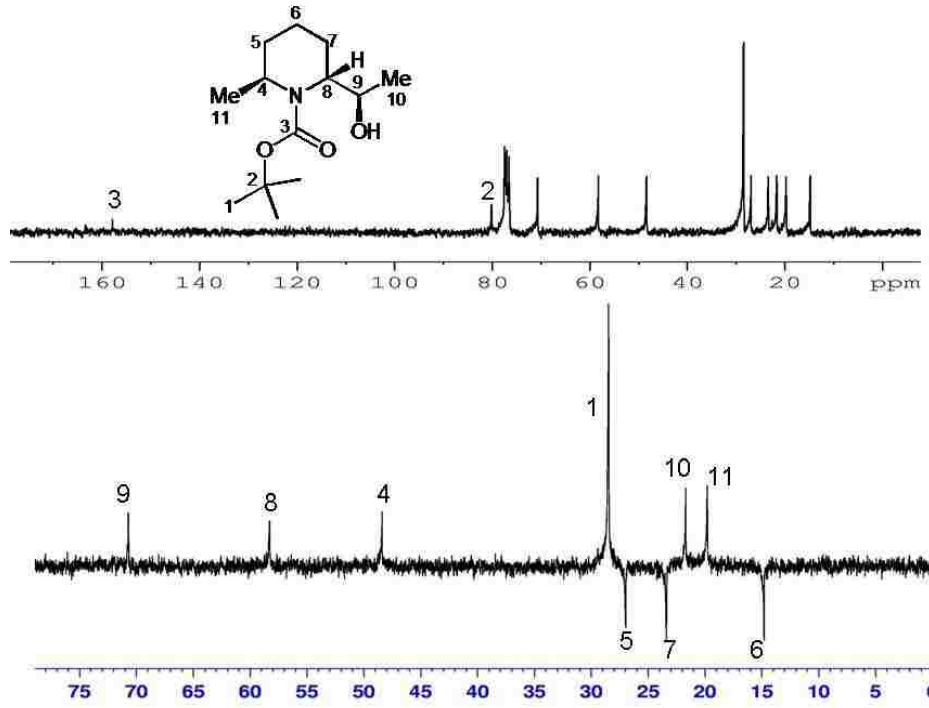

Me
Me
OH
ppm
H6
H7
H11,10
H1,5
10
20
30
40
50
60
70
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

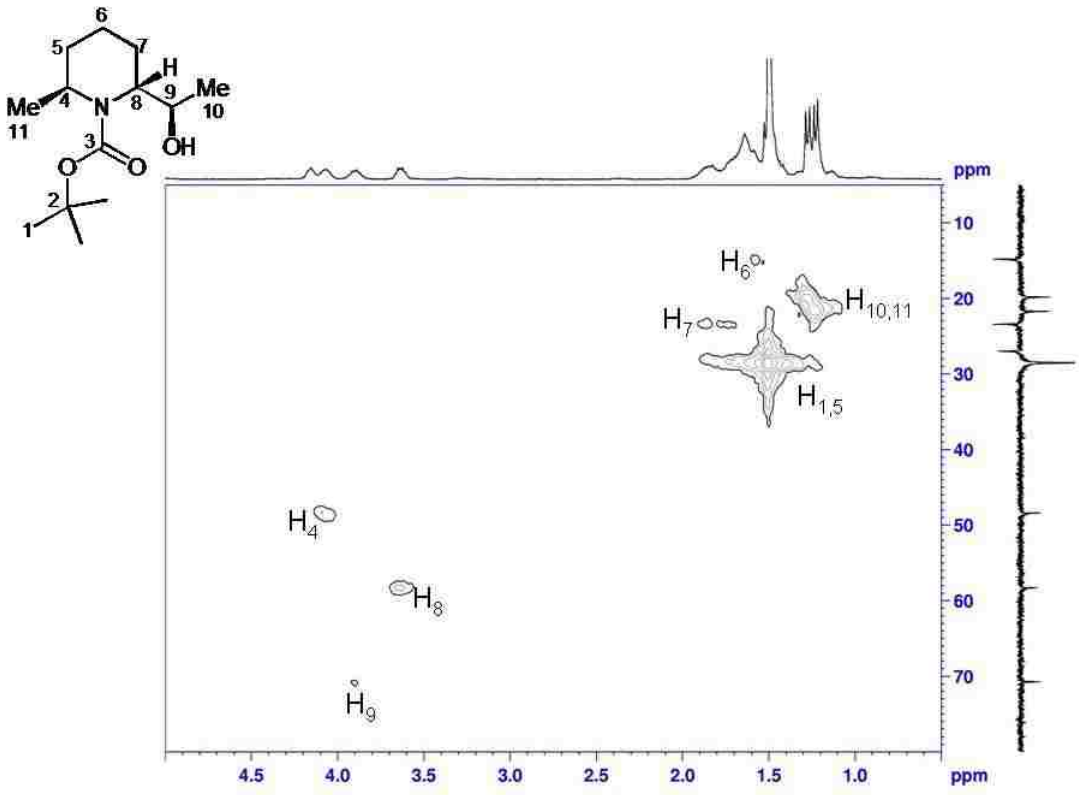

6
5
7
H
9
Me
10
Me
11
4
N
8
OH
3
O
O
2
1
4.0
3.5
3.0
2.5
2.0
1.5
1.0 ppm


Abundance
TIC: 6-ME-BOCPIP-2-ACETMINOR.Didata.ms
9.513
H
Me
Me
N
Boc
OH
MW 243
Time-->
Abundance
Scan 2451 (9.506 min): 6-ME-BOCPIP-2-ACETMINOR.Didata.ms
144
MH+-Boc
170
MH+-CMe3-H2O
MH+
m/z-->

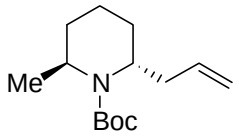
GC

MS


Me
11
4
N
8
H
9
Me
10
OH
3
O
O
2
1
6
5
7
3
2
160
140
120
100
80
60
40
20
ppm
1
9
8
4
10
11
5
7
6
75
70
65
60
55
50
45
40
35
30
25
20
15
10
5
0
ppm


Me
11
4
N
8
H
9
Me
10
OH
3
O
O
2
1
6
5
7
ppm
10
20
30
40
50
60
70
H6
H10,11
H7
H1,5
H4
H8
H9
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm

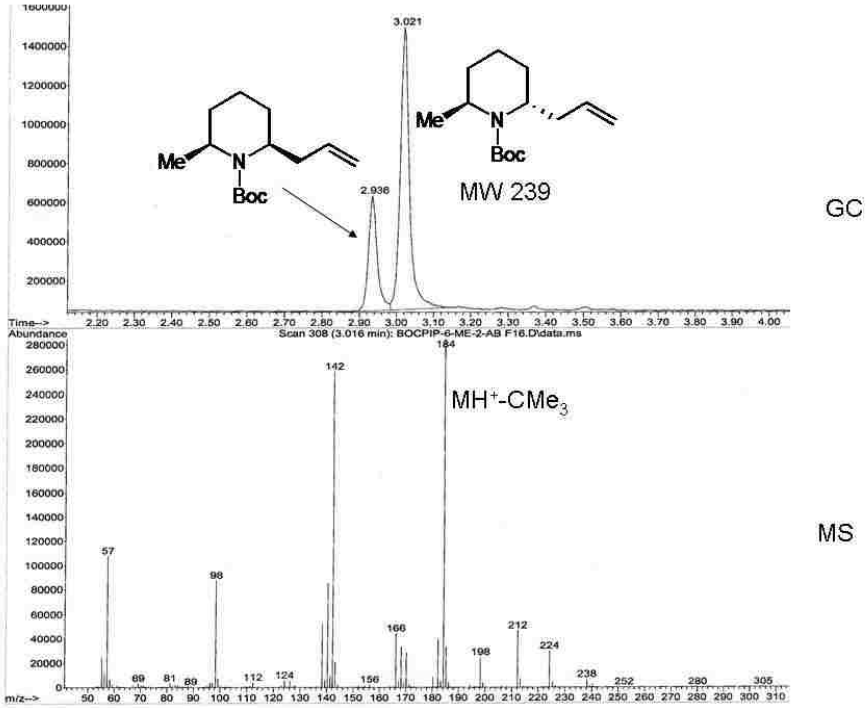
27.10. Electrophilic quench with allyl bromide: Synthesis of 71

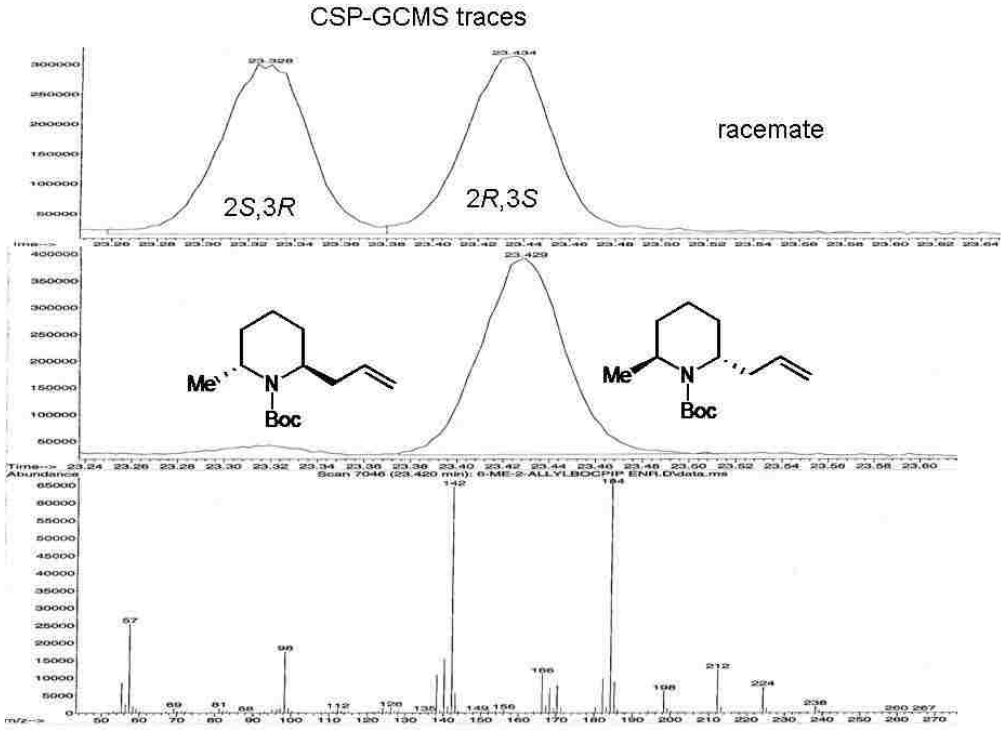


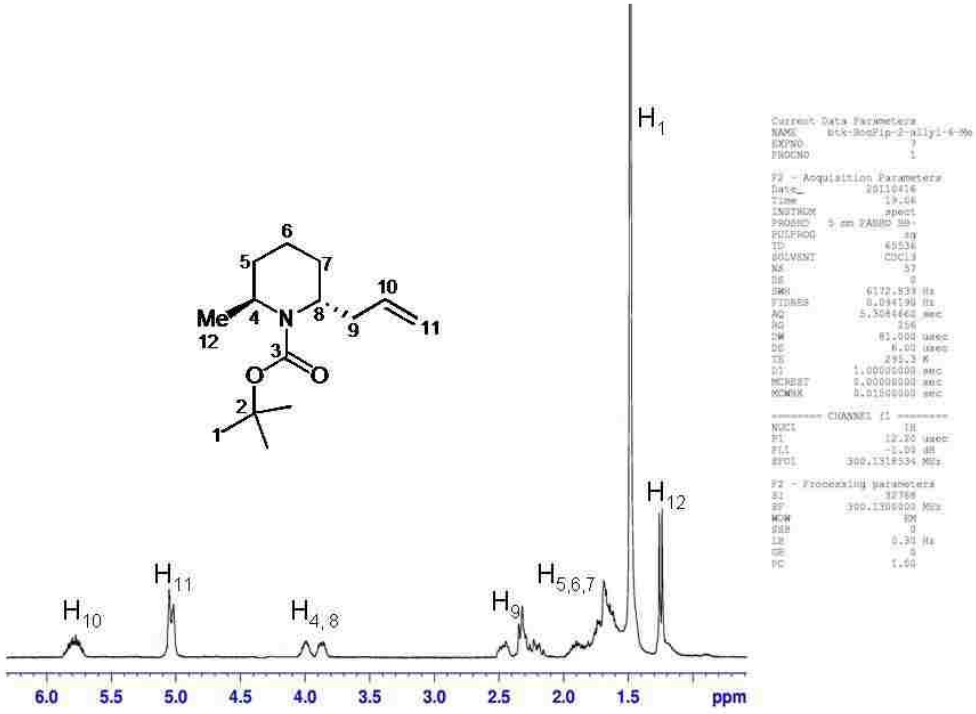
trans-**71**

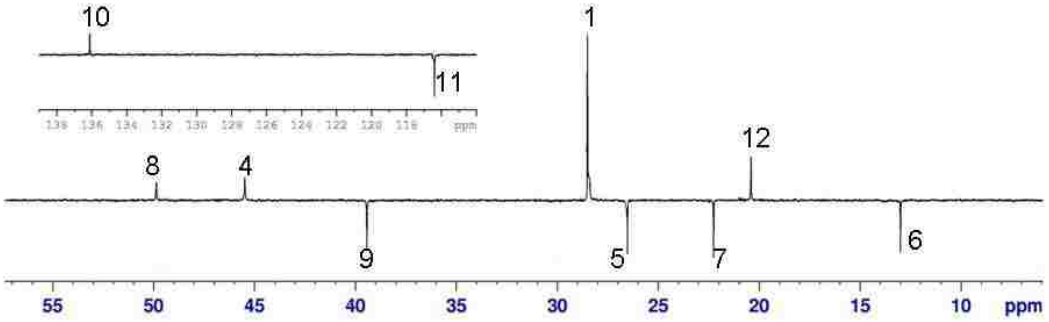
To an oven-dried, septum-capped round bottom flask equipped with a stir bar, was added freshly distilled TMEDA (1.2 mL, 8.0 mmol, 4.0 equiv) in Et_2O (10 mL) under argon. The solution was cooled to –78 °C and s-BuLi (2.4 mL, 2.4 mmol, 1.0 M in cyclohexanes, 1.2 equiv) was added. A solution of S-33 of 96:4 er (398 mg, 2.0 mmol) in Et_2O (5 mL) was added to the flask containing the TMEDA/s-BuLi mixture. After 30 min at this temperature, the mixture was transferred to the bath at –45 °C and allowed to stir for 3 h. After cooling to –78 °C, a solution of $ZnCl_2$ (180 mg, 1.3 mmol, 1.3 equiv) in THF (2 mL), was added. After 30 min, a solution of 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) was added. After 30 min, allyl bromide (150 mg, 1.5 mmol, 1.5 equiv) was added. The mixture was allowed to stir for 10 h at this temperature prior to addition of MeOH (2 mL) and warming to room temperature. A solution of NH_4Cl (5 mL) 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 chromatography eluting with hexane-EtOAc (98:2) afforded 272 mg of 71 as a colorless oil in 57% yield, 76:24 dr (trans:cis) and 96:4 er for the major diastereomer. (the minor diastereomer could not be resolved on our CSP-GC nor CSP-SFC columns). Data for the trans isomer; $[\alpha]_D^{22}$ +20.3 (c = 1.5, $CHCl_3$), lit[7] $[\alpha]_D^{25}$ +23.7 (c = 1.5, $CHCl_3$). All other data as reported.[7] ^{1}H NMR (300 MHz, $CDCl_3$) δ = 5.85-5.63 (1H, m), 5.1 to 4.9 (2H, m), 4.1 to 3.8 (2H, br, NCH), 2.4 to 2.1 (2H, m), 2.0 to 1.3 (15H, m), 1.2 (3H, d, CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 155.2 (C=O), 136.2 (CH), 116.5 (CH_2), 78.6 (C), 51.0 (CH), 46.2 (CH), 39.2 (CH_2), 30.0 (CH_2), 28.5 (3 x CH_3), 22.3

(CH_2), 20.8 (CH_3), 13.9 (CH_2). The er was evaluated by CSP-GC-MS 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, initial temperature = 100 ^{o}C, final temperature = 200 ^{o}C, hold time = 10 min, rate = 5 ^{o}C/min.




CSP-GCMS traces
racemate
2S,3R
2R,3S
23.328
23.434
23.429
Me
N
Boc
Scan 7046 (23.420 min): 6-ME-2-ALLYLBOCPIP ENR.D\data.ms
142
194
57
98
166
212
224
238
200.267


H1
H12
H11
H10
H4, 8
H9
H5,6,7
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
ppm
Me
12
N
4
8
9
10
11
3
O
2
1
5
6
7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11
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12
8
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9
5
7
6
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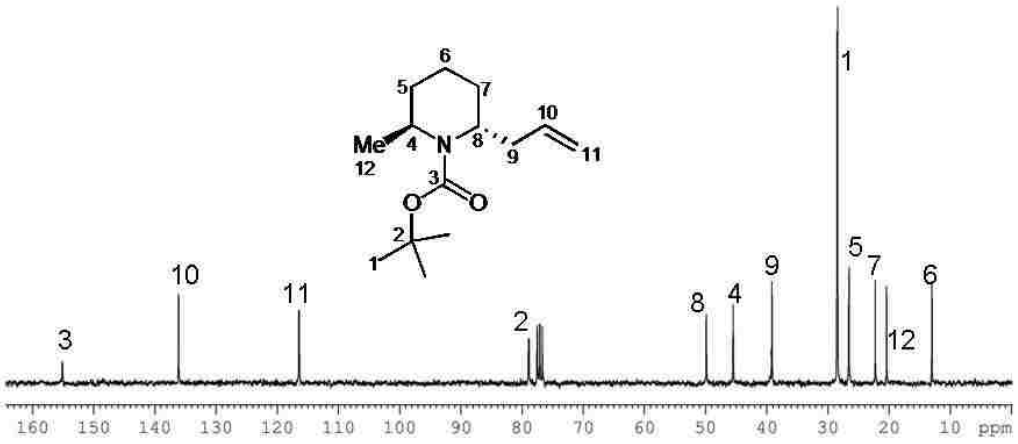
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N
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2
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5
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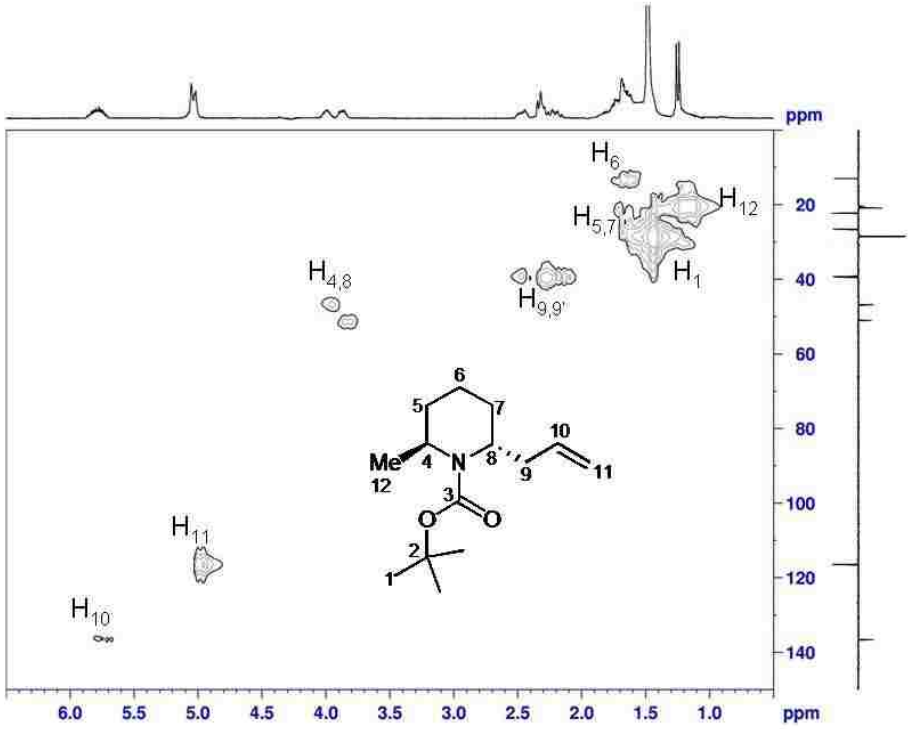
6
12
160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


ppm
H6
H12
H5,7
H1
H4,8
H9,9'
H11
H10
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12
N
O
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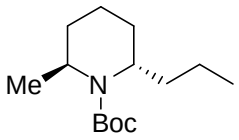
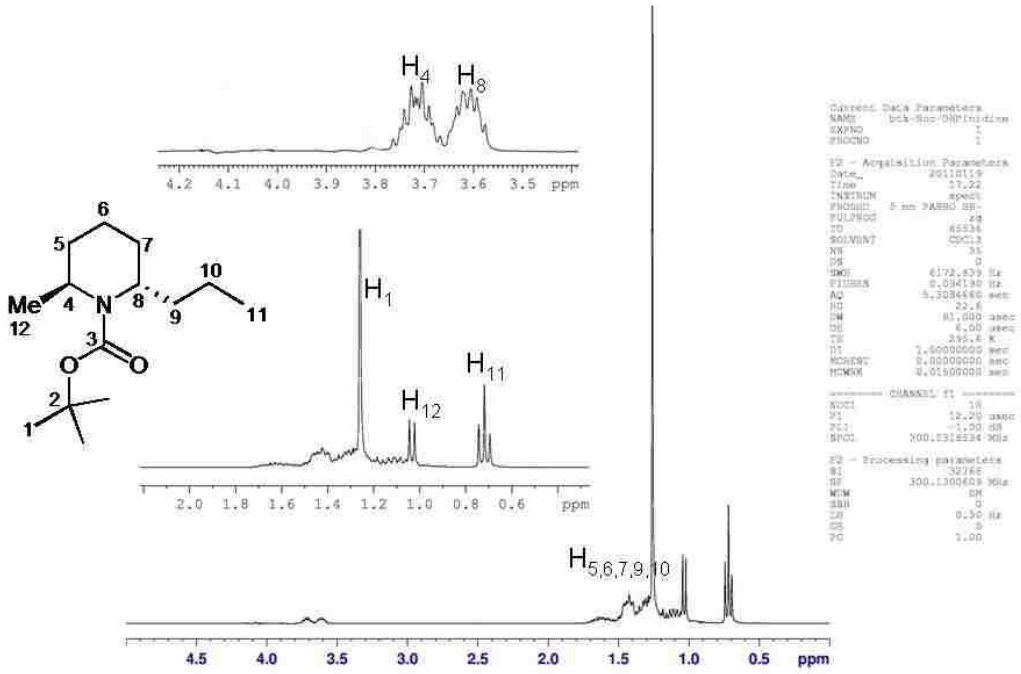
3
4
5
6
7
8
9
10
11
20
40
60
80
100
120
140
6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm

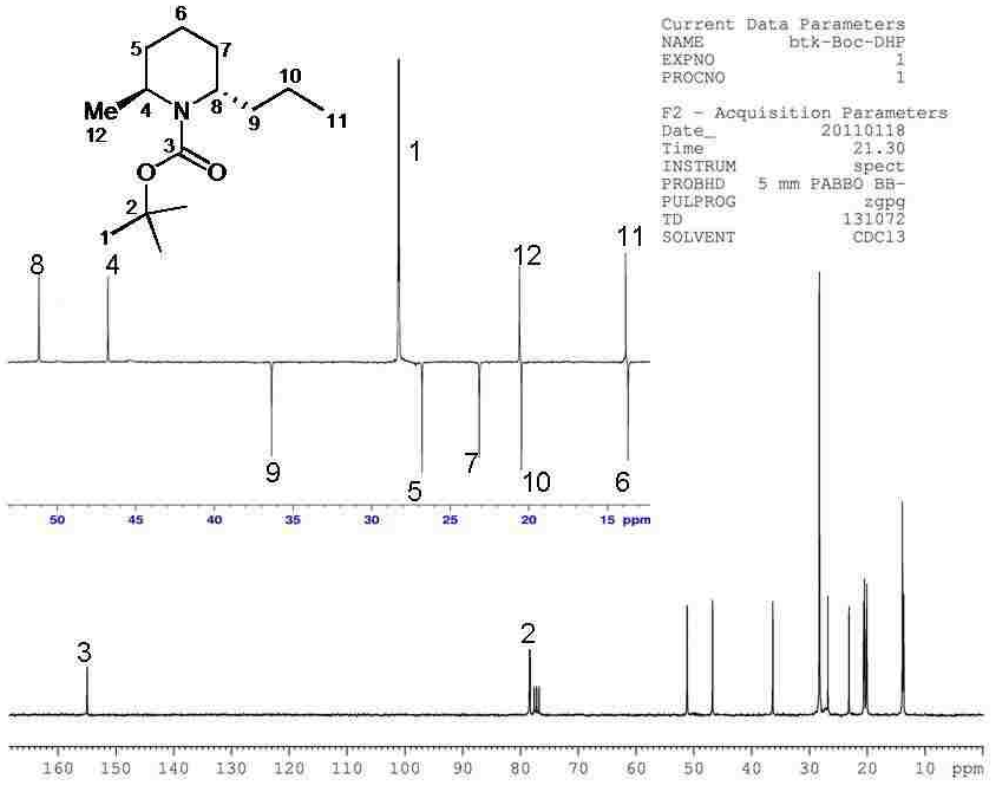
27.11. Synthesis of (–)-N-Boc-epidihydropinidine



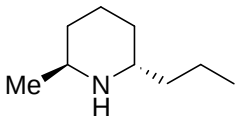
trans-**72**

$Pd(OH)_2$ (24 mg, 0.17 mmol, 40 mol%) was added to a solution of trans-71 (100 mg, 0.42 mmol, 1.0 equiv) in freshly distilled MeOH (5 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 92 mg of 72 in 91% yield. $[a]_D^{22}$ +37.7 (c = 0.25, $CHCl_3$), lit[7] $[a]_D^{25}$ +40.4 (c = 0.25, $CHCl_3$). All other data as reported.[7]





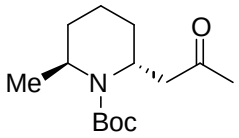
5.12. N-Boc-deprotection of trans-72: Synthesis of (–)-epidihydropinidine



(-)-Epidihydropinidine

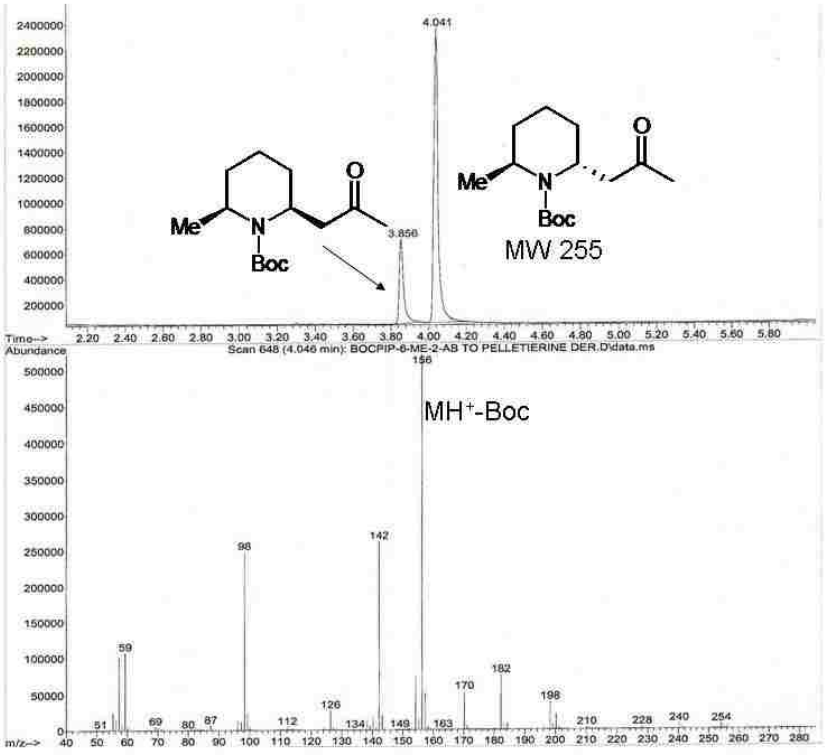
To trans-72 (85 mg, 0.35 mmol) dissolved in CH_2Cl_2 (1.0 mL), was added CF_3CO_2H (0.5 mL) under argon at 0 ^oC. The mixture was stirred for 5 h at this temperature and concentrated in vacuo to obtain the salt. The salt was basified to pH 10 – 12 with 20% $NaOH_{(aq)}$. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 2 mL). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure to give 50 mg of (–)-epidihydropinidine in 100% yield, $[a]_D^{22}$ –2.2 (c = 0.25, $CHCl_3$), lit[7]. for enantiopure (–)-epidihydropinidine $[a]_D^{25}$ –2.7 (c = 0.2, $CHCl_3$).

27.13. Synthesis of N-Boc-epipinidinone: trans-73



73

CuCl (42 mg, 0.42 mmol, 1 equiv) and $PdCl_2$ (8 mg, 0.042 mmol, 10 mol%) were dissolved in 1.0 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 trans-71 (100 mg, 0.42 mmol, 1.0 equiv) in 1.0 mL of DMF:H_2O (10:1) was added to the reaction mixture and stirred for 18 h. After complete conversion of trans-17 as indicated by TLC analysis, the reaction mixture was quenched with 20% $KHSO_4$ (1 mL) and extracted with Et_2O (3 x 2 mL). The combined organic layers were washed with saturated $NaHCO_3$ (1 mL), then with brine (1 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 98 mg of 73 in 92% yield. ^{1}H NMR: o 4.6 (br, m, 1H), 4.3 (br, m, 1H), 2.8-2.5 (m, 2H), 2.2 (s, 3H), 1.8-1.3 (m, 15H), 1.1 (d, 3H); ^{13}C NMR (75.5 MHz): o 206.5, 154.6, 79.1, 48.3, 45.4, 29.9, 29.7, 28.4 (3C), 27.7, 20.0, 13.5.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Boc
O
MW 255
Time-->
Abundance
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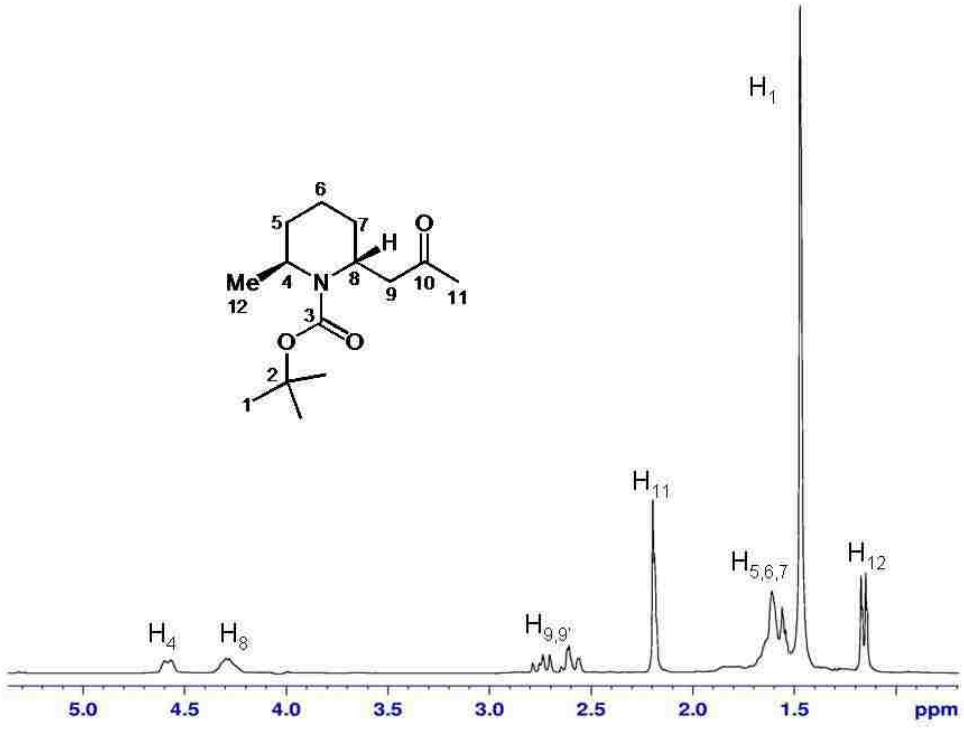
98
142
59
182
170
198
126
GC
MS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H5,6,7
H12
H4
H8
H9,9'
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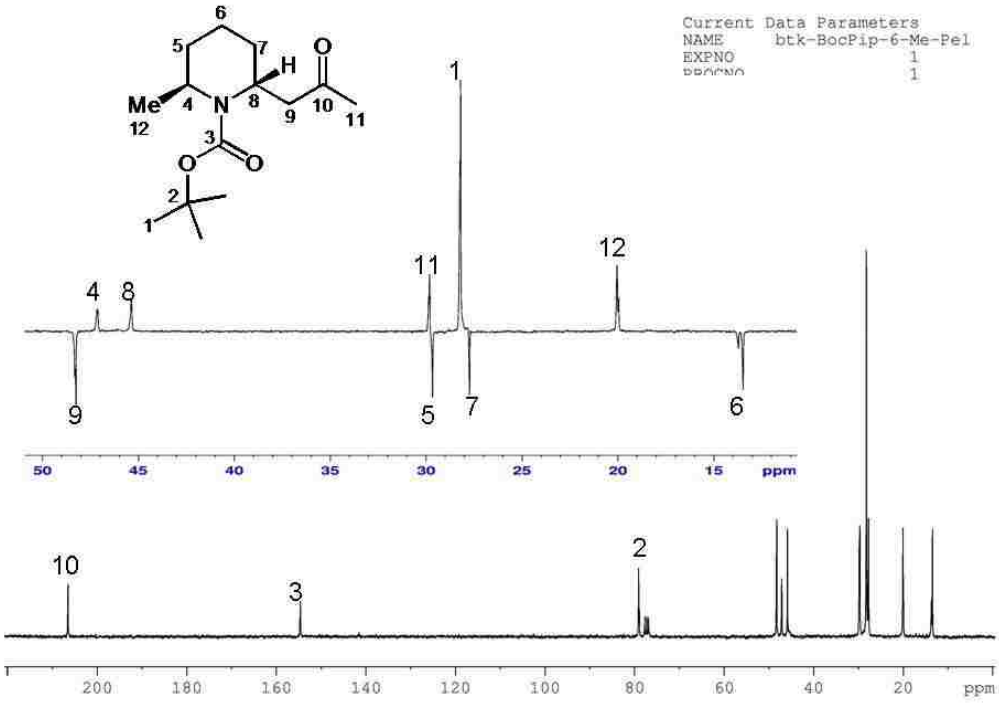
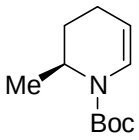
3.0
2.5
2.0
1.5
ppm



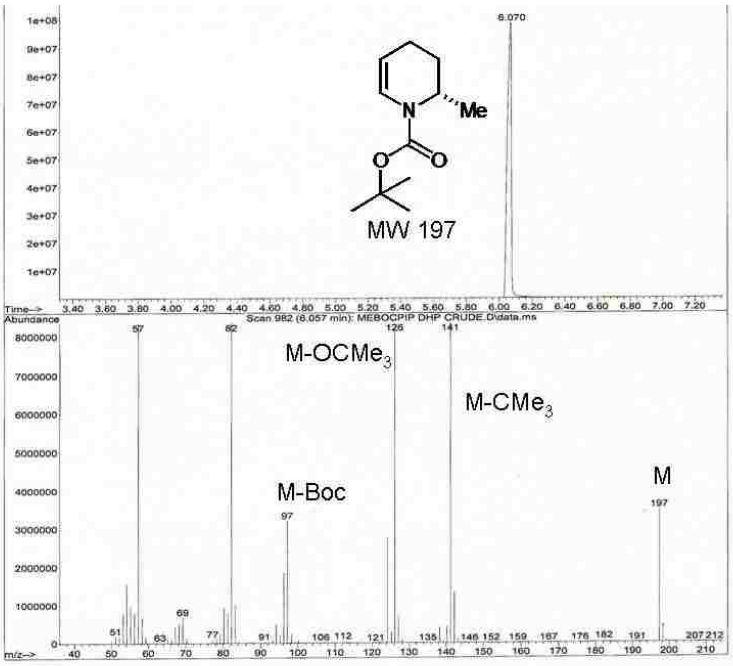
27.14. Electrophilic quench with Iodine: Synthesis of 74

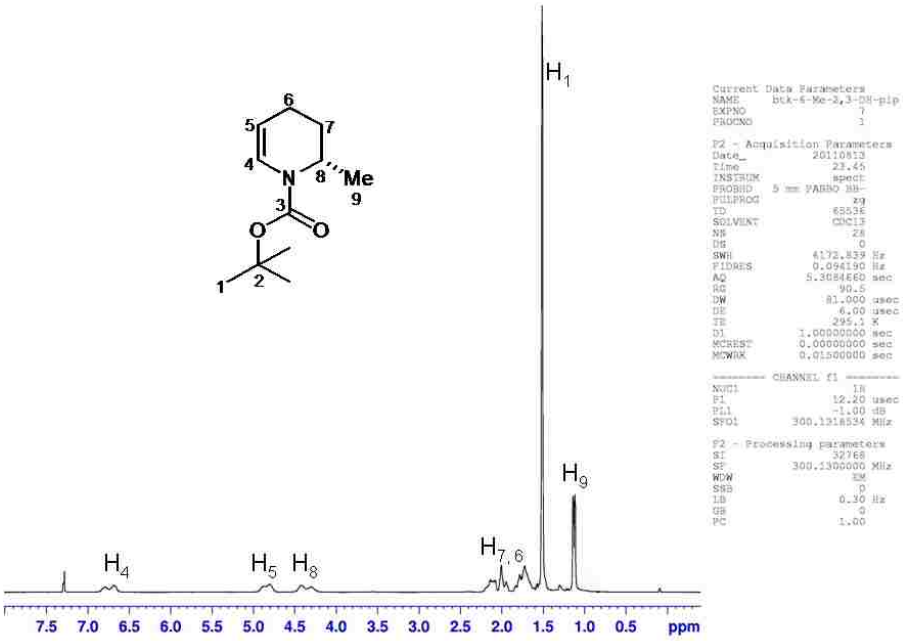


S-**74**

To an oven-dried, septum-capped round bottom flask equipped with a stir bar, was added freshly distilled TMEDA (0.6 mL, 4.0 mmol, 4.0 equiv) in Et_2O (5 mL) under argon. The solution was cooled to –78 °C and s-BuLi (1.2 mL, 1.2 mmol, 1.0 M in cyclohexanes, 1.2 equiv) was added. A solution of S-33 of 96:4 er (199 mg, 1.0 mmol) in Et_2O (5 mL) was added to the flask containing the TMEDA/s-BuLi mixture. After 30 min at this temperature, the mixture was transferred to the bath at –45 °C and allowed to stir for 3 h. After cooling to –78 °C, a solution of $ZnCl_2$ (180 mg, 1.3 mmol, 1.3 equiv) in THF (2 mL), was added. After 30 min, a solution of I_2 in THF (3 mL, 1.0 M, 3.0 equiv) was added. The mixture was allowed to stir for 1 h at this temperature before warming to room temperature slowly. After 18 h, a solution of 10%

NH_4OH(aq) (5 mL) was added dropwise and the mixture was stirred for 20 min. The aqueous layer was extracted with Et_2O (3 x 10 mL) and washed with brine (2 x 10 mL). The combined organic layers were dried over Na_2SO_4 and evaporated to give the crude product. Purification by silica gel chromatography eluting with hexane-EtOAc (99:1) afforded 156 mg of 74 as a colorless liquid in 79% yield 96:4 er. ^{1}H NMR (300 MHz, $CDCl_3$) o 6.8 to 6.2 (1H, m), 4.9 to 4.7 (1H, m), 4.5 to 4.3 (1H, m), 2.2 to 1.3 (13H, m), 1.1 (3H, d); ^{13}C NMR (75.5 MHz, $CDCl_3$), mixture of rotomers, o = 152.4 and 151.8 (C=O), 124.0 and 123.7 (CH), 104.4 and 104.0 (CH_2), 80.1 (C), 46.5 and 45.4 (CH), 28.3 (3 x CH_3), 26.4 (CH_2), 17.3 (CH_2), 17.1 and 16.6 (CH_3).



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PROCNO                      1

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PULPROG                  zg
TD                     65536
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FIDRES              0.063690 Hz
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RG                       90.5
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DE                      6.00 usec
TE                     295.1 K
D1                 1.00000000 sec
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MCWRK              0.01500000 sec

-------- CHANNEL f1 --------
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PL1                    -1.00 dB
SFO1              300.1318554 MHz

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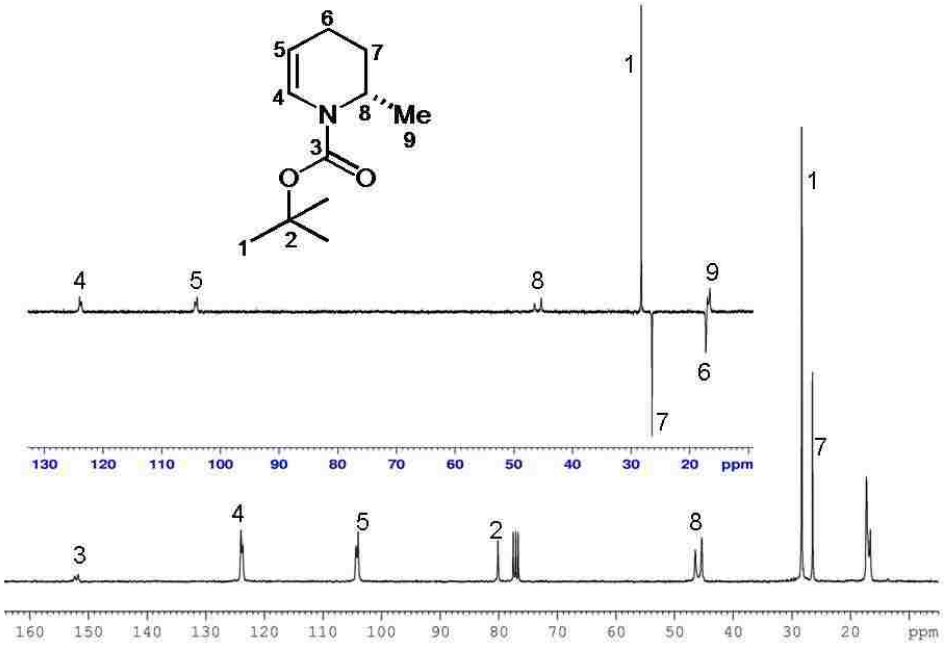
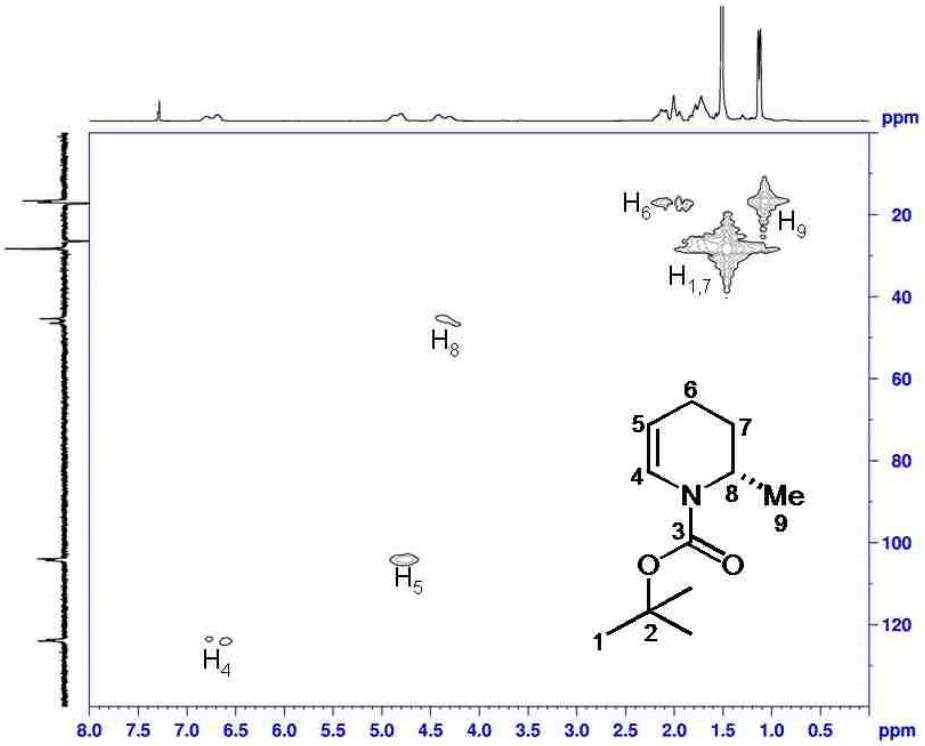
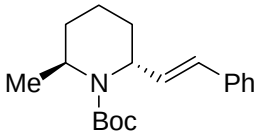




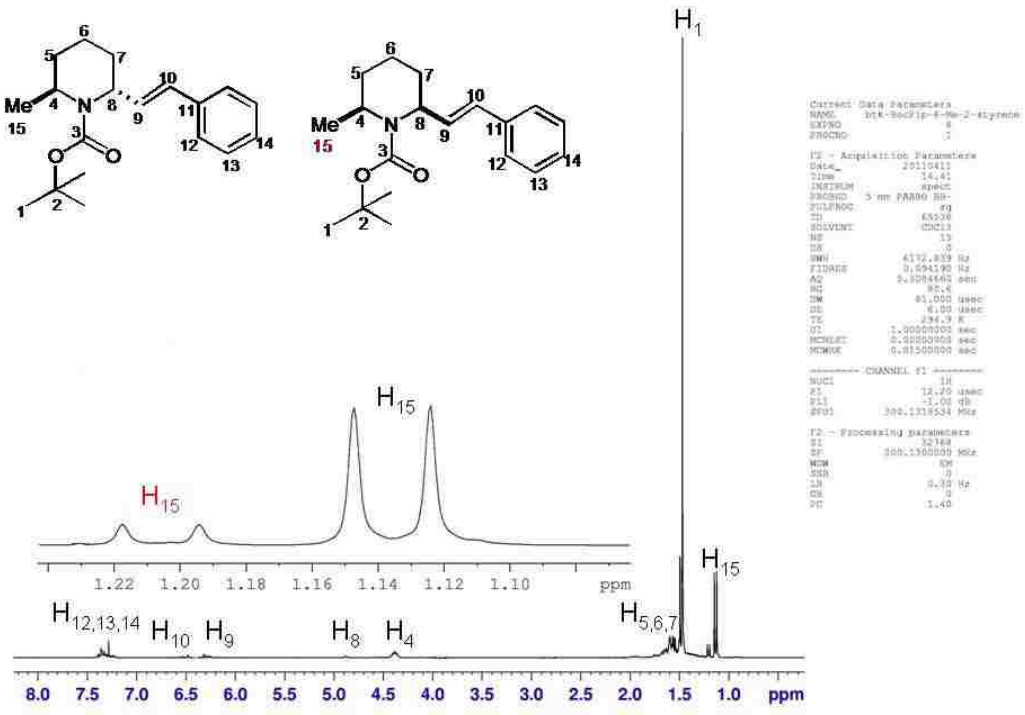
27.15. Electrophilic quench with ℐ-bromostyrene: Synthesis of 75

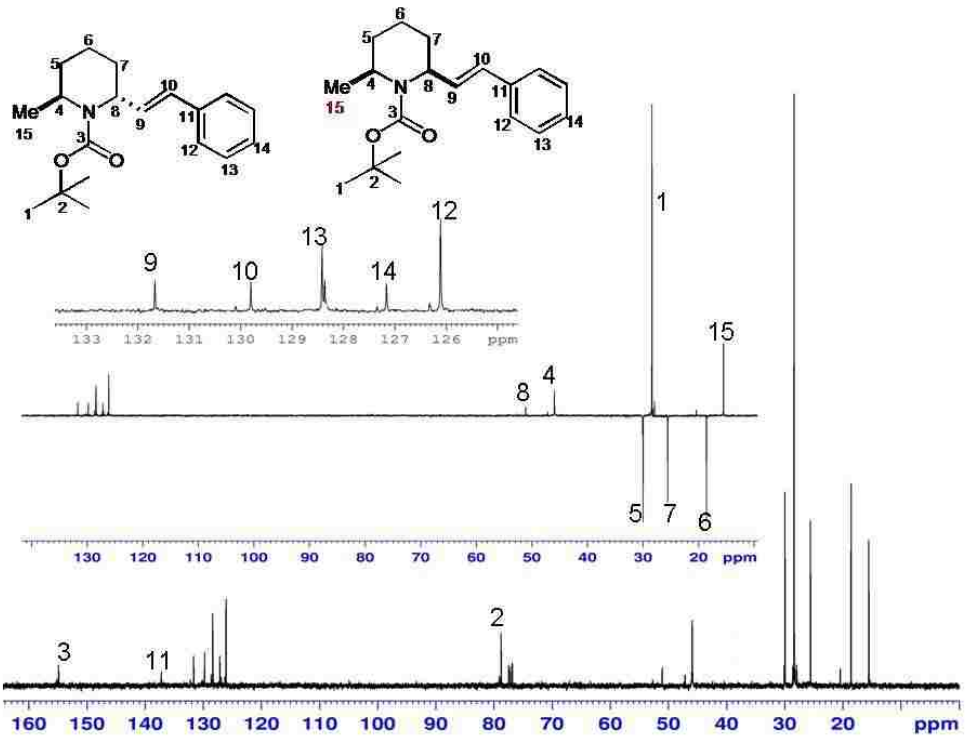


trans-**75**

To an oven-dried, septum-capped round bottom flask equipped with a stir bar, was added freshly distilled TMEDA (1.2 mL, 8.0 mmol, 4.0 equiv) in Et_2O (10 mL) under argon. The solution was cooled to –78 °C and s-BuLi (2.4 mL, 2.4 mmol, 1.0 M in cyclohexanes, 1.2 equiv) was added. A solution of S-33 of 96:4 er (398 mg, 2.0 mmol) in Et_2O (5 mL) was added to the flask containing the TMEDA/s-BuLi mixture. After 30 min at this temperature, the mixture was transferred to the bath at –45 °C and allowed to stir for 3 h. After cooling to –78 °C, a solution of $ZnCl_2$ (180 mg, 1.3 mmol, 1.3 equiv) in THF (2 mL), was added. After 30 min, the mixture was warmed to room temperature slowly. After 30 minutes at room temperature, $Pd(OAc)_2$ (10 mg, 0.04 mmol, 4 mol%), t-$Bu_3P{\cdot}HBF_4$ (23 mg, 0.08 mmol, 8 mol%) and ℐ-bromostyrene (238

mg, 0.18 mL, 1.3 mmol, 1.3 equiv), were added sequentially. After stirring for 18 h at room temperature, NH_4OH (10 mL, 10% aqueous solution) was added dropwise and the mixture was stirred for 30 minutes. The resulting slurry was filtered through Celite and rinsed with 10 mL Et_2O. The filtrate was washed with 1 M $HCl_{(aq)}$ (20 mL), then with water (2 x 10 mL), dried over Na_2SO_4 and evaporated under reduced pressure to obtain the crude product. Purification by silica gel column chromatography eluting with Hexane-EtOAc (98:2) afforded 184 mg of 75 in 61% yield, 89:11 dr (trans:cis), 96:4 er for for both diastereomers. ^{1}H NMR: o 7.38-7.15 (m, 5H), 6.39 (dd, 1H), 6.18 (dd, 1H), 4.95 (br, s, 1H), 4.41 (m, 1H), 1.82-1.40 (m, 15H), 1.1 (d, 3H); ^{13}C NMR (75.5 MHz): o 154.8, 137.2, 131.7, 129.9, 128.4 (2C), 122.3, 126.2 (2C), 78.8, 51.1, 45.9, 38.6, 30.0, 28.4 (3C), 25.6, 18.6, 15.6. The er was determined by CSP-SFC as follows: Column: Pirkle-Whelk-O-1, Flow Rate: 2.0 mL/min, Polarity Modifier %: 2.0% EtOH, Outlet Pressure = 150 psi, Oven Temperature = 35 ^{o}C.

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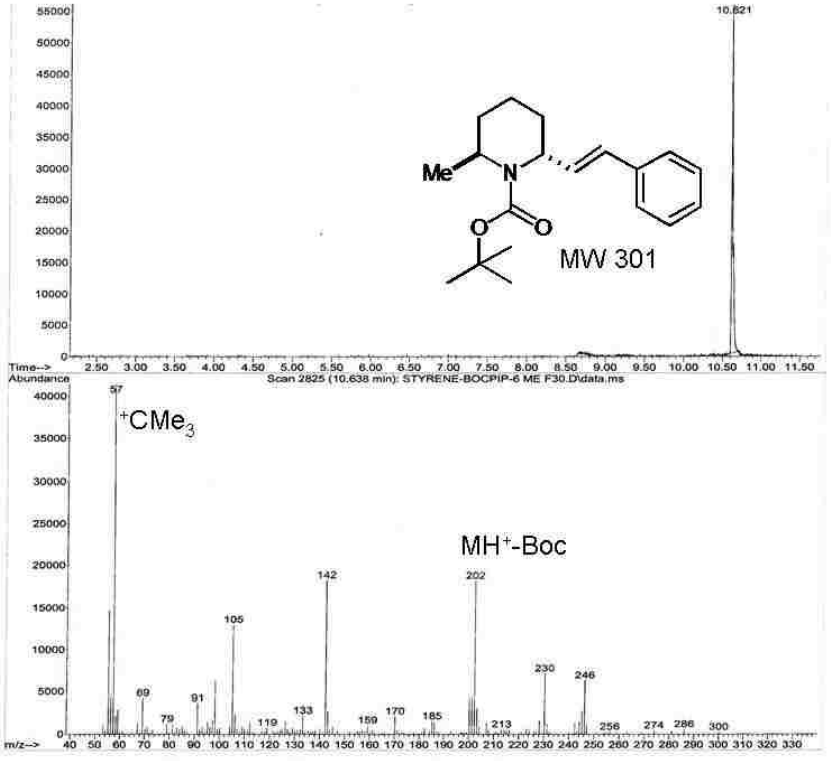
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Abundance
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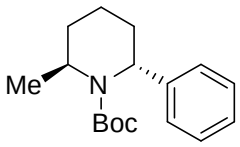
MH+-Boc
m/z-->

GC

MS

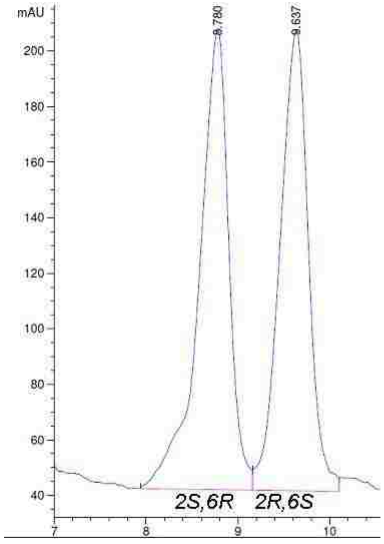
27.16. Electrophilic quench with bromobenzene: Synthesis of 76



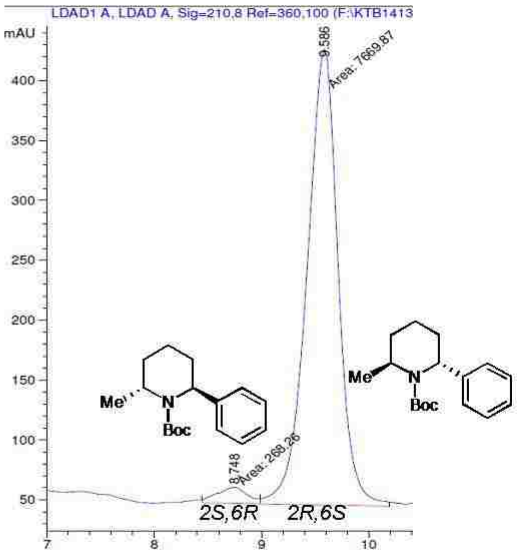
trans-**76**

To an oven-dried, septum-capped round bottom flask equipped with a stir bar, was added freshly distilled TMEDA (1.2 mL, 8.0 mmol, 4.0 equiv) in Et_2O (10 mL) under argon. The solution was cooled to –78 °C and s-BuLi (2.4 mL, 2.4 mmol, 1.0 M in cyclohexanes, 1.2 equiv) was added. A solution of S-33 of 96:4 er (398 mg, 2.0 mmol) in Et_2O (5 mL) was added to the flask containing the TMEDA/s-BuLi mixture. After 30 min at this temperature, the mixture was transferred to the bath at –45 °C and allowed to stir for 3 h. After cooling to –78 °C, a solution of $ZnCl_2$ (180 mg, 1.3 mmol, 1.3 equiv) in THF (2 mL), was added. After 30 min, the mixture was warmed to room temperature slowly. After 30 minutes at room temperature, $Pd(OAc)_2$ (10 mg, 0.04 mmol, 4 mol%), t-$Bu_3P{\cdot}HBF_4$ (23 mg, 0.08 mmol, 8 mol%) and phenyl bromide (0.30 mL, 1.3 mmol, 1.3 equiv), were added sequentially. After stirring for 18 h at room temperature, NH_4OH (10 mL, 10% aqueous solution) was added dropwise and the mixture was stirred for 30 minutes. The resulting slurry was filtered through Celite and rinsed with 10 mL Et_2O. The filtrate was washed with 1 M $HCl_{(aq)}$ (20 mL), then with water (2 x 10 mL), dried over Na_2SO_4 and evaporated under reduced pressure to obtain the crude product. Purification by silica gel column chromatography eluting with Hexane-EtOAc (98:2) afforded 401 mg of 76 in 73% yield, 87:13 dr (trans:cis), 96:4 er for both diastereomers. The er was determined by CSP-SFC as follows: Column: Pirkle-Whelk-O-1, Flow Rate: 1.0 mL/min, Polarity Modifier %: 3.0% EtOH, Outlet Pressure = 150 psi, Oven Temperature = 35 ^{o}C.

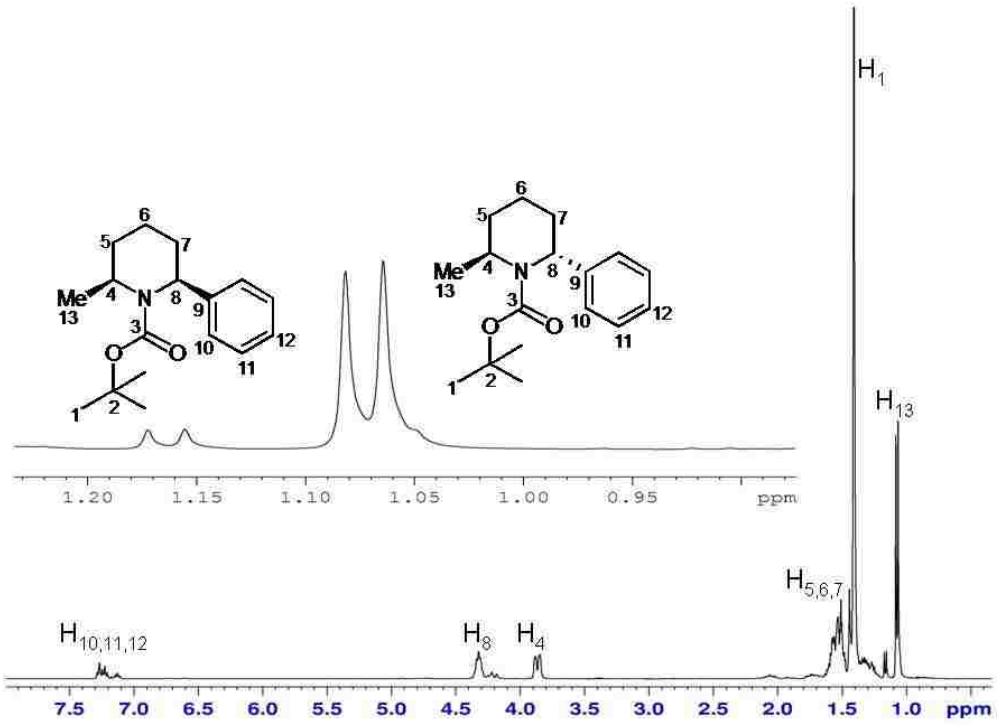
CSP-SFC traces

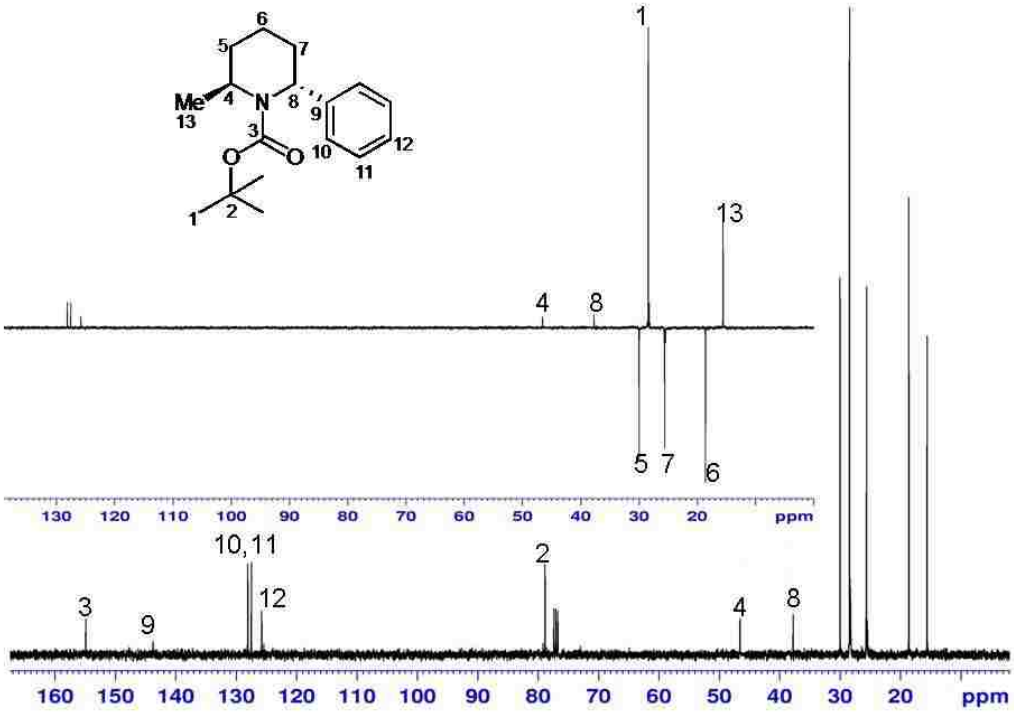


racemate



Enantioenriched

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5 7
6
130 120 110 100 90 80 70 60 50 40 30 20 ppm
10,11
2
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160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm

4.6. References

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Concluding Remarks

Our study on the dynamics and catalytic resolution of selected chiral organolithium species has led to the following important findings:

1. TMEDA facilitates the generation of 4 by deprotonation at low temperatures.
2. Transmetalation of 3 to 4 occurs slowly and 4 exhibits loss of configurational stability in the absence of any ligands even at –78 °C.
3. Excess TMEDA stabilizes the anion configuration of 4.
4. TMEDA accelerates DTR and based on the overall yields and selectivities, other achiral ligands do not enhance the DTR of 4 as effectively as TMEDA.
5. The rate law for the DTR, using excess monolithiated diaminoalkoxide 6, is: $\frac{d[S\text{-}\mathbf{4}]}{dt} = k_{DTR}[R\text{-}\mathbf{4}][TMEDA][\mathbf{6}]^{-0.5}$.
6. DTR of 4 by 6 or 10, in the presence of TMEDA, is mostly entropy controlled.
7. The kinetic order in 10 for dynamic resolution of 4 in the presence of up to one equivalent of 10 is 0.265 ± 0.022, such that the rate increases nonlinearly with increasing [10].
8. The X-ray crystal structure of 10 reveals that 10 is an octomer in its resting state in Et_2O.
9. The relationship between free energy and temperature for enantiomerization of N-trimethylallyl-2-lithiopyrrolidine, N-Boc-2-lithiopiperidine, the ethylene ketal of N-Boc-2-lithio-4-oxopiperidine, and N-Boc-2-lithiopyrrolidine has been determined.
10. The kinetic order for CDR using 15 mol% of 6 is 2nd-order in TMEDA. Therefore, excess TMEDA accelerates the CDR.
11. There is an increase in the rate of CDR as [6] increases up to 1:1 molar ratio. The kinetic order for CDR of N-Boc-2-lithiopiperidine 4 is half-order in monolithiated ligand 6, when 4 is in excess of 6, and one-fourth order in dilithiated ligand 10, when 4 is in excess of 10.

12. The final er of the stoichiometric DTR of 4·6 or 4·10 and the CDR are the same.
13. Careful control of temperature is critical to the success of the catalytic dynamic resolution.
14. The rate law for the CDR, which converts R-4 to S-4, is: $\frac{d[S\text{-}\mathbf{4}]}{dt} = k_{CDR}[R\text{-}\mathbf{4}][TMEDA]^2[\mathbf{6}]^{0.5}$.
15. The asymmetric synthesis of 2-substituted piperidines has been accomplished through catalytic dynamic resolution of N-Boc-2-lithiopiperidine followed by one of three different methods; (i) direct electrophilic quench, (ii) transmetalation and copper-mediated allylation or benzylation, and (iii) transmetalation and palladium-catalyzed (Negishi) arylation or vinylation.
16. Newly discovered diastereomeric ligands 9 and 10 afford opposite configurations of N-Boc-2-lithiopiperidine with excellent enantioselectivity.
17. The asymmetric synthesis of optically active 2-substituted-6-methyl piperidines has been accomplished. In all cases, calculations show that the trans-2,6-disubstituted piperidine is more stable than the cis-2,6-adduct.
18. The CDR of N-Boc-2-lithiopiperidine has been applied to the synthesis of several piperidine medicinal compounds and alkaloids such as ropivacaine, conhydrine, anabasine, coniine, pipecolic acid, pelletierine, epipinidinone, lupetidine, and epidihydropinidine.

The development of powerful methodology for C-C bond formation, which leads to induction of asymmetry on the 2-position of the highly synthetically important piperidine moiety has been accomplished. The application of catalytic dynamic resolution to the synthesis of highly complex targets is ongoing in our laboratory and these results will be communicated in due course.

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Publications

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Teaching

- Organic Chemistry Instructor, University of Arkansas, Fayetteville, Fall 2011.
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- General Chemistry Instructor, Prehealth Outreach Program, East Tennessee State University, ETSU, 2004.
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- General Chemistry Lab Lead Teaching Assistant, Department of Chemistry, Emory University, Atlanta, GA, USA.
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- SI Drill leader, Organic Chemistry 1 & 2, General Chemistry 1 & 2, Organic Physiological Chemistry, University of Arkansas, Fayetteville, AR, USA, 2007 – 2011.

Research Presentations

- Kinetics of Enantiomerization and Resolution of N-Boc-2-lithiopiperidine; Pacifichem 2010; Carbanions: Modern Perspectives in Structure, Reactivity, and Synthesis, Honolulu, Hawaii.
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