Organic Chemistry
Department of Chemistry
Göteborg University
Göteborg
Sweden

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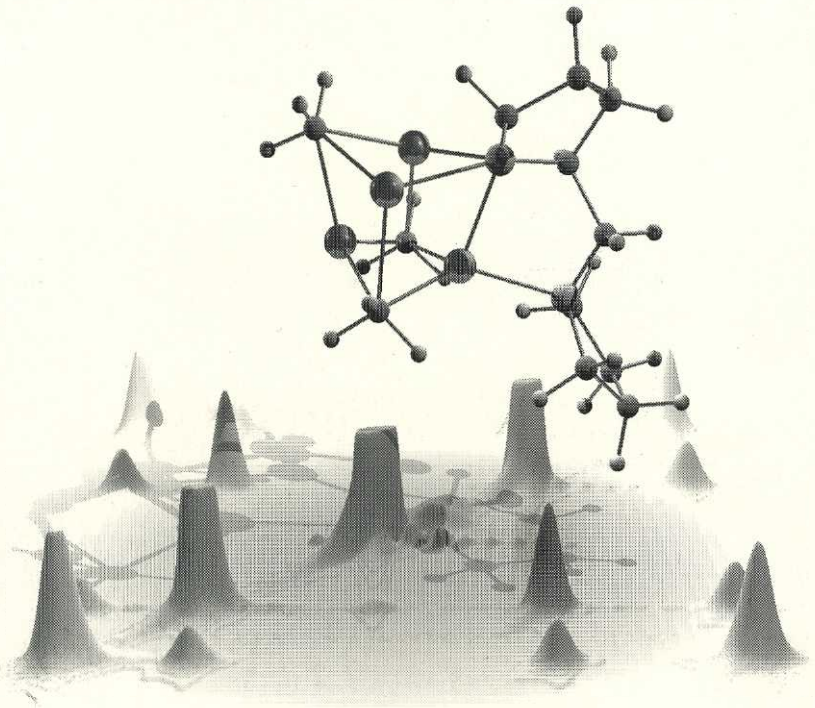
Synthetic, Computational, and NMR Spectroscopic Studies of Aggregation, Solvation, and Selectivity



Per I. Arvidsson

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Per I. Arvidsson

AKADEMISK AVHANDLING

för avläggande av filosofie doktorsexamen i kemi som enligt tjänsteförslagsnämndens ordförandes beslut kommer att försvaras offentligt fredagen den 7 maj 1999 kl. 13.15 i föreläsningssal KA, Kemigården 3, Göteborgs Universitet och Chalmers Tekniska Högskola. Avhandlingen kommer att försvaras på engelska.

Fakultetsopponent är Professor Dr. Gerhard W. Klumpp, Scheikundig Laboratorium, Vrije Universiteit Amsterdam, Holland.

Abstract

Lithium organic reagents find enormous use in organic synthesis; however, little is still known about the structures and reaction mechanisms concerning these supramolecular reagents. This thesis deals with chiral lithium amides; their structures, dynamics, mechanisms, and use in asymmetric synthesis. The reactions studied include the base induced enantioselective rearrangement of *meso*-epoxides to chiral allylic alcohols, an accompanying solvent induced isomerization reaction, and the asymmetric addition of alkyllithium reagents to prochiral aldehydes. Synthesis, theoretical calculations (semi empirical, ab initio, and DFT), and NMR spectroscopy (1D and 2D multinuclear experiments) have been used to investigate the supramolecular aggregates and the origin of stereoselectivity. The main results are summarized below.

A detailed computational study of the activated complexes in the enantioselective rearrangement of cyclohexene oxide to (*S*)-2-cyclohexen-1-ol by the chiral lithium amide Li-**11**, revealed that the observed stereoselectivity is a result of better solvation and less non-bonded interactions in one of the two diastereomeric activated complexes. The calculated enantioselectivity (88% ee) was close to that experimentally observed (80% ee).
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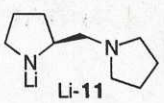

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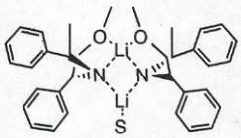

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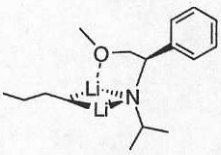

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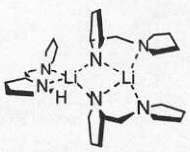

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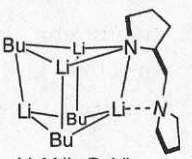

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Synthetic, Computational, and NMR Spectroscopic Studies of Aggregation, Solvation, and Selectivity

by

Per I. Arvidsson

DOCTORAL THESIS

Submitted in partial fulfillment of the requirements for the degree
of
Doctor of Philosophy in Chemistry

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Cover: Ray-traced image of the hypothetical Li-**11**/$(MeLi)_3$ on top of the $^6Li,^6Li$-EXSY spectrum of the observed Li-**11**/$(n\text{-}BuLi)_3$. See section 8.3 for details.
Graphical design: Johan Eriksson & Per I. Arvidsson
Traced by Johan Eriksson using POV-Ray.™

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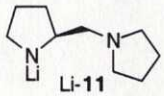

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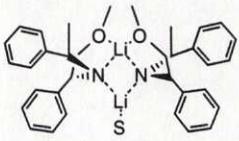

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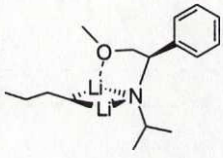

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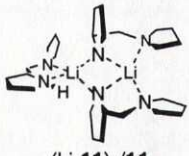

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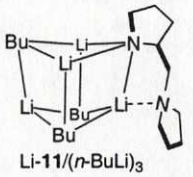

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To my dear Mother & Father,
and my beloved wife Annika.

The most beautiful thing we can experience is the mysterious.
It is the source of all true art and science.
Albert Einstein

The truth is out there!
The X-files

List of Publications

This thesis is partially based on the papers listed below. The papers, referred to by the Roman numerals **I-XII** in the text, are collected at the end of this thesis.

I. Computational Study of Solvation and Stereoselectivity in Deprotonation of Cyclohexene Oxide by a Chiral Lithium Amide
Sten O. Nilsson Lill, Per I. Arvidsson and Per Ahlberg
Tetrahedron: Asymmetry **1999**, *10*, 265-279.

II. A New Chiral Lithium Amide based on (*S*)-2-[1-(3,3-Dimethyl)pyrrolidinomethyl]-pyrrolidine - Synthesis, NMR Studies and use in the Enantioselective Deprotonation of Cyclohexene oxide
Agha Zul-Qarnian Khan, Rimke W. de Groot, Per I. Arvidsson and Öjvind Davidsson
Tetrahedron: Asymmetry **1998**, *9*, 1223-1229.

III. (*S*)-2-(1-Pyrrolidinylmethyl)pyrrolidine•HCl - Crystal Structure and use in the Chiral Lithium Amide Base Mediated Rearrangement of Cyclohexene oxide
Per I. Arvidsson, Göran Hilmersson, Öjvind Davidsson, Agha Zul-Qarnian Khan and Mikael Håkansson
Manuscript

IV. Chiral Lithium Amide/Solute Complexes: X-ray Crystallographic and NMR Spectroscopic Studies
Göran Hilmersson, Per I. Arvidsson, Öjvind Davidsson and Mikael Håkansson
Organometallics **1997**, *15*, 3352-3362.

V. Solvent Induced Isomerization of 2-Cyclohexen-1-ol to 3-Cyclohexen-1-ol by a Chiral Lithium Amide
Agha Zul-Qarnian Khan, Per I. Arvidsson and Per Ahlberg
Tetrahedron: Asymmetry **1996**, *7*, 399-402.

VI. Computational Study of the Mechanism of Isomerization of Allyl Alcohol into Homoallyl Alcohol by Lithium Amide
Sten O. Nilsson Lill, Per I. Arvidsson and Per Ahlberg
Acta Chem. Scand. **1998**, *52*, 280-284.

VII. Solvent-Induced Stereospecific Isomerization of an Allylic Alcohol to a Homoallylic Alcohol Catalyzed by a Chiral Lithium Amide
Per I. Arvidsson, Maria Hansson, Agha Zul-Qarnian Khan and Per Ahlberg
Can. J. Chem. **1998**, *76*, 795-799.

VIII. Rational Design of Chiral Lithium Amides for Asymmetric Alkylation Reactions - NMR Spectroscopic Studies of Mixed Lithium Amide/Alkyllithium Complexes
Per I. Arvidsson, Göran Hilmersson and Öjvind Davidsson
Chem. Eur. J. Accepted for publication

IX. Enantioselective Butylation of Aliphatic Aldehydes by Mixed Chiral Lithium Amide/*n*-BuLi Dimers
Per I. Arvidsson, Öjvind Davidsson and Göran Hilmersson
Tetrahedron: Asymmetry **1999**, *10*, 527-534.

X. Towards Solution State Structure. A $^{6}Li,^{1}H$ HOESY NMR, X-ray Diffraction, Semiempirical (PM3, MNDO), and ab Initio Computational Study of a Chiral Lithium Amide
Göran Hilmersson, Per I. Arvidsson, Öjvind Davidsson and Mikael Håkansson
J. Am. Chem. Soc. **1998**, *120*, 8143-8149.

continued

XI. Stereoselective Diamine Chelates of a Chiral Lithium Amide Dimer: New Insights Into the Coordination Chemistry of Chiral Lithium Amides
Per I. Arvidsson, Göran Hilmersson and Per Ahlberg
J. Am. Chem. Soc. **1999**, *121*, 1883-1887.

XII. Intraaggregate Fluxional Lithium and Carbanion Exchanges in a Chiral Lithium Amide/*n*-Butyllithium Mixed Tetramer Directly Observed by Multinuclear NMR
Per I. Arvidsson, Per Ahlberg and Göran Hilmersson
Chem. Eur. J. **1999**, *5*, 1348-1354.

Contribution Report

The author wishes to clarify his own contributions to the research results presented in the present thesis.

Paper **I**. Significantly contributed to the formulation of the research problem; performed initial calculations on transition states; made some contribution to the interpretation of the results and to the writing of the manuscript.

Paper **II**. Carried out the experimental work in collaboration with the other authors; made equal contribution to the interpretation of the results and to the writing of the manuscript.

Paper **III**. Carried out the experimental work in collaboration with the other authors; made equal contribution to the interpretation of the results and to the writing of the manuscript.

Paper **IV**. Equally contributed to the formulation of the research problem; prepared the new chiral amine and carried out the enantioselective rearrangement reactions; made equal contribution to the interpretation of the results and to the writing of the manuscript.

Paper **V**. Carried out the experimental work in collaboration with the other authors; made equal contribution to the interpretation of the results and to the writing of the manuscript.

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Paper **VII**. Equally contributed to the formulation of the research problem; performed and analyzed the stereospecific isomerization reactions; made significant contribution to the interpretation of the results and to the writing of the manuscript.

Paper **VIII**. Equally contributed to the formulation of the research problem; prepared the chiral amines used, performed the asymmetric alkylation reactions and carried out some of the NMR spectroscopic studies together with the other authors; made equal contribution to the writing of the manuscript.

Paper **IX**. Significantly contributed to the formulation of the research problem; prepared the chiral amines used, performed the asymmetric alkylation reactions together with the other authors; made significant contribution to the writing of the manuscript.

Paper **X**. Prepared the chiral amine and carried out the theoretical calculations; made equal contribution to the interpretation of the results and to the writing of the manuscript.

Paper **XI**. Significantly contributed to the formulation of the research problem; carried out the work together with the other authors; made significant contribution to the interpretation of the results and to the writing of the manuscript.

Paper **XII**. Significantly contributed to the formulation of the research problem; carried out the work together with the other authors; made significant contribution to the interpretation of the results and to the writing of the manuscript.

Abbreviations

AM1	Austin Method 1
B3LYP	Becke's 3 Parameter Hybrid Functional using the Lee-Yang-Parr Correlation Functional
CC	Coupled Cluster
CD	Cyclodextrin
CI	Configuration Interaction
COSY	Correlated Spectroscopy
DABCO	1,4-Diazabicyclo[2.2.2]octane
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
de	Diastereomeric Excess
DEE	Diethylether
DFT	Density Functional Theory
DNMR	Dynamic NMR Spectroscopy
DMAP	4-Dimethylaminopyridine
DMM	Dimethoxymethane
2,5-DMTHF	2,5-Dimethyltetrahydrofuran
DQFCOSY	Double Quantum Filtered Correlation Spectroscopy
ee	Enantiomeric Excess
EQ	External Quench
EXSY	Exchange Spectroscopy
GTF	Gaussian Type Functions
HETCOR	Heteronuclear Correlation Experiment
HF	Hartree-Fock
HMQC	Heteronuclear Multiple Quantum Correlation Experiment
HMPA	Hexamethylphosphoramide
HOESY	Heteronuclear Overhauser Effect Spectroscopy
I	Insensitive (nucleus in NMR pulse sequences)
INADEQUATE	Incredible Natural Abundance Double Quantum Transfer Experiment
IS	Initial State
ISQ	*in situ* Quench
LDA	Lithium Diisopropylamide
NOE	Nuclear Overhauser Effect
NOESY	Nuclear Overhauser Effect Spectroscopy
NPA	Natural Population Analysis
MeLi	Methyllithium
TMEDA	*N, N, N', N'*-Tetramethylethylenediamine
MNDO	Modified Neglect of Diatomic Overlap
MP	Møller-Plesset Perturbation
PM3	Modified Neglect of Diatomic Overlap, Parametric Method Number 3
PMDTA	*N,N,N',N'',N''*-Pentamethyldiethylenetriamine
rt	Room Temperature
S	Sensitive (nucleus in NMR pulse sequences)
s-BuLi	*sec*-Butyllithium
t-BuLi	*tert*-Butyllithium
THF	Tetrahydrofuran
TS	Transition State
TOCSY	Total Correlation Spectroscopy
X-ray	X-ray Diffraction

TABLE OF CONTENTS

1

Introduction

- Lithium organic reagents are among the most widely used reagents in contemporary organic chemistry.
- Preparation of enantiomerically pure chemicals is one of the most important objectives in organic chemistry today.

Given these facts, it seems natural to employ lithium organic reagents for the preparation of enantiomerically pure chemicals, i.e. for asymmetric synthesis. However, despite the enormous utility of lithium organic reagents in synthesis, successful applications of these reagents in asymmetric processes were only recently reported. The meager use of lithium organic reagents in asymmetric synthesis is probably due to an insufficient understanding of the reaction mechanisms involved. Mechanistic detail in this field is itself hampered by incomplete insight into the solution state structures and dynamics of lithium organic reagents. Organolithium chemistry is very complex, with highly reactive compounds present as supramolecular aggregates in solution.

This thesis deals with chiral lithium amides; their structures, dynamics, mechanisms, and use in asymmetric synthesis. The reactions studied in this work include the enantioselective rearrangement of cyclic *meso*-epoxides to chiral allylic alcohols, and the enantioselective alkylation of aldehydes to yield chiral secondary alcohols. During these studies, a solvent induced 1,3-proton transfer reaction was observed. This reaction allows stereospecific conversion of cyclic allylic alcohols to their homoallylic counterparts. Spectroscopic, computational, and synthetic methods have been used to characterize the supramolecular aggregates involved, and for searching the origin of stereoselectivity in lithium organic chemistry.

The impact work of this kind might have on organic chemistry has been eloquently expressed by P. G. Williard:[1]

> *"The material presented may provide fundamental information for the conduct, planning and strategy of organic synthesis. The origin of stereoselectivity in many organic reactions can be put on a more rational basis as more intimate structural details about the intermediates involved in these reactions are discovered. The long term goal and ultimate significance of this structural information is to provide a more thorough basis for accurate prediction and control of stereochemistry in organic reactions."*

This thesis is divided in two parts. Part I is comprised of three chapters. Chapter 2 provides the reader with an essential introduction to lithium organic chemistry. Chapter 3 presents important asymmetric reactions, where chiral lithium amide bases are used as reagents. Chapter 4 gives a short account on the experimental and theoretical methods used. Part II covers five chapters, and is based on the papers **I-XII** collected at the end of this thesis. Chapter 5 concerns the base mediated enantioselective rearrangement of *meso*-epoxides to chiral allylic alcohols. Chapter 6 describes the solvent induced 1,3-proton transfer reaction that transforms cyclic allylic alcohols into their homoallylic counterparts. Asymmetric alkylation of prochiral aldehydes by mixed alkyllithium/lithium amide complexes is outlined in Chapter 7. General work related to the solution state structure of organolithium reagents is collected in Chapter 8. Finally, some suggestions for interesting areas for future research will be presented in Chapter 9.

Part I

2

Lithium Organic Reagents - Background

2.1 General

Organolithium chemistry dates back to 1917 when Schlenk and Holtz reported the preparation of the first alkyllithium compounds, i.e. methyllithium, ethyllithium and phenyllithium.[2] However, it was not until the pioneering work by Wittig,[3-5] Gilman,[6-9] and Ziegler[10] that the large synthetic potential of these reagents was realized.

During time, the definition of the term "organolithium" has broadened. Organolithium now refers to all organic compounds containing lithium linkages, not only compounds with C-Li bonds. Other frequently encountered organolithiums include lithium amides (R_2NLi), lithium alkoxides (ROLi), and lithium enolates ($RC(=CH_2)OLi$).

There is still widespread representation, especially in organic chemistry textbooks, of organolithium compounds as carbanions (R^-) or other organoanions (RO^-, R_2N^-, etc.) with the lithium ion as a passive bystander. This is a severe misconception! Lithium organic compounds are present as solvated aggregates of ion pairs in solution. Monomers are rare species! In order to understand the nature and reactivity of these reagents, knowledge about the structure and degree of aggregation is essential.[11, 12]

2.2 Structure and Dynamics

The nature of the carbon-lithium bond has been a matter of controversy for many years.[13] However, it is now generally accepted that the carbon-lithium and other organo-lithium bonds are mainly ionic.[14-18] Natural population analysis (NPA) of CH_3Li and NH_2Li ascribe 89% ionic character to the C-Li and 90% ionic character to the N-Li bond.[19-21]

In spite of the high number of known X-ray crystal structures containing lithium, there is still little predictability of the coordination number for lithium.[22] Coordination numbers ranging from two through seven, and all values in between, can be found for Li^+.[23] There are also examples of Li-π coordination of aryl anions and conjugated linear anions.[24-27] The coordination geometry of organolithium compounds is primarily governed by the steric requirements of the ligands, i.e. the anion and coordinating Lewis basic molecules/groups. Fortunately, the majority of known structures can be built from a few simple structural patterns.[1, 28]

2.2.1 Aggregation

The basic building block is a dimer with a nearly planar four-membered ring of two lithium cations and two anions (b. in Figure 2.1). The cation in such a dimer is normally coordinated with lone pairs of solvating ligands to make it tetracoordinated. However, exceptions are common. Tri-coordinated lithium centers are prevalent when the anions and/or ligands makes the environment around the lithium center congested.[29, 30]

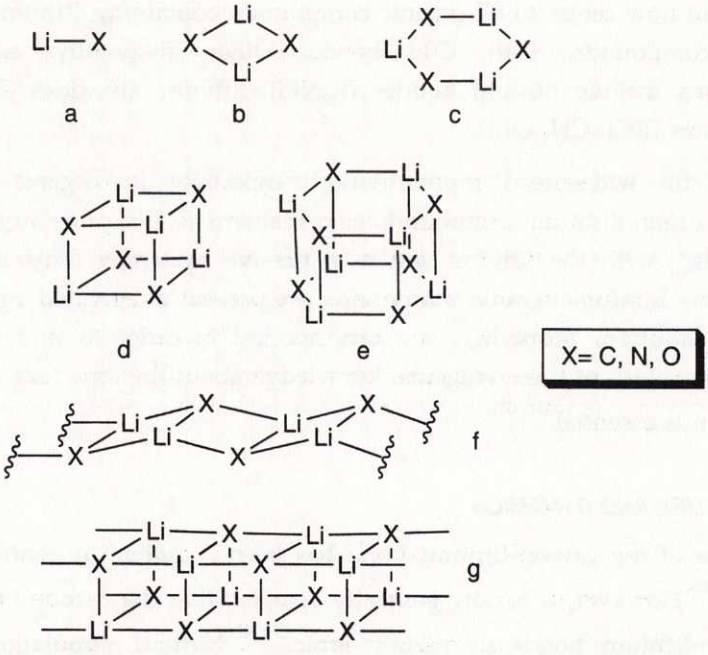


Figure 2.1 Different types of aggregates observed for lithium organic reagents: a. monomer, b. dimer, c. trimer, d. tetramer, e. hexamer, f. infinite ladder, g. infinite stack.

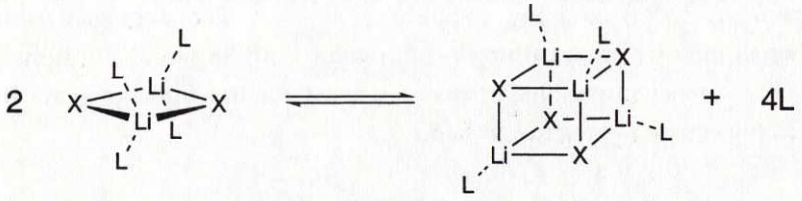
From the dimer, additional aggregates can be constructed. Edge-to-edge combination of dimers gives rise to extended ladder structures (f. in Figure 2.1). Face-to-face combination of two dimeric units yields a cubic aggregate, i.e. a tetramer (d. in Figure 2.1). The cation in such aggregates normally bears one coordinating ligand, again making the lithium atom tetracoordinated. Larger aggregates, e.g. g. in Figure 2.1, may form through further combination of the cubic and ladder motifs. Trimeric rings (c. in Figure 2.1) are another common building block. Stacking of two trimeric rings gives a hexameric aggregate (e. in Figure 2.1). Monomers (a. in Figure 2.1), are only observed under special circumstances (*vide infra*).

Additional structural motifs such as monocyclic tetramers and insoluble infinite polymers are known.

2.2.2 Solvation

The degree of aggregation is mainly determined by the solvent. Thus, solvation has a profound influence on the reactivity, stereochemistry, and regioselectivity of organolithium reagents.[11, 31-37] Monomers are only observed when the lithium cation is solvated by very strong Lewis bases or multidentate ligands such as *N,N,N',N'*-tetramethylenediamine (TMDEA) or *N,N,N',N'',N''*pentamethyldiethylenetriamine (PMDTA), or have very large groups near the anion center.[38] Dimers and tetramers are most prevalent in the presence of coordinating ligands, i.e. coordinating solvent molecules or internally coordinating groups.[39, 40] Trimers and hexamers are the most common states of aggregation in non-coordinating solvents such as hydrocarbons.[41] Smaller aggregates are generally favored in the presence of ligands with high Lewis basicity since these have large affinity for lithium.

The aggregate size is also temperature dependent. Larger aggregates are favored at low temperature in non-coordinating solvents, while smaller aggregates are favored at low temperature in the presence of coordinating ligands, Scheme 2.1.

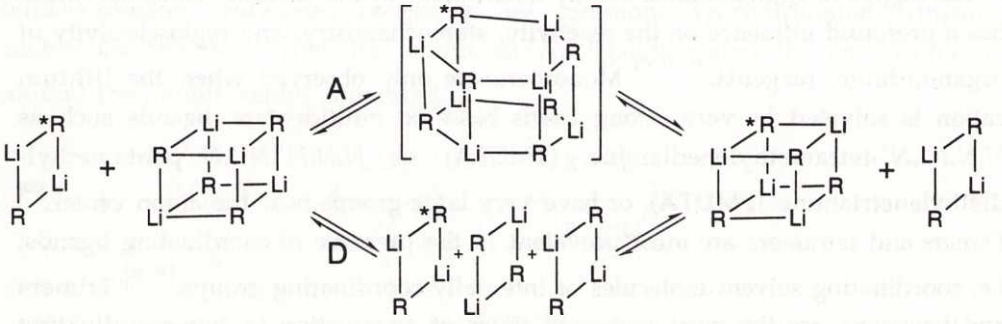


Scheme 2.1

Control of the aggregate size is of importance since the reactivity of lithium organic reagents is highly dependent on the degree of aggregation.[1, 11, 42] Addition of bidentate ligands e.g. TMEDA, increases the reactivity of alkyllithiums presumably through formation of smaller aggregates, i.e. dimers and monomers.[43-47]

2.2.3 Dynamics

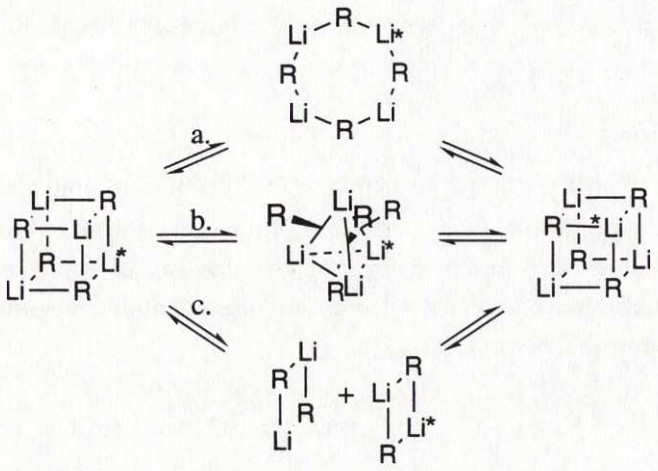
The aggregated organolithiums show inter- and intraaggregate dynamic processes in solution.[42, 48] Inversions at the carbanionic carbons are also observed.[49] Processes of this kind have mainly been studied for alkyllithium reagents using NMR spectroscopy.[50-52] Interaggregate exchange can proceed via an associative mechanism (A in Scheme 2.2) or via a dissociative mechanism (D in Scheme 2.2).[53]



Scheme 2.2

Fraenkel and co-workers have proposed an associative mechanism in which a dimeric aggregate collides with a face of a tetramer, giving a new tetramer and a dimer, possibly through a hexameric intermediate.[51] However, dissociation of a tetramer to dimers followed by recombination is another plausible mechanism.[52]

Intraaggregate exchange in tetrameric RLi aggregates have been extensively studied using $^1J(^{13}C\text{-}^6Li)$ coupling constants.[51, 52, 54, 55] The aggregate is termed fluxional when the carbanion carbons exhibit scalar coupling to all lithiums in the aggregate. Three mechanisms have been proposed for the intraaggregate lithium exchange in tetrameric aggregates, Scheme 2.3.



Scheme 2.3 Three proposed mechanisms for the fluxional lithium- and carbanion-exchange in tetrameric aggregates; a. unfolding/refolding of the tetramer via an eight membered ring, b. concerted center-to-edge rotation, c. dissociation into dimers followed by re-association.

The three mechanisms depicted in Scheme 2.3 are exchange via an eight-membered ring[56] (a. in Scheme 2.3), a concerted center-to-edge rotation of three of the alkyl groups[57] (b. in Scheme 2.3), and dissociation into dimers which recombine[54] (c. in Scheme 2.3). The concerted center-to-edge rotation mechanism was first proposed to explain inversion, observed at stereogenic carbanionic carbons in alkyllithium compounds. It has previously not been established whether it is lithium exchange, carbon exchange, or both carbon and lithium exchange that result in the fluxional lithium-carbon bond exchange.

The dynamic properties of lithium organic compounds are highly dependent on solvent, ligands, and temperature. The static tetramers normally observed at low temperatures are observed to be fluxional at higher temperatures.[54] At even higher temperatures, interaggregate exchange processes begin to be fast. This illustrates the importance of variable temperature NMR spectroscopic measurements on such systems.

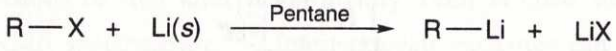
2.3 *UTILIZATION*

The broad usage of lithium organic reagents in organic synthesis makes it impossible to give a detailed account in a book of this size. Instead, only a short summary of the organolithium reagents encountered in this thesis is given below. Another important type of lithium organic reagents, not covered here, are sulfur-

stabilized carbanions.[58] These reagents are intensively used for umpolung reactions.[59]

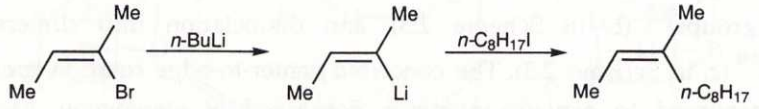
2.3.1 Alkyllithiums

Alkyllithium reagents are the cornerstones of lithium organic chemistry since most other organolithium reagents are prepared starting from them.[60] Alkyllithiums themselves are usually prepared by way of direct synthesis, i.e. reaction of lithium metal with the appropriate organohalide presumably through a radical mechanism, Scheme 2.4.



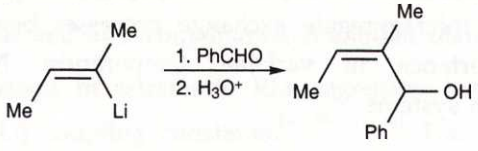
Scheme 2.4

The formed alkyllithium reagent can be used in the Wittig-Gilman reaction, in which the alkyllithium reagent reacts with an alkyl halide to produce a new alkyllithium via metal-halogen exchange. This reaction forms the basis for aryl and alkenyl alkylation reactions, e.g. Scheme 2.5.



Scheme 2.5

The carbanion center in alkyllithium reagents makes the less steric alkyllithium reagents highly potent as nucleophiles. Addition to aldehydes and ketones generates alcohols, while addition to carboxylic acid derivatives gives alcohols or ketones as products. An example of the former reaction is given in Scheme 2.6.



Scheme 2.6

Addition reactions to epoxides and internal alkenes are other well-known reactions of alkyllithium reagents. Alkyllithium compounds are also widely used, as polymerization catalysts, in the industrial production of synthetic rubbers.[61]

The most well known characteristic of lithium organic reagents is perhaps their high basicity. Alkyllithium reagents deprotonate an acidic proton in another molecule if the conjugate acid of the organolithium is a weaker acid than its reactive partner. The product of such a reaction is a new organolithium; hence, the reaction is often entitled metallation reaction. The thermodynamic basicity of alkyllithium reagents increases with increased substitution at the α-carbon, i.e. *t*-BuLi > *s*-BuLi > *n*-BuLi. Despite the invincible thermodynamic base strength of alkyllithium reagents, lithium amide bases are the reagents of choice for deprotonation/lithiation reactions.

2.3.2 Lithium amides

Lithium amides are prepared from alkyllithium reagents through an ordinary acid/base reaction, Scheme 2.7.

$$R_2N\text{-}H + R'\text{-}Li \longrightarrow R_2N\text{-}Li + R'\text{-}H$$

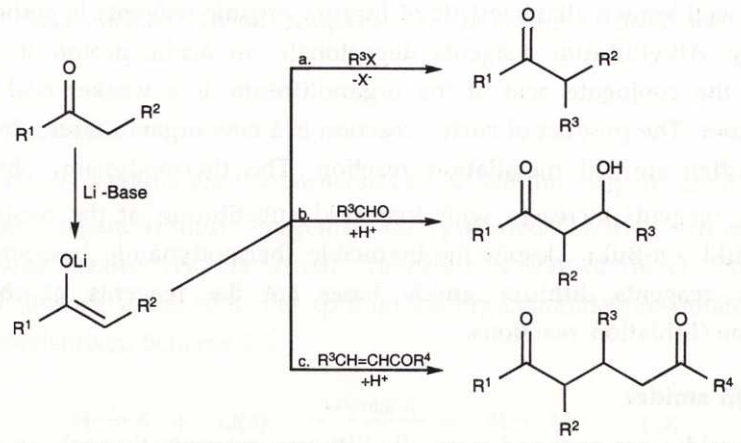
Scheme 2.7

Lithium amides have larger kinetic basicity and lower nucleophilicity compared to alkyllithium reagents.[28] These properties make them the most widely used lithium organic reagents. Lithium amide bases are preferably used for deprotonation/metallation reactions, analogously to the reaction depicted in Scheme 2.5. Since deprotonation is favored over addition to unsaturated groups in the substrate, lithium amides find a particularly important application in the preparation of lithium enolates.

2.3.3 Lithium enolates

The chemistry of enolate anions is of profound importance in organic synthesis since it allows carbon-carbon bond formation. Consequently, much work has been done in this field.[62, 63]

Lithium enolates are prepared through α-deprotonation of a carbonyl compound, preferably by a lithium amide base. The formed enolate may then react further with a suitable electrophilic center, Scheme 2.8.



Scheme 2.8 Formation and reaction of lithium enolates: a. α-alkylation, b. aldol condensation, and c. Michael addition.

Depending on the electrophile, the addition may be any of the well-known reactions: a. α-alkylation, b. aldol condensation, or c. Michael addition (Scheme 2.8). The factors controlling regio- and stereoselectivity in enolate formations are largely influenced by the substrate structure and the base used. The degree of aggregation of the resulting enolate is determined by the enolate structure, the base, solvent, and possible additives.[64, 65] Knowledge about the aggregate structure and size is important since the further reaction with electrophiles is influenced by the overall supramolecular nature of the aggregate.

2.3.4 Lithium alkoxides

Lithium alkoxides are medium strong bases often used for deprotonation of more acidic hydrogens, e.g. C-H moieties with attached electron withdrawing substituents.[66] Furthermore, alkali metal alkoxides are used in conjunction with alkyllithium and lithium amide reagents to form so called "superbases".[67-69] Despite the popularity of such mixed metal—mixed anion superbasic concoctions, their true nature remains to be utterly established. Even the pure lithium alkoxides call for a more thorough exploration.[70-72] Very little is still known about the solution state structure and degree of aggregation among lithium alkoxides.[73-75]

3

Chiral Lithium Amides in Asymmetric Synthesis

The ubiquitous use of lithium amides in organic synthesis suggests a multitude of applications for their chiral counterparts.[76-79] Chiral lithium amide base chemistry offers some unique entries to optically active materials that are highly complementary to other synthetic methods. As chiral base methodology has developed, total syntheses incorporating chiral base mediated steps have become more prevalent.[80-91] A short account on the use of chiral lithium amides in asymmetric synthesis is given below.

Most asymmetric reactions that make use of chiral lithium amide bases can be divided in two categories: a) the chiral lithium amide acts as a chiral base, i.e. it directly abstracts one enantiotopic proton; b) the chiral lithium amide, or the corresponding chiral amine, acts as a non-covalently bound chiral auxiliary, thereby yielding a stereoselective reagent.

3.1 Asymmetric Deprotonations

As might be anticipated, most enantioselective transformations employ the chiral lithium amide as a chiral base. The use of chiral lithium amide bases in enantioselective deprotonation reactions can be divided in three categories: i) deprotonation of conformationally locked prochiral cyclic ketones; ii) aromatic and benzylic functionalization of tricarbonyl (η^6-arene)chromium complexes; iii) rearrangement of epoxides to allylic alcohols.

3.1.1 Enantioselective deprotonation of ketones

The most widely used bases for asymmetric deprotonation of cyclic ketones are shown in Figure 3.1.

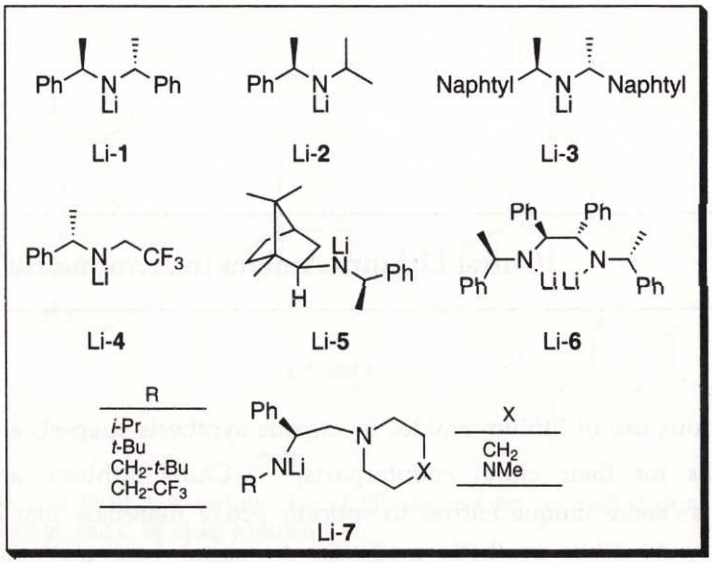
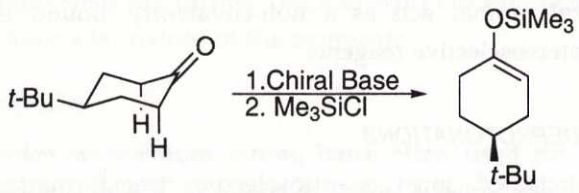


Figure 3.1 Chiral lithium amide bases successfully applied for enantioselective deprotonation of cyclic ketones and tricarbonyl (η^6-arene)chromium complexes.

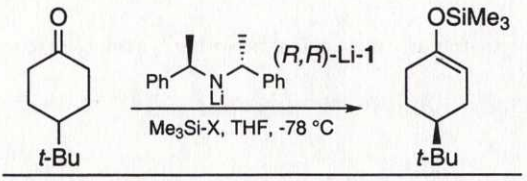
Pioneering work by the research groups of Simpkins,[92, 93] and Koga[76, 94-96] have lead to widespread use of chiral lithium amide bases in enantioselective deprotonation of prochiral cyclic ketones, Scheme 3.1.



Scheme 3.1

In these systems, there are a stereoelectronic preference to remove the axial α-protons. The chiral base discriminates between the two axial protons to preferentially yield one enantiomer of the enolate, usually trapped as the silyl enol ether. It has been shown that *in situ* quench[97] (ISQ i.e. premixing the chiral base with Me_3SiCl prior to addition of the ketone substrate) in contrast to the more traditional method of external quench (EQ i.e. enolization followed by reaction with an electrophile) is needed in order for good enantioselectivities to be obtained.[96] The reason for the increased enantioselectivity under ISQ conditions has been shown to be due to liberation of LiCl as the enolization proceeds.[98] Addition of lithium chloride to reactions conducted under EQ conditions give

comparable enantioselectivities.[84, 98-101] This salt effect is believed to be caused by mixed aggregate formation between the lithium amide and the lithium halide.[102-104] Some typical results in terms of enantiomeric excess (ee) are summarized in Scheme 3.2.[105]

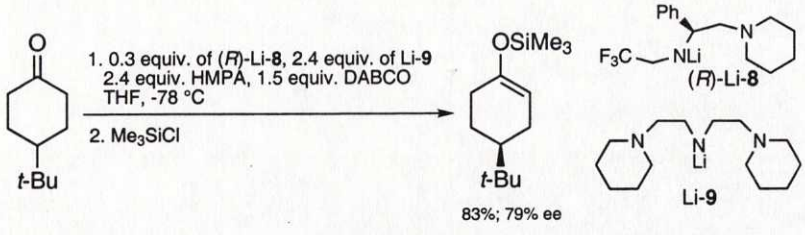


X	Quench	Additive (equiv.)	ee (%)
Cl	ISQ	-	90
Br	ISQ	-	65
I	ISQ	-	31
Cl	EQ	-	44
Cl	EQ	LiCl (0.5)	87
Cl	EQ	LiCl (1.0)	88
Cl	EQ	LiCl (3.0)	88

Scheme 3.2

The scope of this chemistry has extended beyond reactions of carbonyl compounds. Asymmetric deprotonation reactions of this type are also possible with other substrates, e.g. cyclic thiane oxides[106, 107] and imides.[108]

A catalytic modification of the enantioselective ketone deprotonation reaction has recently been developed by Koga, Scheme 3.3.[109, 110] The catalytic cycle is set up with a non-chiral lithium amide Li-**9** as the stoichiometric base, and the chiral lithium amide (*R*)-Li-**8** as the chiral base. The two coordinating nitrogen groups in Li-**9** makes this ligand less reactive in the ketone deprotonation; however, it still deprotonates the corresponding amine of (*R*)-Li-**8** to regenerate the reactive chiral lithium amide.

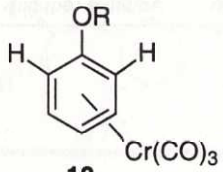


Scheme 3.3

Although, the optimum conditions require the use of excess 1,4-diazabicyclo-[2.2.2]octane (DABCO) and hexamethylphosphoramide (HMPA) as additives, and that the enantiomeric excess of the product was slightly lower than for the corresponding stoichiometric reaction, this result clearly demonstrates the success of a catalytic asymmetric variation of this important reaction.

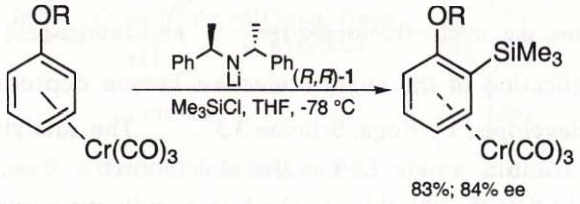
3.1.2 Asymmetric deprotonation of tricarbonyl (η^6-arene)chromium complexes

Tricarbonyl (η^6-arene)chromium complexes, e.g. **10**, are useful intermediates in organic synthesis.[111]



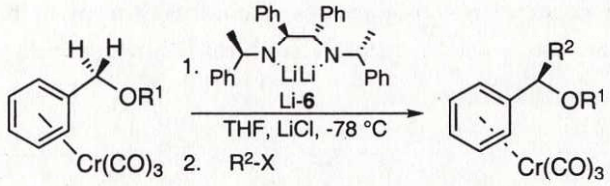
10

Enantiomerically enriched chromium complexes can be prepared using the chiral lithium amide bases Li-**1** to Li-**7** depicted in Figure 3.1 above. The *ortho*-protons in chromium complexes with *ortho*-directing groups are activated to metallation. Thus, direct asymmetric metallation using a chiral base can be used for aromatic functionalization of prochiral chromium complexes,[112-114] e.g. Scheme 3.4.[115]



Scheme 3.4

Chiral lithium amide bases can also be used for benzylic functionalization of chromium complexes.[116-118] An example of this reaction can be found in Scheme 3.5.[119]



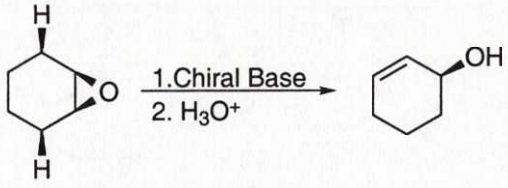
R^1	R^2	Yield (%)	ee (%)
Me	SPh	86	97
Me	Me	96	97
Bn	SPh	95	99
Bn	Me	89	99

Scheme 3.5

Other organometallic compounds with planar chirality, e.g. substituted ferrocenes, may also be prepared through enantioselective *ortho*-lithiation reactions.[120]

3.1.3 Enantioselective rearrangement of epoxides to allylic alcohols

Chiral lithium amide base chemistry has found widespread use for the enantioselective rearrangement of epoxides to yield enantiomerically enriched secondary allylic alcohols.[77, 79, 121-124] The rearrangement of cyclohexene oxide, Scheme 3.6, represent the archetype of this transformation. Cyclohexene oxide is the substrate most frequently studied when new bases are evaluated; although, other substrates usually give higher enantioselectivities.



Scheme 3.6

Whitesell and Felman were the first to report the asymmetric version of this reaction in 1980[125] using the base Li-**1** in Figure 3.1. They obtained the product (*R*)-2-cyclohexen-1-ol in moderate enantiomeric excess (*ca.* 36% based on optical rotation). However, this was the first example of an enantioselective deprotonation by a chiral lithium amide base.

Since then, a number of research groups, including our own, have developed the reaction and the bases used further. The chiral lithium amide bases currently in wide use are shown in Figure 3.2.[82, 122, 126-135]

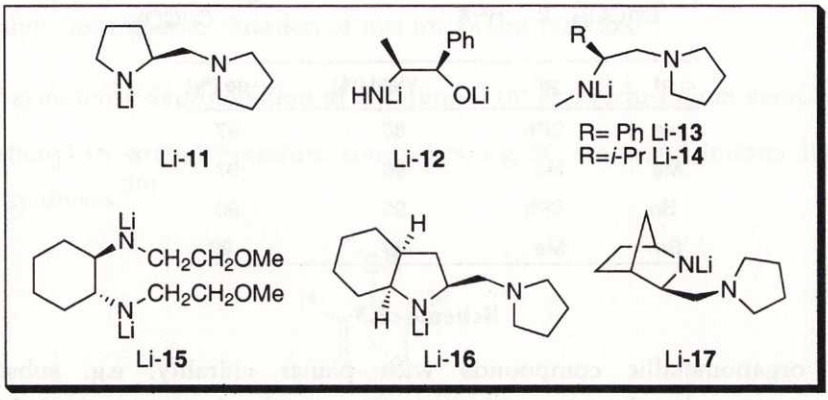
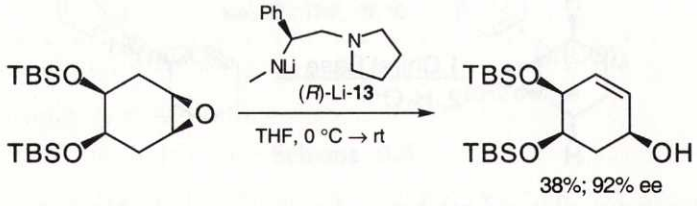


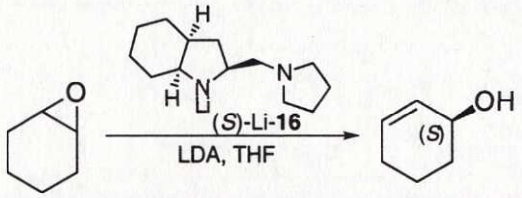
Figure 3.2 The chiral lithium amide bases most widely used for enantioselective rearrangement of epoxides to chiral allylic alcohols.

The most successful bases for this reaction incorporate a coordinating nitrogen atom or alkoxide functionality. The base Li-**11**, developed by Asami in 1984,[136-140] was for long the most utilized base, even so much that it became a commercial product. However, new and highly effective synthetic routes[141-144] to both enantiomers of base Li-**13**[126-128] are making this base the preferred choice for the enantioselective rearrangement reaction. A recent example from the work of O'Brien *et. al.* is shown in Scheme 3.7 below.[82, 122]



Scheme 3.7

Recent results from the laboratory of Asami have employed the chiral lithium amide Li-**16** for catalytic asymmetric rearrangement of epoxides to allylic alcohols. Using lithium diisopropylamide (LDA) as the stoichiometric base and 0.2-0.05 equiv. of the chiral base Li-**16** produced the product (*S*)-2-cyclohexen-1-ol in up to 94% ee, Scheme 3.8.[145]



Equiv. **16**	Equiv. LDA	Temp (°C)	Time (h)	Yield (%)	ee (%)
0.2	1.8	rt	6	95	88
0.05	1.95	rt	12	93	85
0.2	1.8	0	20	89	94

Scheme 3.8

The base Li-**17**, very recently reported by Andersson and co-worker,[130] is also highly effective in the catalytic asymmetric rearrangement reaction when additives like 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) are employed. The catalytic conditions feasible with these bases represent a significant advance in chiral base chemistry. The new chiral bases Li-**16** and Li-**17** also work well in the rearrangement of acyclic *meso*-epoxides, known to be poor substrates for asymmetric rearrangement reactions.

3.2 NON-COVALENTLY BOUND CHIRAL AUXILIARIES

Chiral lithium amide bases may also be used for direct asymmetric carbon-carbon bond formation. In this case, the chiral lithium amide, or the corresponding chiral amine, influences the stereochemical outcome of a reaction by acting as a non-covalently bound chiral auxiliary.

3.2.1 Enantioselective alkylation and aldol reactions with lithium enolates

In contrast to the previously described enantioselective deprotonation of ketones, where the chiral bases were used to prepare chiral silyl enol ethers, the generation of a prochiral enolate via deprotonation using a chiral base followed by subsequent reaction with an electrophile can also produce enantiomerically enriched products. In this case, the enantioselectivity arises because the resulting chiral amine is complexed to the lithium enolate as a non-covalently bound chiral auxiliary.[62, 77, 146-148] The bases most successfully applied for enantioselective alkylation and aldol reactions with prochiral lithium enolates are shown in Figure 3.3.[149, 150]

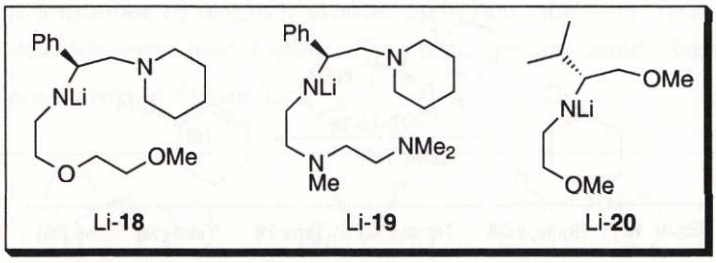
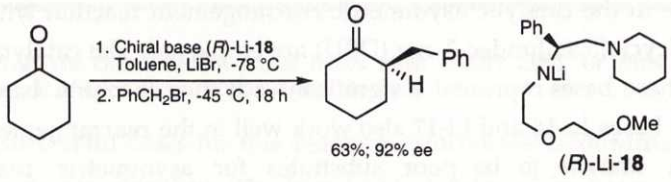
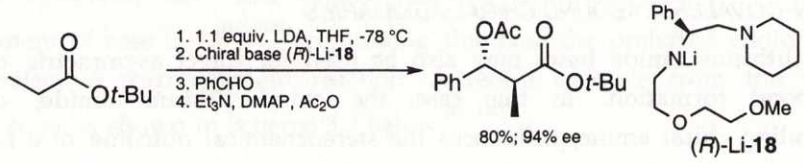


Figure 3.3 Chiral lithium amide bases successfully applied for enantioselective enolate alkylations and aldol condensations.

Koga have used the base Li-**18** for asymmetric alkylation of cyclic ketones and asymmetric aldol reactions[151-153] as illustrated in Scheme 3.9[149] and Scheme 3.10,[154] respectively.



Scheme 3.9



Scheme 3.10

As shown in Scheme 3.9 and Scheme 3.10, it is possible to carry out highly enantioselective alkylations and aldol reactions with prochiral lithium enolates using chiral lithium amide bases. Furthermore, Koga later used base Li-**19** for the reaction in Scheme 3.9 using only a catalytic amount of the chiral base without much loss of enantioselectivity (52%; 90% ee).[155] (DMAP in Scheme 3.10 means 4-dimethylaminopyridine)

3.2.2 Asymmetric alkylations with alkyllithium reagents

Enantioselective addition of alkyllithium reagents to aldehydes and imines yields chiral alcohols and amines, respectively.[156-158] Many chiral ligands[159-161]

have been applied to this reaction, thus also chiral lithium amides. The most successful bases for this reaction are shown in Figure 3.4.[162-167]

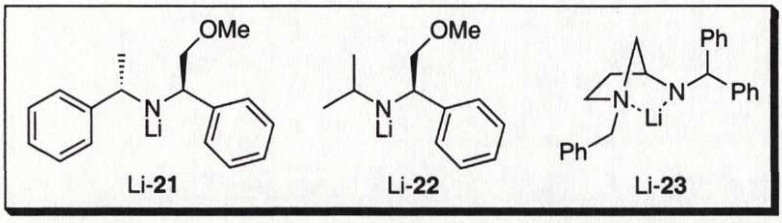
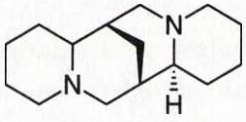


Figure 3.4 Chiral lithium amide bases successfully applied as chiral auxiliaries in the enantioselective alkyllithium alkylation of aldehydes.

As will be shown in Chapter 7, the chiral lithium amide works as a chiral auxiliary in these reactions by forming a one-to-one complex with the alkyllithium reagent.[165, 168, 169]

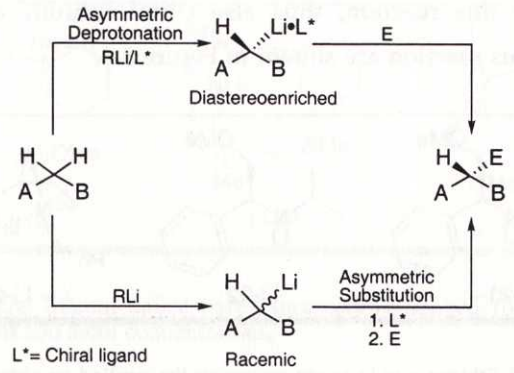
3.3 *OTHER REACTIONS*

Another reaction employing chiral bases, closely related to chiral lithium amide base chemistry, needs to be noted here. Mixed complexes between an alkyllithium reagent and a chiral diamine ligand can be used for asymmetric deprotonation/lithiation reactions. The most studied reagent is composed of *s*-BuLi and the naturally occurring alkaloid (-)-sparteine **24**.



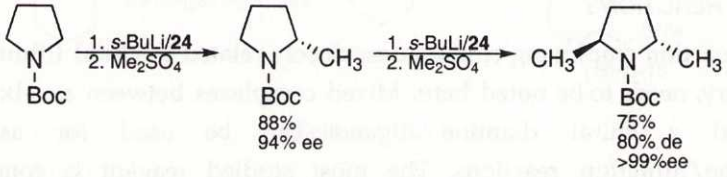
(-)-sparteine
24

Primarily, the research groups of Hoppe,[170-175] and Beak[176-181] have utilized the *s*-BuLi/(-)-sparteine complex for asymmetric transformations. The asymmetric induction can occur through an asymmetric deprotonation where the reagent acts as a chiral base, or through an asymmetric substitution where the chiral ligand acts as an auxiliary, Scheme 3.11.[182]



Scheme 3.11 Asymmetric synthesis using a mixed alkyllithium/chiral ligand complex i.e. *s*-BuLi/(-)-sparteine. The asymmetric induction may occur through an asymmetric deprotonation or through an asymmetric substitution.

An illustrative example of the high utility of this reaction for the preparation of (*S,S*)-2,5-dimethylpyrrolidine is given in Scheme 3.12.[181, 183]



Scheme 3.12

There are many other applications of chiral lithium amides not covered here and new applications are continuously being developed. Some of these include base-induced ring opening of aza- and thiaoxabicycles,[184] asymmetric synthesis of β-amino acids through Michael addition of chiral metal amides,[185] synthesis of enantiomerically pure phospholanes,[186] and asymmetric anionic polymerization reactions.[187]

4

Experimental & Theoretical Methods

4.1 *Enantioselective gas chromatography*

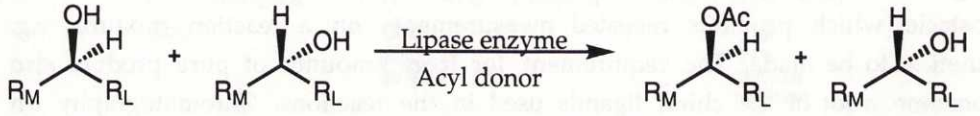
Enantioselective gas chromatography has played a considerable role in this work. When we entered the field of chiral lithium amide mediated asymmetric synthesis, no one used reliable methods for determining the products optical purity. Most stereochemical analyses were made using optical rotation, a method known to have severe limitations.[188, 189] Perhaps the largest disadvantage is that a large amount of highly purified material is needed for analysis. This is an obvious obstacle, which prohibits repeated measurements on a reaction mixture, e.g. kinetics, to be made. The requirement for large amounts of pure product also consume a lot of the chiral ligands used in the reactions. Chromatography on chiral stationary phase is perhaps the most reliable method for enantiomer separation, and hence accurate ee determinations, known today.[190] Capillary gas chromatography on functionalized cyclodextrin phases was found to be the method that best suited our needs for fast, accurate, and reproducible separation of enantiomers and positional isomers.[191] The sensitivity of the method also made it possible to scale down the experiments considerable.

Cyclodextrins (CDs) are cyclic, chiral, torus-shaped macromolecules composed of 6 (α-CD), 7 (β-CD), 8 (γ-CD), or more D-(+)-glucose residues bonded through 1,4-glycoside linkages. The phases used for gas chromatography are modified at the secondary hydroxyl groups located on top of the torus. The separation is presumably a result of formation of reversible inclusion complexes of the eluting enantiomers and the functionalized cavity of the CDs; however, other intramolecular interactions are also believed to play important roles.

The chiral phases used in this work were CP-Chirasil-DEX CB available from Chrompack (Middelburg, The Netherlands) and heptakis (6-O-methyl-2,3-di-O-pentyl)-β-cyclodextrin obtained from Prof. W. König (Hamburg, Germany).[192]

4.2 *BIOCATALYSIS IN ASYMMETRIC SYNTHESIS*

Biocatalysis, i.e. use of isolated enzymes or whole cells, is a powerful complementary synthetic tool for the transformation of organic compounds.[193] Examples of reactions where biocatalysis have been successfully applied include hydrolysis, reduction, oxidation, and carbon-carbon bond formation.[194] Enzyme catalysts often show remarkable regio- and/or stereoselectivity, also for non-natural substrates. The special technique of biocatalysis in non-aqueous media is becoming an increasingly important method for the preparation of enantiopure organic substances.[195] Most such transformations are mediated by lipases. Lipases can accommodate a variety of synthetic substrates, while still showing regio- and/or enantioselectivity.[196] Lipases remain folded even in non-aqueous solvents. This allows the normal ester hydrolysis to be reversed into ester synthesis or interesterification. Thus, lipases are ideal reagents for kinetic resolution of racemic alcohols. The enantiopreference of lipases on secondary alcohols have been rationalized by Kazlauskas, Scheme 4.1.[197]



Scheme 4.1

The preferred enantiomer for acylation is the one having the larger group R_L to the right, when drawn as in Scheme 4.1. This means that if R_L has priority over R_M, i.e. the (*R*)-enantiomer is preferably acylated. This model, known as Kazlauskas' rule, is also supported by crystallographic evidence.[198]

The enzyme employed in this work was immobilized *Candida Antarctica*, preparation SP435,[199] available from Novo Nordisk A/S, Denmark.

4.3 *X-RAY DIFFRACTION*

Single crystal structure analysis is the classical method for elucidation of the three dimensional structure of solid matter.[200] Consequently, cryoscopic single crystal structure analysis is a prevalent technique in the study of organolithium reagents. X-Ray diffraction (X-ray) is the only method available for obtaining a precise view of molecular arrangements. Even reactive intermediates have been characterized using X-ray.[201] Thus, the results obtained using X-ray have had an enormous impact on structural and mechanistic aspects of lithium organic

lithium organic chemistry. However, it is not certain that solid state structures actually relate to the structures present in solution.[202] Since reactions are usually performed in solution, it would be preferred to obtain structural information from solution state nuclear magnetic resonance (NMR) spectroscopy. However, accurate determinations of solution state structures based solely on NMR spectroscopic studies are not always straightforward. In this case, solid state NMR may be used to close the experimental gap between solid state and solution state structures.

The X-ray diffraction analyses in this work were performed by Docent M. Håkansson at the Department of Inorganic Chemistry, Chalmers University of Technology using a Rigaku AFC6R diffractometer. The structures were solved using SHELXS and SHELXL.[203]

4.4 NMR SPECTROSCOPY

Nuclear magnetic resonance (NMR) spectroscopy[204] is undoubtedly the most powerful method for structure elucidation in the liquid state. The entire arsenal of one- (1D) and two- (2D) dimensional ^{1}H and ^{13}C NMR spectroscopic techniques available for structure elucidation can also be successfully applied to the study of lithium organic reagents.[205, 206] Moreover, the nuclear properties of both stable lithium isotopes ^{6}Li and ^{7}Li allow additional NMR spectroscopic techniques to be introduced. The properties of ^{6}Li and ^{7}Li, as well as the other nuclei used in this work, are summarized in Table 4.1.

Table 4.1 Properties of NMR active nuclei relevant to this work.

Nuclei	Natural abundance N (%)	Spin I	Magnetic moment μ (μ_N)	Quadropole moment $Q/10^{-28}(m^2)$	Relative receptivity[a] R_C	Resonance frequency ν at B_o=11.72T (MHz)
^{1}H	99.9	1/2	4.837	-	5.71×10^{3}	500
^{13}C	1.1	1/2	1.217	-	1.0	125.5
^{15}N	0.37	1/2	-0.490	-	3.80×10^{2}	50.7
^{6}Li	7.4	1	1.163	-8.2×10^{-4}	3.64	73.6
^{7}Li	92.6	3/2	4.204	-4.0×10^{-2}	1.55×10^{3}	194.3

[a]Receptivity relative to ^{13}C.[207]

Both of the naturally occurring lithium isotopes have nuclear spin I ≥1, and thus possess quadropole moments. However, the ^{6}Li isotope has the smallest quadropole moment known, and has been termed an "honorary spin-1/2 nucleus".[208] The spin lattice relaxation of ^{6}Li is dominated by factors other than quadropole relaxation. Especially the ^{6}Li,^{1}H dipole relaxation mechanism is of important practical utility, since it allows ^{6}Li,^{1}H- nuclear Overhauser effect (NOE) studies to be performed. This, together with the more confined line width of ^{6}Li, are the prime reasons why most NMR spectroscopic investigations in lithium organic chemistry are done using ^{6}Li enriched material.

Structure assignment based on chemical shift arguments is common for other nuclei, but is difficult for lithium shifts. The reason is the very narrow chemical shift range, *ca.* 12 ppm, of ^{6,7}Li. Chemical shifts of organolithium compounds are also very sensitive to solvent effects, viscosity, temperature, and concentration. The effect of these factors, on the chemical shift, is of the same magnitude as the purely structural effects.

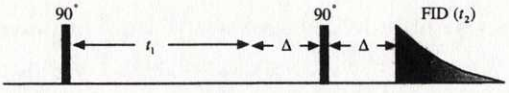
The complex dynamic behavior of organolithium reagents, with many species undergoing exchange processes, requires that NMR spectroscopic studies are done in the slow exchange limit, usually well below -50°C. Characterization and structure determination of the supramolecular aggregates involved, require sophisticated 1D and 2D homo- and heteronuclear NMR experiments. A number of reviews regarding NMR spectroscopy of organolithiums have been published.[55, 209-213] The experiments used in this work are briefly described below.

4.4.1 Methods based on coherent magnetization transfer by scalar spin-spin coupling

Homo- and heteronuclear scalar spin-spin couplings to ^{6,7}Li are of great importance for structural investigations and yields information about chemical bonding between lithium and other elements. Scalar spin-spin coupling is often taken as experimental proof for covalent bonding between the nuclei of interest. Streitwieser, however, has pointed out that coupling between ^{6,7}Li and e.g. ^{13}C may be based on polarization transfer through space.[214] A recent theoretical study indicates that the ^{6,7}Li,^{13}C coupling derive from a small covalent component of the carbon-lithium bond.[20] ^{13}C,^{6}Li coupling constants have been widely used for determination of aggregate size and for studies of intra- and interaggregate dynamics.[26, 51, 52, 54] Two dimensional shift correlated experiments are often needed to resolve complicated spectra and/or small couplings.

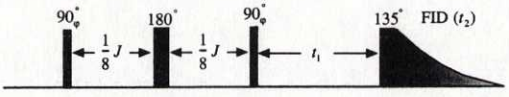
4.4.1.1 Homonuclear spin-spin coupling: ^{6}Li,^{6}Li-COSY and ^{6}Li,^{6}Li-INADEQUATE

The homonuclear shift correlation experiments COSY[215, 216] and INADEQUATE[217-219] have been implemented for lithium by Günther and co-workers.[220] The weak spin-spin coupling between nonequivalent lithium atoms are not resolved in the ordinary 1D ^{6}Li spectrum and consequently require indirect methods for detection. These experiments make it possible to distinguish between ^{6}Li resonances belonging to nonequivalent lithiums in one complex from those resonances resulting from nonequivalent lithiums in another complex.



Eq. 4.1

The original ^{6}Li,^{6}Li-COSY-90 experiment, shown in Eq. 4.1, are sometimes modified with a 45° read pulse to reduce the diagonal intensity. However, this does not always help in reducing signal overlap when there is small chemical shift difference between the signals. In such difficult cases, the phase sensitive ^{6}Li,^{6}Li-INADEQUATE experiment[221] (Eq. 4.2)

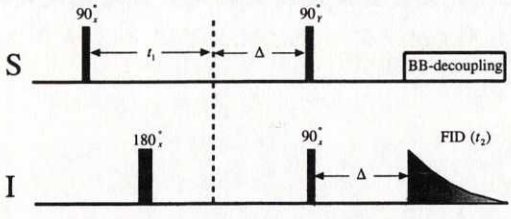


Eq. 4.2

can be employed since no diagonal peaks arise in this experiment.

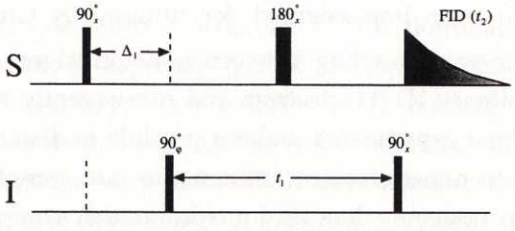
4.4.1.2 Heteronuclear spin-spin coupling: ^{6}Li,^{13}C-HMQC and ^{6}Li,^{15}N-HMQC

Heteronuclear two-dimensional shift correlations can be obtained using two different methods, either through the standard heteronuclear correlation experiment (HETCOR) based on polarization transfer from the sensitive (S) to the insensitive (I) nucleus[222, 223] (Eq. 4.3),



Eq. 4.3

or through the heteronuclear multiple quantum correlation experiment (HMQC) (Eq. 4.4).[224, 225]



Eq. 4.4

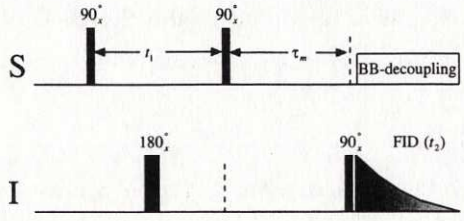
The ^{15}N,^{6}Li-HMQC experiment introduced by Collum[226] allows a wealth of information to be gained about lithiated organonitrogen compounds; however, both ^{15}N and ^{6}Li labeling are required.[38] Notably, the method discriminates between symmetric cyclic dimers and higher oligomers of lithium amides, through homonuclear ^{15}N zero quantum coherence selection.[224, 227, 228]

4.4.2 Methods based on incoherent magnetization transfer

Dipolar interactions between ^{6}Li and neighboring nuclei are favored by the inefficient quadropolar relaxation of ^{6}Li. Wehrli was the first to report the appreciable ^{6}Li,^{1}H nuclear Overhauser effect[229, 230] (NOE).[231, 232] The ^{6}Li,^{1}H NOE in *n*-BuLi in hexane amounts to η=1.19, which can be compared to the theoretically value $\eta=\gamma(^{1}H)/2\gamma(^{6}Li)$=3.40. Similar effects for ^{7}Li are seldom found, because of the larger degree of quadropolar relaxation for this nucleus. The great importance of the ^{6}Li,^{1}H NOE for structural research was recognized independently by two groups in 1984. Avent *et. al.* reported 1D NOE difference experiments[233] while Bauer *et. al.* introduced the ^{6}Li,^{1}H-HOESY experiment[234].

4.4.2.1 ^{6}Li,^{1}H-HOESY

The pulse sequence for heteronuclear Overhauser effect spectroscopy (HOESY) (Eq. 4.5) was first proposed in 1983 by Rinaldi,[235] and Yu and Levy,[236] for ^{13}C,^{1}H- and ^{31}P,^{1}H-spin pairs, but never found widespread use.

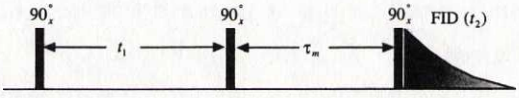


Eq. 4.5

However, since the development of the $^{6}Li,^{1}H$-HOESY experiment by Bauer *et. al.* this has been a valuable tool for detecting short Li-H distances.[212, 237-239] The results obtained provide invaluable information about the 3-dimensional structure of the aggregate under study, including coordinating ligands. Moreover, quantitative information about ^{6}Li-^{1}H distances can be attained through NOE buildup rates.[233, 238, 240, 241] $^{6}Li,^{1}H$-HOESY has also been applied to solution studies of ion pairs.[242]

4.4.2.2 $^{6}Li,^{6}Li$-EXSY

The dynamic nature of most organolithium compounds in solution forms the basis for broad applications of dynamic NMR (DNMR) in this field.[42, 52, 54, 243, 244] Full line shape analysis, the standard techniques available for DNMR investigations,[245] is today supplemented by 2D exchange experiments (EXSY)[246, 247] (Eq. 4.6).



Eq. 4.6

Despite the small homonuclear $^{6}Li,^{6}Li$ NOE, there are wide utilization of 2D $^{6}Li,^{6}Li$-EXSY experiments for systems undergoing slow exchange.[210, 248-250] The cross-peaks in a 2D EXSY spectra show all exchange processes. Furthermore, quantitative comparison between the cross-peak and the diagonal-peak intensities provide accurate determination of rate constants in the region 1-60 s^{-1}.[246, 251-253] $^{7}Li,^{7}Li$ EXSY has also been used for quantitative determinations of exchange rates.[254]

All low temperature NMR spectroscopic studies presented in this work were performed using a Varian Unity 500 spectrometer equipped with three channels. Triple- (^{1}H, ^{13}C and ^{6}Li) or quad- (^{1}H, ^{13}C, ^{6}Li and ^{15}N) resonance probes, custom-built by Nalorac, were used in all low temperature experiments. Some spectra,

obtained at ambient temperatures, were recorded at the Swedish NMR Center at Göteborg University using a Varian INOVA 600 spectrometer.

4.5 COMPUTATIONAL CHEMISTRY

Computational chemistry is a very broad term, covering almost every aspect on the use of computers in chemistry.[255-257] In this work, computational chemistry refers to the use of computational methods to solve quantum chemical problems.

Computational chemistry is becoming a tool of profound importance to the experimental chemist. The increased power and lower cost of computers, the modernized program interfaces and computational methods, together with developments in quantum chemistry are some of the factors that have contributed to this. There are numerous applications of computational chemistry. Today there are accurate computational methods available to obtain good gas phase geometries to complement those derived from X-ray diffraction and NMR spectroscopy. Theoretical calculations also allow the study of transition states and short-lived intermediates. Such species are normally difficult or impossible to study experimentally. Furthermore, molecular modeling on the computer, as compared to the traditional use of molecular models, provides a multitude of additional information, helping the chemist to proof or disproof experimental findings.

The computational methods used in this work are based on molecular orbital calculations.[258] The theoretical foundation for such calculations is the Schrödinger equation.[259] The solution of the Schrödinger equation for a molecular system, i.e. the wave function, gives a complete description of the system.[260] However, the Schrödinger equation has only been solved exactly for the hydrogen atom. For all other systems approximations have to be made.

There are three main methods available for molecular orbital calculations. They differ in the approach used to solve the Schrödinger equation. A short summary, with emphasize on the methods used in this work, will be given below. For a more detailed account, the reader is referred to the many good books written on the subject.[258, 260-263]

4.5.1 ab Initio methods

The ab initio methods solve the Schrödinger equation without any empirical factors, only universal constants are used in the equations. The miscellaneous ab initio methods available differ in the approximations used to obtain the wave function. Most methods approximate the wave function into a product of one-

electron wave functions.[264] Such one-electron wave functions are called atomic- or molecular- orbitals. These orbitals can be expanded using a basis set in order to transform the differential equations to a matrix problem and thereby simplify the calculations.[265] The basis sets most frequently used today are comprised of Gaussian type functions (GTF),[266] and are often of split valence type.[258] The latter means that the outer electrons, involved in the chemistry, are described by more GTFs than the core electrons.

The Hartree-Fock (HF) method[267, 268] was the first ab initio method. This method assumes that each electron moves independently of the others in a field created by the fixed nuclei (Born-Oppenheimer approx.)[269] and the mean-field of the other electrons. HF is the starting point of a hierarchy of models with the objective of getting as accurate solutions to the Schrödinger equation as possible.

With larger basis sets, the HF method yields results closer to the real solution. However, due to the approximations used the exact result is never reached. The lowest energy attainable with HF is called the Hartree-Fock limit. The most serious deficiency of the HF method is an inadequate treatment of correlation between the moving electrons of opposite spin. Furthermore, the HF method does not consider relativistic effects. The electronic correlation energy is the difference between the limiting Hartree-Fock energy and the systems true total energy. The correlation energy error results because the HF method only describes one electron's interaction with all other electrons; i.e. it does not take direct electron-electron correlation into account.

There are different methods for considering the electron-electron correlation. Some of the most widely used methods include the Møller-Plesset perturbation methods[270] (MP2-MP6), the coupled cluster[271] (CC) methods, and the configuration interaction[272] (CI) methods. Density functional theory, described below, is an alternative method for taking electron-electron correlation into account.

The different concepts described above can be summarized in so called theoretical model chemistries, outlined in Figure 4.1.[273]

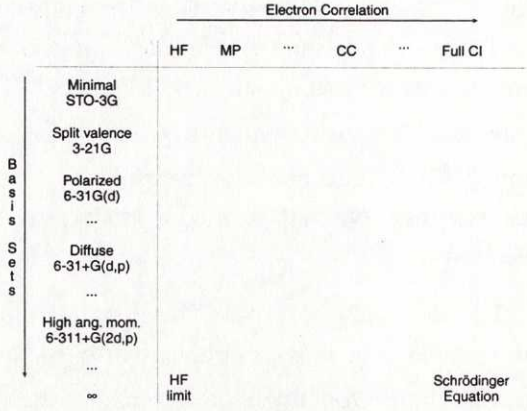


Figure 4.1 Chart showing various model chemistries definable via traditional ab inito methods and standard basis sets.

In Figure 4.1, one can see that going to larger basis sets increases the accuracy. However, the use of a larger basis set also rapidly increases the computational cost. The time requirement for the calculation formally increases with the fourth power of the number of basis functions. Use of correlated methods is also seen to increase the accuracy; however, again at the expense of rapidly increasing computational cost. For these reasons, it is common to do the geometry optimization at a lower level of theory and use this geometry for a single point calculation at a higher level of theory, e.g. MP2/6-31+G(d,p)//HF/6-31G(d). This example demonstrates the terminology used for model chemistries. The model to the left of the double slash shows which model was used to calculate the energy while the model to the right of the double slash shows which model was used for the molecular geometry optimization.

Depending on the actual problem, one always has to choose a suitable theoretical model chemistry for the problem and computer resources at hand.

4.5.2 Semi empirical methods

The computationally most time consuming steps in the ab initio calculations described above are the integral calculations. The matrix elements are composed of integrals over the basis functions describing the different energy components such as: the kinetic energy, the nuclear attraction energy, and the electron-electron repulsion energy. Especially, the many (in the order of 10^6-10^9) electron repulsion integrals are time consuming to calculate. Semi empirical methods simplify the calculations involving the electron repulsion integrals through neglect of differential overlap between atomic centers far apart in the structure. Further approximations and parameterization are normally added to counteract the

omissions. The parameterization is obtained from experiments or from high level ab initio studies on smaller systems. This means that the parameterization incorporates correlation effects, but not in a well defined way.

One often-used semi empirical method is MNDO[274] based on experimental parameterization.[275] The two most recent parameterizations of MNDO, called AM1[276] and PM3,[277] often give qualitatively adequate results. Much larger errors occur when calculations are done on systems different from those used in developing the parameterization.

Anders recently added lithium parameterization[278] to the PM3 method. Since then, this has been the method of choice for semi empirical calculations in lithium organic chemistry.[279-283] This method reproduces geometries of lithium organic molecules well; however, the energies obtained are often unsatisfactory. To overcome this problem single point calculations can be done at a higher level of theory.

4.5.3 Density functional theory

Density functional theory[284-286] (DFT) is based on a fundamentally different approach to quantum mechanics suggested by Thomas and Fermi in 1926.[287, 288] The Thomas-Fermi (TF) approximation does not consider the wave function; instead, the electron density $\rho(r)$ is used to express the energy $E[\rho]$. Kohn later proved the theoretical foundation of this inhomogeneous electron gas approach.[289, 290] However, it took more than twenty years before a functional suitable for molecular systems was obtained.

The functionals employed today partition the electronic energy in several terms.[284, 291-293] One of these terms, the exchange-correlation term, can be further divided into the exchange and the correlation parts. These parts can be of two distinct types: local functionals, which depend only on the electron density, and gradient-corrected functionals, which also depend on the gradient of the density. The most widely used functionals in computational chemistry today are of a third kind, called hybrid functionals. The hybrid functionals define the exchange-correlation term as a linear combination of Hartree-Fock, local, and gradient-corrected exchange terms. This exchange functional is then combined with a local and/or gradient-corrected correlation functional. The best known of these hybrid functionals is probably Becke's three-parameter hybrid functional using the Lee-Yang-Parr correlation B3LYP.[294, 295]

DFT methods constitute a quite new tool for computational chemistry. DFT methods were not incorporated into the well-known Gaussian program until 1992; however, subsequently they have revolutionized the application of quantum chemistry. The best DFT methods available today achieve accuracy comparable to MP2, at a significantly lower computational cost for medium and large systems. Reliable treatment of organolithium compounds by DFT methods have been demonstrated by Pratt and Khan.[296]

All ab initio and density functional calculations presented in this work were done using the Gaussian 94[297] or Gaussian 98[298] program packages. Semiempirical calculations were done using the Spartan program.[299] The calculations were done on the departments own SGI computers (Indy, Power Indigo 2, O2, and Origin 200) or on the Cray C90 at the National Supercomputing Center at Linköping University.

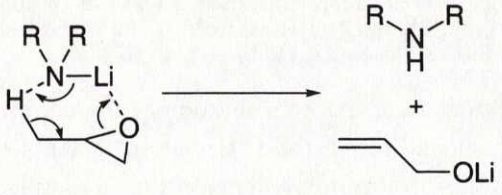
Part II

5

Enantioselective Deprotonation of Cyclohexene oxide

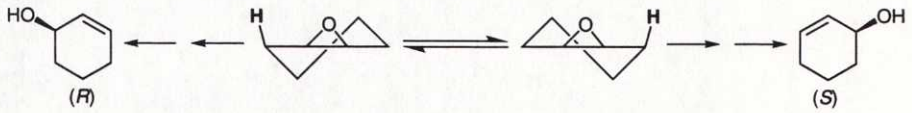
5.1 BACKGROUND

Cope and Tiffany first demonstrated the base induced rearrangement of epoxides to allylic alcohols.[300-305] Later studies, mainly by the research groups of Crandall,[306-311] and Rickborn,[312-315] developed the reaction utilizing lithium amide bases into a synthetically useful and convenient route to allylic alcohols. Mechanistic studies by Thummel and Rickborn showed that the preferred mechanism for proton abstraction from cyclohexene oxide involves *syn* β-elimination of a pseudo-axial proton.[316, 317] The rearrangement is postulated to take place via a cyclic six-membered transition state, Scheme 5.1. Studies on other epoxides have also showed some degree of α-lithiation.[129, 318] The carbenoid thus formed can yield an allylic alcohol, a bicyclic alcohol, or a ketone.[319-321]



Scheme 5.1

As previously described, Whitesell and Felman demonstrated the first enantioselective form of this reaction in 1980.[125] The chiral base Li-**1** (see Figure 3.1) was used to discriminate between the two enantiotopic protons of a prochiral epoxide, i.e. cyclohexene oxide, to yield (*R*)-2-cyclohexen-1-ol in 36% ee (see Scheme 3.6). The enantiotopic proton selection was explained by preferential reaction of the base with one of the rapidly equilibrating enantiomeric half-chair conformations of cyclohexene oxide, Scheme 5.2.



Scheme 5.2

Higher enantioselectivity was observed with the Proline derived chiral lithium amide lithium (*S*)-2-(1-pyrrolidinylmethyl)pyrrolidide Li-**11** (Figure 3.1 and Figure 5.1 below) introduced by Asami in 1984.[137, 140] Using Li-**11** for the rearrangement of cyclohexene oxide produces (*S*)-2-cyclohexen-1-ol in about 80% ee. Asami rationalized the preferred reaction with one of the enantiomeric half-chair conformations in Scheme 5.2 by proposing that the deprotonation occurs preferentially through the transition state (TS) complex where the steric interactions between the cyclohexane ring and the amide are minimized; i.e. TS2, leading to (*S*)-alcohol, is preferred over structure TS1, Figure 5.1.

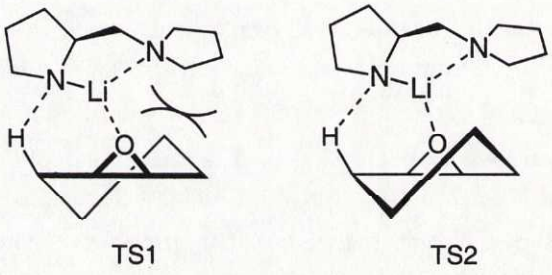


Figure 5.1 Transition state complexes for the enantioselective rearrangement of cyclohexene oxide by the chiral lithium amide Li-**11**, as proposed by Asami. TS1 leading to (*R*)-2-cyclohexen-1-ol is assumed to be disfavored, due to steric repulsions, compared to TS2 leading to (*S*)-2-cyclohexen-1-ol.

No thorough experimental or theoretical study of the enantioselective epoxide opening mechanism, or on initial- and transition state structures, has been reported in the literature. Thus, improvements in the stereoselectivity and yield of this reaction have been guided by trial-and-error structural changes of the chiral amides used. Following the reasoning above, most reported modifications were done by replacing the pyrrolidinyl ring with more congested groups.[139] However, no increase in the product's enantiomeric excess was found by such changes. Instead, higher enantioselectivities were obtained using recently reported chiral amides modified at the pyrrolidide moiety.[145]

5.2 THEORETICAL STUDIES ON THE ENANTIOSELECTIVE REARRANGEMENT (PAPER I)

A computational study was undertaken in order to provide concrete information regarding the origin of stereoselectivity in the rearrangement of cyclohexene oxide by Li-**11**. Geometry optimizations were done using semi empirical (PM3)[277, 278] and ab initio (HF/3-21G)[322] methods. Single point calculations on the optimized structures were done using a DFT method (B3LYP/6-31+G(d)).[294, 295, 323] The study was limited to activated complexes between the epoxide and monomeric lithium amide; although, oligomers of the base may be part of the transition state composition.

5.2.1 Pre-complexes

The lithium amide Li-**11** reacts with both enantiomers of the rapidly interconverting enantiomeric half-chair conformations of cyclohexene oxide and form pre-complexes (**PC1** and **PC2**) in which the deprotonation takes place. The pre-complexes are presumably rapidly interconverting. Thus, the transition states for (*R*)- and (*S*)-alkoxide, **TS1** and **TS2**, respectively, are in equilibrium according to the Curtin-Hammett principle.[324, 325] This means that the stereoselectivity is determined by the difference in free energy ($\delta\Delta G^{\ddagger}$) between the transition states, while the energies of the pre-complexes conduce to the rates of the two routes[326] (Figure 5.2).

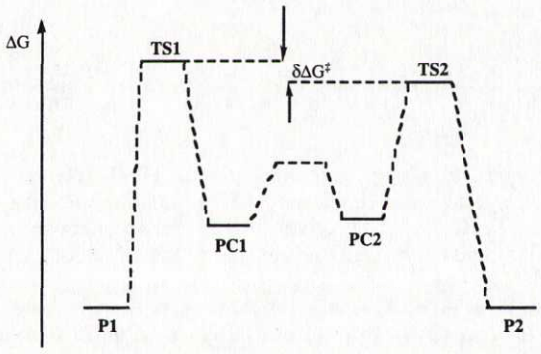


Figure 5.2 Free energy diagram for the enantioselective rearrangement of cyclohexene oxide to 2-cyclohexen-1-ol. The rapidly interconverting enantiomeric pre-complexes between the lithium amide and epoxide (**PC1** and **PC2**), forms enantiomeric products (**P1** and **P2**) via the two diastereotopic transition state structures (**TS1** and **TS2**).

5.2.2 Unsolvated transition state structures

Three transition states leading to the (*R*)-alkoxide (**TS1a-c**) and three transition states leading to the (*S*)-alkoxide (**TS2a-c**) was located at the HF/3-21G level of theory, Figure 5.3.

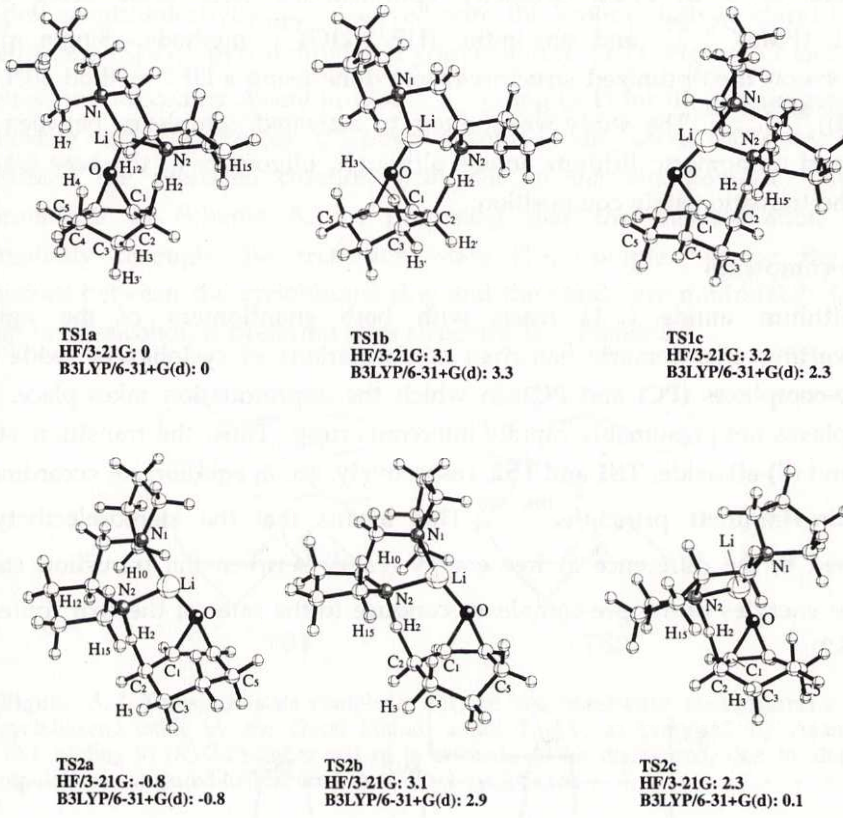


Figure 5.3 Optimized transition state structures at HF/3-21G level of theory for epoxide opening of cyclohexene oxide with Li-**11** yielding (*R*)-alkoxide (**TS1a-c**) and (*S*)-alkoxide (**TS2a-c**), respectively. The relative energies (kcal mol^{-1}), calculated at HF/3-21G and B3LYP/6-31+G(d) levels of theory, respectively, are shown below each structure.

The lithium amide is coordinated above the cyclohexene oxide ring in **TS1a-b** and **TS2c** while the amide is positioned outside the cyclohexene oxide ring in **TS2a-b** and **TS1c**. All transition states have six-membered rings with the lithium atom coordinating to the epoxide oxygen. The epoxide opening is found to be concerted with the proton abstraction by the amide nitrogen (N_2). Furthermore, the proton is found to be slightly more than half-transferred to the nitrogen. The higher energy of the **TS1b** and **TS2b** transition states as compared to **TS1a** and **TS2a**,

respectively, can be attributed to conformational differences in the cyclohexene ring.

The TS yielding the (*S*)-alkoxide, i.e. **TS2a**, is 0.83 kcal mol^{-1} (B3LYP/6-31+G(d)) lower in energy than **TS1a** yielding the *R*-alkoxide. After thermal and entropy corrections, the difference in *free* energy at 298 K is calculated to be 0.83 kcal mol^{-1} at this level. This energy difference corresponds to an ee of 60% at 298 K. Such a small energy difference makes interpretation intricate; however, **TS2a** appears to have less steric interactions between the cyclohexene oxide ring and the lithium amide than **TS1a**. Thus, non-bonded interactions seem to be one reason for the obtained enantioselectivity.

5.2.3 Solvated transition state structures

The role of solvation was studied by specific coordination of one THF molecule to the lithium cation, thus making it tetracoordinated. PM3 optimized solvated activated complexes for the epoxide openings are depicted in Figure 5.4.

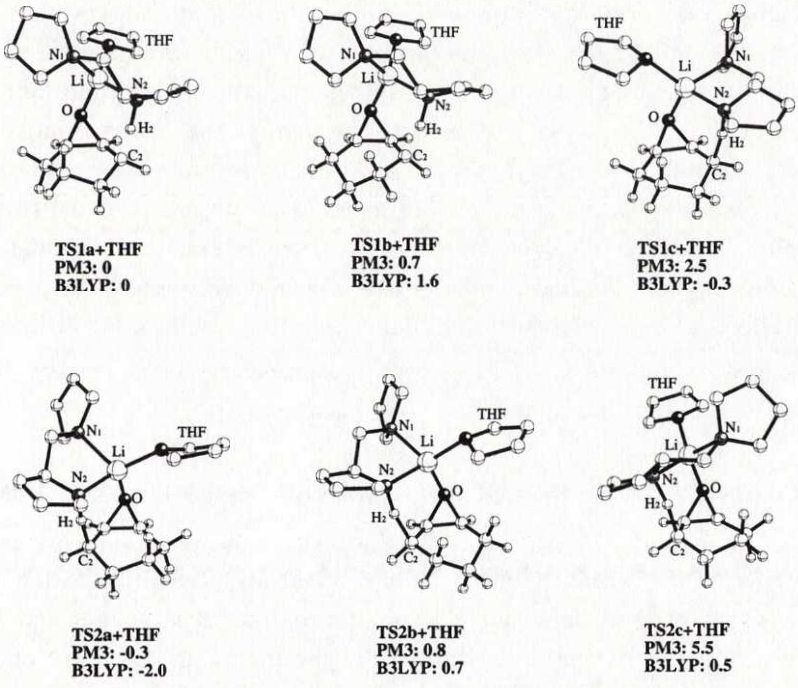


Figure 5.4 PM3 optimized transition states including solvation for the epoxide opening of cyclohexene oxide with Li-**11** yielding (*R*)-alkoxide (**TS1a-c+THF**) and (*S*)-alkoxide (**TS2a-c+THF**), respectively. Some hydrogens are omitted for clarity. The relative energies (kcal mol^{-1}), calculated at PM3 and B3LYP/6-31+G(d) levels of theory, respectively, are shown below each structure.

The structural changes, resulting from the added solvent molecule, are mainly found near the solvated lithium cation. The position of the transferred hydrogen is only slightly affected. A comparison of the lowest transition states yielding (*S*)- and (*R*)-alkoxide indicates that solvation generally causes the energy differences to be larger, i.e. solvation is more effective in the TSs yielding the (*S*)-alkoxide than the (*R*)-alkoxide. Single-point calculations at B3LYP/6-31+G(d) level of theory on the PM3 optimized geometries yield an energy difference of 1.7 kcal mol^{-1} between the lowest TS yielding the (*S*)-alkoxide (**TS2a+THF**) and the lowest TS yielding the (*R*)-alkoxide (**TS1c+THF**). This energy difference corresponding to an ee of 88%, close to the experimental value of 80%.

5.2.4 Summary

The theoretical study of the base induced rearrangement of cyclohexene oxide to 2-cyclohexen-1-ol described above has provided detailed information about the nature of the activated complexes involved. Furthermore, the origin of stereoselectivity observed when the chiral lithium amide Li-**11** is used as base has been rationalized. In contrast to a previous proposal by Asami, suggesting that the stereoselectivity results from steric interactions between the cyclohexene ring and the pyrrolidinyl ring in Li-**11**, this study shows that the most important factor determining the stereoselectivity is better *solvation* of the TS yielding the (*S*)-alkoxide as compared to the TS yielding the (*R*)-alkoxide. Some steric interactions between the cyclohexene ring and the lithium amide were noted in the transition state complex leading to (*R*)-alkoxide; however, these interactions originate from the pyrrolidide moiety in Li-**11** and *not* the pyrrolidinyl moiety as previously proposed. This is in agreement with the higher selectivity obtained with the chiral base Li-**16** (see section 3.1.1).[145] This base is similar to Li-**11**, except for the substitution in the pyrrolidide moiety.

5.3 STRUCTURAL STUDIES AND USE OF LI-**11** AND AN ANALOG (PAPERS II AND III)

Studies of initial state (IS) structures in solution or in the solid state are essential for understanding the actual chemistry behind a reaction. The information gained may, for example, provide new insight into the nature of a reagent and form a basis for reaction mechanism elucidation. Furthermore, in the case of highly exothermic reactions the structure of the IS may well reflect the TS structure according to the Hammond postulate.[327]

An NMR spectroscopic study was initiated to gain further insight into the structure and aggregation of the complex between cyclohexene oxide and Li-**11**. However, the task was complicated by: i) low solubility of Li-**11** in DEE solution,

ii) broad and unresolved ^{6}Li spectrum of Li-**11** in THF at low temperature indicating fast dynamic processes between different aggregates, iii) difficulty with signal assignment due to severe signal overlap in the ^{1}H and ^{13}C NMR spectra.

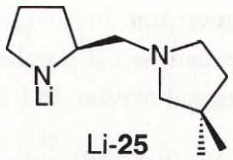
5.3.1 Use of crystalline Li-11 and the hydrochloride salt of the amine precursor 11 for the rearrangement of cyclohexene oxide

The low solubility of Li-**11** in DEE tempted us to grow crystals of Li-**11** suitable for X-ray diffraction studies. Unfortunately, despite repeated attempts, none of the crystals obtained was of sufficiently good quality to allow X-ray analysis. However, we figured that isolation of Li-**11** in the crystalline form could be a method to obtain highly purified Li-**11**. A controversy in the literature,[138, 328, 329] regarding the efficiency of Li-**11** in the enantioselective rearrangement reaction, suggested that possible impurities in the amine precursor **11** could be the cause for the different results obtained. To attest this assumption we crystallized Li-**11** from DEE and used these crystals for the enantioselective rearrangement of cyclohexene oxide. The product (*S*)-2-cyclohexen-1-ol was obtained in 81% ee which is comparable to the 80% ee obtained when "regularly" prepared **11** was used. Thus, it can be concluded that about 80% ee might be the optimum selectivity obtainable with this particular ligand when cyclohexene oxide is used as substrate.

During this study, we also prepared the HCl salt of the amine precursor **11**. This salt is easy to purify through recrystallization, and storage of the amine in this form is advantageous; as compared to storing the amine in the form of an oil, which turns brownish upon prolonged storage. The direct use of this salt for the rearrangement of cyclohexene oxide by *in situ* generation of the lithium amide with two equiv. of *n*-BuLi yielded (*S*)-2-cyclohexen-1-ol in 74% ee. The enantioselectivity was higher (79% ee) in the beginning, but dropped during the course of reaction. This behavior was shown to be related to the presence of LiCl, generated by the *in situ* preparation of the reagent, in the reaction mixture.

5.3.2 NMR spectroscopic studies of an analog of Li-11

The downfield region of the ^{1}H-NMR spectrum of Li-**11** displays severe signal overlap. In order to simplify the spectrum we prepared an analog of Li-**11**, namely lithium (*S*)-2-[1-(3,3-dimethyl)pyrrolidinylmethyl]pyrrolidide Li-**25**. The two methyl groups introduced in the pyrrolidine moiety were hoped to simplify the spectra and form a suitable handle for further structure assignment; hopefully, without altering the selectivity in the epoxide rearrangement reaction.



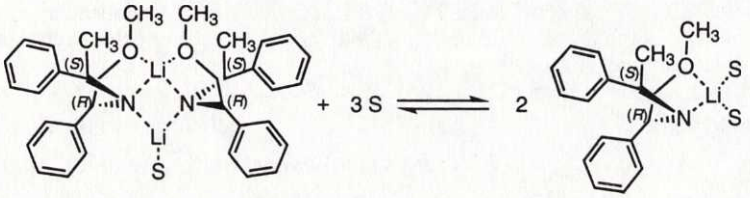
Li-**25**

Complete structure assignment of Li-**25** in THF-d_8 at -10°C was done using routine ^{1}H,^{1}H-DQFCOSY[330] and ^{1}H,^{1}H-NOESY[246] spectroscopy. Lowering the temperature (down to -70°C) resulted in broad unresolved ^{6}Li spectra, preventing a thorough structural investigation. However, upon addition of cyclohexene oxide to the solution of Li-**25** in THF-d_8 at -10°C, we were able to detect weak NOE correlations between protons in the cyclohexene ring and Li-**25**. Interestingly, the strongest NOE correlations were found to the protons in the pyrrolidide moiety of Li-**25**. No correlations to the methyl-substituted pyrrolidinyl moiety were found. One needs to keep in mind that the observed NOEs only give an average picture of the complex between cyclohexene oxide and Li-**25**. However, the obtained results are in accordance with the computational finding of steric interactions between the epoxide and the pyrrolidide ring.

Use of Li-**25** for the enantioselective deprotonation of cyclohexene oxide yielded (*S*)-2-cyclohexen-1-ol in 78% ee. This is close to the 80% obtained with Li-**11**, attesting that the substitution with two methyl-groups had only minor implication on the ligands stereoselectivity.

5.4 RATIONAL DESIGN OF AN IMPROVED CHIRAL LITHIUM AMIDE FOR THE ENANTIOSELECTIVE REARRANGEMENT REACTION THROUGH SOLID STATE AND SOLUTION STATE STRUCTURES OF Li-**21** (PAPER IV)

The solution state structure of the chiral lithium amide lithium (2-methoxy-(*R*)-1-phenylethyl)((*S*)-1-phenylethyl)amide Li-**21** (Figure 3.4), used for the enantioselective addition of alkyllithiums to benzaldehyde, has been extensively studied by workers in our laboratory.[168, 331, 332] Based on multinuclear and multidimensional NMR spectroscopic studies they showed that Li-**21** forms a C_2-symmetric dimer, i.e. (Li-**21**)$_2$·S=DEE in Scheme 5.3, in DEE-d_{10} solution. The dimer was shown solvated by one solvent molecule. Interestingly, the environment occupied by the solvating ligand resembles the binding pocket of an enzyme. This "binding pocket" is capable of stereoselective solvation when a racemic solvent mixture, i.e. 2-methyltetrahydrofuran, is added.[333]



(Li-**21**)$_2$·S Li-**21**·2S

Scheme 5.3 The chiral lithium amide Li-**21** is present as dimer (Li-**21**)$_2$ in DEE solution. In THF, both dimers (Li-**21**)$_2$ and monomers Li-**21** are present. The disolvated monomer is the major aggregate in THF.

Addition of small amounts of THF to a DEE-d_{10} solution of (Li-**21**)$_2$·S=DEE, results in replacement of the solvating DEE molecule by one molecule of THF. In pure THF-d_8, Li-**21** persists as an equilibrium between the dimer (Li-**21**)$_2$·S=THF and the monomer Li-**21**·2S=THF. The disolvated monomer is the major aggregate in THF.

5.4.1 Complexes between Li-21 and cyclohexene oxide

The ^{6}Li NMR spectrum of Li-**21** in DEE at -90°C changed upon addition of cyclohexene oxide. The two lithium signals at δ 2.90 and 3.10, originating from (Li-**21**)$_2$·S=DEE, decreased in intensity and three new lithium signals appeared at δ 2.72, 2.86, and 3.74 (Figure 5.5).

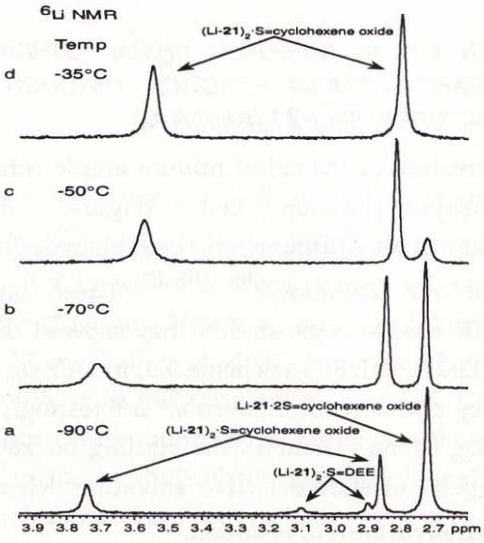


Figure 5.5 ^{6}Li NMR spectra of Li-**21** in DEE-d_{10} with added cyclohexene oxide at -90°C (a). The equilibrium shifts towards the dimer (Li-**21**)$_2$·S=cyclohexene oxide, when the temperature is raised (b to d).

The ^{6}Li,^{1}H-HOESY[234] and ^{6}Li,^{6}Li-EXSY[210, 246] spectra as well as a variable temperature ^{6}Li NMR study of Li-**21** and cyclohexene oxide, revealed that the new ^{6}Li NMR signals emerged from two new cyclohexene oxide/lithium amide complexes. Traces of DEE complexed dimer, i.e. (Li-**21**)$_2$·S=DEE, appear at δ 2.90 and 3.10. The new set of signals at δ 2.86 and 3.74 originate from the cyclohexene oxide complexed dimer, i.e. (Li-**21**)$_2$·S=cyclohexene oxide; the large signal at δ 2.72 emanates from cyclohexene oxide complexed monomer, i.e. Li-**21**·2S=cyclohexene oxide. Furthermore, the intensity of the signal at δ 2.72 increases upon lowering the temperature at the expense of the signals at δ 2.90 and 3.10, Figure 5.6. Thus, this temperature study shows a monomer/dimer equilibrium, where the smaller and more solvated aggregate dominates at low temperature due to the entropy term.

A ^{6}Li,^{1}H-HOESY experiment showed correlations between the lithium signal at δ 2.72 and cyclohexene oxide protons at δ 1.75, 1.92, and 3.04. Weak correlations were also observed between the lithium signal at δ 3.74 and cyclohexene oxide protons, while no correlations between the lithium signal at δ 2.86 and cyclohexene oxide could be detected, Figure 5.6.

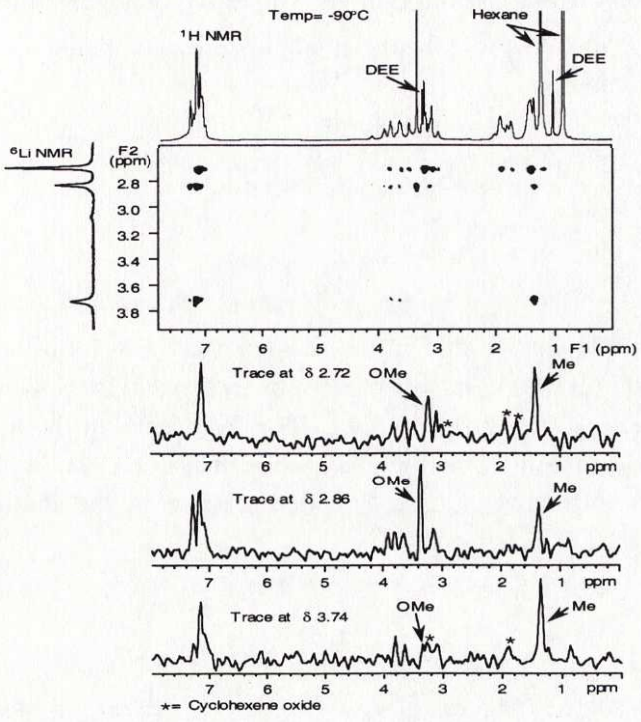


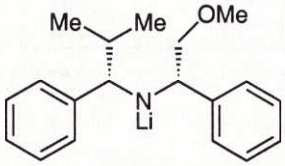
Figure 5.6 Two-dimensional phase-sensitive ^{6}Li,^{1}H-HOESY contour plot of Li-**21** in DEE-d_{10} at -90°C with 2 equiv. of cyclohexene oxide/Li added. The ^{6}Li,^{1}H-HOESY traces at δ 2.72, 2.86, and 3.74 are also shown.

Even though one has to be very careful in interpreting these heteronuclear NOEs, as they originates from an average initial state structure in solution that do not necessarily lead to a similar transition state structure, they show that the transition state for the enantioselective rearrangement reaction may contain a dimeric *or* a monomeric lithium amide base. Both the monomer and the dimer exhibit short distances between lithium and protons in the substrate. Interactions between lithiums and hydrogens are assumed to increase the acidity of carbon-hydrogen bonds.[238, 334, 335]

5.4.2 Design of a dimer with a more congested "binding pocket"

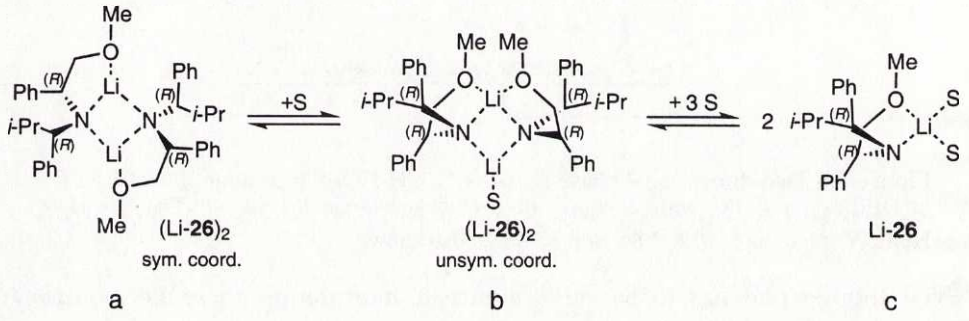
The favorable formation of a dimeric IS complex, i.e. (Li-**21**)$_2$·S=cyclohexene oxide, at higher temperatures suggests that a dimeric TS might be involved. If a dimer of the lithium amide would be the reacting specie, our detailed structural studies on Li-**21** imply that increased selectivity could result if one were to replace the two methyl groups in (Li-**21**)$_2$ with more congested groups. The more congested "binding pocket" thus formed would be a prerequisite for higher

selectivity.[336] To attest this assumption the isopropyl analogue lithium *N*-(*R*)-2-methoxy-1-phenyl-(*R*)-α-isopropylbenzylamide Li-**26** was prepared.



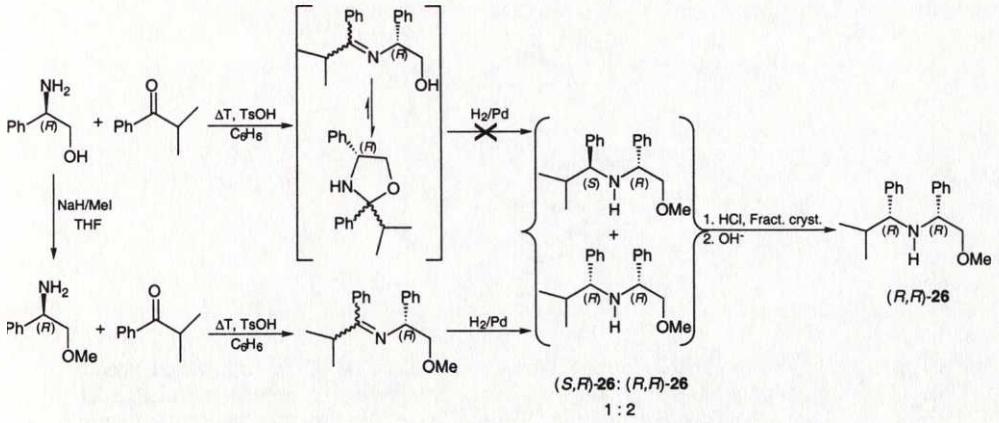
Li-**26**

NMR spectroscopic studies in DEE-d_{10} showed that Li-**26** forms a dimer with symmetric lithium coordination in this solvent, Scheme 5.4a. However, addition of THF, or other strong donor solvents e.g. epoxides, results in the formation of a C_2-symmetric dimer like the one previously described for Li-**21**, i.e. b in Scheme 5.4. At higher concentrations of strongly donating solvents, the equilibrium shifts towards monomers, c in Scheme 5.4.



Scheme 5.4 The chiral lithium amide Li-**26** forms dimers with symmetric lithium coordination in non-coordinating solvents and DEE (a). Addition of solvents/ligands with better coordination affinity towards lithium results in C_2-symmetric dimers (b) and monomers (c).

During synthesis of the amine precursor **26**, outlined in Scheme 5.5, a mixture of the two diastereomers (*R,S*)-**26** and (*R,R*)-**26** was formed in a one-to-two ratio. Resolution of the diastereomers by fractional crystallization of the amines hydrochloride salts gave exclusively the (*R,R*)-**26** diastereomer. Unfortunately, attempts to retrieved the pure (*S,R*)-diastereomer from the mother-liquid were unsuccessful.



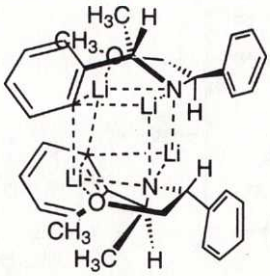
Scheme 5.5 Synthetic route to the amine **26**. The route used to prepare **21** (top) did not succeed for **26** due to formation of a very stable 1,3-oxazolidine. *O*-Methylation of (*R*)-phenylglycinol avoids oxazolidine formation and gives an imine that can be reduced using catalytic hydrogenation.

The outcome of this fortuitous change of configuration at one chiral center, as compared to the original **21** having (*S,R*)-stereochemistry, is that instead of a congested isopropyl substituents interacting with the cyclohexene ring, there is now an phenyl group at this position. However, this is not expected to be crucial since the bulkiness of a phenyl group is similar to that of an isopropyl group.[189]

5.4.3 Structure of dilithiated 21

During studies on mixed complexes between *n*-butyllithium and Li-**21** (*vide infra*) we detected an intramolecular *ortho*-lithiation reaction. One of the *ortho*-protons at the phenyl ring bound to C(10) in Li-**21** is regiospecifically abstracted when the mixed *n*-BuLi/Li-**21** complex in DEE is kept at room temperature for 3-5 hours. The dilithiated specie Li_2-**21** is thus formed.

^{1}H,^{1}H-NOESY, ^{6}Li,^{1}H-HOESY, ^{6}Li,^{6}Li-INADEQUATE,[221] ^{6}Li NMR temperature dependence, titration studies, and T_1 measurements were used to assign the structure of Li_2-**21** in DEE-d_{10}. The details for this structure assignment are outlined in paper **IV** at the end of this book.



27

Figure 5.7 The dimer **27** formed from two molecules of the dilithiated specie Li_2-**21**. The dilithiated compound Li_2-**21** forms when a mixed *n*-BuLi/Li-**21** complex is kept at room temperature in DEE for 3-5 h. The structure have a tetrameric lithium core with one coordinating ligand at each lithium (not shown).

The dilithiated compound Li_2-**21** was shown to form a dimer with a tetrameric lithium core, i.e. **27** in Figure 5.7. Each lithium is proposed to be tetra coordinated by coordinating to one solvent molecule, or by the oxygen atoms in the internal methoxy groups.

5.4.4 Deprotonation of cyclohexene oxide

The results obtained when compounds Li-**21**, Li-**26**, and Li_2-**21** were used for the enantioselective deprotonation of cyclohexene oxide are summarized in Table 5.1.

Table 5.1 Results from the enantioselective rearrangement of cyclohexene oxide using the chiral lithium amides Li-**21**, Li-**26**, and Li_2-**21** in THF or DEE at 20.0°C.

lithium amide	solvent	ee (%)	configuration of 2-cyclohexen-1-ol
Li-**21**	THF	47	*R*
Li-**21**	DEE	47	*R*
Li-**26**	THF	74	*R*
Li-**26**	DEE	70	*R*
Li_2-**21**	DEE	41	*S*

The enantioselectivity in the rearrangement reaction is modest (47% ee of (*R*)-2-cyclohexen-1-ol) when base Li-**21** is used. However, good enantioselectivity (>70% ee of (*R*)-2-cyclohexen-1-ol) is obtained when the modified base Li-**26** is used. Thus, the rational re-design of the substrates "binding-pocket", attained using structural information of the IS complex in conjunction with computational molecular modeling, had the presumed effect of increasing the stereoselectivity.

Furthermore, the stereoselectivity shows no significant solvent dependence, indicating that the major reacting specie is the same in THF and DEE.

The result obtained with the dilithiated specie Li_2-**21** is interesting. The reaction half time is shorter and the configuration of the major product is opposite, as compared to when monolithiated Li-**21** was used. Furthermore, the products enantiomeric excess was at its peak at an early state of the reaction and decreased thereafter when Li_2-**21** was being used up. These results indicate that the deprotonation is initially made by the carbanionic carbon; (*S*)-2-cyclohexen-1-ol and the monolithiated amide Li-**21** are thus formed. The formed Li-**21** then reacts with cyclohexene oxide and forms (*R*)-2-cyclohexen-1-ol; consequently, the enantiomeric excess of the (*S*)-alcohol is lowered.

5.5 CONCLUSION

A computational study on the enantioselective rearrangement of cyclohexene oxide by the monomeric chiral lithium amide Li-**11** gave new insights into the factors controlling the stereoselectivity in this reaction. The main factors were found to be preferred solvation of one of the competing transitions states and steric interactions between the epoxide ring and the pyrrolidide moiety in Li-**11**. Such interactions were also observed in an NMR spectroscopic study of the initial state complex between cyclohexene oxide and Li-**25**, a structural analogue of Li-**11**. Moreover, the theoretically calculated stereoselectivity was very close to that experimentally observed. This close agreement implies that the major reaction path could involve a monomeric lithium amide/substrate complex.

On the other hand, the major pathway for epoxide opening with the chiral lithium amide Li-**21** appears to involve a dimeric aggregated lithium amide, even though an equilibrium between dimers and monomers of the lithium amide are observed by NMR spectroscopy. Compound **26** was prepared as a result of rational re-design of the "binding pocket" in the dimeric Li-**21**. Use of Li-**26** in the epoxide opening reaction raised the enantiomeric excess of the product (*R*)-2-cyclohexen-1-ol from 47% ee to 74% ee, consistent with a presumed major dimeric reaction path.

Altogether, these opposing observations illustrate the large difficulty in understanding, and trying to control, stereoselectivity in this complicated chemistry. To gain further knowledge regarding the species actually reacting in this reaction, kinetic measurements are needed. However, the task is complicated by the delicate equilibrium between the many possible initial state complexes and the even higher number of imaginable transition state complexes. Each of these complexes may be further complexed to; for example, one or more solvent

molecules, the formed lithium alkoxide, the formed amine, or any other additive present in the reaction mixture. Consequently, there are numerous different reaction paths available.

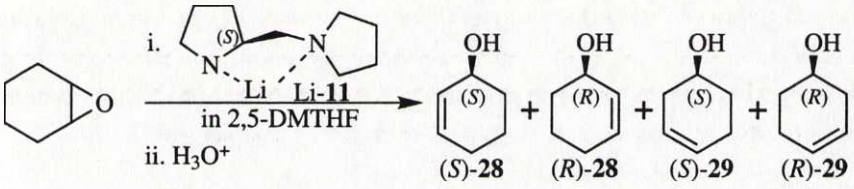
Most likely, the enantioselective rearrangement of epoxides to allylic alcohols by chiral lithium amide bases, proceeds via many competing routes. The enantiomeric excess obtained in the final product reflects the stereoselectivity in all these routes. The results presented in this chapter rationalize the observed stereoselectivity for the ligands studied. However, to use this knowledge to *a priori* design a new chiral base for this reaction is very difficult. Small structural changes in the molecule often lead to tremendous changes in the structure and degree of aggregation. The other species formed in the reaction, i.e. the chiral lithium alkoxide and the chiral amine, may also complicate the issue through formation of mixed aggregates. Thus, to attempt such an adventure, more knowledge regarding the factors controlling aggregate size and structure, and information regarding the exact composition of the transition state, including the number of solvent molecules and other species, are needed. However, armed with such knowledge, gained by NMR spectroscopic studies on IS structures, and kinetic and computational studies on TS structures, it may well be feasible!

6

Isomerization of Allylic- to Homoallylic Alcohol

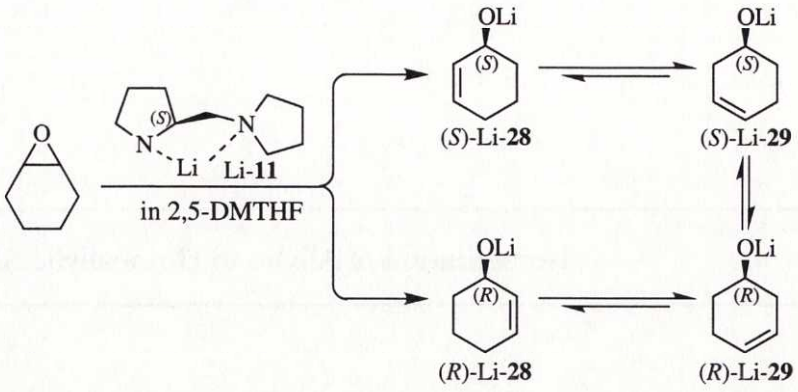
6.1 *Solvent induced isomerization accompanying the enantioselective deprotonation of epoxides (paper V)*

During studies on the use of Li-**11** in the enantioselective rearrangement of cyclohexene oxide to the allylic alcohol 2-cyclohexen-1-ol **28**, we observed a significant solvent effect. A mixture of **28** and the homoallylic alcohol 3-cyclohexen-1-ol **29** was formed when solvents with low propensity to coordinate lithium, i.e. DEE or 2,5-dimethyltetrahydrofuran (2,5-DMTHF), were used, Scheme 6.1.



Scheme 6.1

Compound **29** was shown to be formed from **28**. It was also shown that neither *n*-BuLi, nor the lithium alkoxide of **28** i.e. Li-**28**, or the amine **11**, were able to induce isomerization on their own. Furthermore, the enantiomeric excess of (*S*)-**28** and (*S*)-**29** decreased during the reaction. This observation made us propose a scheme where the homoallylic lithium alkoxide (*S*)-Li-**29** is formed from the allylic lithium alkoxide (*S*)-Li-**28**. The lithium alkoxide (*R*)-Li-**29** may be formed from the lithium alkoxide (*R*)-Li-**28**, or from (*S*)-Li-**29** via further isomerization. Thus, all lithium alkoxides are connected through reversible 1,3-proton transfer reactions, Scheme 6.2.



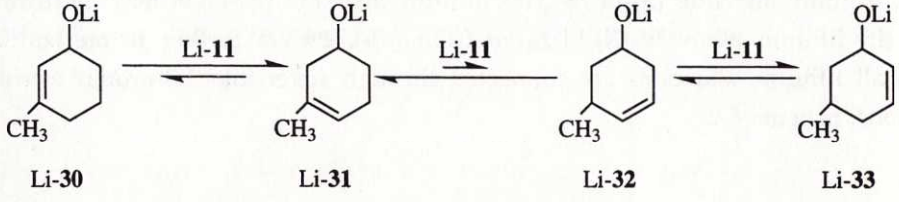
Scheme 6.2

Formation of compound **29** in the rearrangement of cyclohexene oxide by non-chiral lithium dialkylamide bases in DEE solution has previously been described by Kissel and Rickborn.[315] They showed that **29** is a secondary reaction product, formed from **28** by a reversible deprotonation/reprotonation route. The consecutive 1,3-proton transfers proposed in Scheme 6.2 could not be predicted using racemic alkoxides. Interestingly though, they found lithium pyrrolidide to be the most effective base for this isomerization.

The isomerization of (*S*)-Li-**29** to (*R*)-Li-**29** in Scheme 6.2, prevents isolation of the homoallylic alcohol (*S*)-**29** in both high yield and enantiomeric excess. In order to explore the detailed mechanism and the preparative potential of this reaction, a method to inhibit this consecutive 1,3-proton transfer was sought.

6.2 *STEREOSPECIFICITY IN THE ISOMERIZATION REACTION (PAPER VI)*

3-Methyl-2-cylohexen-1-ol, **30**, a compound also known as seudenol, is a sex pheromone of the Douglas fire beetle.[337, 338] This compound was chosen as a substrate for the isomerization reaction since the stabilization of Li-**30** and Li-**31** by their methyl groups was expected to make them thermodynamically more stable than their isomers, Li-**32** and Li-**33**, respectively (Scheme 6.3).



Scheme 6.3

Enzymatic resolution of commercially available racemic **30** gave a mixture of enantiomers with (*S*)-**30** in 76% enantiomeric excess.[339-341] Use of this enantiomerically enriched (*S*)-**30** in the isomerization reaction with Li-**11** in 2,5-DMTHF produced, after work-up, a mixture containing 34% **30** and 66% **31**. Gas chromatographic analysis using a chiral stationary phase column revealed that one of the enantiomers of **31**[342] was formed in 76% ee. Furthermore, the enantiomeric excess of both **30** and **31** remained constant within experimental error during the reaction; i.e. the isomerization reaction is found, within experimental error, to be 100% stereospecific. Thus, it may be concluded that the racemization observed in the isomerization of **28** to **29** in Scheme 6.2 above is caused by consecutive 1,3-proton transfer reactions. Furthermore, the methyl substitution inhibits the isomerization between the homoallylic enantiomers.

The proposed mechanism implies that the configuration at the chiral center is unchanged during the reaction. However, if (*S*)-Li-**31** is the product formed from (*S*)-Li-**30**, then the elution order on the chiral stationary phase column of the two enantiomers of **31** is opposite to that of the enantiomers of **30**. To assign the absolute configuration of the major enantiomer of **31**, we isomerized racemic Li-**30** with Li-**11** in 2,5-DMTHF. To our surprise, both **30** and **31** remained racemic, within experimental error, during the reaction; i.e. there was no stereoselectivity in the isomerization reaction, although a chiral base was used. The isolated mixture of racemic **30** and **31** was then enzymatically resolved using the same enzyme as was used to resolve **30**. According to the rules for lipase enantiospecificity,[197] this resolution gave a mixture enantiomerically enriched in (*S*)-**30** and (*S*)-**31**, respectively. Analysis of this mixture proved the reversed elution order of the enantiomers of **31** on the chiral stationary phase as compared to the enantiomers of **30**. Thus, it is clear that Li-**30** isomerizes to Li-**31** with retention of configuration at the chiral center.

6.3 *LIGAND ACCELERATION*

It was also found that the isomerization of Li-**30** to Li-**31** could be made using only a catalytic amount of Li-**11**; although, the reaction was considerable slower than when an equimolar amount of base was used. However, using excess (0.0-0.28 M) of the amine **11** together with a catalytic amount (0.03 M) of Li-**11** accelerated the isomerization of Li-**30** (0.14 M) considerably. The reaction half-life decreased when the amount of free amine was increased up to 0.14 M. Higher concentrations of the free amine again increased the reaction half-life. This ligand-accelerated reaction is about twice as fast as the equimolar reaction.

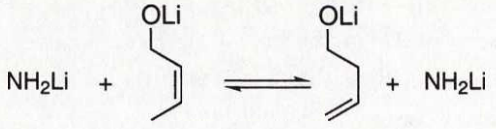
Later studies have shown that amines, preferably containing pyrrolidine rings, i.e. pyrrolidine or the amine **11**, are able to isomerize Li-**30** to Li-**31** without the lithium amide Li-**11**. No isomerization of Li-**30** takes place in the absence of amine ligands. Thus, amines or lithium amides make it possible for the lithium alkoxide Li-**30** to isomerize to Li-**31**. The reason for this still remains unclear; thus, only speculative explanations may be offered. The amine, and the lithium amide, may increase the basicity of the alkoxide functionality, and/or lower the activation energy by stabilizing the transition state more than the initial state. It is also possible that the amine, and the lithium amide, deaggregate the original alkoxide aggregate to smaller, and more reactive aggregates.[343, 344] Combinations of these effects are also conceivable.

6.4 *PRELIMINARY MECHANISTIC STUDIES (PAPERS VI AND VII)*

6.4.1 A preliminary computational study

The chemistry of lithium organic reagents is highly dependent on solvation and coordination at the metal centers.[29, 30, 32] However, the specific role of the solvent and/or other ligands coordinating to the lithium atom is poorly understood.[31] The strong solvent and ligand dependence on the isomerization reaction makes this reaction a useful probe for experimental and theoretical studies on solvation and coordination in lithium organic chemistry.

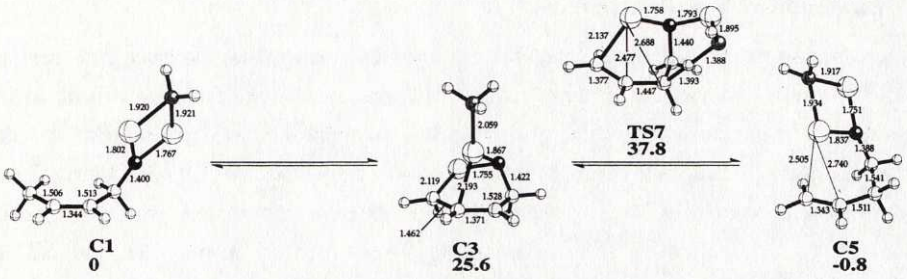
In an initial theoretical study, we investigated a possible mechanism for the 1,3-proton transfer reaction using the model system shown in Scheme 6.4.



Scheme 6.4 Model system for the computational study of the isomerization of an allylic alkoxide into a homoallylic alkoxide catalyzed by a lithium amide.

The model system consists of the lithium alkoxide of *cis*-2-buten-1-ol that is isomerized to the lithium alkoxide of *cis*-3-buten-1-ol, using lithiated ammonia ($LiNH_2$) as catalyst. Geometry optimizations were made at the PM3, HF/6-31+G(d), and B3LYP/6-31+G(d) levels of theory.

The calculated mechanism for a suprafacial 1,3-proton transfer occurring *syn* to the alkoxide functionality is shown in Scheme 6.5.



Scheme 6.5 Calculated mechanism for suprafacial 1,3-proton transfer in the model system occurring *syn* to the alkoxide functionality. The relative energies (kcal mol^{-1}) and selected distances (Å) calculated at the B3LYP/6-31+G(d) level are also shown.

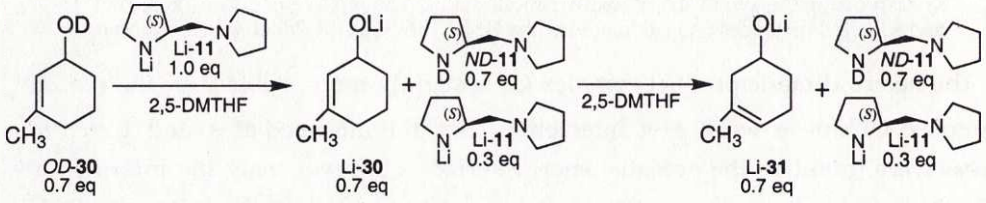
The hetero dimeric product complex **C5** is slightly more stable than the reactant complex **C1** due a weak Li-π interaction. Several intermediates and transition states were found on the potential energy surface. However, only the intermediate **C3** was found to be on the reaction path leading to product. In the intermediate **C3**, the proton is completely transferred to the nitrogen atom in the amide base and a perturbed allylic anion is formed. The two lithiums have different roles; one is coordinating the ammonia, the oxy-anion, and the allylic anion at the former double bond while the other lithium coordinates the oxy-anion and the developing double bond at the C4 carbon. Intermediate **C3** may be reached by two paths, directly via one TS, or indirectly via two intermediates. The energy barriers for the indirect path are lower than that of the direct path. Intermediate **C3** furnishes the product through the rate limiting transition state **TS7**.

The calculated barriers for the isomerization are higher than those found experimentally. However, further calculations indicate that solvation is more effective in the transition states than in the initial state hetero dimer complex.[345] These studies also suggest that there may be two solvent molecules in the transition state, as compared to one solvent molecule in the initial state, when 2,5-DMTHF is used as solvent. In contrast, when THF is used as solvent there are two solvent molecules both in the IS and in the TS. Thus, the lower activation barrier experimentally observed in 2,5-DMTHF may originate from a higher energy of the IS and a lower energy of the TS, as compared to when THF is used as solvent.

Additional computational studies considering also antarafacial proton transfer and proton transfer *anti* to the alkoxide functionality are in progress. These studies will also include solvents and the amine ligands found to accelerate the isomerization.

6.4.2 Intramolecular proton transfer

Ligand acceleration of the 1,3-proton transfer by a diamine, having one tertiary and one secondary nitrogen, suggests that the proton returned to the allylic anion intermediate may come from the coordinating amine, i.e. intermolecular proton transfer. To testify this we deprotonated *O*-deuterated **30**, i.e. *OD*-**30**, using Li-**11**. The resulting alkoxide Li-**30** was then isomerized by a sub-stoichiometric amount of Li-**11** in the presence of the accelerating *N*-deuterated amine **11**, i.e. *ND*-**11**, Scheme 6.6.

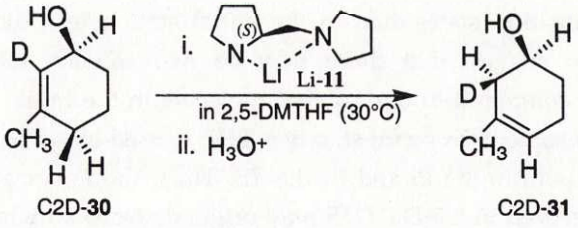


Scheme 6.6

^{1}H- and ^{2}H-NMR spectroscopic analysis on the isolated product mixture showed only traces of deuterium in the allylic- and homoallylic alcohol, respectively. This indicates that the prototropic rearrangement is close to 100% intramolecular.

6.4.3 Suprafacial or antarafacial proton transfer?

Preliminary NMR spectroscopic studies[346] on compound C2D-**31** obtained from isomerization of the substrate C2D-**30** deuterated at C-2, show that the proton being transferred are returned to the opposite side of the hydroxyl group, Scheme 6.7.



Scheme 6.7

To be able to determine whether the proton transfer is antarafacial or suprafacial, a substance specifically deuterated at C-4 is needed. Efforts to prepare such a compound are in progress.

6.5 CONCLUSION

The unexpected finding of almost racemic homoallylic alcohol **31**, as one of the products in the enantioselective rearrangement of cyclohexene oxide by Li-**11** when solvents with little propensity to coordinate lithium were used, made us investigate this interesting reaction. The results obtained so far indicate that the 1,3-proton transfer takes place within a lithium alkoxide aggregate. This aggregate probably also contains amine or lithium amide molecules. A solvent with little propensity for lithium coordination is necessary to induce isomerization. However, presence of small amounts (up to about 1 equiv.) of secondary amines, preferably containing a pyrrolidine moiety, accelerates the reaction. Attempts to accelerate the reaction using other diamine ligands with high affinity for lithium, e.g. (-)-sparteine or TMEDA, have so far been unfruitful. The question whether a secondary amine is necessary, or if a tertiary amine will do equally well, still remains open. Nevertheless, there appears to be a very delicate balance regarding the solvation at the lithium cation in this reaction. The results obtained so far suggest that large aggregates of the alkoxide, e.g. ladders, could exist in solvents with low ability to coordinate the lithium atom.[344, 347] Addition of amines, or lithium amides, likely breaks up these large aggregates into e.g. tetramers, trimers, or dimers.[343] The isomerization could then take place inside such an amine, or lithium amide, coordinated lithium alkoxide aggregate due to an increased reactivity. A sequence of this type also accounts for the decreased reaction rate at high amine concentration, and the lack of ligand acceleration when TMEDA or (-)-sparteine were used, since these conditions would form monomeric lithium alkoxides incapable of isomerization.

Although there are still many unanswered questions regarding this reaction, it appears to be a general preparative procedure for transforming cyclic allylic alcohols to their homoallylic counterparts. The intriguing solvent dependence on this reaction makes it a good model for theoretical and experimental studies on the role of solvent and solvation in lithium organic chemistry. Work to address the questions raised and gain knowledge about the intrinsic reaction mechanism for this 1,3-proton transfer reaction are currently being performed in our laboratory.

7

Asymmetric Alkylation of Aldehydes

7.1 BACKGROUND

Nucleophilic addition of organometallic reagents to carbonyl substrates constitutes one of the most fundamental operations in organic synthesis, mainly because a new carbon-carbon bond is formed.[159, 161, 348] Moreover, through modification of the organometallic compounds by a chiral auxiliary a general method to synthesize optically active alcohols emerges.[349] The use of alkyllithium reagents as nucleophiles in such asymmetric additions has so far been limited.[350] One reason for this is the limited number of chiral auxiliaries available. The chiral auxiliaries used in conjunction with alkyllithium reagents contain amine, ether, lithium alkoxide, or lithium amide functionalities.[326] Unfortunately, most of the chiral auxiliaries reported to date are of limited synthetic application since their preparations often require substantial synthetic efforts. Furthermore, only a few of these chiral auxiliaries give products with enantiomeric excess higher than 60%.[162, 351, 352] Use of alkyllithium reagents as nucleophiles are also complicated by their high reactivity and propensity to assemble in aggregates. For example, it has been suggested that the products may form mixed aggregates with the reagent, and thereby change the reaction conditions.[146, 353-355] However, the property of alkyllithium reagents to aggregate does not necessarily have to be a disadvantage. Instead, formation of a mixed aggregate between the alkyllithium reagent and a chiral additive may be used to introduce a chiral environment at the nucleophilic center.[356] An example was shown in 1984 by Hogeveen and Eleveld, who added *n*-BuLi to benzaldehyde in the presence of the chiral lithium amide Li-**21** at -116°C.[162] They isolated the product (*S*)-1-phenyl-1-pentanol in 74% ee when DEE was used as solvent. A 1:1 solvent mixture of diethyl ether and dimethoxymethane (DMM) was reported to give an enantiomeric excess of 90% in the same reaction. The optimum ratio between benzaldehyde, *n*-BuLi, and **21** was found to be 1: 6.7: 4.

In this section, it will be shown that alkyllithium reagents and chiral lithium amides form one-to-one complexes in solution. Such mixed complexes may be highly stereoselective when used for alkylation of aldehydes.[164-167] Using *n*-BuLi, in the form of a mixed *n*-BuLi/chiral lithium amide complex, for the enantioselective butylation of prochiral aldehydes gives the product in up to 99% enantiomeric excess. NMR spectroscopy, in conjunction with studies of the stereoselectivity in the alkylation reactions, was used to rationalize the factors important for high enantioselectivity.

7.2 NMR SPECTROSCOPIC STUDIES OF MIXED LITHIUM AMIDE/ALKYLLITHIUM COMPLEXES (PAPER VIII)

Earlier NMR spectroscopic studies by Hilmersson and Davidsson on mixtures of *n*-BuLi and the chiral lithium amide Li-**21** (see also Chapter 5) have showed that *n*-BuLi is present in both homo aggregated tetramers and in a mixed one-to-one aggregate with the chiral lithium amide Li-**21**, i.e. Li-**21**/*n*-BuLi.[168] Based on these results it was suggested that the mixed Li-**21**/*n*-BuLi complex is the reactive specie in the asymmetric alkylation reaction reported by Hogeveen and Eleveld. The solvent dependent stereoselectivity reported, might be explained by a solvent dependent equilibrium between homo aggregated Li-**21**, homo aggregated *n*-BuLi, and the mixed aggregate Li-**21**/*n*-BuLi.

To understand and control the reactivity and selectivity of mixed complexes of this type, insight into the solution state structures and dynamics of these mixed complexes are essential. Thus, to gain knowledge about the structure, dynamics, reactivity, and selectivity of mixed dimers we initiated a systematic investigation of the mixed dimers formed from the chiral lithium amides in Figure 7.1 and alkyllithium reagents.

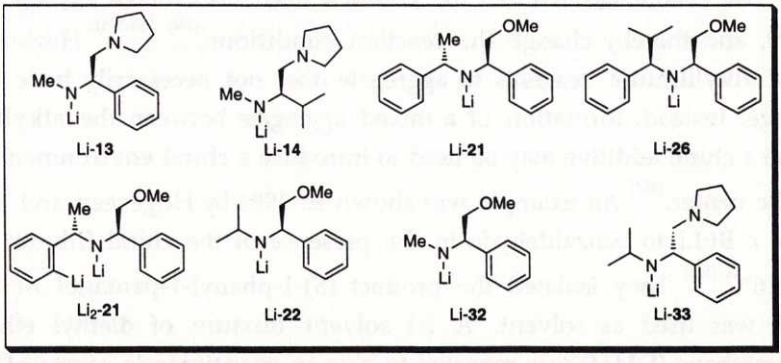


Figure 7.1 The chiral lithium amides whose mixed complexes with alkyllithium reagents were investigated in this work.

7.2.1 Structure of mixed lithium amide/alkyllithium complexes in solution

NMR spectroscopic studies of the chiral lithium amides in Figure 7.1 shows that all these amides are dimeric in DEE-d_{10} solution. Addition of *n*-BuLi to the respective lithium amide dimer results in formation of new species, as shown by ^{1}H, ^{6}Li, and ^{13}C NMR spectroscopy. In addition to the signals from the chiral lithium amide dimers, the ^{6}Li NMR spectrum shows three signals. One signal at δ 1.9 derive from tetrameric *n*-BuLi[355, 357] while the other two signals (present in a one-to-one ratio) originate from the mixed complex between *n*-BuLi and the chiral lithium amide. The ^{13}C NMR spectrum displays two sets of resonances for the chiral lithium amide and two sets of resonances for *n*-BuLi. The signals from the α-carbons of the *n*-BuLi molecules in the mixed complexes are all quintets due to ^{13}C-^{6}Li couplings ($^{1}J(^{13}C,^{6}Li)\approx 8$ Hz).[55] The overall results show that the mixed complexes are dimers, consisting of one molecule of the chiral lithium amide and one molecule of *n*-BuLi.[202]

7.2.2 Complexation ability of lithium amides towards *n*-BuLi

As shown above, an equilibrium between homo dimeric lithium amides, tetrameric *n*-BuLi, and the mixed lithium amide/*n*-BuLi complex exist in solution. The equilibrium constants between the lithium amide homo dimers, $(n\text{-BuLi})_4$, and lithium amide/*n*-BuLi mixed dimers were estimated from intensities in the ^{6}Li NMR spectra at -90°C and the known concentrations of added *n*-BuLi and chiral amine, Table 7.1.

Table 7.1 Equilibrium constants for the formation of mixed lithium amide/*n*-BuLi complexes for four representative lithium amides. The equilibrium constants, determined from intensities in the ^{6}Li NMR spectra, are defined as the equilibrium constant between *n*-BuLi tetramers, lithium amide dimers, and mixed dimers.

Equilibrium	K
$(n\text{-BuLi})_4$ + 2 (Li-**21**)$_2$ $\overset{K}{\rightleftharpoons}$ 4 (Li-**21**)/*n*-BuLi	4 M
$(n\text{-BuLi})_4$ + 2 (Li-**26**)$_2$ $\overset{K}{\rightleftharpoons}$ 4 (Li-**26**)/*n*-BuLi	10 000 M
$(n\text{-BuLi})_4$ + 2 (Li-**22**)$_2$ $\overset{K}{\rightleftharpoons}$ 4 (Li-**22**)/*n*-BuLi	800 M
$(n\text{-BuLi})_4$ + 2 (Li-**33**)$_2$ $\overset{K}{\rightleftharpoons}$ 4 (Li-**33**)/*n*-BuLi	0.14 M

As seen in Table 7.1, there is large variance in the ability of different chiral lithium amides to complex *n*-BuLi. This might be explained by differences in steric interactions and solvation within the lithium amide/*n*-BuLi complexes, as compared to the corresponding lithium amide homo dimers. Compound (Li-**33**)$_2$ with intramolecular pyrrolidine coordination shows only a weak tendency to coordinate *n*-BuLi.

7.2.3 Complexation ability of different alkyllithium reagents towards Li-21

To testify if the size of the alkyl group in the alkyllithium reagent is important for formation of mixed lithium amide/alkyllithium complexes, we investigated the tendency of Li-**21** to form mixed complexes with alkyllithiums of different congestion. The equilibrium constants, determined from intensities in the ^{6}Li NMR spectra at -80°C in DEE-d_{10}, for formation of mixed complexes between Li-**21** and MeLi, *n*-BuLi, *s*-BuLi, and *t*-BuLi are shown in Table 7.2.

Table 7.2 Equilibrium constants for the formation of mixed complexes with Li-**21** for different alkyllithium reagents. The equilibrium constants, determined from intensities in the ^{6}Li NMR spectra, are defined as the equilibrium constant between homo aggregated alkyllithium (R-Li)$_x$, (Li-**21**)$_2$, and the mixed dimers R-Li/Li-**21**.

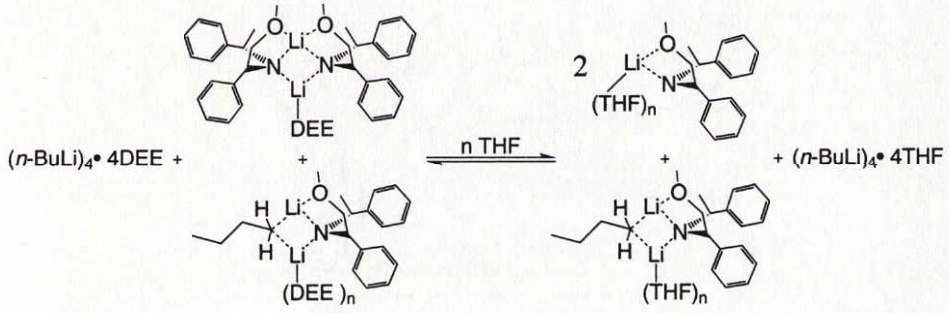
Equilibrium	K	ΔG_{193K}
(MeLi)$_4$ + 2 (Li-**21**)$_2$ $\overset{K}{\rightleftharpoons}$ 4 (Li-**21**)/MeLi	0.001 ± 0.009 M	11 kJ mol^{-1}
(*n*-BuLi)$_4$ + 2 (Li-**21**)$_2$ $\overset{K}{\rightleftharpoons}$ 4 (Li-**21**)/*n*-BuLi	1.22 ± 0.41 M	-0.32 kJ mol^{-1}
(*s*-BuLi)$_4$ + 2 (Li-**21**)$_2$ $\overset{K}{\rightleftharpoons}$ 4 (Li-**21**)/*s*-BuLi	150 ± 70 M	-8.0 kJ mol^{-1}
(*t*-BuLi)$_2$ + (Li-**21**)$_2$ $\overset{K}{\rightleftharpoons}$ 2 (Li-**21**)/*t*-BuLi	0.4 ± 0.3	1.5 kJ mol^{-1}

The homo aggregates of MeLi, *n*-BuLi, and *s*-BuLi are all tetrameric in DEE solution at -80°C; *t*-BuLi, on the other hand, is dimeric under these conditions.[358] From the equilibrium constants in Table 7.2, it is clear that *s*-BuLi is superior over the other alkyllithium reagents in the formation of mixed dimers with the chiral lithium amide Li-**21**. The equilibrium constant between homo and hetero complexes is dependent on the steric requirements of the substituents on the α-carbon. The branching at the carbanion carbon in *s*-BuLi yields crowding at the carbanions close to the lithiums. This disfavors *s*-BuLi homo tetramers compared to the Li-**21**/*s*-BuLi mixed dimers. In contrast, *t*-BuLi is only sparingly found as

mixed complexes with Li-**21**. Since *t*-BuLi is homo dimeric in DEE a homo dimer—mixed dimer equilibrium results; comparisons of the equilibrium constants are therefore complex.

7.2.4 Solvent dependence upon mixed complex formation

Addition of THF to a DEE solution of the mixed complex Li-**21**/*n*-BuLi shows that the equilibrium between homo and hetero complexes is solvent dependent, Scheme 7.1.



Scheme 7.1 The equilibrium between homo aggregated Li-**21**, homo aggregated *n*-BuLi, and mixed Li-**21**/*n*-BuLi complexes is affected by THF.

The ^{6}Li NMR spectra in Figure 7.2 shows the effect of THF addition to a mixture of (Li-**21**)$_2$, Li-**21**/*n*-BuLi, and (*n*-BuLi)$_4$ in DEE. In agreement with previous observations,[331] addition of THF rapidly lowers the concentration of the DEE solvated (Li-**21**)$_2$ (δ 2.72 and 3.14), while the THF solvated (Li-**21**)$_2$ (δ 2.70 and 3.16) is formed together with the THF solvated monomer (δ 2.28). The signals for Li-**21**/*n*-BuLi at δ 2.40 and 3.68 were also affected by THF. At first, the most downfield ^{6}Li NMR signal at δ 3.68 shifted slightly downfield, possibly due to replacement of one DEE molecule by one THF molecule in the solvated mixed Li-**21**/*n*-BuLi complex. At THF concentrations above 8%, the ^{6}Li signals from the THF solvated Li-**21**/*n*-BuLi shift upfield towards that of Li-**21**/*n*-BuLi in pure THF, Figure 7.2b.

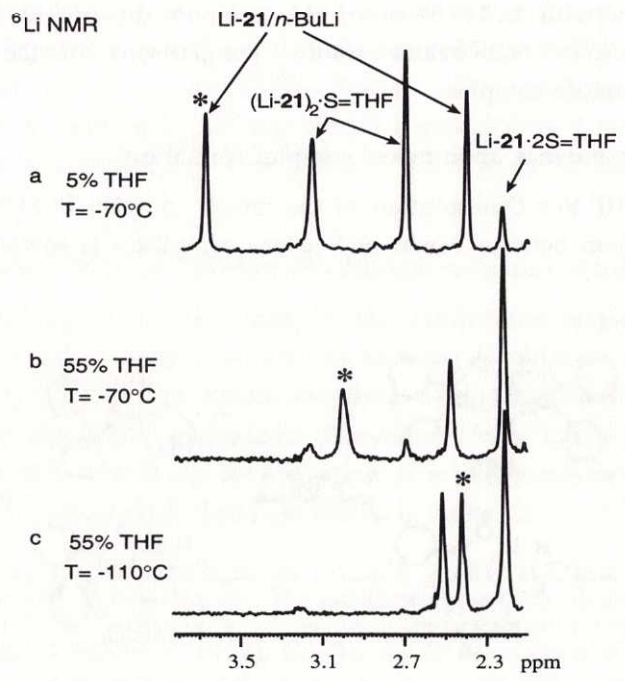


Figure 7.2 Part of ^{6}Li NMR spectra of the mixture of dimeric and monomeric Li-**21** as well as the mixed Li-**21**/*n*-BuLi complex in DEE-d_{10} with (a) 5% added THF and (b) 55% THF. The large temperature dependence on the marked (*) signal are also shown (c).

At 55% THF in DEE the most downfield ^{6}Li resonance from Li-**21**/*n*-BuLi (originally at δ 3.68) was observed about 0.6 ppm upfield (now at δ 3.04). These chemical shift changes are likely the effect of an increased coordination number for one of the lithiums in Li-**21**/*n*-BuLi.

The shift of this signal also showed large temperature dependence in the ^{6}Li NMR spectra. Upon lowering the temperature from -70°C to -110°C, the ^{6}Li NMR signal at δ 3.04 shifts upfield to δ 2.42. Interestingly, the chemical shift for this ^{6}Li NMR signal seems to merge the ^{6}Li NMR chemical shift of the tetra-coordinated lithium in Li-**21**. The second ^{6}Li NMR signal from Li-**21**/*n*-BuLi in DEE, originally at δ 2.40, showed only small chemical shift changes upon THF addition. This indicates a preserved coordination around this lithium. Presumably, this lithium is solvated by the oxygen in the methoxy group; this coordination persists also in THF.

Addition of TMEDA to a DEE solution of Li-**21**/*n*-BuLi, Li-**21** dimers, and (*n*-BuLi)$_4$ resulted in a large fraction of TMEDA-solvated monomers of Li-**21**, i.e. Li-**21**/TMEDA and TMEDA solvated *n*-BuLi dimers. No TMEDA solvated mixed

Li-**21**/*n*-BuLi complexes were observed. Similar results were obtained upon addition of THF or TMEDA, respectively, to the other mixed dimer complexes in DEE.

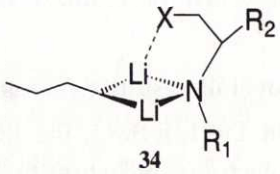
The overall results demonstrate a preference for coordination at one lithium center in Li-**21**/*n*-BuLi; the lithium center originally found at δ 3.68 in the ^{6}Li NMR spectrum. Structurally this implies that the internal coordination by the methoxy group is very strong,[359] as it persists even in the presence of a strong polar solvent such as THF. Tentatively, this implies that solvents as well as substrates initially coordinate to the non-methoxy coordinated lithium cation. A further consequence of the strong internal methoxy coordination is that the substituents at the methylene carbons between the amide nitrogen and the methoxy group will be locked in a "well defined" spatial arrangement. Thus, an incoming substrate will be regioselectively directed to one of the lithium atoms and, once there, forced to adopt a geometry that minimizes the steric interactions with the lithium amide moiety (*vide infra*).

Since the stereoselectivity for the asymmetric alkylation of benzaldehyde was reported to improve in a 1:1 solvent mixture of DEE and DMM, as compared to pure DEE, we investigated the effect of DMM on the above equilibrium. However, no changes were observed in the ^{6}Li NMR spectra for Li-**21**/*n*-BuLi or Li-**22**/*n*-BuLi upon addition of 50% (v/v) DMM to the DEE solution. This indicates that DMM only has marginal effect on the above equilibriums and structures.

7.3 EVALUATION OF CHIRAL LITHIUM AMIDES FOR ASYMMETRIC ALKYLATION REACTIONS

To acquire a relationship between the structure of the mixed lithium amide/alkyllithium complex and the selectivity obtained in the asymmetric alkylation of aldehydes, we performed the asymmetric addition of *n*-BuLi to benzaldehyde. DEE was used as solvent in these reactions; although, a 1:1 mixture of DEE and DMM has been reported to give higher stereoselectivity. The use of DEE allows a direct comparison with the NMR spectroscopic results. The results obtained using the mixed complexes between *n*-BuLi and the chiral lithium amides in Figure 7.1 are shown in Table 7.3.

Table 7.3 Results for the asymmetric alkylation of benzaldehyde in presence of the chiral lithium amides in Figure 7.1. The following molar ratios were used: lithium amide (1 equiv.), *n*-BuLi (0.45 equiv.), and benzaldehyde (0.25 equiv.). All reactions were carried out at -116°C in DEE. The substituents R_1, R_2 and X are shown in structure **34**.



34

amide	R_1	R_2	X	ee % (GC)
Li-**21**		Ph	OMe	72 (*S*)
Li-**26**		Ph	OMe	75 (*S*)
Li_2-**21**		Ph	OMe	8 (*S*)
Li-**13**	Me	Ph		7 (*R*)
Li-**14**	Me	*i*-Pr		7 (*R*)
Li-**22**	*i*-Pr	Ph	OMe	82 (*S*)
Li-**32**	Me	Ph	OMe	2 (*S*)
Li-**33**	*i*-Pr	Ph		26 (*S*)

From the results in Table 7.3 it is possible to identify some structural features in the lithium amide that are important for controlling the enantioselectivity in the alkylation reactions. The steric requirement of the R_1 substituent is crucial for the reaction, i.e. high stereoselectivity is dependent on a large group at R_1; a methyl group is too small (see the entries with compounds Li-**13**, Li-**14**, and Li-**32** in Table 7.3). Congested R_1-groups, like those in Li-**21**, Li-**26**, and Li-**22** gave high enantioselectivities. Furthermore, compound Li-**22**, in which one of the chiral centers of Li-**21** has been removed, did not result in a drop in stereoselectivity; instead, the product ee increased to 82%. This observation shows that R_1 does not have to be chiral and indicates that the asymmetric induction is controlled by the chiral center between the R_2 substituent and the chelating group.

The configuration of the product 1-phenyl-1-pentanol was reversed, considering the absolute configuration of the lithium amide, when the amides Li-**13**, Li-**14**, and

Li-**33** were used. Furthermore, the enantioselectivity was low when these ligands were used. Obviously, the pyrrolidine group forces the benzaldehyde into a different transition state geometry. Two important factors can be noticed when Li-**33** is used. The isopropyl group in R_1 would imply a high selectivity for (*S*)-alcohol; however, this effect is biased by the large pyrrolidine group that favors a transition state yielding the (*R*)-alcohol.

Hogeveen and Eleveld reported an enantiomeric excess of 90% for (*S*)-1-phenyl-1-pentanol when a 1:1 mixture of DEE and DMM was used as solvent.[162] However, despite repeated attempts, we only obtained (*S*)-1-phenyl-1-pentanol in 72% ee using Li-**21** in this solvent mixture. The observed difference may be connected to the way the optical purity of the product was determined. Hogeveen and Eleveld determined the ee from the optical rotation, whereas we used GC on chiral stationary phase. Surprisingly, the addition of DMM to the reaction performed with Li-**22** as chiral inducer resulted in a large increase in stereoselectivity. (*S*)-1-phenyl-1-pentanol was now formed in 91% ee. The reason for this improved stereoselectivity is not unambiguously determined; it is likely an effect of increased solvation in the transition state with DMM.

7.4 ASYMMETRIC ALKYLATION OF PROCHIRAL ALDEHYDES BY MIXED LITHIUM AMIDE/ALKYLLITHIUM COMPLEXES (PAPER IX)

Aliphatic aldehydes have traditionally been poor substrates for enantioselective alkylation reactions using organolithium reagents. However, encouraged by the high stereoselectivity obtained using Li-**21** and the new chiral ligand[153] Li-**22** we studied the enantioselective addition of *n*-BuLi to the various aldehydes shown in Figure 7.3.

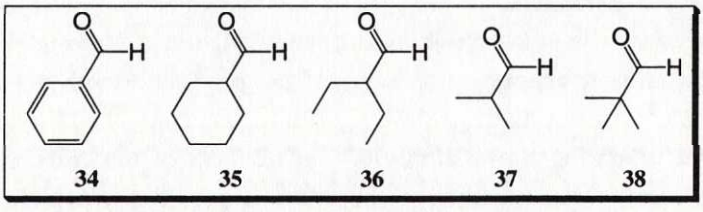


Figure 7.3 Aldehydes used as substrates for the enantioselective addition of *n*-BuLi using the chiral lithium amides Li-**21** and Li-**22** as chiral auxiliaries.

The results obtained when the prochiral aldehydes in Figure 7.3 were butylated with the mixed complexes Li-**21**/*n*-BuLi and Li-**22**/*n*-BuLi, respectively, are summarized in Table 7.4.

Table 7.4 Enantioselective addition of *n*-BuLi (0.45 equiv.) to prochiral aldehydes (0.25 equiv.) in the presence of the chiral lithium amides Li-**21** or Li-**22** (1 equiv.) in (50/50 v/v) DEE/DMM solution at -116°C.

Entry	Lithium amide	Aldehyde	Product	ee (%)
1	Li-**21**	**34**	1-phenyl-1-pentanol	72
2	Li-**22**	**34**	1-phenyl-1-pentanol	91
3	Li-**21**	**35**	1-cyclohexyl-1-pentanol	91
4	Li-**22**	**35**	1-cyclohexyl-1-pentanol	>98.5
5	Li-**21**	**36**	3-ethyl-4-octanol	90[a]
6	Li-**22**	**36**	3-ethyl-4-octanol	65[a]
7	Li-**21**	**37**	2-methyl-3-heptanol	96
8	Li-**22**	**37**	2-methyl-3-heptanol	>98.5
9	Li-**21**	**38**	2,2-dimethyl-3-heptanol	58
10	Li-**22**	**38**	2,2-dimethyl-3-heptanol	11

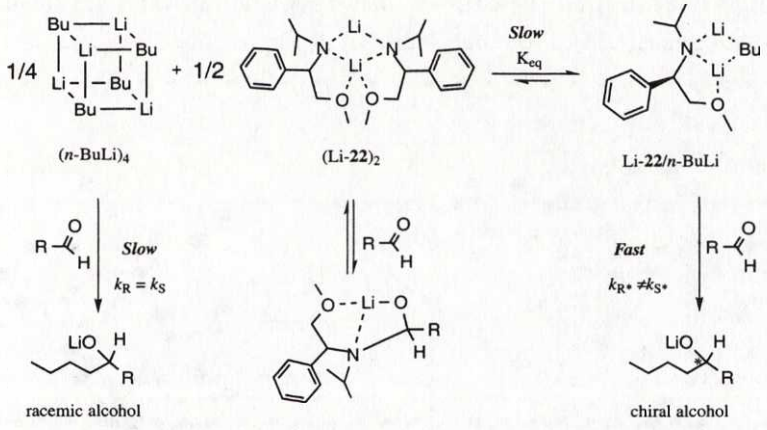
[a] The peaks were not fully resolved; reported values are estimates of enantiomeric excess.

As described in the preceding section, the asymmetric butylation of aldehydes is likely to proceed through an activated complex in which the aldehyde is coordinated to one of the two stereogenic lithium atoms in the mixed lithium amide/*n*-BuLi dimer. The spatial complementary of the aldehyde to this mixed dimer is important for the asymmetric induction. The aldehydes in Table 7.3 differ in their steric requirements at the α- and β-carbons. 1-Cyclohexyl carboxaldehyde **35** is more congested than benzaldehyde **34**. This difference is reflected in an increased enantiomeric excess of the product 1-cyclohexyl-1-pentanol. 2-Ethyl-butyraldehyde **36** is even more congested; a low enantiomeric excess of the product 3-ethyl-4-octanol was obtained when Li-**22** was used as chiral ligand. *i*-Butyraldehyde **37** is a small aldehyde, and the enantiomeric excess of the product 2-methyl-3-heptanol is again high, >98.5% using Li-**22** and 96% with Li-**21**. Both Li-**21** and Li-**22** are efficient in discriminating between the *Re*- and *Si*-faces of the carbonyl group in the above aldehydes. However, when the very congested pivalaldehyde **38** was used, the enantiomeric excess of the resulting 2,2-dimethyl-3-heptanol dropped significantly. Similar results were also observed in an attempt to butylate acetophenone in the presence of Li-**22**. The resulting product 2-phenyl-2-hexanol was obtained in only 10% ee. Thus, it is clear that the enantioselectivity in the addition reaction is *extremely* sensitive to the steric requirement of the R-group attached to the carbonyl carbon.

7.4.1 Ligand accelerated alkylation and an attempt to catalytic turnover

The reactivity of organolithium reagents is known to increase upon deaggregation, i.e. dimers of *n*-BuLi are more reactive than their tetrameric analogues.[31, 355] Thus, it seems likely that *n*-BuLi within the hetero dimers Li-**22**/*n*-BuLi would be more reactive than *n*-BuLi present as dimeric and tetrameric aggregates. To test this hypothesis, we estimated the reaction rates at -116°C for the butylation of **35** and **37** from the observed half-life of the aldehydes, in the absence and presence of Li-**22**. The rate of butylation using the mixed complex Li-**22**/*n*-BuLi was found to be too fast to be determined with the method used, i.e. reaction quenching followed by GC analysis. However, the butylation of **35** and **37** *without* added Li-**22**, i.e. with dimeric and/or tetrameric *n*-BuLi, was much slower ($T_{1/2}$ > 10 min).

The increased reactivity of the Li-**22**/*n*-BuLi complex, as compared to tetrameric *n*-BuLi, encouraged us to attempt the butylation reaction using only a catalytic amount of the chiral lithium amide. The product alcohol was isolated in high enantiomeric excess but in low chemical yield. Prolonging the reaction time increased the chemical yield; however, at expense of the stereoselectivity. These observations were caused by two factors, Scheme 7.2.



Scheme 7.2 The chiral lithium amide Li-**22** dissociates the tetramers of *n*-BuLi into hetero dimers Li-**22**/*n*-BuLi, which are more reactive towards the aldehyde than the *n*-BuLi tetramers. The formation of Li-**22**/*n*-BuLi is slower than the reaction between the aldehyde and Li-**22**/*n*-BuLi. The lithium amide, present as (Li-**22**)$_2$, undergoes 1,2-addition to the aldehyde in absence of *n*-BuLi.

The rate of formation of the mixed complex Li-**22**/*n*-BuLi from the lithium amide dimer and tetrameric *n*-BuLi was found slower than the reaction between Li-**22**/*n*-BuLi and the aldehyde. Furthermore, there appears to be a loss of the

chiral amide due to a 1,2-addition to the aldehyde[164, 166, 360-362] in the absence of *n*-BuLi. Thus, catalytic turnover is hampered in a one-pot synthesis. However, turnover for the asymmetric butylation could be demonstrated by a repetitive cycle comprised of: 1) formation of the mixed complex Li-**22**/*n*-BuLi at room temperature (by the addition of 0.5 equiv. *n*-BuLi to Li-**22**), 2) cooling down to -116°C followed by addition of **35** (0.5 equiv.). This cycle was repeated 5 times to yield 1-cyclohexyl-1-pentanol in quantitative chemical yield (GC) and 82% ee using a sub-stoichiometric amount of Li-**22**. Since the chemical yield and enantioselectivity was found high, there does not seem to be any interference from the product.

7.5 PROPOSED ACTIVATED COMPLEXES

The NMR spectroscopic study suggested that solvents as well as the aldehyde substrate initially binds to the non-methoxy coordinated lithium atom in the mixed Li-**21**/*n*-BuLi complex. Thus, the aldehyde is likely to form a pre-complex with the mixed Li-**21**/*n*-BuLi complex; addition of the *n*-BuLi moiety in Li-**21**/*n*-BuLi to the aldehyde then occurs within this pre-complex. Based on this reasoning, we initiated a computational study on possible transition states for the nucleophilic addition of ethyllithium to benzaldehyde in the presence of the chiral lithium amide Li-**26**. Initial calculations at the semi empirical PM3 level located the two diastereomeric transition states shown in Figure 7.4.

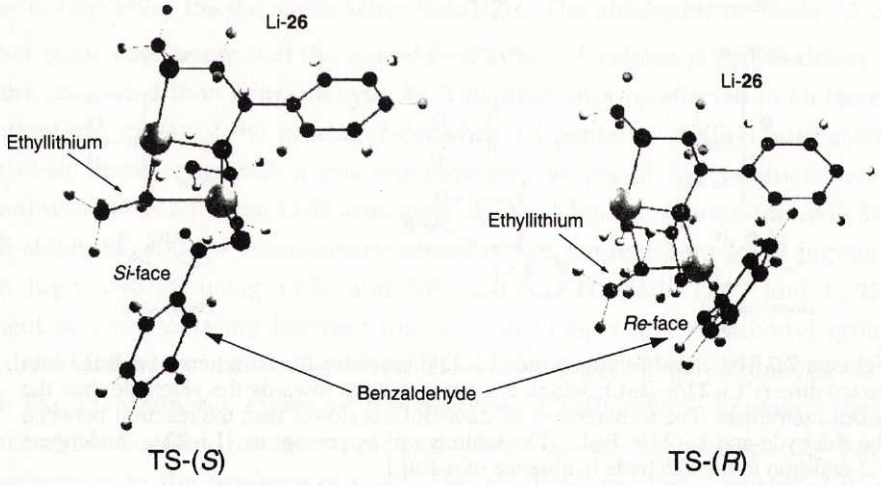


Figure 7.4 PM3 optimized transition states for the nucleophilic addition of ethyllithium, present as a mixed aggregate with Li-**26**, to benzaldehyde.

The transition state leading to (*S*)-1-phenyl-1-pentanol, i.e. attack by the ethyllithium to the *Si*-face of the aldehyde, was found to be favored when single point DFT calculations were performed on the PM3 geometry (2.9 kcal mol^{-1} p-BP86/DN*, 0.2 kcal mol^{-1} B3LYP). As seen in Figure 7.4, the transition state leading to the (*R*)-alcohol has unfavorable non-bonded interactions between the phenyl-ring in Li-**26** and the phenyl-ring in benzaldehyde. Although, these calculations correctly predict the stereochemical outcome of the addition reaction, no solvation was included in this initial study. Based on the experimental results, coordinating solvent molecules are expected to have a large effect on the relative energies of the transition states. A more detailed study, also including solvent molecules, is in progress.

7.6 CONCLUSION

NMR spectroscopic studies have showed that mixed complexes between chiral lithium amides and alkyllithium reagents are formed in solution. These mixed complexes are composed of one molecule of the chiral lithium amide and one molecule of the alkyllithium reagent. The equilibrium constants for formation of mixed complexes reveal large differences among structurally related lithium amides in their ability to form mixed complexes. Lithium amides having a methoxy-group as internally coordinating ligand form more stable mixed complexes than lithium amides containing a pyrrolidine moiety. There are also large differences among various alkyllithium reagents to form mixed complexes. Homo aggregates of congested alkyllithium reagents are disfavored for steric reasons; this leads to favorable mixed complex formation.

The mixed complexes of chiral lithium amides and alkyllithium reagents can be used for asymmetric carbon-carbon bond formation. Nucleophilic addition of the complexed alkyllithium reagent to prochiral aldehydes produces chiral secondary alcohols in high yields and enantiomeric excesses. Enantioselective addition of *n*-BuLi to benzaldehyde in the presence of various chiral lithium amides indicated the structural features of the lithium amide that control stereoselectivity. Based on these findings we designed a new chiral lithium amide, giving higher stereoselectivity in alkylation reactions than the parent lithium amide. Furthermore, this new ligand can be prepared through a short and efficient synthetic route. Comparing the equilibrium constants for mixed complex formation for some lithium amides demonstrate that a high tendency to form mixed complexes does not necessarily imply a high stereoselectivity in the alkylation reaction. However, it was found that the alkyllithium reagent in the mixed complex is more reactive than the homo aggregated reagent. Thus, the

prerequisite for catalytic asymmetric alkylation exists. Unfortunately, catalytic turnover in the alkylation reaction is hampered by a retarded mixed complex formation. Furthermore, the lithium amide accumulating in the reaction mixture is lost through reaction with the aldehyde. However, enantioselective addition using only catalytic amounts of the chiral ligand was demonstrated through a sequential addition of alkyllithium reagent and aldehyde followed by a short temperature jump to allow formation of the mixed complex.

8

Solution State Studies on Lithium Organic Reagents

The previous sections of this thesis have described reactions where the chiral lithium amide base acts as a reagent or is used as a chiral auxiliary. Most of the structural studies presented have dealt with the ligand itself or initial state complexes between the ligand and a substrate. However, no molecular structure is static, there are always various intramolecular motions taking place. In supramolecular structures, like aggregates of lithium organic reagents, additional dynamic processes are possible. Examples of such processes include exchange between different aggregates;[363, 364] i.e. interaggregate exchange, and exchange of solvents, lithiums, anions, and other ligands within the same aggregate, i.e. intraaggregate exchange.[53] This section will focus on structural and dynamic properties of the aggregates themselves.

8.1 Solution state structure through the combination of X-ray diffraction, computational, and NMR spectroscopic studies (paper X)

8.1.1 Background

Quantitative structural studies in lithium organic chemistry have traditionally relied almost exclusively on X-ray diffraction.[1, 13] However, it can be difficult to obtain single crystals suitable for X-ray diffraction analysis. Furthermore, the obtained structure does not necessarily reflect the actual solution state structure. Today, computational methods may also be used to gain structural information, even for large systems including coordinated solvent molecules and other ligands. The obvious obstacle with this approach is that an initial guess of possible structures is needed before geometry optimizations are initiated. Again, there is no guarantee that the optimized structure of lowest energy actually represents the solution state structure.

The average solution state structure may be quantitatively determined from NMR spectroscopy using transient NOE experiments.[365] However, this approach requires a reference distance. This distance may be obtained from an X-ray diffraction study or, as will be shown here, through a computational geometry optimization. In order to evaluate how good solid-state and gas-phase geometries model solution state structures, and to compare geometries obtained using different methods and aggregation states, we undertook a quantitative $^{6}Li,^{1}H$-HOESY study of the dimeric lithium amide (Li-**21**)$_2$·S=THF, previously discussed in Scheme 5.3.

8.1.2 Solid state structure of Li-21

A single-crystal X-ray diffraction study revealed that the solid state structure of Li-**21**, crystallized from a hexane-THF solution is dimeric, i.e. (Li-**21**)$_2$·S=THF. The dimer, having one three-coordinated and one tetra-coordinated lithium center with an almost planar Li_2N_2 core is found to be close to C_2-symmetric as previously proposed from the NMR spectroscopic studies, see Figure 5.5.

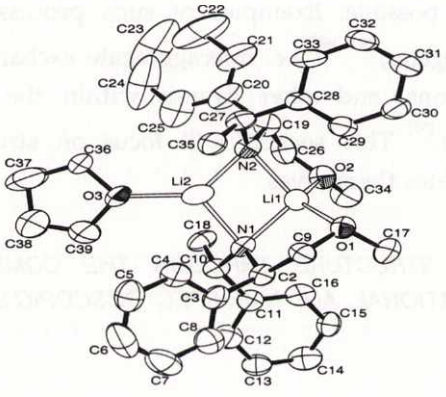


Figure 8.1 ORTEP drawing showing the crystallographic numbering of (Li-**21**)$_2$·S=THF crystallized from a hexane-THF solution.

Comparison of the solid state structure of (Li-**21**)$_2$·S=THF with other structures,[366] containing Li-N and Li-O bonds, found in the Cambridge Structural Database (CSD)[23] revealed that the obtained structure is representative for lithium amides in general. Using the solid state structure (Li-**21**)$_2$·S=THF as a reference for distance calculations is thus feasible.

8.1.3 Gas phase (computationally optimized) structure

Computational studies on a smaller dimeric model system revealed that B3LYP/6-31+G(d) and HF/6-31(d) are the methods that structurally best describe

system of this kind, i.e. show largest structural similarity with the X-ray structure. However, very close structural agreement is also obtained using the computationally less demanding semi empirical PM3 method. The accuracy of the PM3 method for geometry optimizations in lithium organic chemistry has also recently been supported by Schleyer *et. al.*[367]

Geometry optimizations of the full (Li-**21**)$_2$·S=THF system were done at the PM3, MNDO, HF/STO-3G, and HF/6-31G(d) levels of theory. Reasonable agreements with the solid state structure were noted for the geometries obtained using the ab initio and PM3 methods. The MNDO-calculated geometry, on the other hand, showed large deviations. As might be expected for gas-phase geometries, the calculated Li-H distances were generally found to be somewhat longer (0-0.4 Å) than those measured in the solid state structure.

8.1.4 Solution state structure

As in the determination of homonuclear ^{1}H-^{1}H distances through ^{1}H,^{1}H-NOESY experiments, internuclear ^{6}Li-^{1}H distances may be derived from ^{6}Li,^{1}H-HOESY spectra.[233, 240, 241] The initial buildup rates, f, of transient heteronuclear NOEs are related to the corresponding distances r through Eq. 8.1.[365]

$$\{f(^6\text{Li-H}^A)/f(^6\text{Li-H}^X)\}^{1/6} = r(^6\text{Li-H}^X)/r(^6\text{Li-H}^A) \qquad \text{Eq. 8.1}$$

Here, H^A denotes a proton of known distance from the lithium nucleus, whereas H^X is a proton of unknown lithium separation. The known reference distance may be taken from X-ray diffraction measurements or, as will be shown below, from computational studies. Thus, all Li-H distances of an organolithium compound in solution can be determined from the ^{6}Li,^{1}H NOE buildup rates and a known reference distance.

The NOE buildup curves of (Li-**21**)$_2$·S=THF in toluene-d_8 at -85°C were determined through a series of 2D ^{6}Li,^{1}H-HOESY experiments with varying mixing times (0-4 s). The buildup rates for the transient heteronuclear NOEs were determined from linear fits of the NOE cross-peak intensities to the mixing times (initial buildup range 0-0.5 s). Consequently, all Li-H distances in (Li-**21**)$_2$·S=THF could be determined using the buildup rates and Eq. 8.1. In the analysis, we separately used all Li-H distances shorter than 5Å in the geometries obtained from X-ray, PM3, and HF/6-31G(d) as reference distances. A list of values for one particular distance is thus produced. The distances shown in Table 8.1 represent the mean average of this list of values.

Table 8.1 Solution state Li-H distances in (Li-**21**)$_2$·S=THF obtained using heteronuclear buildup rate correlations are shown together with reference distances taken from the X-ray-, PM3-, and HF/6-31G(d)-geometries, respectively.

	measured distances[c]			calculated distances from NOE buildup rates[d]		
proton	X-ray	PM3	HF/ 6-31G(d)	X-ray	PM3	HF/ 6-31G(d)
methyl-CH_3	3.03[a]	3.11[a]	3.15[a]	3.05[a]	3.01[a]	2.97[a]
C(18,35)	3.82[b]	3.91[b]	3.97[b]	3.65[b]	3.79[b]	3.58[b]
methoxy-OCH_3	5.25[a]	5.63[a]	5.48[a]	4.58[a]	4.47[a]	4.57[a]
C(34,17)	3.35[b]	3.32[b]	3.45[b]	3.34[b]	3.70[b]	3.30[b]
C(9,26)	4.49[a]	4.80[a]	3.88[a]	4.14[a]	4.14[a]	4.03[a]
	3.57[b]	3.78[b]	3.23[b]	3.34[b]	3.67[b]	3.38[b]
THF(α)	3.22[a]	3.14[a]	3.34[a]	3.46[a]	3.45[a]	3.37[a]
C(36,39)	5.45[b]	5.48[b]	5.50[b]	5.08[b]	4.67[b]	4.96[b]
THF(β)	4.74[a]	4.99[a]	4.79[a]	4.16[a]	3.95[a]	3.82[a]
C(38,37)	7.19[b]	7.20[b]	7.17[b]	5.26[b]	4.97[b]	5.37[b]

[a]For Li(2) at δ 3.16 (THF-coordinated lithium). [b]For Li(1) at δ 2.70 (methoxy coordinated lithium). [c]Distances measured in respective geometries. [d]The distances in each row calculated with eq 8.1 are average distances (the slopes of the initial NOE build-up curves obtained from the HOESY experiments were used together with several X-ray or calculated distances).

Most of the data in Table 8.1 indicate a similar structure in the solid state, in solution state, and in the gas phase (calculated). Furthermore, for distances less than 4 Å, there are only small differences of less than 0.2 Å between the distances obtained using X-ray diffraction, computational geometry optimizations, and heteronuclear NOE buildup rates from ^{6}Li,^{1}H-HOESY experiments. However, distances longer than 4 Å are measured less accurately. The prime reasons for this are problems with small NOEs and spin diffusion.

8.1.5 Conclusion

Heteronuclear NOE buildup rates, obtained from ^{6}Li,^{1}H-HOESY experiments, in conjunction with a reference distance may be used to quantitatively measure Li-H distances in aggregated lithium organic compounds in solution. This study has shown that the necessary reference distance may be taken from X-ray diffraction studies *or* from a computationally optimized geometry. In the field of lithium organic chemistry, the HF/6-31G(d) and PM3 levels of theory provide sufficiently accurate geometries to be used in structural studies of this kind. Thus, solution state geometries of large aggregated lithium organic compounds may be obtained, without access to crystals suitable for single X-ray diffraction measurement, using the computationally very cheap PM3 method.

8.2 NEW INSIGHTS INTO THE COORDINATION CHEMISTRY OF CHIRAL LITHIUM AMIDES (PAPER XI)

8.2.1 Background

Lithium amide bases are mainly used for deprotonation/lithiation reactions. Thus, an amine is inevitably formed from the corresponding lithium amide in these reactions. Since amines are known to be strong ligands for lithium cations, they are likely to interact with the aggregates present in solution.[29, 36, 38, 368] The amine-coordinated aggregates thus formed may successively influence the reactivity and selectivity of the original reagent. Consequently, much effort has been made to understand the influence of amines in these reactions.[62, 146]

In this section, characterization of a novel type of complex, consisting of a dimeric chiral lithium amide chelated by the parent diamine, is described. This complex allowed us to illustrate how an amine ligand may effect the structure of a reagent and gain insight into the dynamic processes involved.

8.2.2 Amine chelates of Li-11

The difficulties associated with NMR spectroscopic investigations of Li-**11**, in terms of low solubility in DEE and rapid dynamic processes in THF, was outlined in Chapter 5. Addition of *n*-BuLi to a DEE-d_{10} solution of the amine **11** (0.1 M) immediately results in precipitation of Li-**11**. However, addition of 0.5 equiv. of the amine **11** to the precipitate results in complete dissolution of the solid material. The ^{1}H, ^{13}C, and ^{6}Li NMR spectra all display sharp resonances. Nine carbon signals were observed for each of **11** and Li-**11**. Thus, rotation of the pyrrolidine rings in both Li-**11** and **11** are slow on the NMR time scale (-90°C) indicating a complexation between the two. The intensities of the ^{13}C signals suggest that Li-**11** and **11** form a 2:1 chelate, i.e. (Li-**11**)$_2$/**11**. Two resonances of equal intensity and line shape are observed in the ^{6}Li NMR spectrum of (Li-**11**)$_2$/**11**. The line shapes of the signals suggest that both lithiums are tetracoordinated. The overall results indicate that Li-**11** is a dimer, with one of the lithium atoms coordinated by the two pyrrolidine nitrogens in the amide ligands. The other lithium atom is chelated by the nitrogens in **11**, Figure 8.2a.

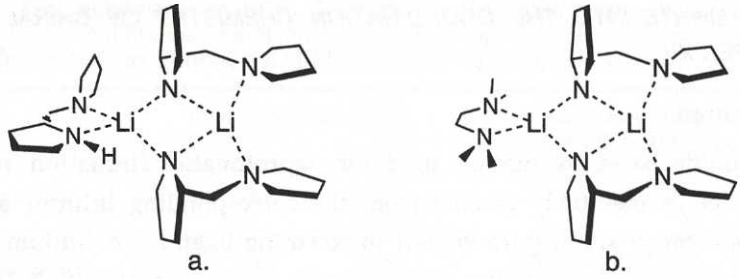


Figure 8.2 Proposed structure of the chelate (Li-**11**)$_2$/**11** (a) and (Li-**11**)$_2$/TMEDA (b).

Similarly, the widely used lithium-chelating diamine TMEDA is found to dissolve Li-**11** in DEE, presumably by formation of the complex (Li-**11**)$_2$/TMEDA shown in Figure 8.2. However, TMEDA needs to be in excess relative to Li-**11** to fully dissolve the crystals. No monomers were observed even at high TMEDA concentrations.

As previously noted the ^{6}Li, ^{1}H, and ^{13}C NMR spectra of Li-**11** in THF-d_8 at low temperatures are characterized by broad and unresolved signals. However, addition of one equiv. of **11** to a THF solution of Li-**11** gives a spectrum very similar to that of (Li-**11**)$_2$/**11** in the DEE mixture above. In the ^{13}C spectrum at -105°C both uncoordinated and coordinated **11** are observed. Thus, it is concluded that **11** is competing effectively with the bulk solvent THF for (Li-**11**)$_2$.

8.2.3 Computational studies

The large stability of the (Li-**11**)$_2$/**11** chelate was also demonstrated in a computational study. The complexation energy for dimethylether (used instead of DEE due to lower computational cost), TMEDA, and **11** are shown in Table 8.2.

Table 8.2 PM3 and B3LYP/6-31+G(d) complexation energies[a] for the dimer (Li-**11**)$_2$ with different ligands **L**.

(Li-**11**)$_2$ + **L** $\rightleftharpoons$ (Li-**11**)$_2$/**L**

L	PM3	B3LYP/ 6-31+G(d)//PM3
Me_2O	-9.891	-8.253
TMEDA	-15.55	-13.94
11	-19.60	-18.15

[a]Energies in kcal mol^{-1}

In agreement with the NMR spectroscopic results, the coordination of amine **11** yields the most stable complex. The PM3-optimized structure of (Li-**11**)$_2$/**11** is shown in Figure 8.3.

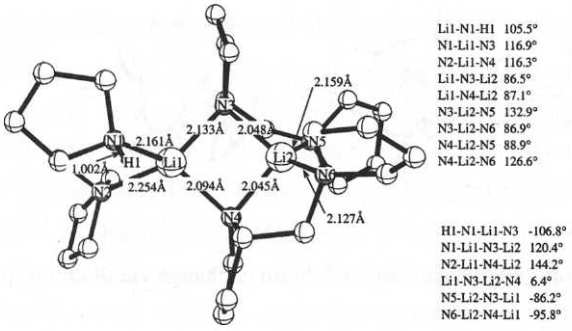


Figure 8.3 Structure of the PM3 optimized geometry of (Li-**11**)$_2$/**11**. Hydrogens are omitted for clarity.

The two amides form a "C_2-symmetric" dimer with a nearly planar (Li-N)$_2$ arrangement. This plane is almost perpendicular to the plane defined by one lithium atom and the two nitrogen atoms in the solvating diamine. The bond lengths and angles are typical for lithium amide dimers, Figure 8.3.[28]

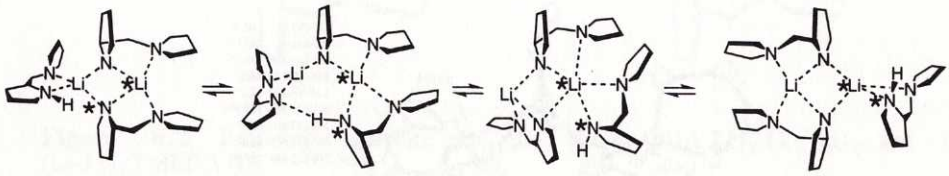
8.2.4 Ligand exchange in (Li-**11**)$_2$/**11**

The ^{13}C NMR resonances for the complexed **11** in (Li-**11**)$_2$/**11** appear shifted relative to the signals for uncomplexed **11** in DEE at -105°C. The signals for **11** in (Li-**11**)$_2$/**11** broaden upon addition of **11** indicating slow ligand exchange on the NMR time scale. At -98°C coalescence results, corresponding to $\Delta G^{\ddagger}_{175K}$= 7.8 kcal mol^{-1} for the ligand exchange.[245] The rate constant for exchange is concentration-independent in the interval 10 mM to 500 mM of uncomplexed diamine. This shows that the ligand exchange follows a dissociative mechanism.[53]

8.2.5 Diamine-lithium amide interconversion in (Li-**11**)$_2$/**11**

At ambient temperatures, only one set of ^{13}C NMR resonances for **11** and Li-**11** is observed, indicating rapid interconversion of diamine and lithium amide. The interconversion is due to the degenerate lithiation of the diamine **11** by Li-**11**. The coalescence temperature for signals from Li-**11** and coordinated **11** is approximately 268 K, corresponding to a free energy of activation of 10.9 kcal mol^{-1}. Furthermore, the rate constant for diamine-lithium amide interconversion was found

independent of the concentration of **11**, thus indicating that the interconversion proceeds *within* the chelate (Li-**11**)$_2$/**11**. A possible pathway for this degenerate rearrangement via diamine-lithium amide interconversion is shown in Scheme 8.1.



(Li-**11**)$_2$/**11** (Li-**11**)$_2$/**11**

Scheme 8.1 Proposed mechanism for lithium exchange via diamine-lithium amide interconversion.

8.2.6 Li-Li-exchange in (Li-11)$_2$/11

Quantitative ^{6}Li,^{6}Li-EXSY measurements were used to estimate the rate constants[252] for the lithium exchange at -91°C $k_{exch,182K}$= 0.5 s^{-1} and at -66°C $k_{exch,207K}$= 22 s^{-1}. This corresponds to $\Delta G^{\ddagger}_{182K}$= 10.7 kcal mol^{-1} and $\Delta G^{\ddagger}_{207K}$= 10.7 kcal mol^{-1}, respectively. Coalescence of the two ^{6}Li resonances occurred at -48°C corresponding to a $\Delta G^{\ddagger}_{225K}$ of 10.6 kcal mol^{-1}. This temperature independence suggests that the entropy of activation is close to zero for this process. Moreover, the exchange rate constant is independent of the concentration of $[\mathbf{11}]_{free}$, showing that the major pathway for the lithium exchange does not involve free amine. The exchange rate constant is also independent of [(Li-**11**)$_2$/**11**], consistent with an intramolecular lithium exchange mechanism. The similarity of the barrier for Li-Li exchange ($\Delta G^{\ddagger}_{182K}$= 10.7 kcal mol^{-1}) and the diamine-amide interconversion ($\Delta G^{\ddagger}_{268K}$= 10.9 kcal mol^{-1}) is striking and suggests that these processes are coupled, as suggested in Scheme 8.1.

8.2.7 Conclusion

A chelate, in which the parent chiral amine chelates a dimer of the chiral lithium amide, i.e. (Li-**11**)$_2$/**11**, has been structurally characterized for the first time. Complexes of this type are expected to be present and influence the reactivity in the reaction mixtures from asymmetric enolizations, deprotonations, and other lithiation reactions. Furthermore, there are a number of inter- and intraaggregate processes taking place in a chelate of this type. These include lithium-lithium exchange, diamine ligand exchange, and degenerate diamine-lithium amide interconversion.

8.3 ON THE MECHANISM OF INTRAAGGREGATE (FLUXIONAL) LITHIUM AND CARBANION EXCHANGE IN TETRAMERS (PAPER XII)

8.3.1 Background

Alkyllithium compounds, and mixed aggregates containing alkyllithiums, are known to undergo both interaggregate and intraaggregate (fluxional)[369] exchange in solution (see section 2.2.2).[42] A thorough understanding of the structures involved, as well as the rates and mechanisms of the exchange processes, are fundamental for realizing and controlling reactivity of alkyllithium compounds. Studies of dynamic intraaggregate processes, primarily performed in the research groups of Fraenkel,[51] Seebach,[52] and Thomas,[54] have all relied on studies of $^1J(^{13}C\text{-}^6Li)$ couplings constants by variable temperature NMR. Further investigations of the fluxional lithium exchange processes in alkyllithiums have not been possible, due to the high symmetry of the aggregates.

The unexpected formation of a mixed *tetrameric* complex between one chiral lithium amide molecule and three molecules of *n*-butyllithium, produces an asymmetric tetrameric aggregate that serves as a probe for kinetic measurements on intraaggregate lithium- and carbon-exchange.

8.3.2 Structure of Li-11/(*n*-BuLi)$_3$

Addition of the amine **11** to a DEE-d_{10} solution containing *n*-BuLi results in the formation of a mixed complex containing four non-equivalent lithium centers. The ^{6}Li NMR spectrum of the resulting solution at -90°C contains four singlets with equal integrals at δ 2.30, 2.12, 1.64, and 1.32 in addition to the signal from excess tetrameric *n*-BuLi at δ 1.87,[355, 357] Figure 8.4a.

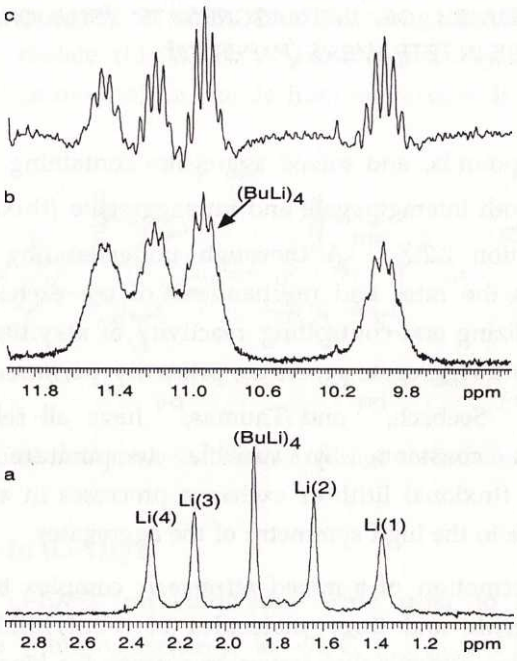


Figure 8.4 a) ^{6}Li NMR spectrum at -90°C of a mixture of Li-**11**/(*n*-BuLi)$_3$ and (*n*-BuLi)$_4$. b) Upfield part of a ^{13}C NMR spectrum of Li-**11**/(*n*-BuLi)$_3$ showing four different α-carbons of *n*-BuLi (complexed and uncomplexed) at -90°C. c) Same as in b but with resolution enhancement.

The ^{13}C NMR spectrum at -90°C shows three non-equivalent α-carbon signals from *n*-BuLi in the complex Li-**11**/(*n*-BuLi)$_3$ in addition to the α-carbon signal (septet) from the excess tetrameric *n*-BuLi at δ 10.90, Figure 8.4b.[55] The two signals at δ 9.87 and 11.2 are septets (J=5.0 to 5.5 Hz), indicating that each carbon is coupled to three lithium atoms (I=1), Figure 8.4c. The complex pattern of the third signal is likely caused by different coupling constants between this carbanion and the three non-equivalent lithium nuclei.

The solution state structure of the mixed Li-**11**/(*n*-BuLi)$_3$ complex was assigned using ^{1}H,^{1}H-TOCSY,[370, 371] ^{1}H,^{1}H-DQFCOSY, ^{1}H,^{1}H-NOESY, ^{6}Li,^{6}Li-COSY and ^{6}Li,^{1}H-HOESY experiments. The PM3 optimized structure of Li-**11**/(*n*-BuLi)$_3$ is shown in Figure 8.5.

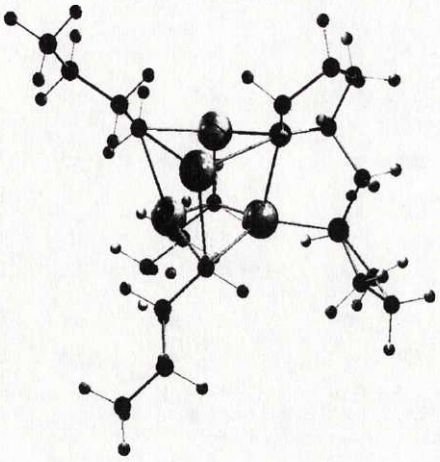


Figure 8.5 PM3 optimized structure of Li-**11**/(*n*-BuLi)$_3$; coordinating solvent molecules are omitted for clarity.

The calculated structure of Li-**11**/(*n*-BuLi)$_3$ contains a distorted cubic tetramer core. Similar core arrangements have also been observed for alkyllithium tetramers in the solid state.[39]

8.3.3 Rate of exchange in Li-**11**/(*n*-BuLi)$_3$

At ambient temperature, interaggregate exchange is observed for both carbanions and lithiums in Li-**11**/(*n*-BuLi)$_3$. However, by lowering the temperature it is possible to study the intraaggregate exchange independently of the interaggregate exchange. The only method available for simultaneous determination of multiple site to site rate constants is quantitative 2D NMR exchange spectroscopy (EXSY).[246] The cross-peaks in an EXSY spectrum give a graphical display of all the exchange processes. Furthermore, the rate constant, k, for an exchange process can be obtained from the ratio between cross-peak and diagonal-peak intensities.[252]

To map out the exchange pathways in Li-**11**/(*n*-BuLi)$_3$ several quantitative ^{6}Li,^{6}Li-EXSY experiments, with mixing times ranging from 0.025 s to 0.450 s, were performed at -76°C and -81°C, respectively. The ^{6}Li,^{6}Li-EXSY spectrum with mixing time 0.450 s is shown in Figure 8.6. No interaggregate exchange between lithium atoms in Li-**11**/(*n*-BuLi)$_3$ and lithium atoms in (*n*-BuLi)$_4$ was observed at these temperatures.

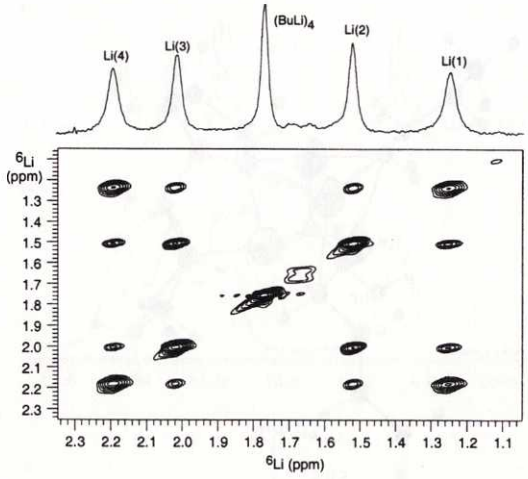


Figure 8.6 The ^{6}Li,^{6}Li-EXSY spectrum (τ_m=0.450 s) of Li-**11**/(*n*-BuLi)$_3$ at -81°C in DEE-d_{10}.

Our data suggest that Li-**11**/(*n*-BuLi)$_3$ undergoes intraaggregate degenerate rearrangements by which the four different lithium nuclei exchange. The ^{6}Li,^{6}Li-EXSY spectrum indicates that the intraaggregate degeneracy of the complex is a result of two-site exchanges. There are six different two-site exchanges with the rate constants k_{12}, k_{13}, k_{14}, k_{23}, k_{24} and k_{34}, respectively. Analysis of the ^{6}Li,^{6}Li-EXSY data using the matrix formalism developed by Perrin and Gipe,[251] either manually or with the program D2DNMR (by Abel *et. al.*),[372] provided the rate constants for direct two-site exchanges as shown in Table 8.3.

Table 8.3 Rate constants for the intraaggregate degenerate Li exchange within complex Li-**11**/(*n*-BuLi)$_3$; determined from a ^{6}Li,^{6}Li-EXSY spectrum (τ_m=0.450 s) at -81°C in DEE-d_{10}.

Two-site exchange	Rate constant[a]/s^{-1}
k_{12}	0.37± 0.08
k_{13}	0.50± 0.08
k_{14}	2.96± 0.19
k_{23}	0.75± 0.01
k_{24}	0.24± 0.06
k_{34}	0.07± 0.12

[a]Error analysis was performed using D2DNMR that only estimates errors in rate constants based on errors in peak intensities.

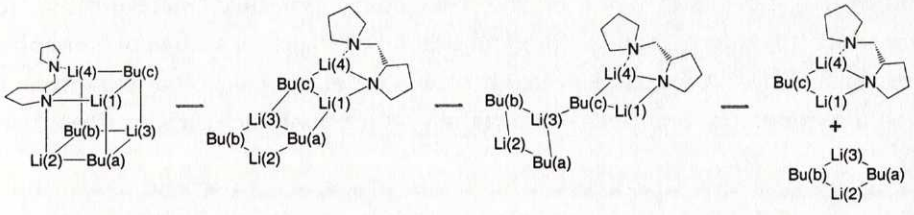
Similarly, through a $^{13}C,^{13}C$-EXSY experiment at -81°C we could ascertain that the carbon exchange in Li-**11**/(n-BuLi)$_3$ proceeds through an intraaggregate pathway. The rate constant for this intraaggregate carbon exchange was estimated to $2 \pm 1\ s^{-1}$.

8.3.4 Proposed mechanism

The three exchange mechanisms previously proposed in the literature were shown in Scheme 2.3 of this thesis. These involve rearrangement of the tetrameric cube through an eight-membered ring,[56] concerted center to edge rotation of the carbanions,[57] and dissociation into dimers[54] followed by recombination. It has not been established whether lithium exchange, carbanion exchange, or both, result in the fluxional lithium-carbon bond exchange.

However, none of the previously proposed mechanisms is in accordance with the kinetics observed in this study. The lack of cross-peaks between signals from Li-**11**/(n-BuLi)$_3$ and (n-BuLi)$_4$ clearly excludes mechanism in which the tetramer dissociates into free dimers. Furthermore, the difference in rate constants for the direct two-site lithium exchanges also exclude mechanisms with coupled two-site exchanges such as the 8-membered ring mechanism.

A mechanism consistent with the observations is presented below. A possible mechanism for the well-known dissociation of a mixed tetramer (A) to dimers (D) via a ladder intermediate (B) is shown in Scheme 8.2. It involves reversible stepwise breaking of core bonds. Expected accompanying solvation changes are not shown in Scheme 8.2.



A **B** **C** **D**

Scheme 8.2 Proposed intermediates (B) and (C) on the pathway from tetramers (A) to dimers (D). The mechanism for the fluxional exchange in tetramers is proposed to proceed via key structure (B) and (C). Only one of two possible ladder structures (B) is shown. Solvation is excluded for clarity.

Breaking a core bond in the ladder structure yields an intermediate in which a mixed dimer is bound to a homo dimer by a single bond (C). Other C-type structures can be obtained by breaking a different triple of core bonds in the

tetramer in Scheme 8.2. Such intermediates may undergo degenerate rearrangements via rotation around the bond connecting the two dimers. Rotation of the mixed dimer unit around the single bond connecting the two dimers, followed by a change of pyrrolidine coordination from Li(4) to Li(1), and return to the mixed tetramer, yields a tetramer structure in which only two lithium sites have exchanged, i.e. Li(1) and Li(4). On the other hand, rotation of the homo dimer unit around the single bond connecting the two dimers in C, followed by return to a tetramer, yields a mixed tetramer in which only the butyl anions a and b have exchanged. The processes described above results in non-coupled two-site exchanges and account for all the observed two-site exchanges. This process resembles the dissociative mechanism c in Scheme 2.3, however, without complete dissociation into free dimers.

The observed rate of carbon exchange, within the mixed tetramer, is comparable to the rates for the lithium exchanges. It is interesting to note that the pathway in Scheme 8.2 also predicts inversion of the carbanionic carbons. This explains why racemization is observed for e.g. lithium organic compounds containing stereogenic carbanionic carbons.[49, 50]

8.3.5 Conclusion

The processes responsible for lithium- and carbanion-exchange in Li-**11**/(*n*-BuLi)$_3$ are probably similar to those in pure alkyllithium tetramers. The characterization of this mixed lithium amide/alkyllithium tetramer made direct observation of the fluxional lithium- and carbanion-exchange possible for the first time. Furthermore, the rate constants for all site to site exchanges could be determined from quantitative ^{6}Li,^{6}Li- and ^{13}C,^{13}C-EXSY spectroscopy. The results thus obtained show that none of the previously proposed mechanisms, for lithium and carbanion exchanges in alkyllithium tetramers, is sufficient to explain the present findings. A mechanism that accounts for all the observed exchanges, as well as the previous reported racemization at carbanionic carbons, has been outlined.

9

Interesting Areas for Future Research

The Holy Grail in lithium organic chemistry embraces the knowledge of how to form aggregates with pre-defined structure, solvation, and reactivity. Knowledge of this kind will allow us to use simple building blocks like alkyllithiums, lithium amides, lithium alkoxides, solvents, and other additives to assemble tailor-made reagents for a particular application. With full control of aggregate stability and dynamics, one may also imagine putting together a sequence of reactions where the product of one step moves on to a new aggregate, where another reaction takes place, and so forth. Lithium organic reagents wide utility and high propensity to aggregate would make them destined for such "multiple transformation reactions". However, much work remains to be done until we are able to predict what a structural modification might do to the aggregates size, solvation, and reactivity. Studies directed to answer such questions are of prime importance for future developments in this field.

Intervention by the product in the reagent aggregate is also an exciting topic, since it is a prerequisite for autocatalysis.[373-377] There has been one example in lithium organic chemistry where the product alkoxide in an asymmetric aldehyde alkylation influence the formation of it's own formation, i.e. asymmetric autocatalysis.[353] Lithium organic reagents high propensity to aggregate merits further studies on asymmetric autocatalysis with these reagents in the future.

Another topic closely related to asymmetric autocatalysis is the subject of nonlinear effects, i.e. a nonlinear relationship between the reagents ee and the products ee.[378-380] Nonlinear effects may be used as a complement to ordinary kinetic methods in mechanistic studies.[381-383] Studies of nonlinear effects in lithium organic chemistry would make it possible to investigate the relative stability and reactivity of different complexes present in solution.

The meager exploration of lithium alkoxides has previously been noted in this thesis. Further detailed studies on the structure, reactivity, and use of lithium

alkoxides are of interest. Studies of mixed complexes containing lithium alkoxides are also of importance, since this will bring about a better understanding of the chemistry of superbases.[67, 68, 73-75]

Related to this is the still largely unexplored chemistry of mixed-metal chemistry.[384] Aggregates containing a combination of different alkali metals, or a combination of alkali and other metals, are of considerable interest since these reagents have unique chemical behavior compared to their single-metal components. New and exciting chemistry is expected to evolve from increased studies on mixed-metal systems.

A more direct extension of the work presented in this work involves use of the mixed lithium amide/alkyllithium reagents for enantioselective alkylation of imines to form chiral secondary amines.[157, 158] Application of a polymer supported ligand, for easy recycling and catalytic turnover, would be another interesting extension of this work.

The topics outlined above represent only a few suggestions for future research in this field. However, knowledge how to control structure, dynamic, reactivity, and selectivity are of fundamental importance for all research in this area. The way to gain knowledge in this field, is the same as in all fields of chemistry. Using irrational methods, such as trial-and-error synthesis and combinatorial approaches, we will be able to explore chemistry and find new reactions. However, to be able to control and thereby improve chemistry, understanding is required. Such detailed understanding can only be obtained by solid physical organic studies.

Thus, let me finally end this with the initial citation: "The truth is out there!" — However, it remains for us to ask the right questions!

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Research is never the work of one man; it is the joint venture of many skilled persons. Thus, many people have contributed to the work presented in this thesis, and deserve my sincere gratitude.

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continued

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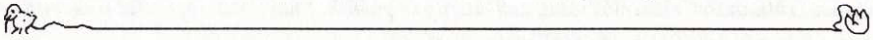
Per Arvidsson

Göteborg, Eastern 1999



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