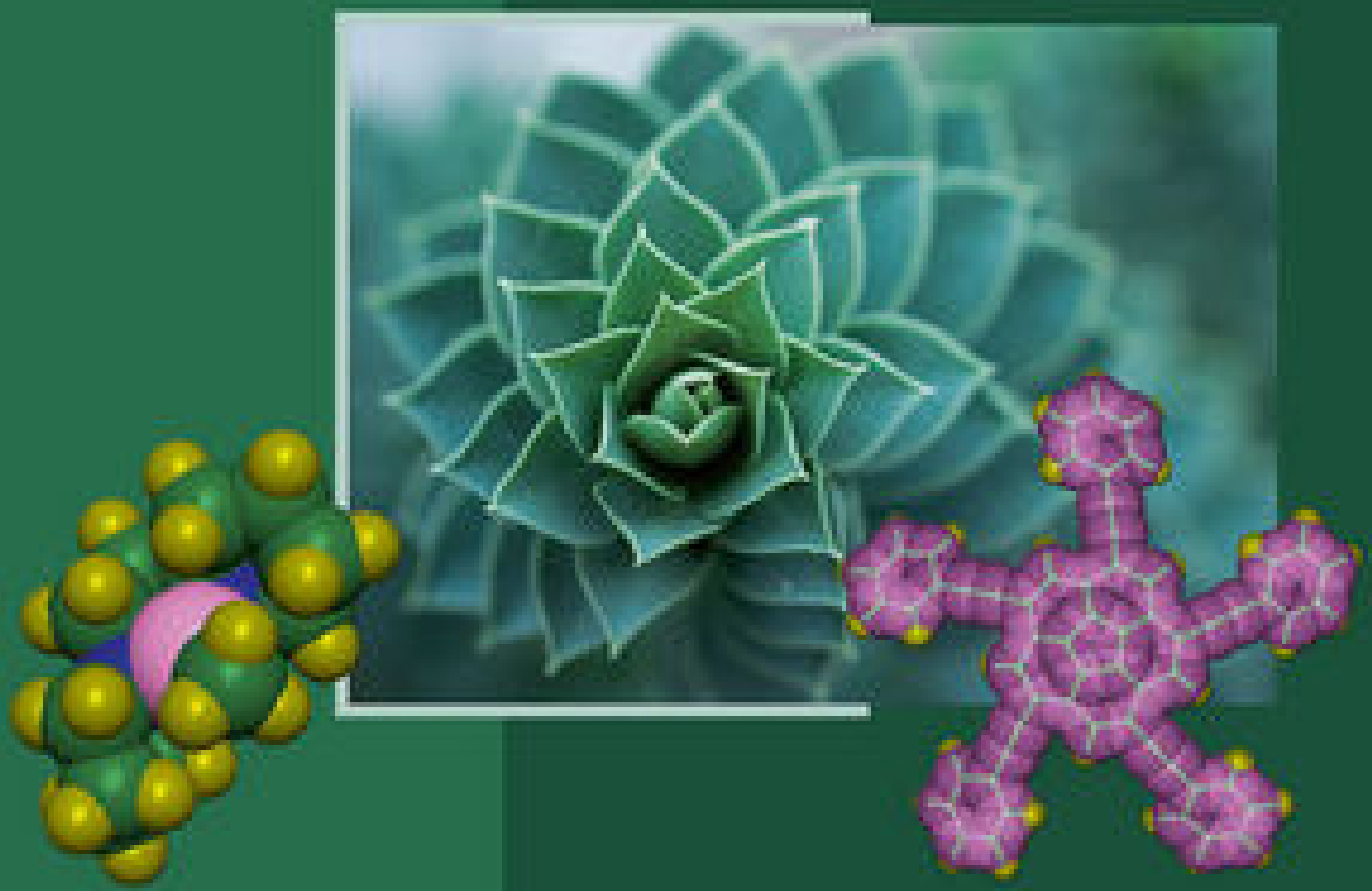
Topics in Stereochemistry

Volume 26

Jay S. Siegel (Ser. Ed.)

Robert E. Gawley (Ed.)

Stereochemical Aspects of Organolithium Compounds



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Stereochemical Aspects of Organolithium Compounds

Stereochemical Aspects of Organolithium Compounds Edited by Robert E. Gawley

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Foreword

Volume 26 of *Topics in Stereochemistry* marks the end of an era, while developing a bridge to the next generation. Traditional book series like *Topics in Stereochemistry* have had to evolve through the last decade of enormous change in publishing, influenced by e-publishing, abstracting services and library acquisition policy. This decade of discovering how best to serve the authors and readers of *Topics* brought us to a fundamental reorganization, one that will steer *Topics* toward new frontiers in Stereochemistry and will provide a superior scholarly publication for our contributors and community.

The process began with Scott Denmark's singular vision to breath life back into the Eliel's creation. With volume 22, Scott single handedly took on the task to reproduce the kind of epic volume, which founded the reputation of the series. In volume 24, I joined the team to help with pushing the project forward. Recently, Scott has received the call to take over another classic Wiley series, Organic Synthesis. I will miss working with him and thank him wholeheartedly for his service to *Topics in Stereochemistry*.

Stereochemistry has changed since the active time of greats like Prelog and Mislow. The philosophical and fundamental discovery era rooted in the 1800's and continuing to the 1980, has shifted to an industrial revolution, wherein the now well tested principles of stereochemistry can provide keys for unlocking the mysteries of life science and materials engineering. From selective pharmaceuticals to sustainable photovoltaics, stereochemistry sits at the throne of molecular science.

A new generation in publishing, parallel to a new generation in Stereochemistry mandated a new venue and modus operandi for Topics. Zurich, the home of Werner and Wislicenus, has a unique heritage in Stereochemistry. Fortunately, the Wiley family's publishing partnerships include *Verlag Helvetica Chimica Acta*, a house with a reputation for superior quality in publishing. Indeed, within the pages of its namesake periodical, *Helvetica Chimica Acta*, one finds many of the seminal research works of stereochemistry's giants. As such, a transfer of editorial operations to Zurich and a collaboration bringing *Topics* as a series closer to periodical status provides a growth platform for the future.

It is my special honor, to work with Dr. Volkan Kisakürek, Director of *Verlag Helvetica Chimica Acta*, on this project of transforming *Topics*. Dr. Kisakürek brings not only his editorial prowess to the project, but also a love and understanding for Stereochemistry that no other editor/publisher could offer. From his expertise in all things nomenclatural, to his long history

of working with great authors of stereochemistry, he adds a special flare to *Topics*. I welcome him and look forward to a highly successful partnership.

Special thanks are due to Professor Robert Gawley, Guest Editor for Volume 26. Bob has had to deal with numerous issues associated with the transatlantic voyage of *Topics*. Luckily, he does not become seasick easily and he has remained at the helm to bring this volume into port on time and with full cargo. The details of his theme of carbanion stereochemistry appear in his preface, and I applaud his work in collecting such a high quality set of authors for this volume.

The new *Topics in Stereochemistry* has many factors for the future that shine brightly. Readers and librarians can rely on a regular schedule of scholarly publications. Authors will benefit from ISI abstracting and bibliometric monitoring. *Topics in Stereochemstry* will serve the full breadth of the molecular science community, and thereby have a strong impact as the site for practioneers depending on a molecular level understanding of life and the material world.

JAY S. SIEGEL

Preface

Organolithium compounds are of unparalleled importance among organometallic compounds in synthetic organic chemistry. In this volume, we highlight stereochemical features of these compounds, which are of special interest to synthetic chemists. We begin with a chapter by Simpkins and Weller on the use of chiral lithium amides in stereoselective deprotonation reactions. This is followed by a chapter by Carlier and colleagues on the self-regeneration of stereocenters wherein the chirality center is destroyed in a deprotonation step, and replaced by a labile chirality axis.

In both of these introductory chapters, the lithium is often on oxygen in the reactive intermediate or product; the remaining chapters describe systems that primarily feature compounds having carbon–lithium bonds. A chapter by Gawley provides an overview of carbanion dynamics and electrophilic substitutions. This is followed by a contribution from Florio and colleagues on the use of lithiated oxiranes, which are normally configurationally stable, as chiral synthons. Since chiral organolithiums have varying degrees of configurational stability, a chapter by Hoffmann describes the utility and historical development of the "Hoffmann Test" of configurational stability on the time scale of the reaction with an electrophile. A chapter by Kizirian describes enantioselective deprotonations using alkyllithium/sparteine bases. The chapter by Coldham and Sheikh details various techniques for dynamic resolution of organolithiums, which provides an opportunity to begin with a racemic organolithium and produce nonracemic products with the aid of chiral ligands on the lithium.

It is hoped that these chapters will be useful to readers who seek an introduction to the stereochemical aspects of organolithium chemistry.

Robert E. Gawley
August 13, 2009

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Contents

Chapter 1

Asymmetric Deprotonations Using Chiral Lithium Amide Bases

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I. INTRODUCTION

Chiral lithium amide bases have been of significant interest over the past 20 years or so, in reactions that can be broadly described as enantioselective deprotonations. Developments in the methodology, including design and exploration of novel bases, moves towards catalysis, and applications to new types of substrates, have opened up the scope of the chemistry considerably. The use of chiral lithium amides for conversion of prochiral cyclic ketones into chiral, non-racemic enolates, has become a reasonably well-established strategy in organic synthesis, and has seen significant application in target synthesis.

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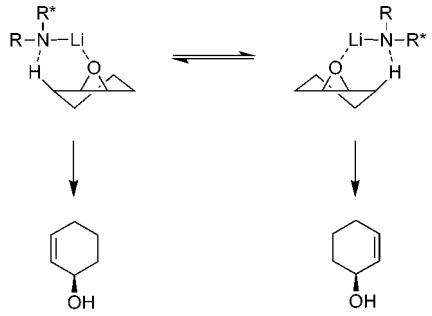
This article aims to give a broad overview of the area, whilst focusing primarily on more recent developments that have not been covered in previous reviews.[1–4] The ketone asymmetric enolisation method has been applied to numerous target molecules, and has required opening the chemistry up to new types of ketone - both in terms of ring size and substitution pattern. New substrates have also been successfully employed, particularly cyclic imides, and the chiral products used in synthesis. The chemistry is described only in outline, and the reader is directed to the published articles, and to previous reviews for more details.

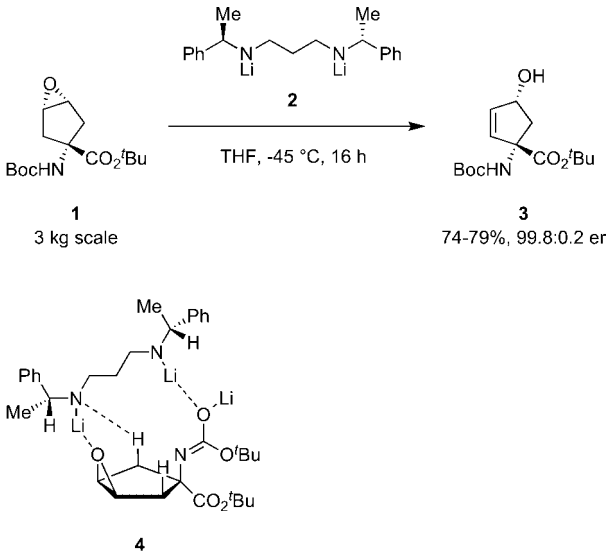
II. ENANTIOSELECTIVE CONVERSION OF EPOXIDES INTO ALLYLIC ALCOHOLS

The base-mediated rearrangement of an epoxide to an allylic alcohol is a well-investigated process. When the base is a chiral lithium amide and the epoxide is prochiral, this results in a selective rearrangement to afford enantiomerically-enriched products. In general, it is understood that this proceeds via a cyclic *syn* β-elimination pathway (Scheme 1.1).[5] The α-elimination pathway is possible however in the case of the unsubstituted cyclopentene oxide.[6] It has been three decades since the pioneering study by Whitesell that first demonstrated this process with cyclohexene oxide as the substrate.[7] Since this category of asymmetric deprotonation has been the subject of several reviews already,[1–3,8] we shall limit our discussion here to some valuable recent studies and, in particular to the latest successful attempts to perform this transformation using sub-stoichiometric quantities of chiral base.

Recently, scientists at Eli Lilly and Co. have demonstrated scale-up of the desymmetrisation of a *meso*-epoxide during studies directed at synthesising the metabatropic glutamate receptor agonist LY459477.[9] Treatment of *meso*-epoxide **1** (3 kg scale) with 2.4 equivalents of chiral bis-lithium amide **2** in THF led to the formation of allylic alcohol **3** in good yield with essentially complete enantioselectivity (Scheme 1.2). A bidentate chelation model



Scheme 1.1.

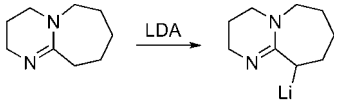


Scheme 1.2.

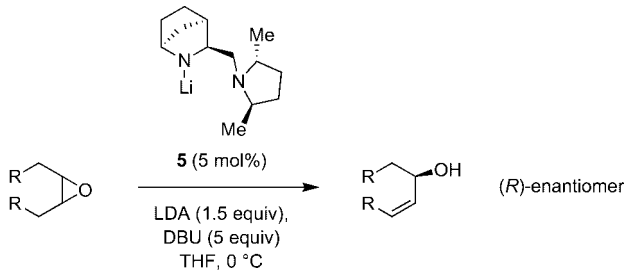
4 was proposed for this efficient asymmetric process, which involved deprotonation of the carbamate NH and chelation of the chiral base to both the lithiated carbamate and the epoxide. This example neatly illustrates the applicability of chiral lithium amides in industrial synthesis.

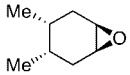
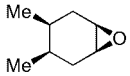
Epoxides have proved to be the best performing substrates in asymmetric deprotonations using sub-stoichiometric quantities of chiral lithium amide. Pioneering studies in this area were provided by the groups of Asami[10,11] and Alexakis.[12] These early examples of the catalytic enantioselective rearrangement of epoxides were well-described in the review by O'Brien[3] and therefore we shall not discuss them here. Andersson reported exceptional yields and enantioselectivities for the isomerisation of epoxides to allylic alcohols using **5** as the chiral amide base.[13] Treatment of a range of epoxides with **5** (5 mol%) and LDA (1.5 equiv) in THF at 0 °C gave the corresponding allylic alcohols (Scheme 1.3). The presence of DBU (5 equiv) in the catalytic reaction was found to lead to a more rapid conversion of the epoxide and improved enantioselectivities.† Particularly impressive is the successful re-

† LDA in THF has been shown to reversibly deprotonate DBU to yield lithiated DBU.[14]



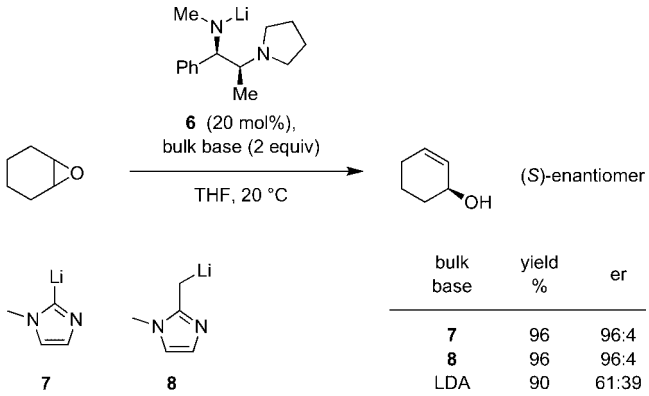
The lithiated DBU forms heterodimers with chiral lithium amides and these might function as the active species for enantioselective deprotonation. Lithiated DBU might otherwise function as a bulk base, or DBU itself could be a solvating ligand. It is worth noting that in Asami's most successful catalytic system it was possible to dispense with the use of DBU as an additive.[11]



	yield %	er		yield %	er
	81	98:2[a]		94	99:1
	95	>99:1		85	>99:1
	93	>99:1		80	95:5

a) Run at rt.

Scheme 1.3.

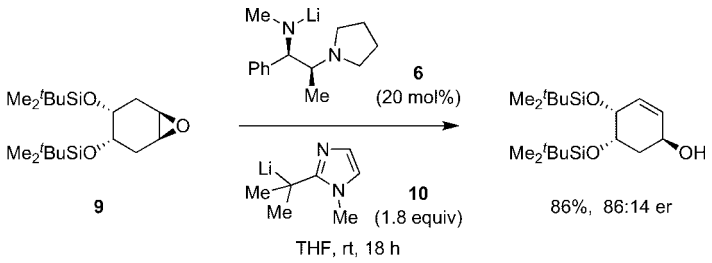


bulk base	yield %	er
7	96	96:4
8	96	96:4
LDA	90	61:39

Scheme 1.4.

arrangement of the notoriously difficult substrates cyclopentene oxide and (*Z*)-4-octene oxide. Similar findings were reported in the asymmetric deprotonation of silacyclopentene oxides.[15]

The catalytic deprotonation of cyclopentene oxide can be performed using novel bulk bases, which include azoles.[16] The best results by Ahlberg *et al.* are summarised in Scheme 1.4 and involved the use of sub-stoichiometric quantities (20 mol%) of chiral lithium amide **6**. The bulk bases **7** and **8**



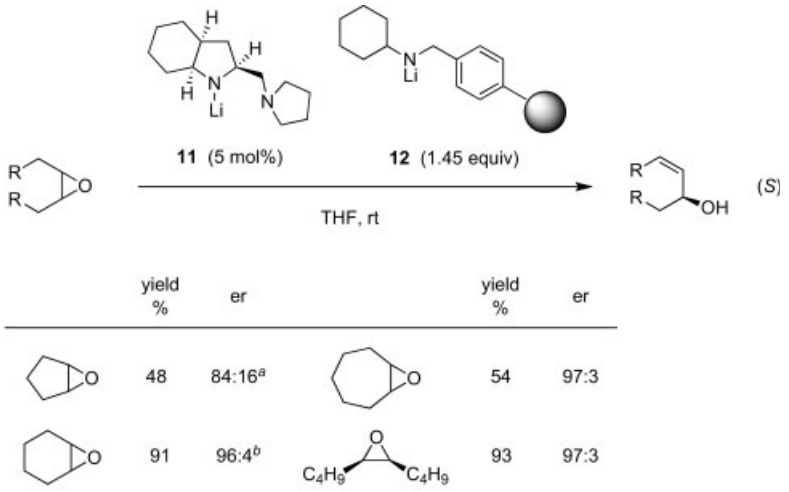
Scheme 1.5.

showed significantly enhanced performance with respect to enantioselectivities versus LDA. Unfortunately, the performance of these catalytic systems at lower loadings of chiral base was not reported.

O'Brien *et al.* have expanded the substrate scope of the Ahlberg system to functionalised cyclopentene and cyclohexene oxides, such as **9** (Scheme 1.5). In doing so, the authors detected some reaction manifolds not previously noted for cyclohexene oxides, such as the competing background deprotonation (leading to racemic product) and nucleophilic ring-opening of the epoxide by bulk base **8**.[17] These troublesome side-reactions were apparently circumvented by changing the bulk base from **8** to lithiated imidazole **10**.

The bulk base for catalytic enantioselective deprotonation of epoxides can be a polymer-bound lithium amide.[18] Thus, treatment of a range of *meso*-epoxides with chiral lithium amide **11** (5 mol%) and polymer-bound lithium amide **12** (1.45 equiv) in THF afforded the corresponding allylic alcohols in good yield and enantioselectivity (Scheme 1.6). The enantioselectives were higher than those obtained by the corresponding solution-state version (*i.e.* when LDA was used as the bulk base).[11] This could be attributed to the lower reactivity of solid-supported lithium amides, which makes the non-enantioselective background reaction less favoured. Furthermore, computational approaches were employed to probe the rearrangement of cyclohexene oxide using lithium amides based on 2-(dialkyl aminomethyl)pyrrolidines (Asami-type bases).[19] For example, MM3 force field calculations predict that, for chiral base **11**, the population of reaction intermediate complexes leading to the generation of (*S*)-cyclohex-2-en-1-ol was 99.6% at 298 K. A good correlation between experimentally determined er values and the MM3 calculated populations was identified for a range of Asami-type lithium amides. This is expected to assist with the further design of chiral bases for the conversion of epoxides into allylic alcohols.

It has also been reported that α-pinene based chiral lithium amides can be used for the catalytic enantioselective deprotonation of cyclohexene oxide.[20] Reactions were performed at 0 °C using 20 mol% of chiral lithium amide with LDA (1.25 equiv) as the bulk base, and a maximum er of 97:3 was obtained using the amide generated from (–)-*N*,*N*-diisopinocamphenylamine.



Scheme 1.6.

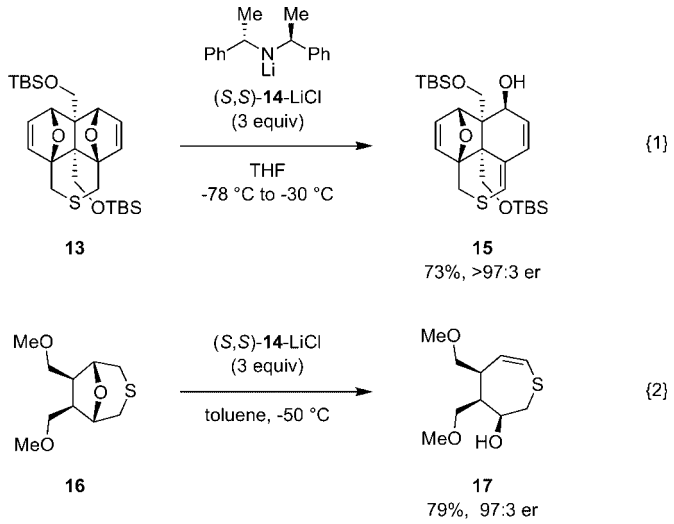
III. ENANTIOSELECTIVE DEPROTONATIONS ADJACENT TO SULFUR

A variety of chiral base mediated deprotonations have been reported, which involve deprotonation adjacent to sulfur at various oxidation states.

Certain types of oxa-bicyclic frameworks can be converted into unsaturated alcohols by ring-opening, in a fashion akin to the conversion of epoxides into allylic alcohols (see Section II).[21] As an impressive illustration of this strategy, thiapyran substrate **13**, having two fused oxa-norbornene systems, was deprotonated using three equivalents of the lithium amide (*S*,*S*)-**14**-LiCl to give alcohol **15** in high yield and enantioselectivity (Scheme 1.7 eq 1).

In this example, as in many others, a mixture of lithium amide base and LiCl was formed by treatment of the appropriate secondary amine hydrochloride salt with two equivalents of butyllithium. The presence of LiCl facilitates many of the metallations and enolisations described herein, and can also enhance the levels of enantioselectivity observed. This LiCl effect has been discussed previously, and it will not be described in detail here.

This methodology in Scheme 1.7 was developed as part of a project towards polysubstituted *cis*-decalins. The chiral amide-induced ring-opening of a range of thiaoxa[3.2.1] and -[3.3.1]bicycles was also investigated by the

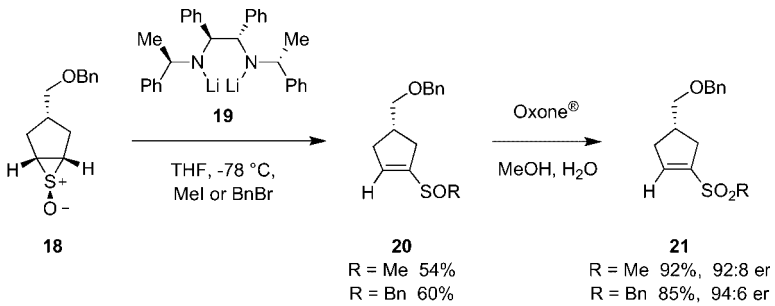


Scheme 1.7.

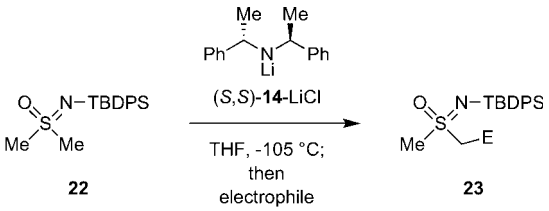
Lautens group.[22] For example, substrate **16** was ring-opened using chiral base (*S*,*S*)-**14**-LiCl to provide alcohol **17** (Scheme 1.7 eq 2).

For a limited range of substrates, episulfoxides can be converted into alkenyl sulfoxides using chiral lithium amides.[23] For example, episulfoxide **18** was deprotonated using chiral bis-lithium amide **19** to form an intermediate alkenyl sulfenic acid anion, which was alkylated using either methyl iodide or benzyl bromide (Scheme 1.8). Before determining the extent of asymmetric induction, the alkenyl sulfoxide product **20** was first converted into its corresponding sulfone **21** using Oxone®. The chiral base approach was found to be moderately selective with a small group of such episulfoxides, including norbornene derivatives (*i.e.* 82:18–92:8 er).[24]

The desymmetrisation of *N*-trialkylsilyl dimethyl sulfoximines has been investigated by Bolm *et al.*[25] Dimethyl sulfoximine **22** was deprotonated us-



Scheme 1.8.

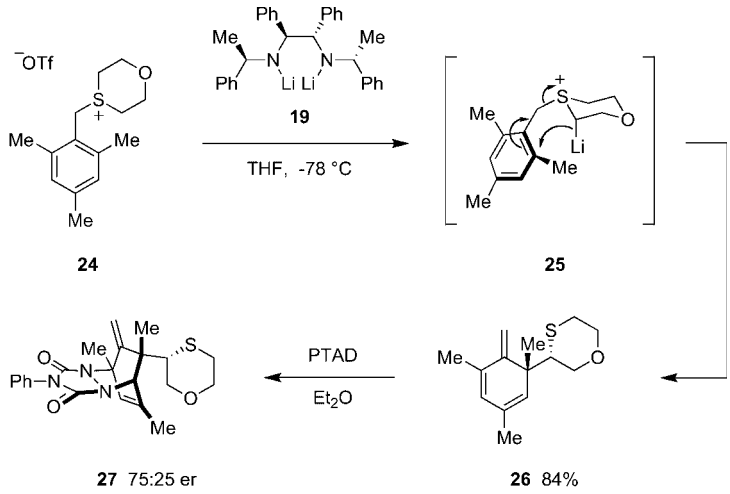


electrophile	yield **23** %	er of **23**
Me_3SiCl	58	80:20
$Ph_2C{=}O$	86	85:15
$Ph_2C{=}NTs$	30	64:36
$2\text{-}BrC_6H_4CH_2Br$	70	78:22

Scheme 1.9.

ing chiral base (*S*,*S*)-**14**-LiCl and captured using a variety of electrophiles (Scheme 1.9). Enantioenriched sulfoximines such as **23** have not proved to be readily available by other approaches, although at present the variable yields and levels of selectivity require further development of the chiral base method.

An interesting process for the dearomatisation of benzene rings is the thia-Sommelet rearrangement (*i.e.* the [2,3] sigmatropic rearrangement of benzylsulfonium ylides). Recently, this was performed enantioselectively (up to 75:25 er) using the chiral base approach.[26] Treatment of benzylsulfonium salt **24** with bis-lithium amide **19** resulted in the generation of benzyl-

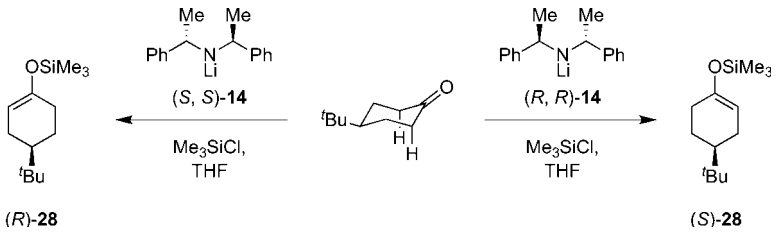


Scheme 1.10.

sulfonium ylide **25** followed by rearrangement to give cyclohexa-1,3-diene **26** in 84% yield (Scheme 1.10). The enantiomeric ratio of the product **27** was determined after Diels-Alder adduct formation with 4-phenyl-[1,2,4] triazole-3,5-dione (PTAD).

IV. ENANTIOSELECTIVE DEPROTONATION OF CYCLIC PROCHIRAL KETONES

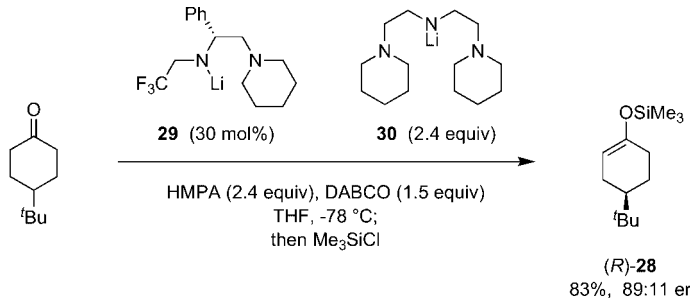
Probably the most important category of chiral-base mediated processes is the symmetry-breaking enolisation reaction, involving cyclic prochiral ketones. In conformationally locked cyclohexanones, such as 4-*tert*-butylcyclohexanone, there is a stereoelectronic preference for removal of the axial protons, and chiral lithium amides (*e.g.* **14**) are able to discriminate between the two enantiotopic protons (Scheme 1.11). It is therefore possible to generate preferentially one enantiomer of silyl enol ether **28** by trapping with chlorotrimethylsilane (usually in an excess, *ca.* 5 equiv). The research groups of Simpkins,[1,27] Koga,[4,28] and Majewski[29] have been very active in this research area. As the chemistry prior to 1998 was the subject of the excellent review by O'Brien,[3] we shall focus almost exclusively on developments in the methodology that have emerged since that time.[30]



Scheme 1.11.

A. Important Methodology Developments

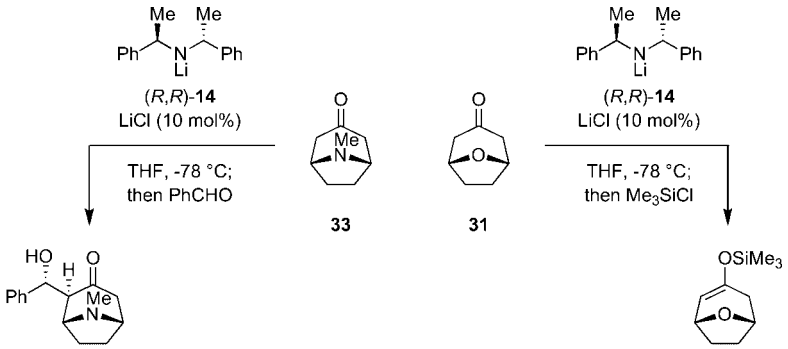
There has been continued interest in the discovery of new chiral lithium amide bases, including polymeric types, and bis-lithium amides. It is also worth reiterating the important discovery of Koga and co-workers, who showed that the enantioselective deprotonation of 4-substituted cyclohexanones can be performed using *catalytic* quantities of chiral lithium amide.[31] Use of the combination of chiral lithium amide **29** (30 mol%) with bulk base **30** (2.4 equiv) in the presence of HMPA and DABCO in THF led to the formation of silyl enol ethers upon addition of chlorotrimethylsilane (Scheme 1.12). At present, this remains the only successful implementation of catalytic



Scheme 1.12.

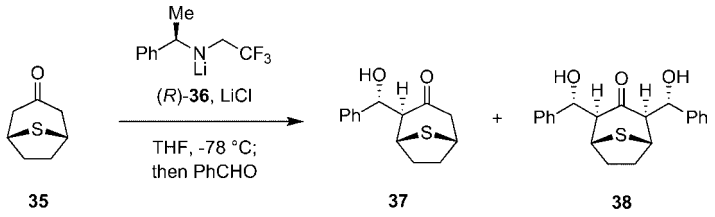
asymmetric deprotonation of cyclic ketones using chiral base methodology. In light of the advances made in the catalytic asymmetric deprotonation of *meso*-epoxides (see Section II), this is somewhat surprising. Perhaps this is because the relative rate of the background deprotonation by the bulk base is faster with cyclohexanones than it is with epoxides. The remainder of this Section will therefore cover the developments with regards to the stoichiometric process.

Important substrates used to probe the asymmetric deprotonation of cyclic ketones include oxa-, aza- and thiabicyclo[3.2.1]octan-3-ones. The conversion of these substrates into silyl enol ethers has been explored under a variety of conditions.[32,33] Higher enantioselectivities were often observed when the electrophile, chlorotrimethylsilane, was premixed with the base prior to addition of the ketone (in situ quench conditions) rather than added to the enolate (external quench conditions). As mentioned previously, it was



a) the values in parentheses are the er's obtained when lithium chloride was omitted from the reaction mixture.

Scheme 1.13.



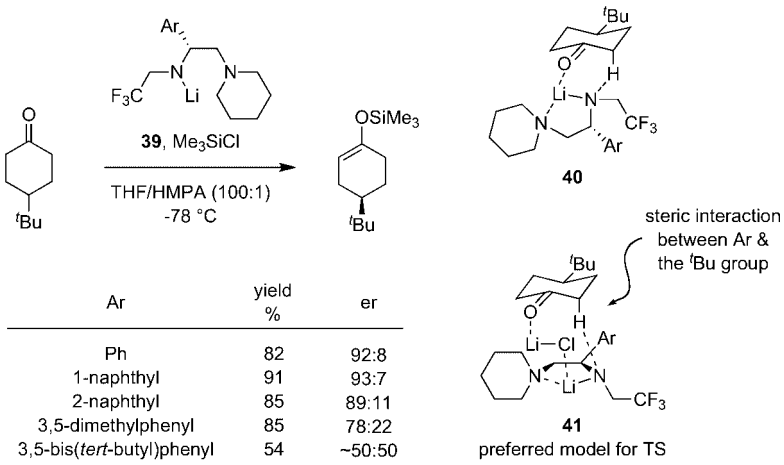
35 37 38

36 conc. [M]	37/38	yield 37 %	er of 37
0.12	86:14	55	73:27
0.10	88:12	61	76:24
0.05	80:20	65	82:18
0.035	84:16	72	85:15

Scheme 1.14.

subsequently found that the enantioselectivity for reactions under external quench conditions was dramatically enhanced by the addition of lithium chloride (see **31**→**32** and **33**→**34** in Scheme 1.13) or zinc(II) chloride. Under in situ quench conditions, rapid trapping of the enolate by chlorotrimethylsilane would provide an increasing amount of LiCl over the course of the reaction, which explains the similarly enhanced er levels observed using this approach. In fact, chlorotrimethylsilane has also been shown to not be fully compatible with LDA, and even at low temperature LiCl is generated to some extent.[34] Lithium chloride, even in low concentration, is therefore important for achieving the high enantioselectivities in many examples shown, most likely by forming mixed aggregates with the lithium amide.

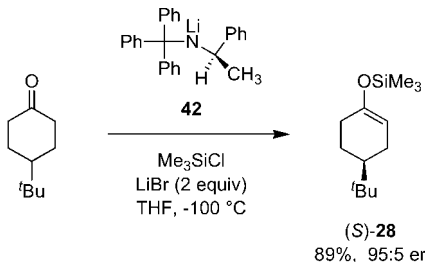
Majewski and co-workers have examined the behaviour of the thiabicyclo[3.2.1]octan-3-one framework upon asymmetric deprotonation because of concerns about reproducibility when using this substrate class.[35] They found that treatment of **35** with chiral lithium amide (*R*)-**36** followed by addition of benzaldehyde led to the formation of mono-aldol product **37** as the major product and bis-aldol product **38** in typically 10–15% yield (Scheme 1.14). The formation of a product where two aldol reactions had taken place on the same molecule was unexpected and had not been observed previously using ketones **31** and **33**. The authors noted that the er of product **37** clearly increased as the reaction mixture was made more dilute (see table in Scheme 1.14). Although it was speculated that the formation of the bis-aldol product **38** might be responsible for such variations in the enantioselectivity, perhaps through a kinetic resolution process, there seems to be no correspondence of the observed er with the amount of **38** formed. It is known that concentration (amongst other factors) can influence the aggregation state and reactivity of lithium enolates[36,37] but a more detailed investigation of the processes responsible for this trend in enantioselectivity has yet to emerge.



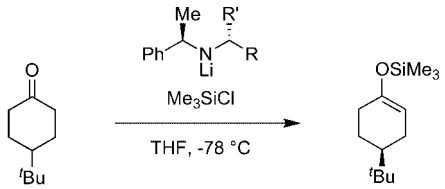
Ar	yield %	er
Ph	82	92:8
1-naphthyl	91	93:7
2-naphthyl	85	89:11
3,5-dimethylphenyl	85	78:22
3,5-bis(*tert*-butyl)phenyl	54	~50:50

Scheme 1.15.

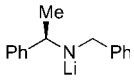
Koga *et al.* have studied bidentate chiral lithium amides **39** having a bulky group other than phenyl on the stereogenic carbon.[38] These bases were assessed for their performance in deprotonation reactions of 4-substituted cyclohexanones. It was found that changing the phenyl group to a more bulky substituent did not lead to an improvement in selectivity and, on the contrary, in several cases led to an erosion in enantioselectivity (Scheme 1.15). On the basis of these results, Koga revised his proposed mechanism for the present enantioselective deprotonation reaction. Rather than proceeding through a six-membered (Ireland-type) transition state **40**,[39] it was suggested that this transformation involves an eight-membered cyclic transition state **41** which includes LiCl. As stated previously, under the in situ quench conditions a small quantity of lithium chloride is generated by trapping of the intermediate enolate with chlorotrimethylsilane. Transition state model **41** places the aryl group of the chiral base considerably closer to the *tert*-butyl substituent of the substrate. It therefore better explains the effect of increasing the steric bulk of the aryl group on the enantioselectivity of the reaction.



Scheme 1.16.



R	R'	yield %	er
Me	H	55	70:30
CH_2F	H	61	71:29
CHF_2	H	66	79:21
CF_3	H	98	94:6
CF_2CF_3	H	92	91:9
Ph	Me	73	84:16
Ph	H	71	75:25



(*R*)-**43**

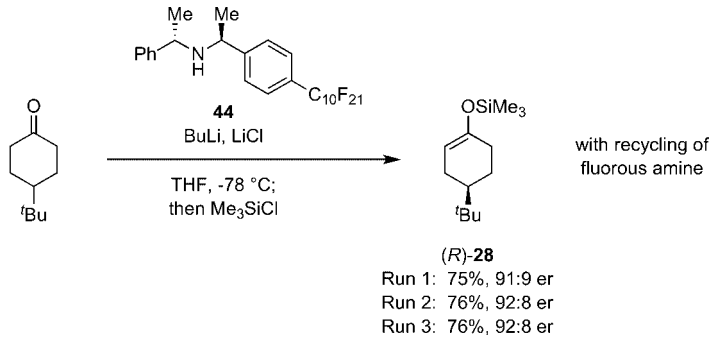
Scheme 1.17.

Corey has investigated the use of chiral lithium amide **42** having a trityl group on nitrogen for the enantioselective deprotonation of 4-*tert*-butylcyclohexanone.[40] Reaction of this substrate with **42** in the presence of chlorotrimethylsilane (in situ quench conditions) and lithium bromide (2 equiv) gave the silyl enol ether (*S*)-**28** in 89% yield and 95:5 er (Scheme 1.16). Contrary to the results in the previous example, it appears that the substantial increase in steric bulk of the chiral base does not impair its performance in this enantioselective deprotonation.

Koga has also investigated 1-phenylethylamine-derived chiral lithium amides, which have an achiral alkyl group or a fluorine-containing alkyl group on the amide nitrogen.[41] The best yields and selectivities were obtained using chiral lithium amides having a 1,1,1-trifluoroethyl or 1,1,1,2,2-pentafluoropropyl group on the amide nitrogen (Scheme 1.17). These chiral bases outperform the popular chiral bases (*R*,*R*)-**14** and (*R*)-**43** for this transformation (entries 6–7 of the table in Scheme 1.17).[42]

An increasingly useful method for the purification and recycling of expensive reagents is the application of a fluorous biphasic system.[43] Ryu *et al.* have demonstrated the use of fluorous-tagged chiral lithium amides for asymmetric deprotonation.[44] For example, chiral amine **44**, which has a perfluorodecyl chain attached to one phenyl group, was used for conversion of 4-*tert*-butylcyclohexanone into (*R*)-**28** (Scheme 1.18). The presence of the fluorous tag apparently had no appreciable detrimental effect on the selectivity of lithiation. Unfortunately, the authors state that extraction of **44** using FC-72 (perfluorohexanes) at the end of reactions was rather tedious. The fluorous-tagged chiral amine was instead recycled using silica gel chromatography.

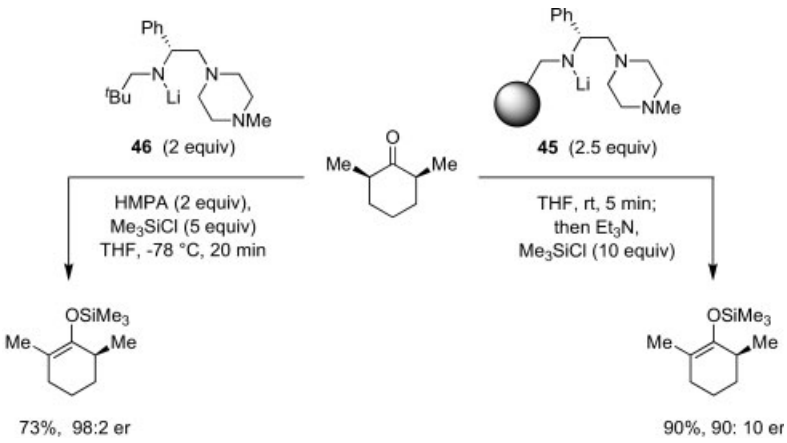
Polymer-supported chiral amines have also been shown to undergo recycling and re-use without loss of reactivity or selectivity.[45] Williard has de-



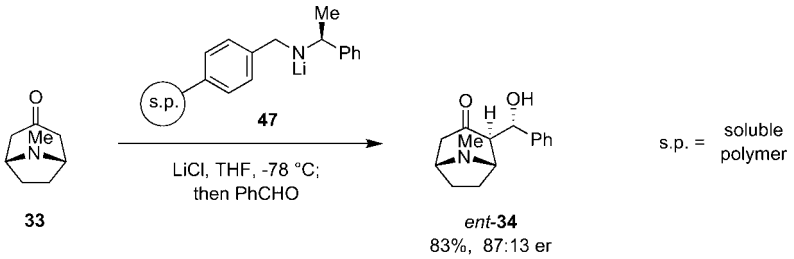
Scheme 1.18.

veloped chiral amides attached to Merrifield resin, such as **45**, which were efficient in the asymmetric deprotonation of *cis*-2,6-dimethylcyclohexanone (Scheme 1.19). A significant result of this study was that the polymeric reagents did not require sub-ambient temperatures to generate high enantioselectivities, and performed well at room temperature. This approach compares favourably with the corresponding solution-state reaction using chiral base **46**. In this case, it was necessary to carry out the reaction at low temperatures (–78 °C) with the addition of one equivalent of hexamethylphosphoric triamide (HMPA).[46]

The group of Majewski have also been active in examining chiral lithium amides attached to solid support.[47] Non-crosslinked (soluble) polystyrene supports were employed as well as the Merrifield resin approach. The authors found that, for the deprotonation and aldol reaction of tropinone, the soluble polymers were considerably better than Merrifield resin-based reagents at facilitating the asymmetric transformation. Thus, reaction of tropi-



Scheme 1.19.



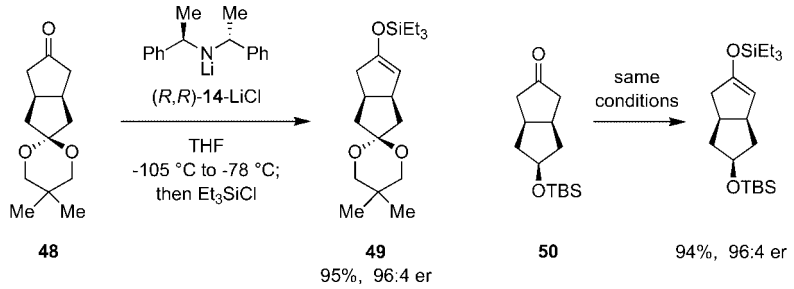
Scheme 1.20.

none **33** with chiral lithium amide **47** followed by addition of benzaldehyde gave the aldol product *ent*-**34** in 83% yield and 87:13 er (Scheme 1.20). The corresponding reaction where a Merrifield resin support was used instead of a soluble polymer support gave *ent*-**34** in only 45% yield and 62:38 er.

There seems to be room for further development of immobilised chiral lithium amide bases, both to facilitate scale-up reactions and base recovery, and also in the design of multi-base systems for catalytic chiral base chemistry.

B. Applications of Chiral Lithium Amides in Synthesis

Two decades ago, Koga *et al.* showed that certain monoacetals of bicyclo[3.3.0]octan-3,7-diones can be deprotonated enantioselectively to afford chiral synthons towards the carbocyclins.[48] The group of Gais *et al.* have been particularly active at expanding this area of research. Thus, ketone **48** was converted into silyl enol ether **49** using (*R*,*R*)-**14**-LiCl as the chiral base (Scheme 1.21). Alternatively, bicyclo[3.3.0]octane **50**, where the acetal was replaced by a silyloxy group, was employed. Asymmetric deprotonations of this kind were used to prepare analogues of prostacyclin, such as 3-oxacarbacyclin and 3-oxaisocarbacyclin,[49] cicaprost and isocicaprost,[50] as well as 16*S*-

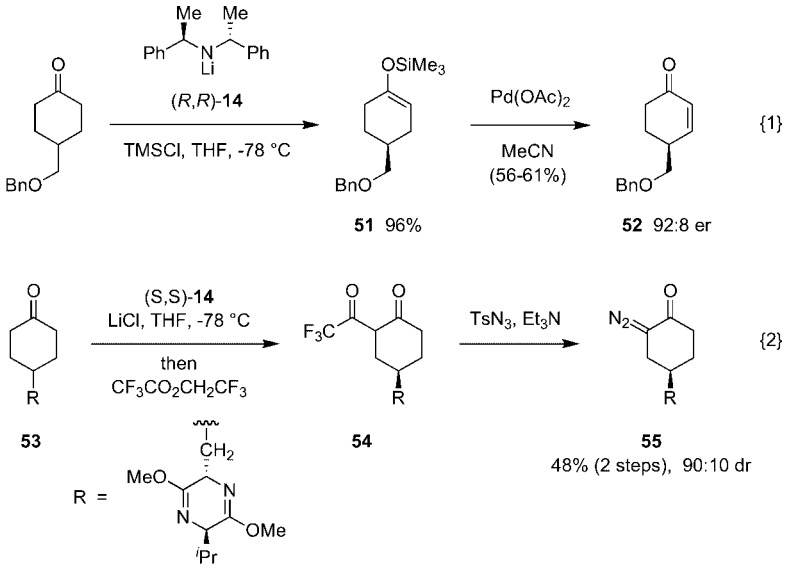


Scheme 1.21.

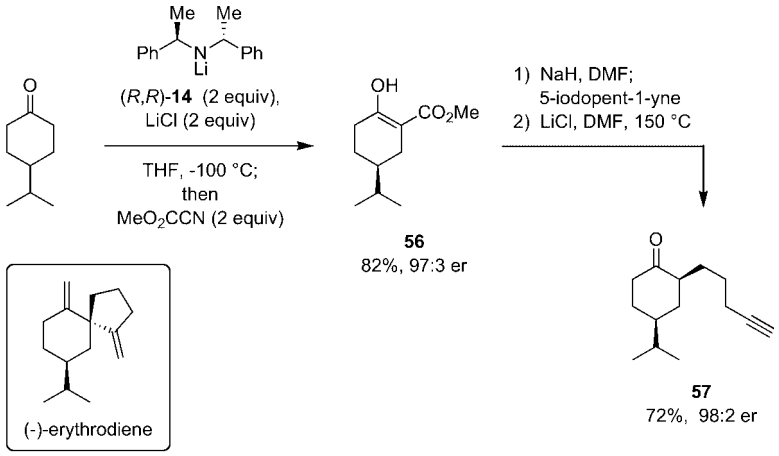
iloprost and 16*S*-3-oxa-iloprost,[51] amongst others.[52] In related work, Abe *et al.* have explored the asymmetric deprotonation of *meso*-bicyclo[3.1.0]hexan-3-one systems.[53]

1. Deprotonations of Substituted Monocyclic Cyclohexanones

The desymmetrisation of an achiral, 4-substituted cyclohexanone using chiral base (*R*,*R*)-**14** was employed by at an early stage in the total synthesis of the fungal metabolite penitrem D.[54] Exposure of 4-(benzyloxymethyl)cyclohexanone to (*R*,*R*)-**14** in the presence of chlorotrimethylsilane resulted in the formation of silyl enol ether **51** in 96% yield (Scheme 1.22 eq 1). The enantioselectivity of this step was determined to be 92% upon conversion of **51** into enone **52** under the standard conditions for this transformation (*i.e.* palladium(II) acetate in acetonitrile).[55] Wild has used chiral base (*S*,*S*)-**14** in the total synthesis of the antifungal natural products chlorotetaine, bacilysin and anticapsin.[56] In this case, rather than prepare the silyl enol ether from **53**, the enolate that was formed in situ was *C*-acylated using 2,2,2-trifluoroethyl trifluoroacetate to afford 1,3-diketone **54** (Scheme 1.22 eq 2). In this case the ketone possesses remote chirality, in the form of the *bis*-lactim ether substituent, and so this is formally a case of double asymmetric induction. Further examples of this type of process, where the substrate is already chiral (either enantiopure or racemic) can be found later in the review. In this case, subsequent diazotisation of diketone **54** using tosyl azide



Scheme 1.22.

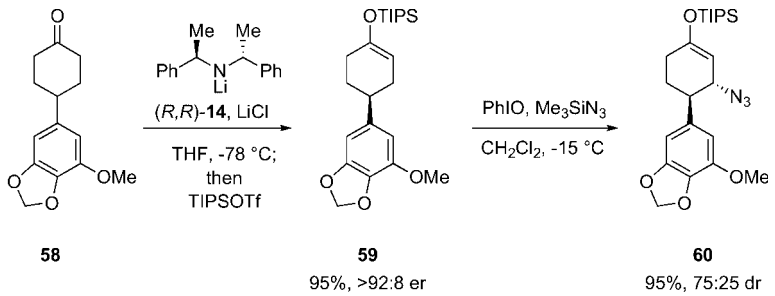


Scheme 1.23.

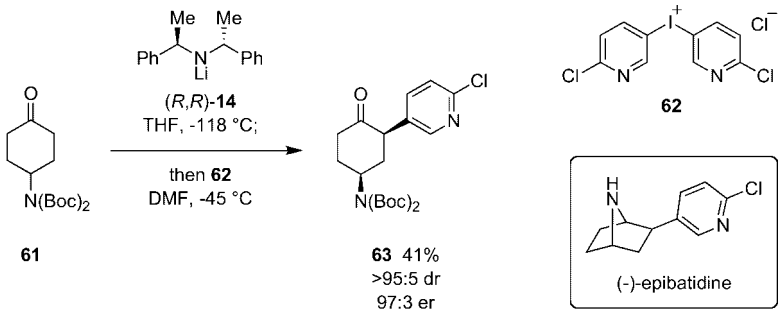
and triethylamine led to the formation of α-diazo ketone **55** in 48% overall yield and 90:10 dr.

Asymmetric deprotonation was utilised by Renaud *et al.* in the total synthesis of (–)-erythrodiene.[57] Treatment of 4-(isopropyl)cyclohexanone with chiral lithium amide (*R*,*R*)-**14** and methylcyanoformate gave β-keto ester **56** which was isolated as the enol form (Scheme 1.23). Compound **56** was converted into acetylene **57** by alkylation with 5-iodopent-1-yne followed by Krapcho decarboxylation. The target (–)-erythrodiene was accessed from **57** in four additional steps, which included a radical spirocyclisation as the key transformation.

Magnus *et al.* have employed the chiral base approach for the total synthesis of (+)-pancratistatin[58] and a synthesis of the lycorane core structure in non-racemic form.[59] Enantioselective deprotonation of cyclohexanone **58** using chiral base (*R*,*R*)-**14**, followed by trapping of the enolate with triisopropylsilyl trifluoromethanesulfonate resulted in the formation of silyl enol



Scheme 1.24.

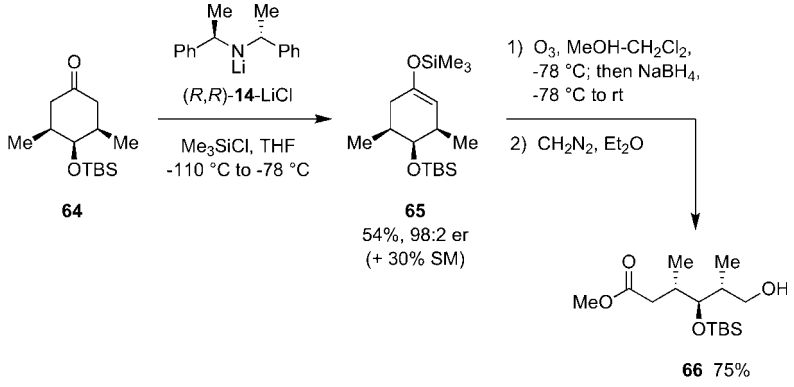


Scheme 1.25.

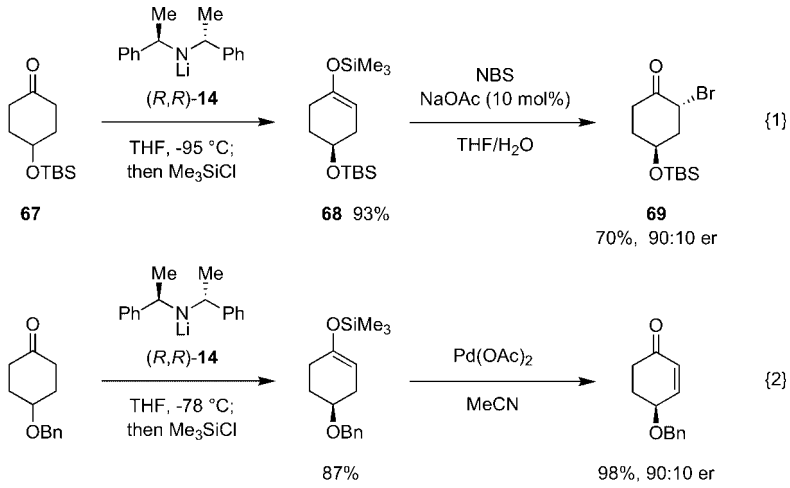
ether **59** in excellent yield and good enantioselectivity (Scheme 1.24). Silyl enol ether **59** was subjected to a β-azidonation reaction using iodosylbenzene and trimethylsilyl azide, to afford **60**.

Diaryl iodonium(III) salts are an attractive class of electrophilic aryl reagents which undergo couplings with enolates.[60] Aggarwal *et al.* have developed the enantioselective α-arylation of cyclohexanones using diaryl iodonium salts and applied this to the synthesis of (–)-epibatidine.[61] Thus, cyclohexanone **61** was deprotonated using chiral base (*R*,*R*)-**14** and arylated with dipyridyl iodonium salt **62** to afford **63** with high diastereo- and enantioselectivity (Scheme 1.25).

The chiral base desymmetrisation of a cyclohexanone has been used for the preparation of the C5–C11 fragment of bafilomycin A_1.[62] Deprotonation of *meso*-cyclohexanone **64** using chiral base (*R*,*R*)-**14**-LiCl and silylation gave, as expected, silyl enol ether **65** of high enantiopurity (Scheme 1.26). This compound was converted into the open-chain methyl ester **66** by the sequence of ozonolysis, reduction and esterification.



Scheme 1.26.

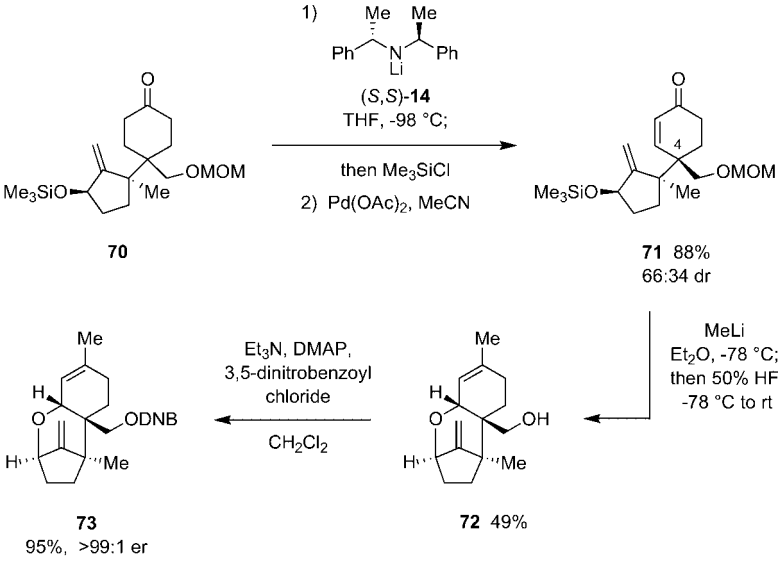


Scheme 1.27.

Enantioselective deprotonation was employed by Parker *et al.* as the starting point for their synthesis of the enyne A-ring synthon of the 1α-hydroxy vitamins D.[63] Treatment of cyclohexanone **67** with chiral base (*R*,*R*)-**14** and silylation gave silyl enol ether **68** in 93% yield (Scheme 1.27 eq 1). The enantiopurity was determined for the α-bromo ketone **69** after bromination using *N*-bromosuccinimide (NBS). Similarly, Kibayashi *et al.* used the enantioselective deprotonation of 4-(benzyloxy)cyclohexanone to prepare either enantiomer of 4-(benzyloxy)cyclohex-2-en-1-one (Scheme 1.27 eq 2).[64]

The strategy of silyl enol ether synthesis via asymmetric deprotonation and Saegusa reaction was used by Ihara *et al.* during the formal synthesis of 4-deoxyverrucarol.[65] Treatment of cyclohexanone **70** with lithium amide (*S*,*S*)-**14** followed by chlorotrimethylsilane generated the corresponding silyl enol ether (Scheme 1.28). Upon exposure to palladium(II) acetate in acetonitrile, this afforded enone **71** in 88% yield as an inseparable mixture of diastereomers (corresponding to the two epimers at C4). Enone **71** was then cyclised into tricyclic pyran **72** by reaction with methyllithium followed by 50% hydrogen fluoride. The enantiomeric purity of **72** was determined to be >99:1 er after formation of its 3,5-dinitrobenzoyl derivative **73**.

The first examples of intramolecular cyclisation of prochiral cyclohexanones using chiral lithium amides were reported by Weinreb.[66] The intramolecular S_N2 reaction was shown to be feasible, and could be effected with good enantioselectivities. For example, exposure of cyclohexanone **74**, which has an iodopropyl group at C4, to the lithium amide (*S*,*S*)-**14**-LiCl resulted in the formation of bicycle **75** in 62% yield and 87:13 er (Scheme 1.29, conditions A). Alternatively, the reaction between **76**, which has an iodoethyl group at C4, and chiral amide **36** (conditions B) gave bicycle **77** in 70% yield



70

71 88%
66:34 dr

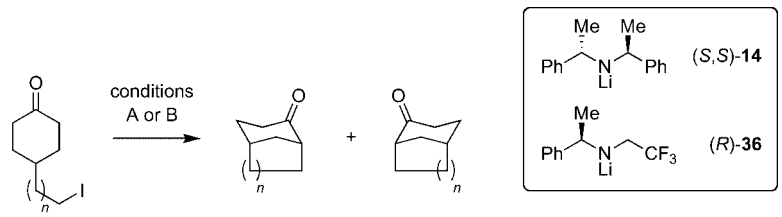
72 49%

73
95%, >99:1 er

Scheme 1.28.

and 90:10 er. The authors remark that this intramolecular cyclisation was highly dependent on the reaction conditions and that they were unable to identify any obvious trends within their experimental data.

Ihara and co-workers have shown that an intramolecular Michael-addition–aldol sequence can be an effective approach for the formation of tricyclic cyclobutane derivatives.[67] Combining this strategy with an initial asymmetric deprotonation enables the rapid asymmetric synthesis of some complex polycyclic frameworks. Thus, reaction of 4-substituted cyclohexa-



74 (n = 2)
76 (n = 1)

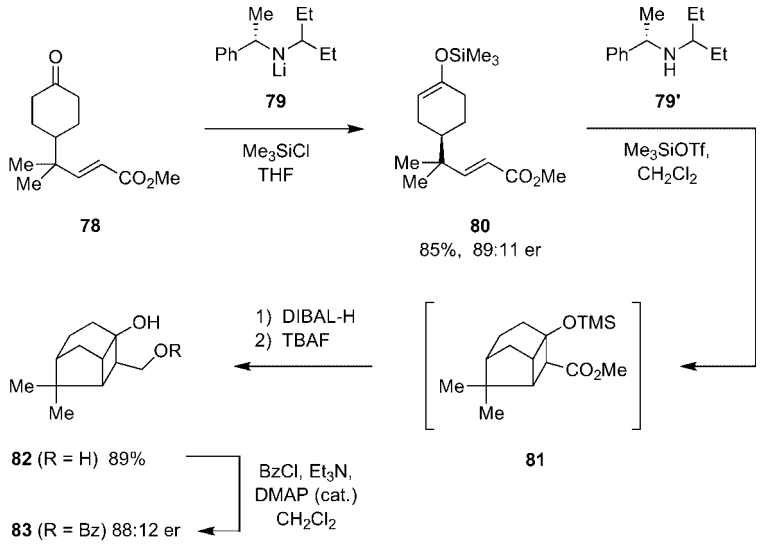
75 (n = 2)
ent-**77** (n = 1)

ent-**75** (n = 2)
77 (n = 1)

62%, 87:13 er (using A)
70%, 10:90 er (using B)

conditions
A: chiral amide (*S,S*)-**14**-LiCl (1.5 equiv), LiCl (1 equiv), THF, -60 °C to -20 °C
B: chiral amide (*R*)-**36** (1.05 equiv), LiCl (1 equiv), THF, -80 °C to -40 °C

Scheme 1.29.

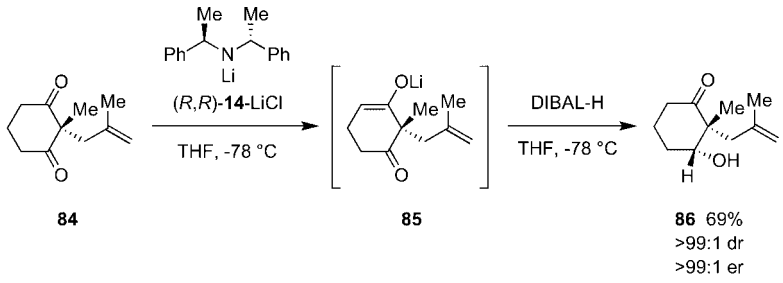


Scheme 1.30.

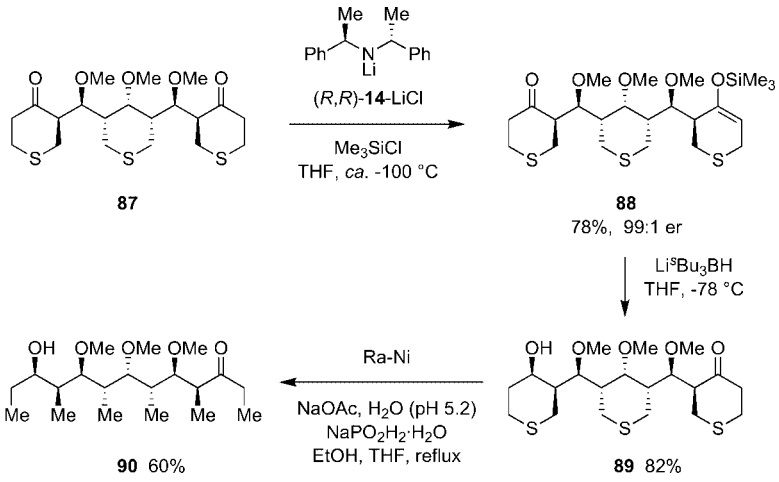
none **78** with lithium amide **79** and chlorotrimethylsilane afforded silyl enol ether **80** in good yield (Scheme 1.30).

Exposure of **80** to the chiral amine **79′** and TMSOTf resulted in cyclisation to the tricyclic cyclobutane **81**. On account of the difficulty to isolate pure **81**, this was immediately converted into diol **82** in 89% overall yield by reduction with diisobutylaluminium hydride and desilylation. The enantiopurity of the diol product was determined after its conversion into benzoate **83** (88:12 er). It is worth noting that the intramolecular Michael-aldol reaction was lower-yielding (54%, 89:11 er) when triethylamine was used in place of chiral amine **79′**.

Highly selective enolisation of cyclic 1,3-diketones is possible using chiral lithium amides and this provides a new method for enantioselective diketone reduction.[68] The best diastereo- and enantioselectivities were observed



Scheme 1.31.



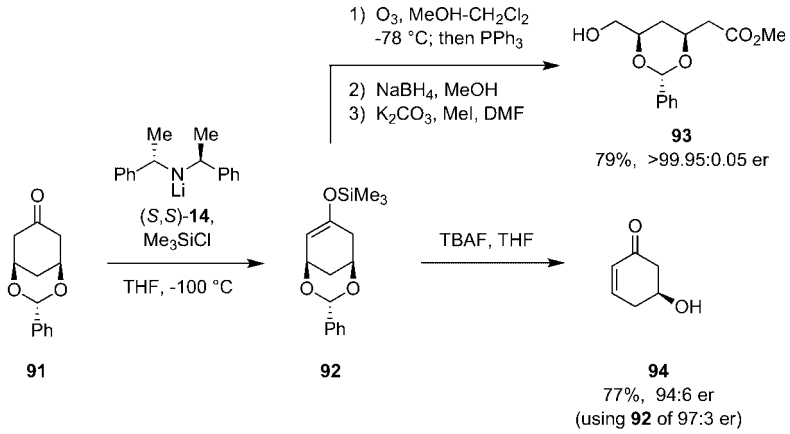
Scheme 1.32.

when six-membered rings were employed as substrates. Thus, treatment of 1,3-diketone **84** with the chiral base (*R*,*R*)-**14**-LiCl generated the intermediate lithium enolate **85** (Scheme 1.31). This was reduced using diisobutylaluminium hydride to afford β-keto alcohol **86** in 69% yield, >99:1 dr and >99:1 er. Hence the formation of a mono lithium enolate allowed for selective protection of the corresponding ketone, enabling selective reduction of the non-enolised carbonyl function.

A conceptually similar approach was devised by Ward and co-workers.[69] They showed that *meso*-1,9-diketone **87** could be desymmetrised using chiral lithium amide (*R*,*R*)-**14**-LiCl in the presence of chlorotrimethylsilane. This afforded silyl enol ether **88** in 78% yield and 99:1 er (Scheme 1.32). As a result, the remaining ketone group was primed for reduction by L-Selectride® to give **89**. Finally, the desired open-chain polypropionate **90** was accessed by desulfurisation using Raney nickel.

2. Deprotonations of Bicyclic Cyclohexanones

Honda has employed the enantioselective deprotonation of a prochiral 3,5-disubstituted cyclohexanone as a key reaction in a formal synthesis of the antiobesity agent (–)-tetrahydrolipstatin,[70] as well as an inositol phosphatase inhibitor.[71] Enantioselective deprotonation of rigid bicyclic cyclohexanone **91** using (*S*,*S*)-**14** in the presence of chlorotrimethylsilane led to the formation of the corresponding silyl enol ether **92** (Scheme 1.33). The deprotonation of **91** was observed to afford the silyl enol ether with a higher enantiomeric excess (>99:1 er) compared to when 3,5-di(benzyloxy)cyclohexanone

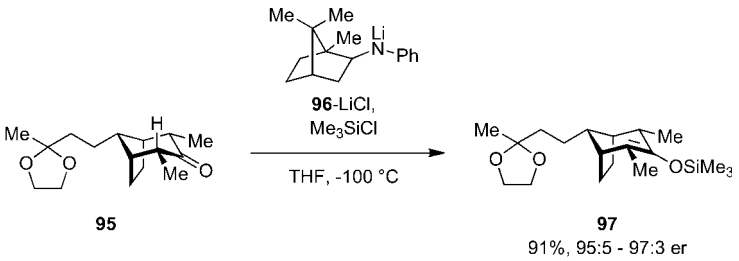


Scheme 1.33.

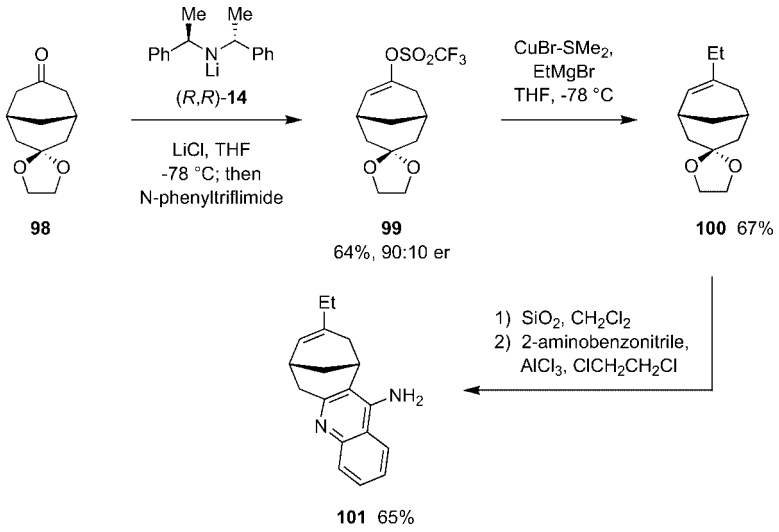
was used as the substrate (87:13 er). This improvement was attributed to the increased rigidity of the bicyclic compound. The product **92** was either ring-opened under ozonolysis conditions and then converted into methyl ester **93**, or used to prepare enone **94** by treatment with TBAF. Some slight erosion of er was observed in the latter process.

As part of a strategy directed towards the synthesis of the potent antiviral agent (–)-reiswigin A, MaGee *et al.* carried out an enantioselective deprotonation of *meso*-ketone **95**.[72] Treatment of **95** with lithium amide **96**-LiCl in the presence of chlorotrimethylsilane led to the formation of silyl enol ether **97** in high yield and excellent enantioselectivity (Scheme 1.34). The sense of asymmetric induction observed is in agreement with the very first published asymmetric enolisations described using this base, back in 1986.[73]

Enantioselective deprotonation was used as a key step by Camps *et al.* for the preparation of a tacrine-huperzine A hybrid.[74] The starting *meso*-ketone **98** was converted enantioselectively into enol triflate **99** by reaction with chiral base (*R*,*R*)-**14** and capturing of the resulting enolate with *N*-phenyltriflimide (Scheme 1.35). The product was then subjected to a

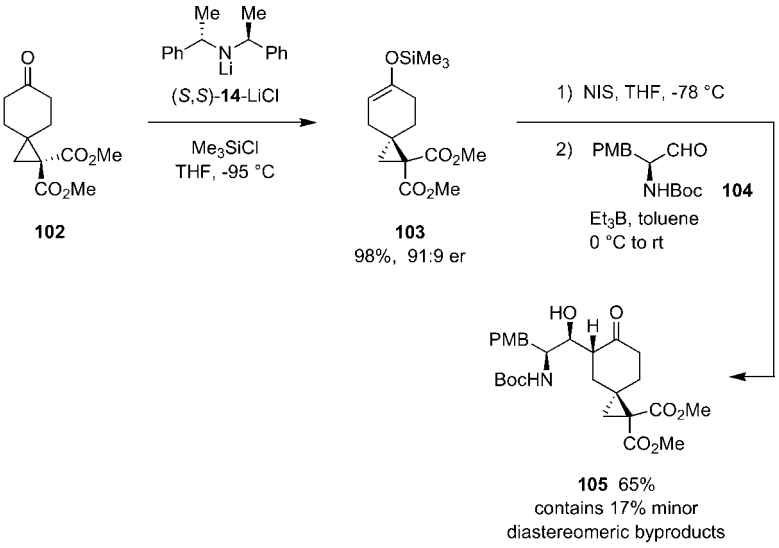


Scheme 1.34.

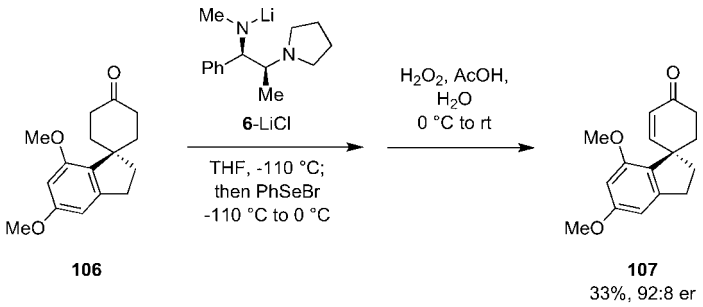


Scheme 1.35.

copper-mediated cross-coupling with ethylmagnesium bromide (Kant's modification of the McMurry protocol)[75] to give olefin **100**. Removal of the cyclic acetal by hydrolysis gave the corresponding ketone and a Friedländer reaction with 2-aminobenzonitrile gave tacrine-huperzine A hybrid **101** in 65% yield. In related work, Reissig and co-workers have demonstrated that *O*-nonaflation of 4-*tert*-butylcyclohexanone could be carried



Scheme 1.36.



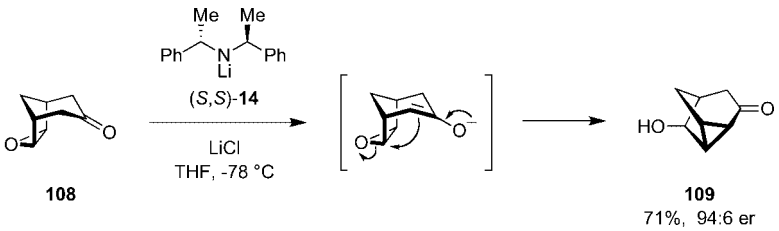
Scheme 1.37.

out asymmetrically via its silyl enol ether (94:6 er using chiral base (*R*,*R*)-**14** at –100 °C) and that the resulting enol nonaflates were good substrates for Heck couplings.[76]

FR901483 is an inhibitor of purine biosynthesis and has been compared to leading immunosuppressive agents such as cyclosporin A and FK-506. For the synthesis of this interesting natural product, Kerr and co-workers employed, at an early stage, the asymmetric deprotonation of cyclohexanone **102**.[77] Silyl enol ether **103** was prepared in the standard way using chiral lithium amide (*S*,*S*)-**14**-LiCl in the presence of chlorotrimethylsilane (Scheme 1.36). This was converted into the corresponding α-iodo ketone by exposure to *N*-iodosuccinimide, which was coupled with aldehyde **104** via a Et_3B-mediated Reformatsky type reaction.[78] This afforded β-keto alcohol **105** with an acceptable degree of selectivity.

Similarly, Braun *et al.* used the chiral lithium amide formed from **6**-LiCl to prepare non-racemic *O*-methylcannabispirenone **107** from cyclohexanone **106**.[79] In this instance, the enolate obtained by enantioselective deprotonation was converted into the corresponding enone by the sequence of selenation, oxidation and spontaneous elimination (Scheme 1.37).

In a novel transformation, Abe *et al.* have performed an enantioselective deprotonation which leads to a transannular C–C bond forming process.[80] In order to achieve this, bicyclic keto-epoxide **108** was used as the substrate (Scheme 1.38).



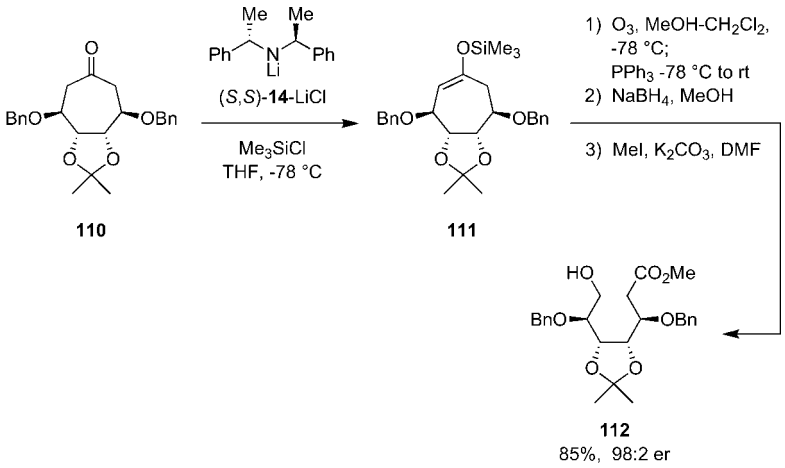
Scheme 1.38.

On deprotonation using chiral lithium amide (*S*,*S*)-**14**, this compound undergoes enolisation followed by intramolecular epoxide-opening to afford keto alcohol **109** in 71% yield and 94:6 er.

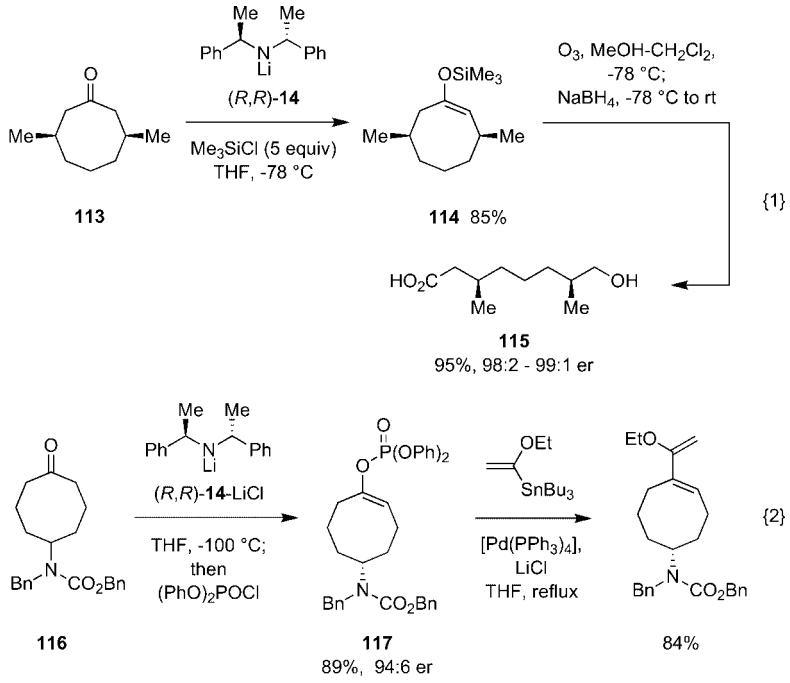
3. Deprotonations of Cycloheptanones and Cyclooctanones

The enantioselective deprotonation of a *meso*-cycloheptanone was performed by Honda and co-workers as part of their approach to pseudomonic acid B.[81] Treatment of cycloheptanone **110** with chiral lithium amide (*S*,*S*)-**14**-LiCl and silylation gave silyl enol ether **111** (Scheme 1.39). Ozonolysis resulted in cleavage of the double bond that had been introduced and two additional steps (reduction and esterification) gave methyl ester **112** in 85% overall yield and 98:2 er.

The asymmetric deprotonation of *meso*-cyclooctanones has also been investigated. Berkovitz used the enantioselective deprotonation of eight-membered cyclic ketone **113** to prepare a C10 chiral intermediate applicable to the synthesis of archaebacterial lipids.[82] Thus, *meso*-3,7-dimethyl-cyclooctanone **113** was deprotonated in a highly enantioselective manner using chiral base (*R*,*R*)-**14** to make the silyl enol ether **114** in 85% yield (Scheme 1.40 eq 1). Ozonolytic cleavage followed by reduction gave the open chain carboxylic acid **115** in 95% yield with ≥98:2 er. Similarly, Aggarwal *et al.* performed an enantioselective deprotonation of cyclooctanone **116** in their formal synthesis of (–)-anatoxin-a.[83,84] Here the resulting enolate was captured with diphenyl chlorophosphate to form the enol phosphate **117**, which successfully participated in a Stille coupling with 1-ethoxy-1-tributylstannylethene (Scheme 1.40 eq 2).

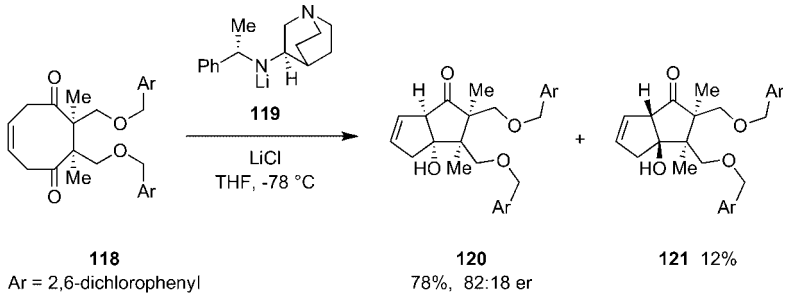


Scheme 1.39.

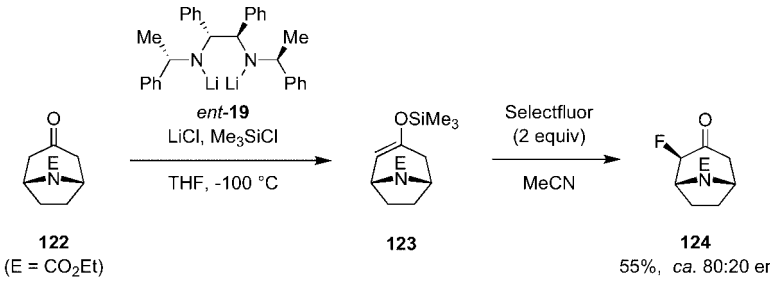


Scheme 1.40.

A chiral base-induced enantioselective desymmetrisation strategy was devised by Inoue and co-workers, as part of the synthesis of (+)-merrilactone A.[85] The key step involved the transannular aldol reaction of eight-membered *meso*-diketone **118**, and this was performed asymmetrically using chiral lithium amide **119** (Scheme 1.41). The authors observed that an increased steric bulk of the hydroxy protecting group in the substrate (here they used 2,6-dichlorobenzyl) was required to favour the formation of the desired diastereoisomer **120** over **121**. The enantioselectivity of this reaction was



Scheme 1.41.



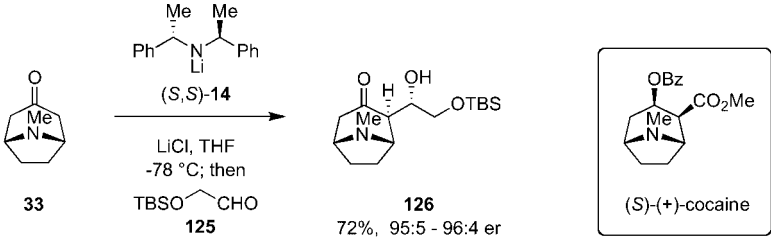
Scheme 1.42.

only moderate (82:18 er), although the product could be enantiomerically enriched to >99:1 er by recrystallisation.

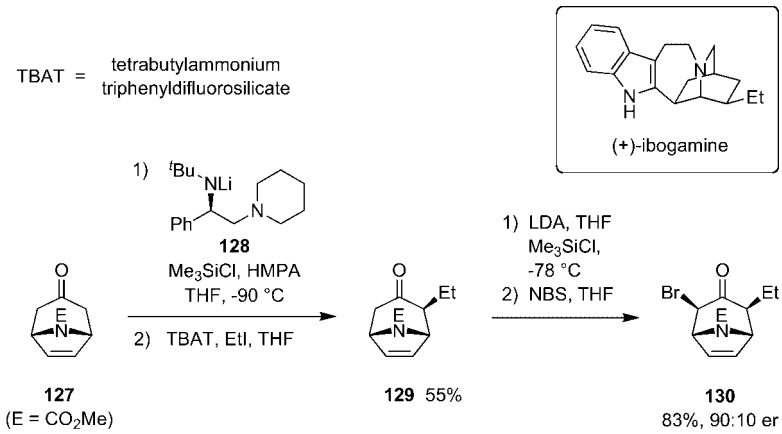
This intramolecular aldol example is one of a small, but interesting, group of chiral base reactions that involve intramolecular electrophilic trapping, which includes the alkylations shown in Schemes 1.29 and 1.38, and the Michael addition in Scheme 1.30. This appears to be a synthetic strategy of some promise, which should prove useful in target synthesis.

As mentioned in Section IV.A, heteroatom bridged cycloheptanones, particularly tropinones, have been studied extensively in chiral base reactions, not least because of the obvious applications in alkaloid synthesis. In a complementary application, Armstrong has used chiral α-fluoro ketone **124** as an asymmetric epoxidation catalyst.[86] It was prepared from tropinone **122** by the asymmetric deprotonation approach. Treatment of **122** with bis-lithium amide *ent*-**19**, in the presence of lithium chloride and chlorotrimethylsilane furnished the corresponding silyl enol ether **123** (Scheme 1.42). Exposure of **123** to Selectfluor® in acetonitrile led to the formation of **124** in 55% yield with an er of *ca.* 80:20. The relatively modest enantioselectivities in enolisation of *N*-acylated tropinones, compared to the N-Me variants, had been observed previously in a total synthesis of anatoxin-a.[84] The enantiopurity of **124** was enhanced to >99:1 er by recrystallisation.

The unnatural (+)-(*S*)-enantiomer of cocaine was prepared using the chiral base approach by Cha *et al.*[87] In their synthesis, tropinone **33** was deprotonated using chiral lithium amide (*S*,*S*)-**14** and trapped in situ with aldehyde



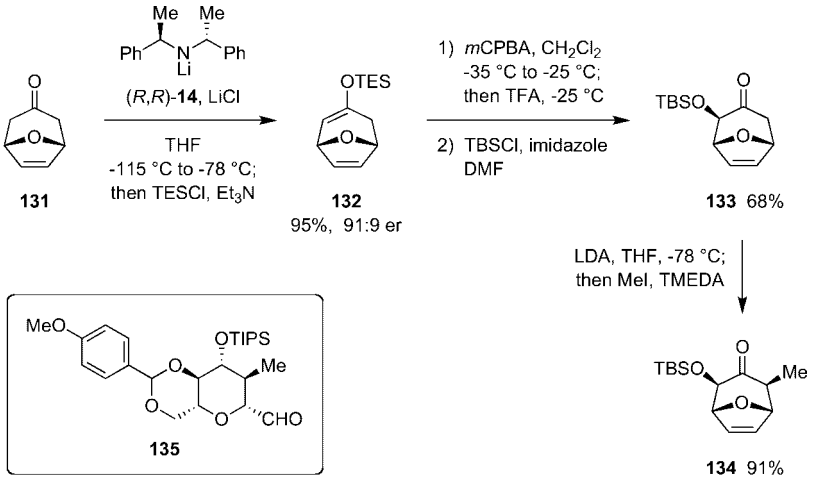
Scheme 1.43.



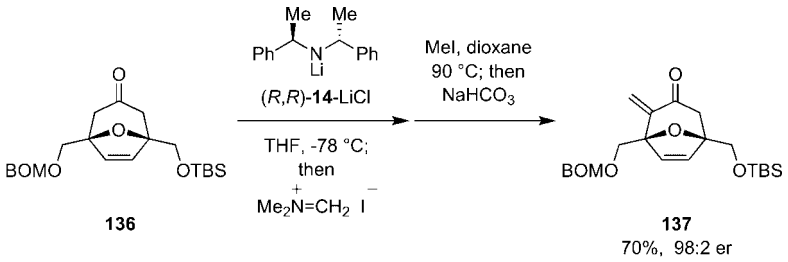
Scheme 1.44.

125 (Scheme 1.43). This gave β-keto alcohol **126** in 72% yield and ~95–96% enantioselectivities.

Hodgson *et al.* have completed a synthesis of (+)-ibogamine which includes the asymmetric deprotonation of tropenone **127**.[88] The approach involved conversion of **127** into the corresponding silyl enol ether using chiral base **128** and chlorotrimethylsilane (Scheme 1.44). This was then subjected to a TBAT-induced ethylation to afford alkylated tropenone **129** in 55% yield (86% yield based on recovered **127**). Bromination of the kinetic silyl enol ether of **129** (LDA, chlorotrimethylsilane) using NBS gave the α,α′-disubstituted ketone **130** in 83% yield and 90:10 er.



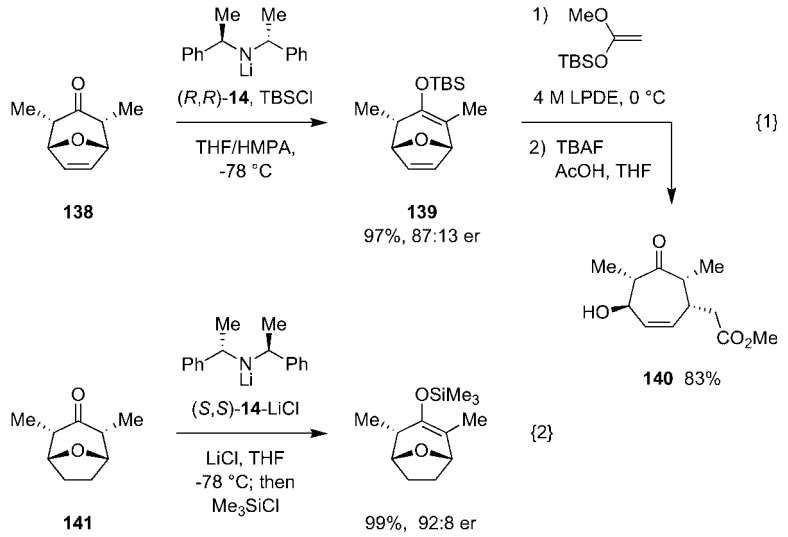
Scheme 1.45.



Scheme 1.46.

Synthesis of the C38–C44 segment of spongistatin 1 (**135**) was accomplished by Hoffmann *et al.* using the chiral base approach.[89] Enantioselective deprotonation of oxabicyclo[3.2.1]octene **131** and silylation gave silyl enol ether **132** in 95% yield and 91:9 er (Scheme 1.45). This was derivatised into α-(tert-butyldimethylsilyloxy) ketone **133** and methylation of the kinetic silyl enol ether of **133** (LDA, methyl iodide) gave the α,α′-disubstituted ketone **134** in 62% overall yield. The Hoffmann group have used similar chiral base methodology to prepare the C18–C24 unit of lasonolide A and to prepare a full set of hydroxymethyl C-glycosides.[90,91]

The enantioselective deprotonation of an oxabicyclo[3.2.1]octene was also performed by Cha *et al.* during the synthesis of (+)-phorbol.[92] Thus, treatment of oxabicyclo[3.2.1]octene **136** with the chiral amide (*R*,*R*)-**14**-LiCl, followed by Mannich condensation and elimination according to Eschenmoser's method gave the enone **137** in 70% yield in essentially enantiomerically pure form (Scheme 1.46).



Scheme 1.47.

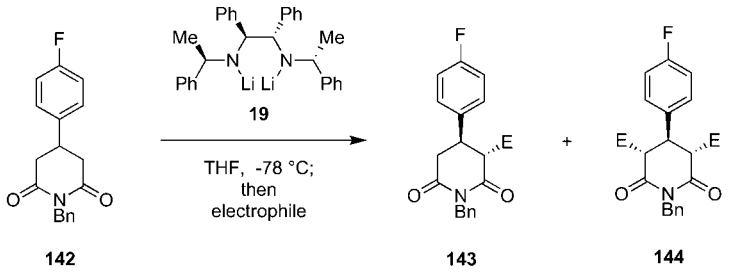
Greico and co-workers have also performed enantioselective deprotonation of an oxabicyclo[3.2.1]octene ring system in their synthesis of the chiral C(19)-C(26) and C(27)-C(32) fragments of scytophysin C.[93] For example, oxabicyclo[3.2.1]octene **138** was converted into silyl enol ether **139** using chiral base (*R*,*R*)-**14** (Scheme 1.47 eq 1). Interestingly, the authors reported the inverse sense of asymmetric induction than would be expected for this deprotonation. For example, Montaña *et al.* have carried out the deprotonation of oxabicyclo[3.2.1]octane **141**, where the ring system is saturated, and found that, with (*S,S*)-**14**, enantioselective deprotonation proceeds in the expected fashion (Scheme 1.47 eq 2).[90,94] It appears that the facial selectivity of the chiral base is different for each substrate in Scheme 1.47, and the reasons for this apparent discrepancy are not clear at present. Treatment of silyl enol ether **139** with two equivalents of 1-methoxy-1-(*tert*-butyldimethylsilyloxy) ethylene in 4 M lithium perchlorate-diethyl ether, followed by exposure of the crude product to TBAF, gave the ring-opened adduct **140** in 83% yield.

V. DESYMMETRISATION OF CYCLIC IMIDES

Application of the chiral base enolisation method to cyclic imides was identified as a potentially attractive entry to chiral alkaloids. This idea has been explored by Simpkins and co-workers in several interesting modifications.

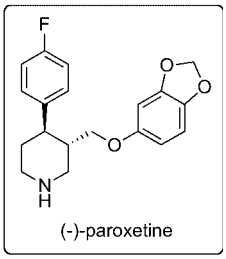
Certain 4-aryl glutarimides can undergo asymmetric deprotonation with high levels of selectivity using chiral bis-lithium amide bases.[95,96] Thus, 4-fluorophenyl glutarimide **142** was deprotonated using bis-lithium amide base **19** and alkylated using a variety of reagents (Scheme 1.48). It was found generally that, in circumstances where an appreciable quantity of the di-alkylated product **144** was formed, the er of the desired product **143** was enhanced. This was attributed to a favourable kinetic resolution process, where the minor enantiomer of the product **143** was consumed in a fast second alkylation. This asymmetric desymmetrisation process was subsequently employed in the asymmetric synthesis of the selective seratonin reuptake inhibitor (–)-paroxetine.

The desymmetrisation of cyclopropyl-fused succinimides constitutes another entry to the range of reactions that can be carried out using chiral lithium amide bases.[97,98] For example, treatment of cyclopropyl imide **145** with chiral base (*R*,*R*)-**14**-LiCl, in the presence of chlorotrimethylsilane gave mono-silylated product **146** in good yield and excellent enantioselectivity (Scheme 1.49). The product **146** could be further elaborated in a number of ways. For example, by further deprotonation using LDA-LiCl, and trapping with a variety of electrophiles gave products **147**. Silyl imide **146** was also shown to undergo highly regioselective reduction and thionation reactions, to give **148** and **149**, respectively.



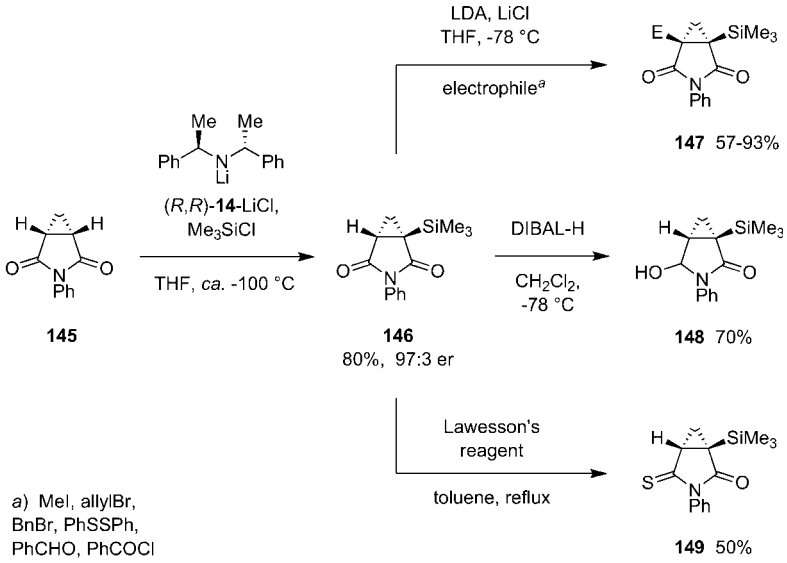
electrophile	**143**/**144**[a]	yield **143** %	er of **143**
MeI	3:1 (14)	64	>98:2
allylbromide	nd (7)	52	95:5
BnBr	2:1 (22)	61	>98:2
PhCHO	nd	40[b]	>98:2
MeO_2CCN	6.5:1	71	>98:2

a) Figures in parentheses are isolated yields of **144**
b) Isolated as a single diastereoisomer

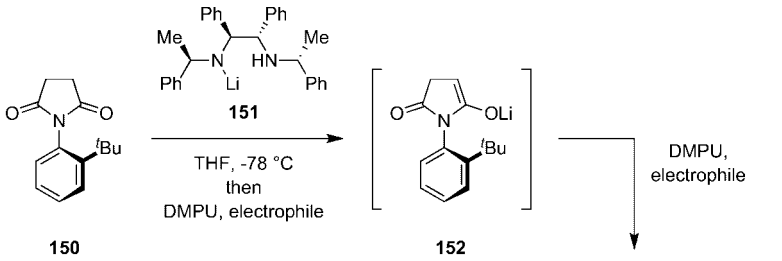


Scheme 1.48.

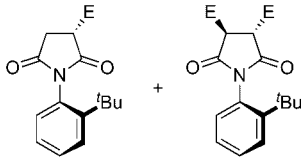
The deprotonation of imide **150** is a very special and unusual example of a chiral base enantioselective enolisation, since the starting molecule does not possess any pro-stereogenic carbon centres.[99] In this case, position-selective enolisation was expected to generate an atropisomeric enolate intermediate, **152**, which would then react with electrophiles in a face selective fashion



Scheme 1.49.

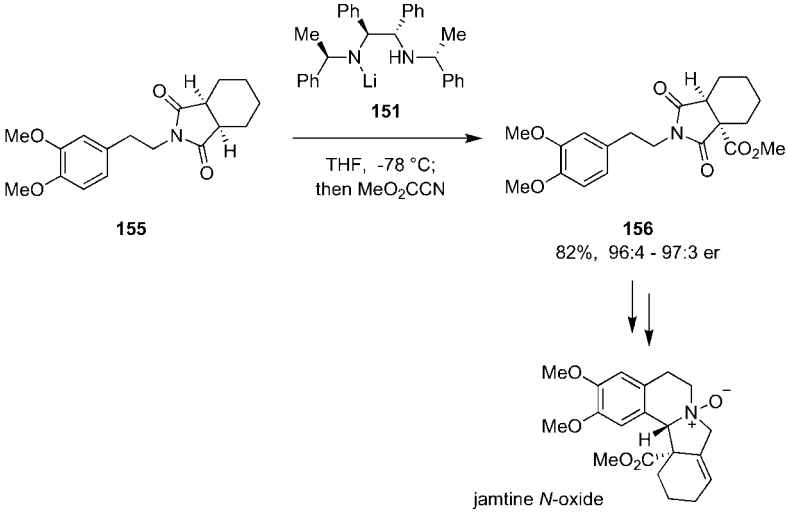


alkylating agent	yield **153** %	er of **153**	yield **154** %
MeI	56	92:8	0
allylBr	55	97:3	7
BnBr	50	96:4	6
piperonylBr	40	97:3	7

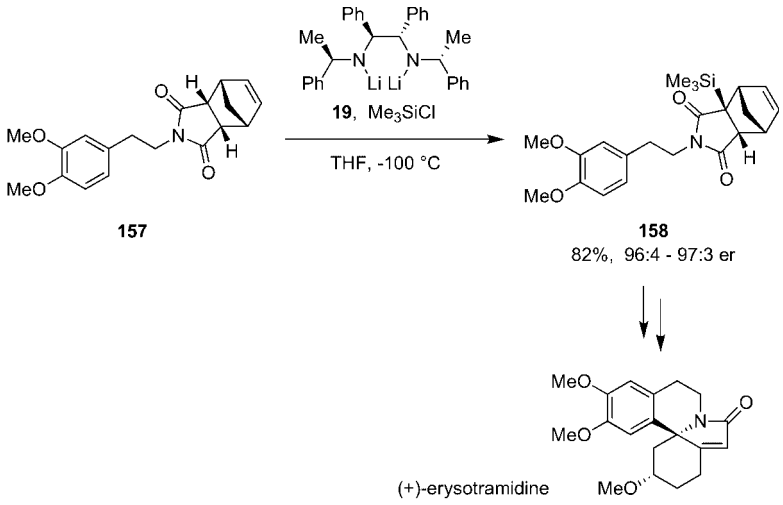


Scheme 1.50.

to give chiral imide product **153** (Scheme 1.50). For the successful implementation of this strategy, Simpkins *et al.* observed that it was necessary to use mono-lithiated base **151** for the deprotonation, whilst alkylation had to be carried out using reactive alkyl halides in the presence of DMPU. This gave the mono-alkylated succinimides **153** in reasonable yield and excellent enantioselectivity. When the bis-lithiated base **19** was employed however, the di-alkylated product **154** (predominantly as the *trans* isomer) was obtained as the major product in an almost racemic form. In a similar fashion to the glutarimide work (see Scheme 1.48), the enantiopurity of the mono-



Scheme 1.51.



Scheme 1.52.

alkylated product appeared to be slightly enhanced in runs where some dialkylation was evident. Again this could be due to a kinetic resolution of the first formed product being superimposed on the initial asymmetric deprotonation.

The asymmetric deprotonation of ring-fused imides has proved very useful in the synthesis of bioactive target molecules. The proposed structure of the unusual alkaloid jamtine *N*-oxide was prepared by Simpkins *et al.* using the chiral base approach.[96,100] Thus, deprotonation of ring-fused imide **155** using mono-lithiated diamine base **151**, followed by carboxymethylation using Mander's reagent gave **156** in 82% yield and 96–97% enantioselectivity (Scheme 1.51). The product ester was converted into jamtine *N*-oxide in five additional steps. As a consequence, it was found that the NMR data for the synthetic material did not agree with those reported for the natural compound, but showed excellent agreement with those by Padwa *et al.*[101] The original structure assignment for this natural product must therefore be incorrect.

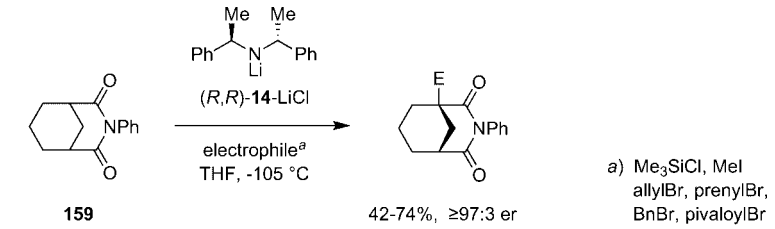
The erythrinan alkaloid (+)-erysotramidine was prepared in highly enantiomerically enriched form using similar methodology.[102] Ring-fused imide **157** was reacted with bis-lithium amide **19** in the presence of chlorotrimethylsilane. This resulted in the isolation of silylated imide **158** in 82% yield and high enantioselectivity (Scheme 1.52). The target natural product was synthesised from this point in ten additional steps.

VI. ENANTIOSELECTIVE DEPROTONATION AT BRIDGEHEAD CARBONS

Previous sections have illustrated asymmetric variants of rather conventional enolisation reactions. However, the chiral base method has also proven useful in metallations at bridgehead positions, in which the enolate structure may be more carbanion-like.[103] A small number of these, somewhat surprising, asymmetric metallation–substitution reactions have been accomplished.

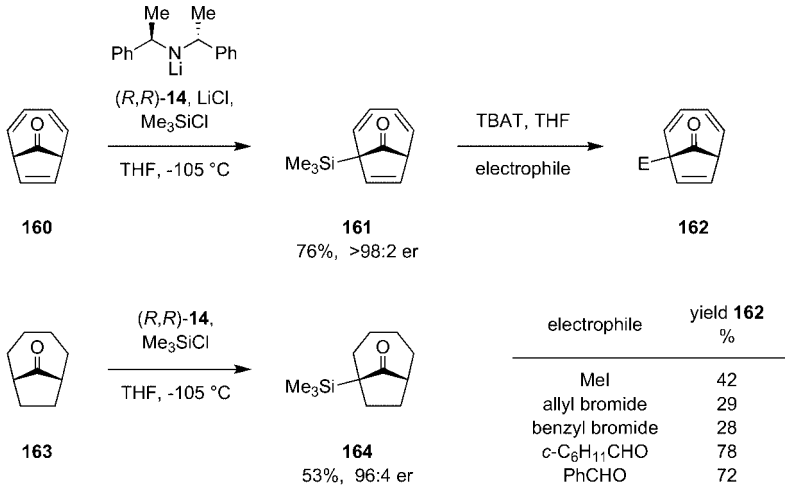
Bridged imide **159** proved to be a highly satisfactory substrate with regards to its asymmetric deprotonation and subsequent functionalisation.[104] Addition of chiral base (*R*,*R*)-**14**-LiCl to a mixture of imide **159** and an appropriate electrophile (in situ quenching conditions) led to enantioselective silylation, alkylation or acylation at the bridgehead position (Scheme 1.53).

The enantioselective generation of bridgehead carbanions can also be accomplished starting from bridged ketones. For example, Simpkins *et al.* have shown that bridged ketones **160** and **163** can be deprotonated using chiral lithium amide (*R*,*R*)-**14**.[105] Electrophilic trapping by chlorotrimethylsilane



159 42-74%, ≥97:3 er

Scheme 1.53.



160 **161** 76%, >98:2 er **162**

163 **164** 53%, 96:4 er

electrophile	yield **162** %
MeI	42
allyl bromide	29
benzyl bromide	28
c-$C_6H_{11}CHO$	78
PhCHO	72

Scheme 1.54.

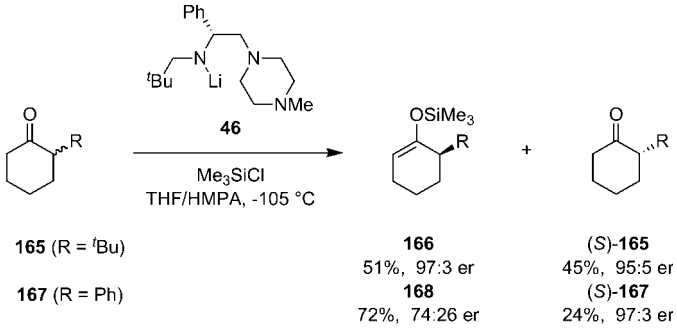
(under in situ quench conditions) resulted in the formation of the monosilylated bridged ketones **161** and **164**, respectively, in reasonable yield and excellent enantioselectivity (Scheme 1.54). Unfortunately the in situ quench approach was incompatible with most electrophiles; indirect access to products **162** was achieved however using the silyl exchange reaction with tetrabutylammonium triphenyldifluorosilicate (TBAT).

One further notable example of enantioselective bridgehead metallation–substitution has been reported in the context of natural products chemistry. This was carried out in kinetic resolution mode and so is included in the next section.

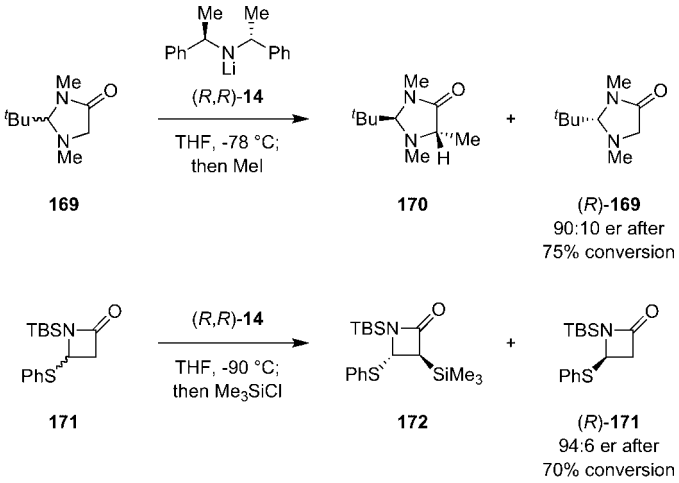
VII. KINETIC RESOLUTION PROCESSES

Only a few kinetic resolution processes involving chiral lithium amide bases are known. In these reactions a deficiency of base is employed in order to convert the fast reacting enantiomer present in the mixture into its corresponding product, whilst the slow reacting enantiomer is recovered. Asami and co-workers have demonstrated the viability of this idea for racemic epoxides as substrates.[106] Koga *et al.* have investigated the kinetic resolution of 2-substituted cyclohexanones.[107] For example, using lithium amide base **46** (1.0 equiv), the (*R*)-enantiomer of 2-(*tert*-butyl)cyclohexanone **165** was converted into silyl enol ether **166** to afford (*S*)-**165** in 45% yield and 95:5 er (Scheme 1.55). Similarly, racemic 2-(phenyl)cyclohexanone **167** was resolved into **168** and (*S*)-**167** using the same chiral base (1.3 equiv).

The racemic imidazolidinone **169** and β-lactam **171** have been shown to be appropriate substrates for kinetic resolutions using chiral lithium amide (*R*,*R*)-**14**.[108] Thus, treatment of imidazolidinone **169** with chiral base (*R*,*R*)-**14** followed by methyl iodide resulted in conversion of the (*S*)-enantiomer into methylated product **170** and enantiomeric enrichment of the (*R*)-enantiomer (Scheme 1.56 eq 1). Likewise, deprotonation of β-lactam **171** and silylation



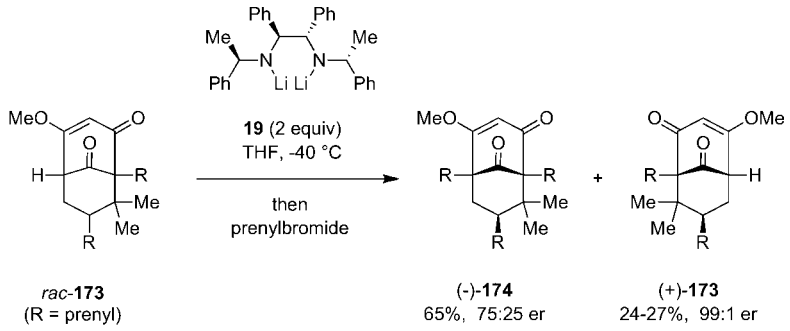
Scheme 1.55.



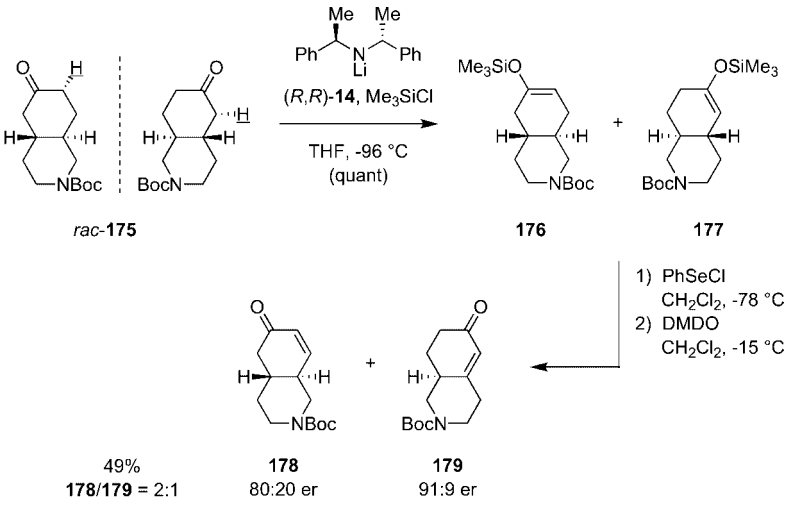
Scheme 1.56.

with chlorotrimethylsilane led to conversion of the (*S*)-enantiomer into silyl enol ether **172** whilst the (*R*)-enantiomer reacted more slowly (Scheme 1.56 eq 2).

A chiral lithium amide base was employed by Simpkins *et al.* for the kinetic resolution of a key intermediate in the total synthesis of (+)-clusianone.[109] Prior to this work, the absolute configuration of this polycyclic polyprenylated acylphloroglucinol (PPAP) had not been assigned. Bridged ketone *rac*-**173** was reacted with two equivalents of bis-lithium amide **19** followed by prenyl bromide (Scheme 1.57). Under these conditions, the prenylated product (–)-**174** was isolated in 65% yield and with an er of about 75:25, and the recovered starting material, (+)-**173**, was isolated in 24–27% yield in an enantiomerically enriched form (>99:1 er). This eventually allowed the authors to establish the absolute configuration of the (+)-isomer of this natural product.



Scheme 1.57.

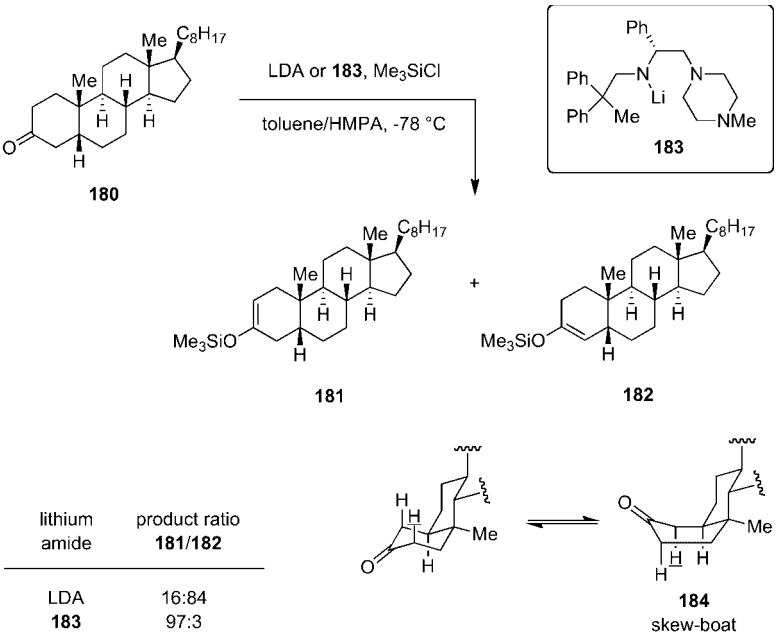


Scheme 1.58.

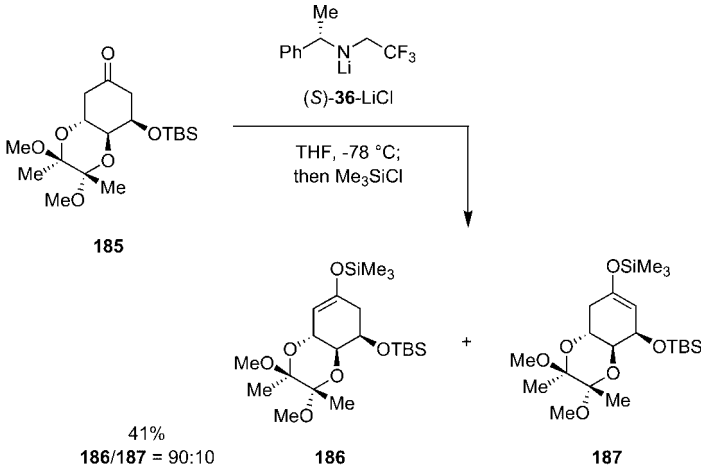
Simpkins and co-workers developed a novel resolution of bicyclic ketone *rac*-**175**.[110] In this reaction, reagent control by chiral base (*R*,*R*)-**14** results in the two enantiomers of the substrate *rac*-**175** being converted into enolate constitutional isomers. This generated a mixture of silyl enol ethers **176** and **177** in quantitative yield (Scheme 1.58). The mixture was converted to the enones **178** and **179** by the process of selenation, oxidation and spontaneous elimination. Enones **178** and **179** were separated and their enantiomeric ratios were found to be 80:20 and 91:9, respectively. This confirmed the successful implementation of a novel mutual kinetic resolution.

Chiral lithium amides have been used in the regioselective enolisation of certain 3-keto steroids.[111] For example, reaction of 3-keto steroid **180** under the standard conditions for forming the kinetic enolate (*i.e.* using LDA) gave a mixture of silyl enol ethers **181** and **182** in a ratio of 16:84 (Scheme 1.59). When chiral lithium amide **183** was employed (instead of LDA), this selectivity was reversed to give **181** and **182** in a ratio of 97:3. A deuterium-labelling study supported the hypothesis that the cyclohexanone ring in **180** adopts a skew-boat conformation **184** before it is deprotonated.[112] The chiral base then removes a proton from **180** with the selectivity that would be expected for this reagent.

A chiral lithium amide base was used by O'Brien and co-workers to overcome the regiochemical preference of lithium bis(trimethylsilyl)amide (LiHMDS) when deprotonating bicyclic cyclohexanone **185**.[113] Treatment of **185** with LiHMDS followed by chlorotrimethylsilane gave silyl enol ethers **186** and **187** in a ratio of 2:98 (Scheme 1.60). When the chiral base (*S*)-**36**-LiCl was employed however, the regioselectivity was reversed to give **186** and **187** in a ratio of 90:10.



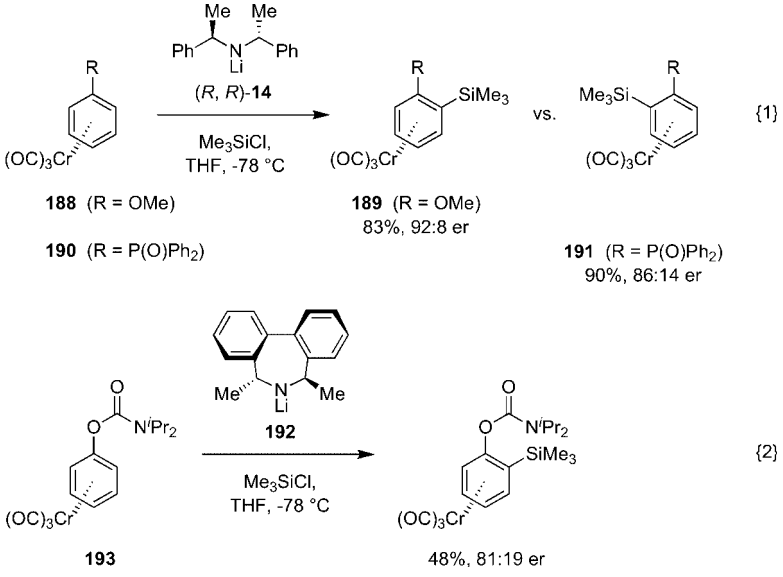
Scheme 1.59.



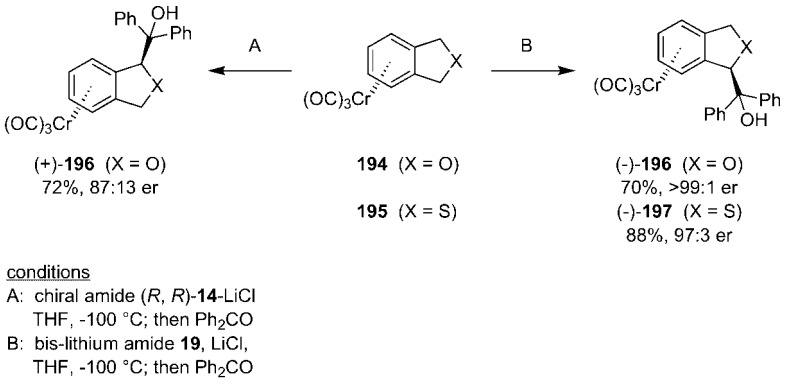
Scheme 1.60.

VIII. ENANTIOSELECTIVE DEPROTONATION OF TRICARBONYL(η^6-ARENE)CHROMIUM COMPLEXES

Asymmetric functionalisation of tricarbonylchromium(0) complexes of arenes has received much attention in organometallic chemistry.[114] Complexation of an arene ring to a tricarbonylchromium(0) unit leads to an increase in the acidity of both (i) the hydrogens attached to the aromatic ring, and (ii) any benzylic hydrogens associated with the arene. This makes tricarbonyl(η^6-arene)chromium complexes ready substrates for deprotonations using lithium amide bases. For example, anisole complex **188** is deprotonated by chiral base (*R*,*R*)-**14** and silylated to give **189** in 83% yield and 92:8 er (Scheme 1.61 eq 1).[115] Reaction of the corresponding phosphine oxide complex **190** under identical conditions resulted in the formation of **191** in 90% yield and 86:14 er.[116,117] Significantly, the sense of asymmetric induction in the reaction was opposite to that seen for the previous substrate. This is probably due to the different situations for directed metallation in these systems. In the anisole system, coordination to oxygen in an unhindered environment can prelude deprotonation via a six-membered transition state. In the phosphine oxide example the system is much more hindered, and if coordination to oxygen is important then a seven-membered arrangement is required. Kündig *et al.* have prepared 6,7-dihydro-5*H*-dibenz[c,e]azepine **192** as a new chiral lithium amide, which incorporates a chiral biaryl bond as a stereogenic element. This base was applied to the enantioselective deprotonation of Cr arenes.[118] Thus, for the enantioselective deprotonation of carbamate complex **193** (Scheme



Scheme 1.61.

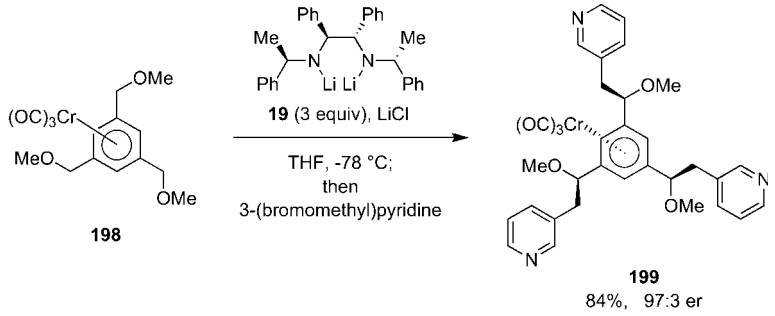


Scheme 1.62.

1.61 eq 2), it was found that the enantioselectivity was improved when chiral base **192** was used (81:19 er) rather than chiral base (*R*,*R*)-**14** (69:31 er).

Other arene complexes that have been investigated using the chiral base approach include phthalan complex **194** and 1,3-dihydroisobenzothiophene complex **195**.[117,119] For example, desymmetrisation of phthalan complex **194** using chiral base (*R*,*R*)-**14**-LiCl with benzophenone as the electrophile gave alcohol (+)-**196** in 72% yield and 87:13 er (Scheme 1.62). This base gave very poor results however when reacted with its sulfur ananlogue **195** (~ 52:48 er). Changing the base to bis-lithium amide **19** in the presence of lithium chloride led to much improved results: the product (–)-**197** was obtained in 88% yield and 97:3 er. In general, for the enantioselective deprotonation of benzylic ethers,[120] benzylic thioethers[121] and benzylamine derivatives[122] it is best to carry out the reaction using bis-lithium amide **19**-LiCl as the chiral base.

Gibson *et al.* have devised an approach to enantiomerically pure C_3-symmetric ligands by deprotonating Cr arenes at the benzylic position.[123] An impressive example of this methodology is shown in Scheme 1.63. The 1,3,5-trisubstituted arene tricarbonylchromium(0) complex **198** was tri-functionalised by its reaction with three equivalents of bis-lithium amide **19** and



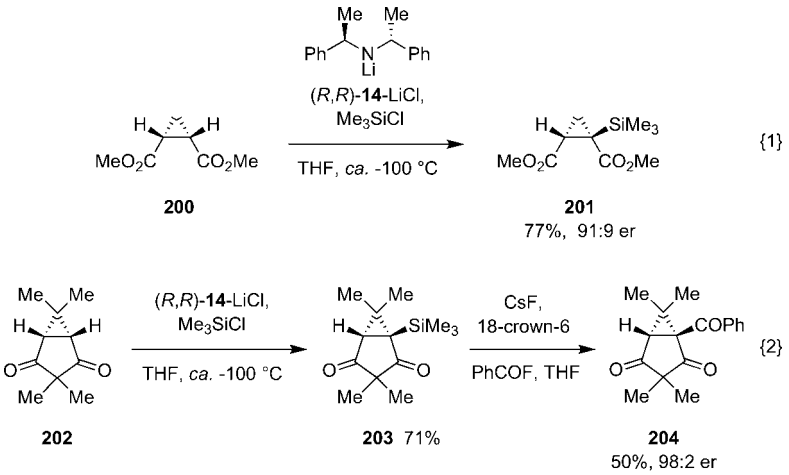
Scheme 1.63.

trapping with 3-(bromomethyl)pyridine. This resulted in the formation of the C_3-symmetric ligand **199** in 84% yield and ≥97:3 er. The viability of **199** as a chiral ligand was demonstrated by its subsequent complexation to a ruthenium metal centre.[124]

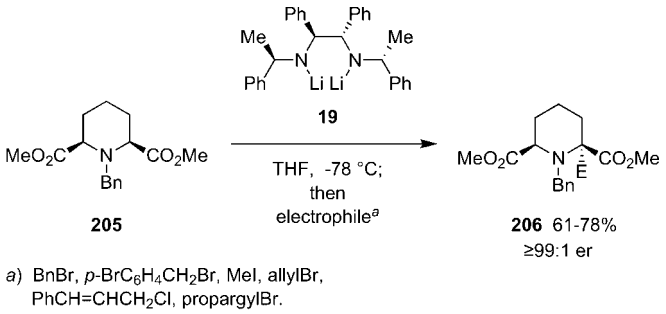
IX. OTHER TRANSFORMATIONS

In work closely associated to the asymmetric deprotonation of cyclopropyl imides (see Scheme 1.49), Simpkins and co-workers demonstrated that cyclopropane derivatives could also be silylated with high enantioselectivity.[98] Treatment of cyclopropane **200**, possessing two ester groups in a 1,2-*cis* configuration, with chiral base (*R*,*R*)-**14**-LiCl under in situ quench conditions with chlorotrimethylsilane gave the product **201** with a good degree of enantioselectivity (Scheme 1.64 eq 1). Better enantioselectivity was observed using bicyclic 1,3-diketone **202** as the substrate (Scheme 1.64 eq 2). The enantiomeric purity of the product **203** proved difficult to assay and so it was converted first into benzoyl derivative **204**. Krief and co-workers have used the enantioselective deprotonation of **202** as part of their synthesis of non-racemic (1*R*)-*cis*-chrysanthemic acid.[125]

The deprotonation of *meso*-piperidine diesters can be performed with excellent enantioselectivity using chiral bis-lithium amide base **19**.[126] Thus, treatment of piperidine diester **205** with bis-lithium amide **19** in THF at -78 °C followed by addition of the electrophile led to the formation of alkylated piperidine diester **206** in good yield and ≥99:1 er in all cases (Scheme 1.65). This chiral base desymmetrisation procedure was subsequently combined with ring-closing metathesis as a route towards chiral azaspirocycles.[127]



Scheme 1.64.

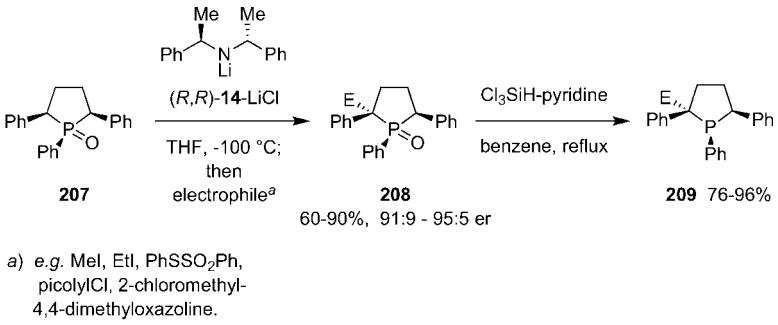


Scheme 1.65.

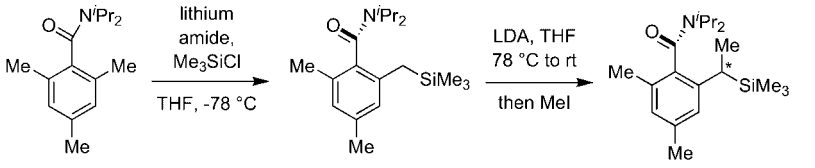
Similarly, Clive and co-workers have used the asymmetric allylation of **205** to synthesise azaspirocycles related to the marine natural products halichlorine and pinnaic acid.[37,128]

Prochiral cyclic phosphine oxides have proved to be good substrates for the chiral base-mediated asymmetric deprotonation reaction.[129] This approach might be very useful, as chiral phosphines, such as **209**, are frequently employed as ligands for asymmetric catalysis. Thus, lithium amide (*R*,*R*)-**14**-LiCl was used to discriminate between the two acidic sites of phospholane **207**, and the resulting organolithium species was functionalised using a range of electrophiles (Scheme 1.66). The phosphine oxide products **208** could be reduced to give the corresponding chiral phosphines **209** using the combination of trichlorosilane and pyridine in benzene.

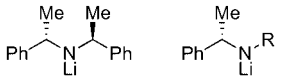
Enantiomerically enriched atropisomeric amides were accessed by the desymmetrisation of *N*,*N*-dialkylmesitamides.[130] Clayden *et al.* demonstrated that *N*,*N*-diisopropylmesitamide **210** could be deprotonated by chiral lithium amides (*S*,*S*)-**14**, (*S*)-**211**, or (*S*)-**43** and trapped with chlorotrimethylsilane to give **212** in 81:19–94:6 er (Scheme 1.67). This afforded hindered tertiary aromatic amide **212** where the atropisomerism is exhibited about the Ar–CO bond. The authors then showed that **212** could be lithiated regioselectively using LDA to afford methylated product **213** as a single regioisomer.



Scheme 1.66.

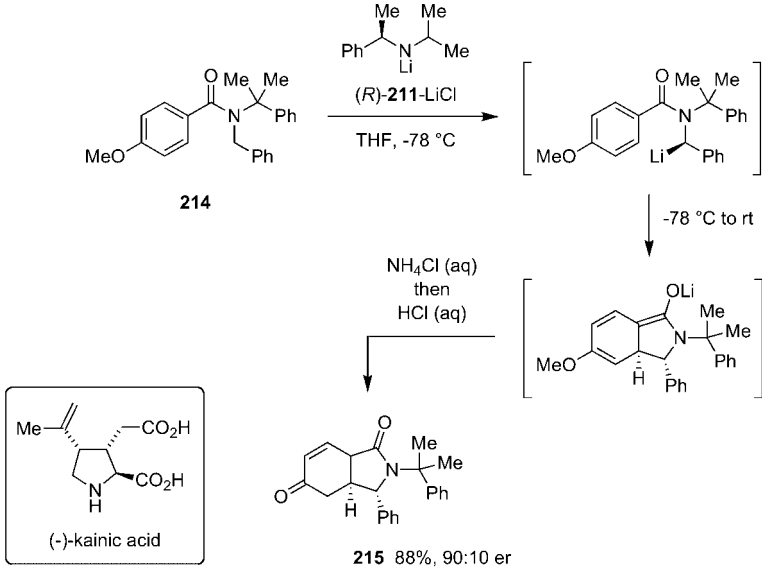


lithium amide	yield **214** %	er of **214**
(*S*,*S*)-**14**	55	94:6
(*S*)-**211**	64	81:19
(*S*)-**43**	45	89:11

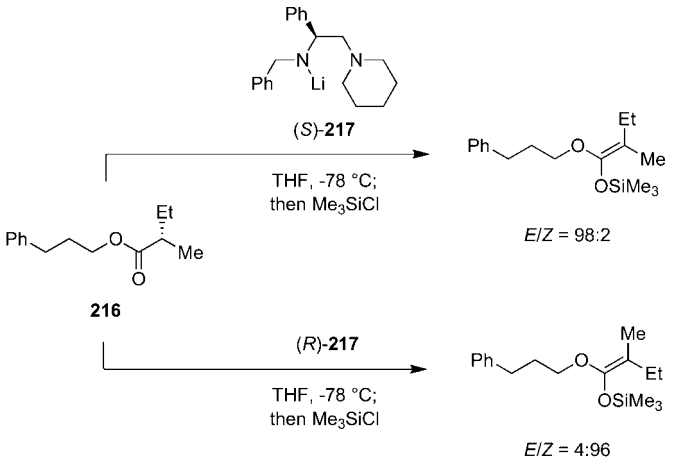


Scheme 1.67.

A chiral lithium amide base was also employed in a dearomatising cyclisation reaction that delivered chiral saturated isoindolones (see Scheme 1.10 for another dearomatisation strategy using a chiral base). Again, this involved the formation of an enantiomerically enriched benzylic organolithium and in this case it was applied to the synthesis of (–)-kainic acid.[131] Thus, deprotonation of *N*-benzyl anisamide **214** with lithium amide (*R*)-**211**-LiCl resulted in enantioselective deprotonation at its benzylic site, which on warming led to cyclisation (Scheme 1.68). An aqueous quench and acidic work-up afforded the enone **215** in 88% yield and



Scheme 1.68.



Scheme 1.69.

90:10 er. The target natural product was prepared in fourteen additional steps.

Zakarian and co-workers have developed the selective production of *E* or *Z* enolates by deprotonation of α-branched esters, such as **216**, using chiral lithium amides. This was put to use recently in the Ireland-Claisen rearrangement[132] and the synthesis of the spiroimine fragment of spirolide C.[133] Here, the chiral base **217** does not discriminate between two enantiotopic protons, since there is only one proton available for removal (Scheme 1.69). Instead, it exerts an influence over the geometry of the double bond formed in the enolate. Impressively, this can distinguish between a methyl and an ethyl group at the carbon α to the ester carbonyl group. Such stereodefined enolates are promising reagents for a variety of asymmetric transformations.

X. CONCLUSIONS

The fundamental nature of metallation and enolisation processes, and their importance for synthesis has resulted in a broad range of corresponding asymmetric deprotonation chemistry. The most venerable of these, involving the chiral base rearrangement of epoxides into allylic alcohols is now an attractive option for synthesis because of the scope to use the chiral base in a sub-stoichiometric quantity.

The asymmetric deprotonation of prochiral cyclic ketones is arguably the most broadly applicable of all chiral base strategies, although a key limitation is the lack of a truly effective catalytic protocol. Despite the advances in competitive approaches using organocatalysis, a highly effective catalytic chiral lithium amide base system (especially one generally applicable at ambient

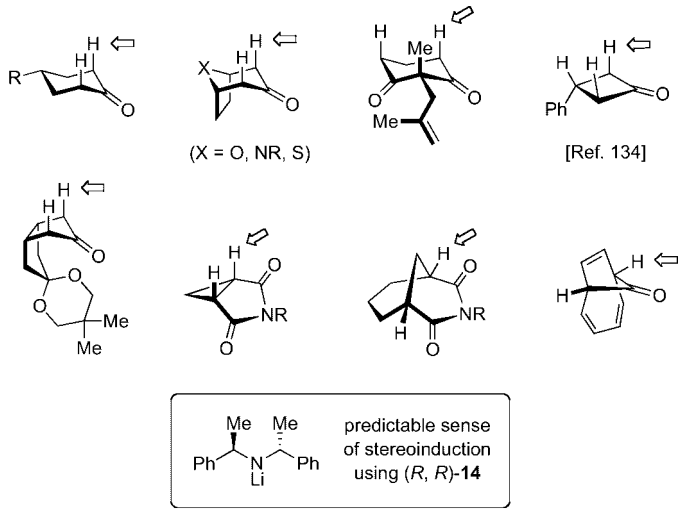


Figure 1.1.

temperatures) would be well worth developing. In spite of this shortcoming, the asymmetric enolisation process is obviously very useful, as shown by the numerous applications illustrated in Section IV.B, and ingenious developments involving intramolecular alkylation, transannular aldol, and cascade reactions, are worthy of note.

In principal, the chiral base approach should be applicable to many alternative, symmetrical carbonyl, or polycarbonyl systems, but only a limited number of examples have emerged to date. Cyclic imides are one such category of substrates, which have performed well with chiral lithium amides, and which provide products suitable for further transformation towards alkaloid targets.

Despite one apparent anomaly, mentioned in Scheme 1.47, the chiral lithium amides show remarkable consistency in the sense of asymmetric induction across a wide range of substrates. For example, the most widely used base **14**, delivers synthetically useful levels of selectivity with numerous ketones, as well as imides, and even bridgehead substrates, and, despite the varied stereoelectronics involved (not to mention possible interference from additional functional groups present in many cases), the sense of induction is predictable, Figure 1.1.

The use of bis-lithium amides for deprotonations is a relatively new development, and the chemistry of these systems is even less well understood than that of simpler lithium amides. The improved reactivity and selectivity seen with base **19**, compared to base **14**, in a number of cases (sometimes involving only the mono-lithiated base) requires further study. Again however, the enolisation reactions seem to follow a trend, enabling the sense of stereoinduction to be predicted, Figure 1.2.

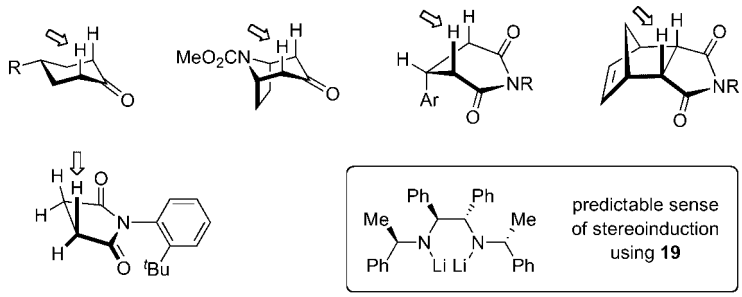


Figure 1.2.

Although the majority of asymmetric enolisations involve prochiral substrates, applications to kinetic resolution have also appeared, although not in large numbers. This approach should be useful where no easy route to a chiral product presents itself, but the racemic counterpart is readily available via a key enolisation step.

As well as enolisations, it is clear that the synthesis community has embraced the use of chiral lithium amides for a wide range of other types of metallation, particularly the enantioselective functionalisation of tricarbonyl(η^6-arene)chromium complexes. Applications involving a potpourri of other functional groups, particularly phosphorous and sulfur containing systems have also been explored.

We anticipate further developments in the future, both in the design of new reagents and catalysts, the detailed understanding of the asymmetric proton transfer steps, and applications to target synthesis.

ACKNOWLEDGEMENT

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Chapter 2

Self-Regeneration of Stereocenters (SRS) via Stereolabile Axially Chiral Intermediates

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I. INTRODUCTION

In a seminal paper in 1991, Professor Fuji posed a question: in the absence of any external chiral controller, can stereoselective α-alkylation of an enantiopure carbonyl compound such as **A** be achieved?[1] Reactions that proceed through the corresponding enolate **B** would appear doomed to give racemic product **C**, because the sole stereogenic center of **A** should be destroyed in the deprotonation step (Scheme 2.1). In fact, some eleven years earlier (1980) Braña and coworkers reported that (*S*)-**1a** could be stereospecifically transformed to (*S*)-**1b** by a deprotonation/methylation sequence.[2] The authors' subsequent retraction of this claim (**1b** was found to be racemic!)[3] only highlights the challenge inherent in non-racemizing α-alkylation of compounds like **A**. In 1981, just one year after Braña's initial claim, Wasmuth

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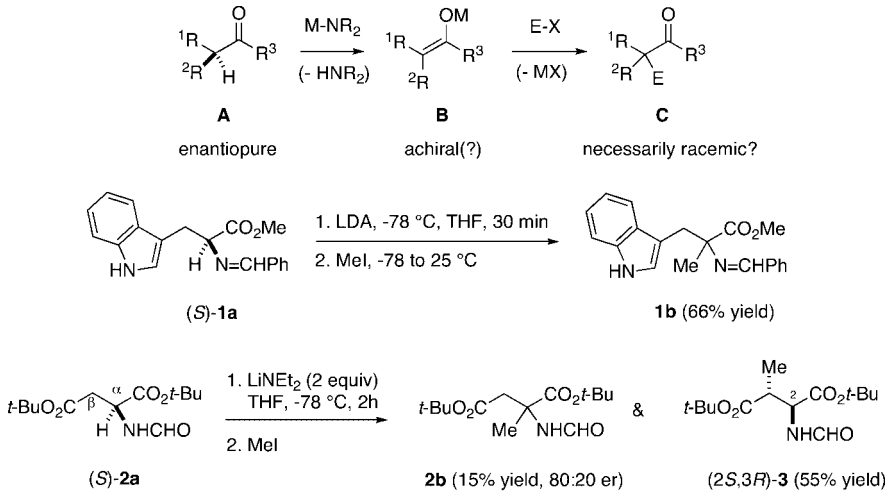
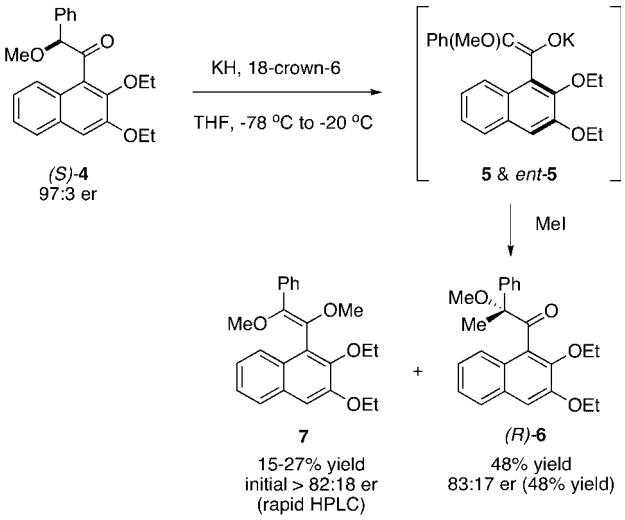


Scheme 2.1.

and Seebach reported the non-racemizing α-alkylation of a different amino acid derivative (*S*)-**2a**.[4] Although the desired product, **2b**, was obtained in only 15% yield, chiral shift reagent ^{1}H NMR spectroscopic studies indicated significant enantiomeric enrichment (80:20 er). Note that the major product (2*S*,3*R*)-**3** results from β-deprotonation, wherein the stereogenic center at C_α remains intact. The authors proposed two possible limiting explanations for formation of **2b** in enantiomerically enriched form. First, the enolate derived from α-deprotonation of (*S*)-**2a** could be axially chiral by virtue of the orientation of the C_α–N bond. Second, enantiomerically enriched **2b** could arise from methylation of a mixed aggregate comprised of the *chiral enantiopure* enolate resulting from β-deprotonation of (*S*)-**2a**, and the achiral enolate resulting from α-deprotonation of **2a**. Although in a subsequent publication the authors favor the mixed aggregate explanation,[5] it is important to note that the concept of an axially chiral enolate goes back to at least 1981.

With this background in place, the importance of Fuji's pioneering 1991 work can be better appreciated. He was the first to unequivocally achieve non-racemizing α-alkylation of an enantiopure compound *through the intermediacy of an axially chiral enolate* (Scheme 2.2). Deprotonation of (*S*)-**4** at –78 to –20 °C, followed by treatment with methyl iodide afforded (*R*)-**6** in 48% yield and 83:17 er.[1] Strong evidence for the axial chirality of the proposed potassium enolate intermediate **5** was obtained by the isolation of enol ether **7** as a minor by-product. Direct HPLC analysis (chiral stationary phase) following a short workup indicated **7** possessed an er exceeding 82:18. Subsequent studies determined that **7** racemized at 21 °C with a half-life of 53 minutes.[6] Thus it appeared that the stereochemical information encoded in the nearly pure (*S*)-configuration of the starting ma-

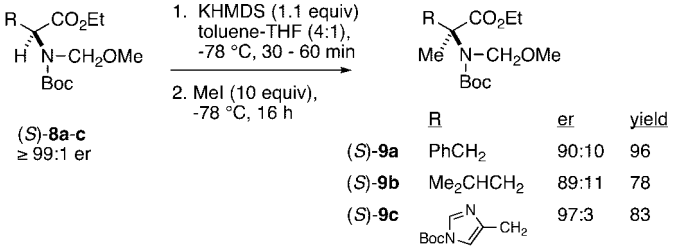


Scheme 2.2.

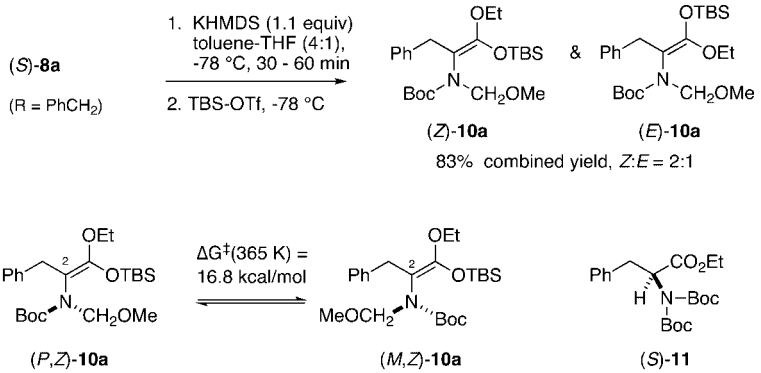
terial (**4**) was largely captured in the conformation of a non-racemic axially chiral reactive intermediate **5**. Stereoselective trapping of this intermediate lead to the enantiomerically-enriched, centrally chiral product (*R*)-**6**.

Fuji and co-workers soon developed an even more successful embodiment of this principle in alkylations of *N*-Boc-*N*-MOM-protected α-amino acid esters (Scheme 2.3).[7,8] Deprotonation of (*S*)-**8a–c** with KHMDS at –78 °C, followed by the addition of methyl iodide, gave the desired α-methylated α-amino acid esters (*S*)-**9a–c** in good yields and in good enantiomeric ratios (89:11 to 97:3).

Kawabata reported four other examples that gave similar enantiomeric ratios and yields; we have reviewed this work in detail previously.[9] Trapping of the potassium enolate of phenylalanine-derived (*S*)-**8a** with *tert*-butyldimethylsilyl triflate gave the corresponding silyl enol ether **10a** as an *E*/*Z* mixture (Scheme 2.4). ^{1}H NMR spectroscopic analysis of **10a** indicated diastereotopic methylene protons in the MOM groups of both (*Z*)- and (*E*)-**10a**, demonstrating that the enol ethers were *chiral*. Thus the C2–N bond in **10a**



Scheme 2.3.

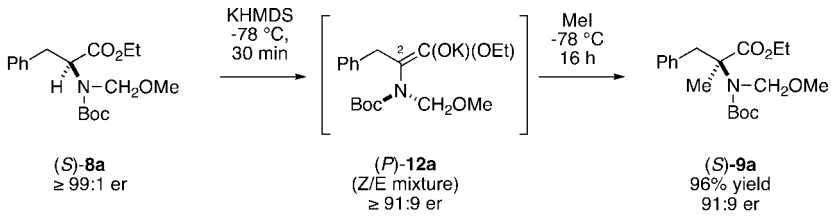


Scheme 2.4.

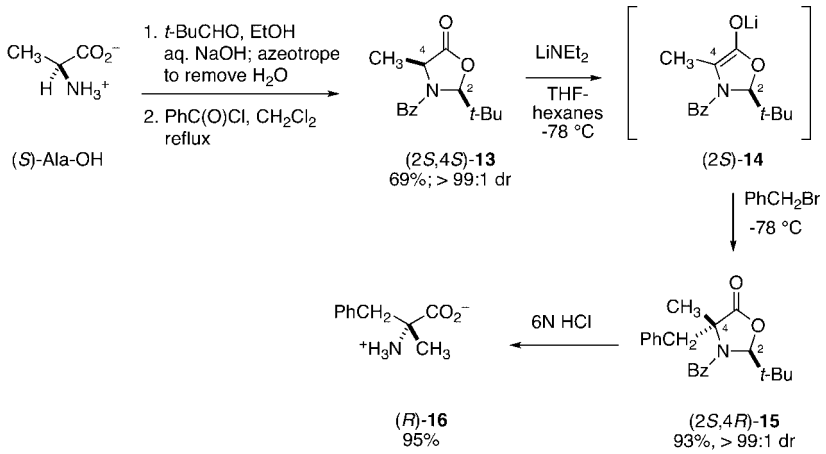
must be twisted in such a way to place the amino protecting groups above and below the plane of the alkene. Enantiomeric conformations of (*Z*)-**10a** can be described using the (*P*)- and (*M*)-helical descriptors;[10] dynamic ^{1}H NMR spectroscopic studies of (*Z*)-**10a** indicated an enantiomerization barrier of 16.8 kcal/mol (365 K).[11]

Note that enol ether (*Z*)-**10a** (and its corresponding potassium enolate) are chiral simply by virtue of two different protecting groups on nitrogen. If two identical protecting groups were employed, the derived enolate would be achiral and would thus give racemic alkylation product. To confirm that axially chiral enolate intermediates were indeed responsible for successful stereochemical information transfer from (*S*)-**8a**–**c**, *N*,*N*-di-Boc analogue (*S*)-**11** was applied in the protocol described in Scheme 2.3. As predicted, the methylated product was obtained in racemic form.[11]

From these and other observations, Fuji and Kawabata proposed a detailed mechanism for the retentive deprotonation/methylation of (*S*)-**8a**–**c**.[12] Below we present a highly simplified schematic (Scheme 2.5). Deprotonation of (*S*)-**8a** at –78 °C is proposed to give axially-chiral potassium enolate **12a** with a preponderance of the (*P*)-enantiomer. Approach of the electrophile is expected to be sterically controlled; since the MOM group is smaller than the Boc group, methylation of (*P*)-**12a** gives (*S*)-**9a**. The overall process is retentive.



Scheme 2.5.



Scheme 2.6.

With a plausible mechanism in hand we now turn to a very practical question. *How can we best describe the process of stereochemical information transfer in these and related reactions?* Fuji suggested the term "memory of chirality" since in his words "the central chirality at a carbon alpha to a carbonyl group is preserved as transient axial chirality of the intermediate enolate and is then regenerated as central chirality in the reaction product (memory of chirality)." In the context of Scheme 2.5, "memory" of the (*S*)-configuration of the starting material is retained in the (*P*)-conformation of potassium enolate **12a**. Fuji's term "memory of chirality" is vivid and concise, and to date has been adopted by many researchers, ourselves included. However, the term is imprecise, and tends to evoke misunderstanding. As we have pointed out, it is not the *chirality* of the starting material that is memorized in the intermediate, but rather the *sense* of chirality or *configuration*.[13]

But is there a better term than "memory of configuration?" Recently Wolf has described Fuji's reactions as examples of "self-regeneration of chiral elements with stereolabile intermediates."[14] We believe this description is considerably more precise than the original phrase "memory of chirality." Furthermore, Wolf's term makes a strong conceptual link to the seminal "self-regeneration of stereocenters (SRS)" work of Seebach.[5, 15] In SRS an enantiopure starting material such as (*S*)-alanine is reacted with an achiral molecule (pivalaldehyde) so as to generate a diastereomerically pure oxazolidinone (2*S*,4*S*)-**13**, that contains an additional stereogenic center (Scheme 2.6).[16] This second stereogenic center (C2) is considered "temporary", because it is removed once it has served its purpose. Its configuration is directed by that of the sole stereogenic center of the starting material (subsequently C4 in the oxazolidinone **13**). Whereas the original stereogenic center (C4) is destroyed by deprotonation to enolate **14**, the "temporary"

stereogenic center (C2) directs the trajectory of enolate alkylation, giving (2*S*,4*R*)-**15** in high yield. The temporary stereogenic center is finally removed by hydrolysis to (*R*)-**16**.[16]

There is a clear parallel between the "temporary" stereogenic center in SRS with the chiral axis in Fuji's work. In each case the sole stereocenter in an enantiopure starting material directs the installation of a new "temporary" chiral controller (C2 in **13** or the C2–N axis of **12a**), prior to (or concurrent with) trigonalization of the original stereocenter. Then, under the direction of the "temporary" chiral controller, the original stereocenter is regenerated, with a new ligand attached to it. Of course, there are critical differences between SRS as originally conceived and "memory of chirality." First, as we have pointed out,[9] the chiral controller in reactions involving stereolabile axially chiral intermediates is truly "temporary." Axially chiral intermediates **5** and **12a** will racemize on the alkylation timescale if the reaction temperature is too high, whereas centrally chiral (2*S*)-**14** faces no such danger. Second, whereas the configuration of the chiral control element is assured in SRS, generation of a homochiral, axially chiral control element is far from straightforward. Thus to describe the reactions covered in this review we propose to modify Wolf's description only slightly to "SRS via stereolabile axially chiral intermediates." We believe this term pays appropriate homage to the important and unique contributions of both Seebach and Fuji. The "SRS" (i.e. self-regeneration) portion of this description also clearly differentiates it against other asymmetric reactions involving stereolabile intermediates, such as electrophilic substitution of *C*-chiral organometallics (see the chapter by Gawley in this volume).[17,18] The "stereolabile axially chiral intermediate" portion of the description clearly differentiates these reactions from SRS reactions believed to depend on mixed aggregates for asymmetric induction.[4,19] Finally, as several reviews of the field have been published, it is appropriate that we discuss our coverage. Following their "Concepts" article in 1998,[6] Fuji and Kawabata reviewed the literature to 2000 in an earlier volume of this series.[12] Subsequently Kramer and Griesbeck reviewed work through 2002,[20] and Wolf reviewed work through 2005.[14] Since our previous review covered the field to 2004,[9] in this chapter we will focus on reports published from 2005 through 2008. Our goal in each case is to illustrate the factors contributing to stereochemical control. Wherever possible we rely upon the author's own explanations, but in several cases we, for clarity, provide additional commentary and stereochemical nomenclature. Finally, it is well known that metal enolates exist as aggregates, and thus a complete explanation of enolate reaction stereoselectivity would acknowledge the possible differential reactivity of higher and lower aggregation states.[21] However, in the absence of detailed structural and kinetic data implicating reaction via a specific aggregation state, we have chosen to explain reaction stereoselectivity in terms of monomers or the corresponding free anions.

II. KINETIC REQUIREMENTS FOR SRS VIA STEREOLABILE AXIALLY CHIRAL INTERMEDIATES

As alluded to above, SRS via stereolabile axially chiral intermediates can be difficult to achieve. As we described in our 2005 review,[9] at least three requirements must be met. In the context of a deprotonation/electrophilic trapping sequence, deprotonation of the stereogenic center in the enantiopure starting material (*S*)-**A**-H must generate an axially chiral reactive intermediate (*M*)-**A**$^-$ with high enantioselectivity (Figure 2.1). Here the choice of (*M*)-helicity is purely arbitrary; the point is that the two deprotonation rate constants k_1 and $k_{1'}$, must differ greatly ($k_1 >> k_{1'}$), or the axially chiral intermediate will not have a high er. This scheme also suggests that variation of reaction conditions might allow selective generation of either antipodal intermediate (i.e. (*M*)- or (*P*)-**A**$^-$), at will, from a single enantiomer of the starting material. Below we will describe successful demonstrations of this principle. Secondly, (*M*)-**A**$^-$ must not readily enantiomerize, at least not on the time scale of the desired subsequent reaction. The chapter by Hoffmann in this volume discusses a method for evaluating the relative rates of racemization and bimolecular electrophilic quenching reactions. Assuming pseudo-first order trapping, and first order enantiomerization, high asymmetric induction requires $k_{MP} << k_2$[E-X]. As will be seen in several examples below, high [E-X] and modulation of k_2 by variation of the leaving group X can be critical to achieving high enantioselectivity. Thirdly, the axially chiral intermediate must react with the electrophile in high enantioselectivity to produce (*S*)-**A**-E ($k_2 >> k_{2'}$). Again, the choice of (*S*)-configuration is arbitrary: the point here is that formation of a slowly racemizing, enantiopure intermediate is not sufficient to guarantee success in SRS via stereolabile axially chiral intermediates. Stereoselectivity in the trapping reaction is essential. Finally, we would note that Figure 2.1 is most relevant to intermolecular reactions. As will be seen below, in enolate cyclization reactions deprotonation is often the enantiodetermining step; geometric constraints then dictate how the (*M*)- or (*P*)-configuration of the axially chiral intermediate stereoselectively determines the (*R*)- or (*S*)-configuration of the product.

Before proceeding much further some discussion of the often confused terms "enantiomerization" and "racemization" is merited. Enantiomeriza-

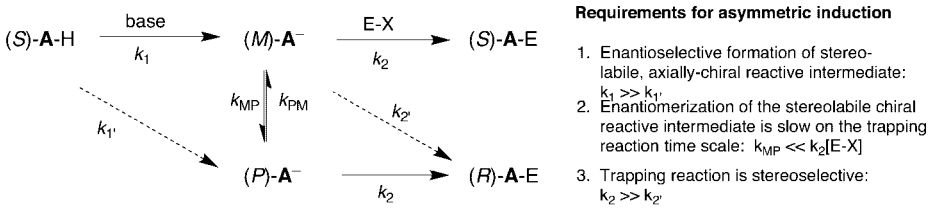


Figure 2.1.

tion is the conversion of one enantiomer into another, e.g. (*M*)-**A**$^-$ to (*P*)-**A**$^-$, and occurs with the rate constant k_{MP}. (Figure 2.1). In an achiral or racemic medium, $k_{MP} = k_{PM}$, and in transition state theory this rate derives from the activation free energy for enantiomerization $\Delta G^{\ddagger}$. On the other hand, racemization is the conversion of an enantiopure, or enantiomerically enriched compound to the racemate (50:50 er). For a reversible first order racemization, $k_{rac} = k_{MP} + k_{PM} = 2 \cdot k_{MP}$,[22] and the expression for k_{MP} derives from the Eyring equation:[23]

$$k_{rac} = k_{mp} + k_{pm} = 2\left(\frac{\kappa k T}{h}\right) e^{\left(\frac{-\Delta G^{\ddagger}}{RT}\right)} \qquad (1)$$

where κ is the transmission coefficient (taken as unity), k is Boltzmann's constant, h is Planck's constant, R is the gas constant, T is the absolute temperature, and $\Delta G^{\ddagger}$ is the activation free energy for enantiomerization. The half-life for racemization $t_{1/2}$(rac) then follows:

$$t_{1/2}(\text{rac}) = (\ln 2)/k_{rac} \qquad (2)$$

As we have pointed out previously,[9] for a given enantiomerization barrier $\Delta G^{\ddagger}$, $t_{1/2}$(rac) can vary rather dramatically with temperature (Table 2.1). As shown in Table 2.1, at the common cryogenic temperature of –78 °C, racemization half-lives vary dramatically as the enantiomerization barrier is increased from 10 to 20 kcal/mol. At –78 °C, a reactive intermediate with an enantiomerization barrier of 16 kcal/mol could undergo slow intermolecular reaction without significant racemization. However, at room temperature, the same intermediate would racemize two million times faster, and intramolecular reaction or solvent trapping would appear to provide the only way to

Table 2.1
Racemization half-lives as a function of enantiomerization barrier and temperature.

Enantiomerization barrier $\Delta G^{\ddagger}$ (kcal/mol)	$t_{1/2}$(rac) at –100 °C	$t_{1/2}$(rac) at –78 °C	$t_{1/2}$(rac) at 0 °C	$t_{1/2}$(rac) at 25 °C
10	0.41 s	1.4×10^{-2} s	6.2×10^{-6} s	1.2×10^{-6} s
12	2.3 min	2.4 s	2.5×10^{-4} s	3.5×10^{-5} s
14	13 h	7 min	9.8×10^{-3} s	1.0×10^{-3} s
16	180 d	20 h	0.39 s	3.0×10^{-2} s
18	> 100 y	148 d	16 s	0.9 s
20	> 100 y	70 y	10 min	26 s
22	> 100 y	> 100 y	6.9 h	13 min
24	> 100 y	> 100 y	12 d	6.2 h
26	> 100 y	> 100 y	1.3 y	7.6 d

achieve enantioselective reaction. Thus low temperatures are often essential to achieve SRS via stereolabile axially chiral intermediates. Further inspection of Table 2.1 reveals that if the enantiomerization barrier is lowered to 12 kcal/mol, intermolecular quenching at –78 °C will likely be unsuccessful. However, in such cases, lowering the reaction temperature to –100 °C may allow enantioselective trapping if the intermediate is generated in the presence of the electrophile.

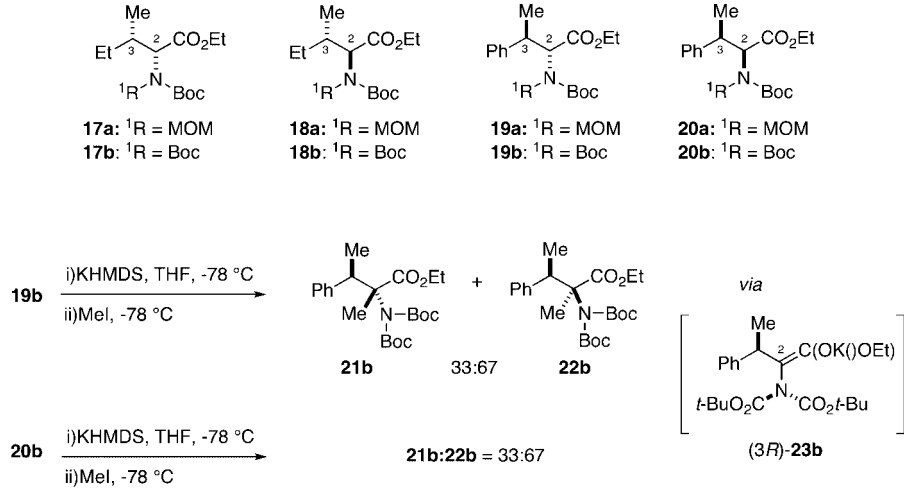
From a design standpoint, therefore, SRS via stereolabile axially chiral intermediates often relies upon hindered rotation around sp^2-sp^2 bonds, since barriers in excess of 16 kcal/mol are easily achieved.[24] All of the reactions described in this chapter, and most of those covered in our previous review[9] fall in this category. In contrast, it is difficult to achieve SRS via stereolabile axially chiral intermediates based on hindered rotation around sp^3-sp^3 or sp^3-sp^2 bonds, since such bonds typically have barriers to rotation of less than 7 kcal/mol.[25] In cases where success has been realized, solvent quench[26] or intramolecular reaction[27, 28] provides the necessary fast trapping of the stereolabile axially chiral intermediate.

III. SRS VIA STEREOLABILE AXIALLY CHIRAL ENOLATES

A. α-Amino Acid Ester-Derived Enolates

In Section I, we described Fuji & Kawabata's pioneering work in SRS via stereolabile axially chiral enolates derived from α-amino acid esters.[1, 6, 7, 11] The key insight for success in this area was the use of two different protecting groups on the α-amino nitrogen atom, which renders the C2–N axis in (*P*)-**12a** stereogenic (Scheme 2.5). Following their landmark enolate alkylation paper in 2000, they published several papers on intermolecular[8, 29, 30] and intramolecular (i.e. cyclizing)[31] alkylation reactions of stereolabile axially chiral α-amino acid ester-derived enolates; we have previously reviewed these reports.[9] In 2005, Kawabata & Fuji published an extension of their previous examination of the effect of additional stereogenic centers on SRS via stereolabile axially chiral enolates.[32]

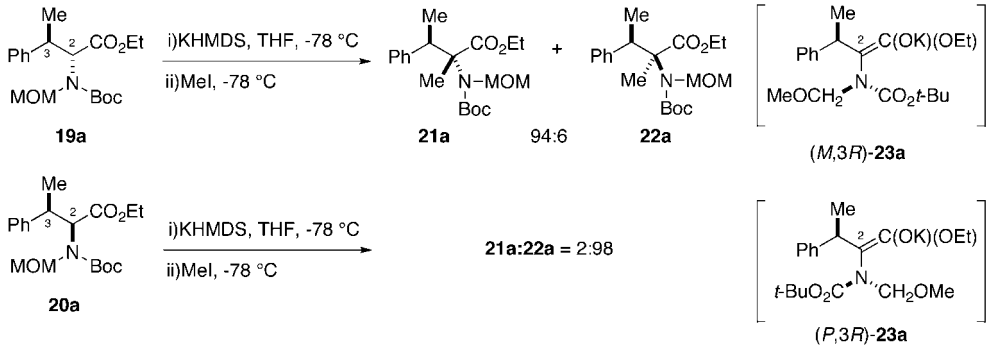
Earlier work demonstrated that deprotonation/methylation reactions of L-isoleucine derivative **17a** and D-*allo*-isoleucine derivative **18a** at –78 °C (Scheme 2.7) proceeded with a very high degree of retention at C2 (93:7 and 94:6 dr, respectively).[8] The authors thus concluded that the stereogenic center at C3 had very little influence on the alkylation trajectory. It is clear however, that the two substituents at C3 in **17** and **18** (ethyl and methyl) are sterically and electronically similar. It could well be argued that the configuration at C3 would be more influential if the two C3 substituents were better differentiated. Thus β-methyl phenylalanine derivatives **19** and **20** were examined. To isolate the effect of the C3 stereogenic center on alkylation dia-



Scheme 2.7.

stereoselectivity, the di-*N*-Boc derivatives **19b** and **20b** were subjected to the deprotonation/methylation protocol. The ratio of diastereomers (**21b**:**22b**) was identical for both substrates, suggesting a common enolate intermediate, (3*R*)-**23b**. The degree of diastereoselectivity was low (33:67), but greater than had been previously observed for **17b** and **18b** (54:46). Thus greater differentiation of the C3 substituents did in fact lead to increased stereoselectivity. *N*-Boc,*N*-MOM analogues **19a** and **20a** were then examined to see if the C2–N axis still dominated stereocontrol (Scheme 2.8).

Subjection of **19a** to the deprotonation/methylation protocol gave diastereomeric products **21a** and **22a** in a 94:6 ratio; in contrast **20a** gave **21a** and **22a** in a 2:98 ratio. Thus **19a** and **20a** must give rise to different reactive intermediates; the highly retentive outcomes can be rationalized as proceeding from diastereomeric enolates (*M*,3*R*)- and (*P*,3*R*)-**23a**. The authors noted



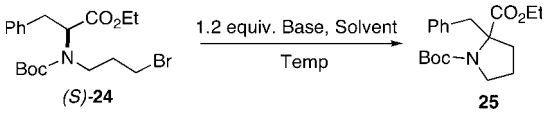
Scheme 2.8.

that the non-identical diastereoselectivities exhibited by **19a** and **20a** suggest "mismatched" and "matched" cases respectively. Nevertheless, the chiral C2–N axis is more influential than the C3-stereogenic center in directing methylation. Interestingly, even in the mismatched case (**19a**) diastereoselectivities are higher than observed for the simple phenylalanine derivative (*S*)-**8a** (Scheme 2.5). One way to rationalize this unexpected outcome is that the diastereoselectivity in deprotonation of **19a** is greater than enantioselectivity realized in deprotonation of **8a**, a conclusion that highlights the importance of generating stereolabile axially chiral intermediates in high enantiopurity (cf. Figure 2.1 and accompanying discussion).

The competing deprotonation pathways depicted in Figure 2.1 raise a question: could simple variation of experimental conditions allow one to generate antipodal enantioenriched stereolabile axially chiral intermediates from a single enantiopure starting material? Kawabata's recent results in asymmetric cyclization can be accounted for by such a mechanism. Deprotonation of (*S*)-**24** with KHMDS in DMF at –60 °C gives (*S*)-**25** in 99:1 er and 94% yield (Table 2.2, entry 1).[31] However, stunningly, use of LiTMP in THF at 20 °C gives the enantiomeric product (*R*)-**25** in 4:96 er and 93% yield (Table 2.2, entry 5).[33]

Thus (*S*)-**24** can undergo highly retentive or invertive cyclization, depending on whether deprotonation is carried out with KHMDS in DMF, or LiTMP in THF (Table 2.2, entries 1, 5). Invertive cyclization is also observed with LDA in THF (Table 2.2, entry 6). Interestingly, cyclization is retentive with LiHMDS in DMF, but slightly invertive with LiHMDS in THF (Table 2.2, entries 3,4). Similarly enantiodivergent cyclizations were seen in deprotonations of related substrates (Figure 2.2). Deprotonation of (*S*)-**26**–**28** gives the corresponding proline analogues: in each case KHMDS/DMF gives retention, and LiTMP/THF gives inversion. Homologues (*S*)-**29**–**30** exhibit enantiodivergent cyclization to

Table 2.2
Enantiodivergent cyclizations of phenylalanine derivative (*S*)-**24**.[33]



(*S*)-**24** **25**

Entry	Base	Solvent	Temp, Time (h)	Yield (%)	er (*S*:*R*)
1	KHMDS	DMF	–60 °C, 0.5	94	99:1
2	KHMDS	THF	–78 °C, 0.5	92	95:5
3	LiHMDS	DMF	–60 °C, 0.5	60	89:11
4	LiHMDS	THF	–60 °C, 1	10	43:57
5	LiTMP	THF	20 °C, 0.5	93	4:96
6	LDA	THF	20 °C, 0.5	69	9:91

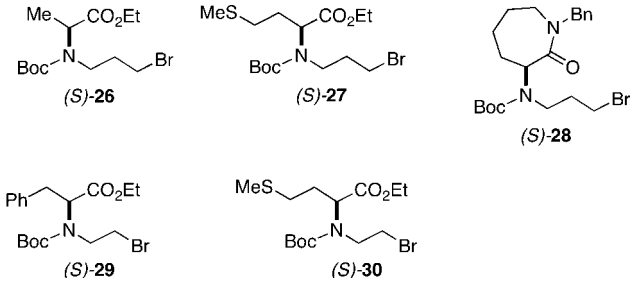
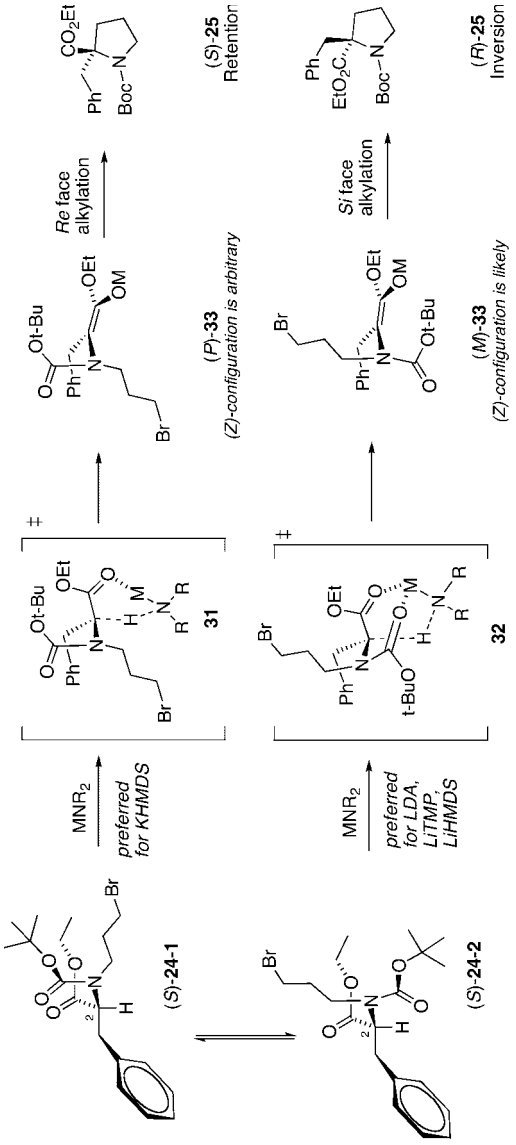


Figure 2.2.

the corresponding azetidines; some variation in optimum conditions is required, but K/NaHMDS gives retention, and LiTMP/LiHMDS gives inversion.

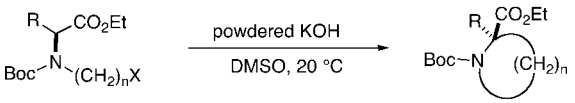
To rationalize these divergent outcomes, Kawabata proposed the following mechanism (Scheme 2.9). Conformational search on (*S*)-**24** identified (*S*)-**24-1** and (*S*)-**24-2** as the lowest energy conformers, which differ in the relative orientation of the C2 and N substituents. These two rotamers provide a reasonable foundation for competing deprotonation transition structures **31** and **32**. Deprotonation via transition structure **31** gives enolate (*P*)-**33**, which will cyclize to give the retentive product (*S*)-**25**, if cyclization is faster than C2–N bond rotation. In contrast, deprotonation transition structure **32** would give the antipodal enolate (*M*)-**33** and thus the invertive product (*R*)-**25**. Kawabata proposed that unfavorable steric interactions between the KHMDS and the Boc group in the deprotonation transition structures would render **31** lower in energy than **32**, causing (*S*)-**25** to predominate. However, in the case of the more tightly coordinating lithium, chelation to the Boc group in **32** could render it lower in energy than **31**, causing (*R*)-**25** to predominate. Whatever the case, it is important to realize that if C2–N bond rotation is slow relative to cyclization, *deprotonation is the enantiodetermining step of the overall reaction.* The orthogonality of the nitrogen substituents to the enolate plane, and the stereoelectronic constraint posed by the forming 5-membered ring, permit only *Re* face alkylation of (*P*)-**33**, producing (*S*)-**25**. Similarly, (*M*)-**33** can only undergo *Si* face alkylation, and thus can only give (*R*)-**25**.

Further process optimization of the retentive cyclizations was achieved through the use of powdered KOH as base in DMSO (Table 2.3).[34] As can be seen, enantiomeric ratios using this protocol are very high, and in several cases are higher than those obtained using KHMDS in DMF at –60 °C. Chemical yields are also excellent for the formation of 4-, 5-, and 6-membered rings. Solution (DMF) kinetic studies of racemization of the potassium enolate derived from (*S*)-**24** indicate an enantiomerization barrier of 15.5 kcal/mol at –78 °C. Fast intramolecular alkylation is thus key to high enantioselectivity in these cyclizations. The improved enantiomer ratios afforded by iodides


MNR2
preferred for KHMDS
MNR2
preferred for LDA, LiTMP, LiHMDS
(S)-24-1
(S)-24-2
31
32
Re face alkylation
Si face alkylation
(P)-33
(Z)-configuration is arbitrary
(M)-33
(Z)-configuration is likely
(S)-25
Retention
(R)-25
Inversion

Scheme 2.9.

Table 2.3
Asymmetric cyclization of α-amino acid derivatives with KOH/DMSO.[34]



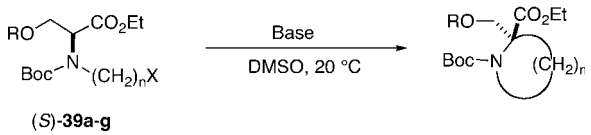
(*S*)-**29-38**

Entry	Substrate	n	R	X	Time (h)	Yield	er
1	(*S*)-**29**	2	$PhCH_2$	Br	2	82	>99:1 (*R*)
2	(*S*)-**31**	2	Me_2CH	Br	2	79	>99:1
3	(*S*)-**30**	2	$MeSCH_2CH_2$	Br	1	85	>99:1 (*S*)
4	(*S*)-**24**	3	$PhCH_2$	Br	2	91	>99:1 (*S*)
5	(*S*)-**32**	3	Me_2CH	Br	2	94	99:1
6	(*S*)-**27**	3	$MeSCH_2CH_2$	Br	2	91	99:1 (*S*)
7	(*S*)-**33**	4	$PhCH_2$	Br	12	73	95:5
8	(*S*)-**34**	4	Me_2CH	Br	17	74	97:3
9	(*S*)-**35**	4	$MeSCH_2CH_2$	Br	4	86	94:6
10	(*S*)-**36**	4	$PhCH_2$	I	2	97	99:1
11	(*S*)-**37**	4	Me_2CH	I	18	90	99:1
12	(*S*)-**38**	4	$MeSCH_2CH_2$	I	3	89	99:1

(*S*)-**36–38** relative to the corresponding bromides (*S*)-**33–35** (Table 2.3, cf. entries 10–12 and 7–9), can thus be understood to arise from an increase in the alkylation rate constant and a concomitant reduction in enolate racemization. Similar improvements in enantioselectivity arising from leaving group effects had been observed earlier by Carlier and co-workers in their studies of benzodiazepine enolate alkylations.[35, 36]

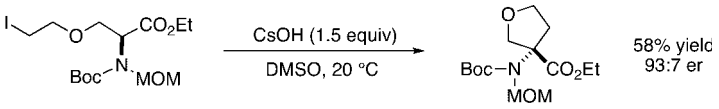
The high enantiomer ratio achieved in cyclizations of phenylalanine, valine, and methionine derivatives with KOH at ambient temperatures inspired Kawabata to apply these reaction conditions to the corresponding *O*-benzyl serine derivatives.[37] Deprotonation/alkylation of protected serine derivatives typically is plagued by β-elimination; however, application of the KOH protocol to serine derivative (*S*)-**39a** gave the intended cyclization product in 97% yield and 88:12 er (Table 2.4, entry 1). Use of RbOH or CsOH in place of KOH did not significantly affect er (Table 2.4, entries 1–3), but use of the corresponding iodide (*S*)-**39b** did provide improved er, presumably due to an increase in the alkylation rate constant and consequent reduced racemization of the stereolabile axially chiral enolate (Table 2.4, cf entries 3, 4). Using CsOH as base and iodide as the leaving group allowed high er to be achieved as the oxygen protecting group (R = Me, PMB, *t*-Bu) and tether length (n = 2–4) were varied (Table 2.4, entries 5–9). Finally, Kawabata and co-

Table 2.4
Asymmetric cyclization of β-alkoxy-α-amino esters.[37]



(*S*)-**39a-g**

Entry	Substrate	R	X	n	Base (equiv)	Time (min)	Yield	er
1	(*S*)-**39a**	Bn	Br	3	KOH (3.0)	60	97	88:12
2	(*S*)-**39a**	Bn	Br	3	RbOH (1.5)	20	93	85:15
3	(*S*)-**39a**	Bn	Br	3	CsOH (1.5)	20	91	89:11
4	(*S*)-**39b**	Bn	I	3	CsOH (1.5)	30	84	93:7
5	(*S*)-**39c**	Me	I	3	CsOH (1.5)	10	75	91:9
6	(*S*)-**39d**	PMB	I	3	CsOH (1.5)	30	88	96:4
7	(*S*)-**39e**	*t*-Bu	I	3	CsOH (1.5)	30	89	97:3
8	(*S*)-**39f**	*t*-Bu	I	2	CsOH (1.5)	20	74	96:4
9	(*S*)-**39g**	t-Bu	I	4	CsOH (1.5)	60	77	97:3



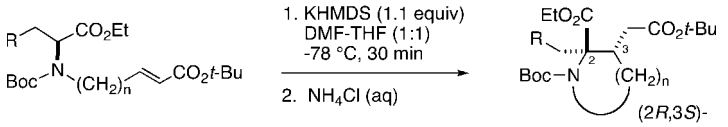
(*S*)-**40** (*S*)-**41**

Scheme 2.10.

workers applied their protocol to serine derivative (*S*)-**40** to provide a synthesis of novel THF amino acid (*S*)-**41** (Scheme 2.10).[37]

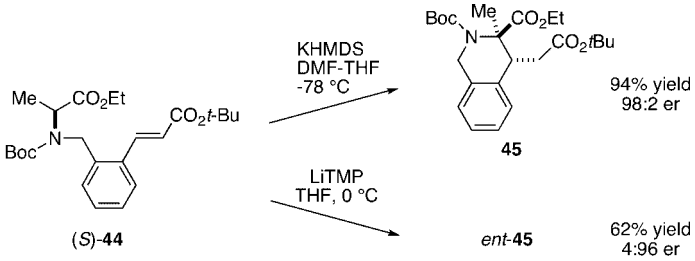
In addition to alkylation of stereolabile axially chiral α-amino acid ester enolates, Kawabata and co-workers have also reported intramolecular conjugate addition reactions of these species.[38] Amino acid ester derivatives (*S*)-**42a–d** bearing pendant Michael acceptors were deprotonated with KHMDS in THF-DMF at –78 °C. As can be seen, cyclization to give 5-membered, 6-membered, and 7-membered rings occurs in high enantioselectivity (Table 2.5). The highly functionalized cyclic products **43a–d** represent enantioenriched, constrained α-alkylated glutamic acid esters. All feature retentive substitution at the stereogenic carbon of the starting materials, but diastereoselectivity varies. In the case of (*S*)-**42d**, a 16% yield of the (2*R*,3*R*)-diastereomer is obtained (97:3 er), but for (*S*)-**42b–d** no trace of the (2*R*,3*R*)-diastereomers is seen. The authors give no explanation for the varying diastereoselectivity. Kawabata then applied this protocol to the synthesis of tetrahydroisoquinoline derivatives by deprotonation of (*S*)-**44** (Scheme 2.11).

Table 2.5
Intramolecular conjugate addition of enolates derived from (*S*)-**42a–d**.[38]



(*S*)-**42a-d** → **43a-d**

Substrate	n	R	% yield	er
(*S*)-**42a**	2	$PhCH_2$	65	94:6
(*S*)-**42b**	3	$PhCH_2$	66	99:1
(*S*)-**42c**	3	4-EtO-C_6H_4-CH_2	74	99:1
(*S*)-**42d**	4	$PhCH_2$	19	94:6

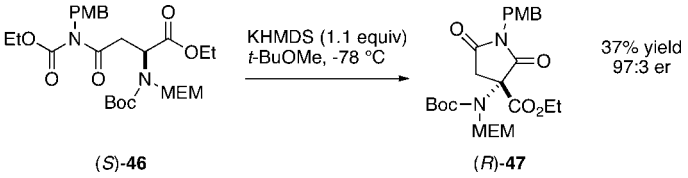


Scheme 2.11.

Either enantiomer of product **45** can be obtained in high enantioselectivity, depending on the base employed. As was seen in Table 2.5, use of KHMDS gives retentive conjugate addition, producing **45** (98:2 er). However, use of LiTHP gives *ent*-**45** (4:96 er), presumably due to the intermediacy of the antipodal enolate, as was proposed for deprotonative cyclizations of (*S*)-**24** (Table 2.2 and Scheme 2.9, above). In both cases only a single diastereomer was observed, consistent with the high diastereoselectivities seen in reactions of (*S*)-**42b–c**, which also form six-membered rings.

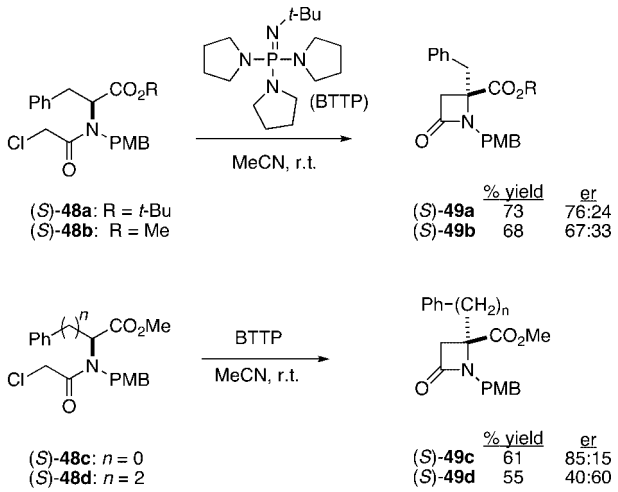
A logical extension of cyclization by intramolecular Michael addition would involve enolate acylation. Thus Kawabata and co-workers reported work towards asymmetric Dieckmann condensation based on α-amino acid ester derivative (*S*)-**46** (Scheme 2.12).[39] Although the yield was low, cyclization to (*R*)-**47** was highly retentive (97:3 er). Extensive variation of solvent, base, and protecting groups did not improve the yield or enantioselectivity.

In the period 2005–2008 a number of other workers published reactions of amino acid ester-derived enolates that embody the principle of "SRS via stereolabile axially chiral intermediates." González-Muñiz and co-workers continued their studies in β-lactam synthesis from *N*-chloroacetyl-α-amino



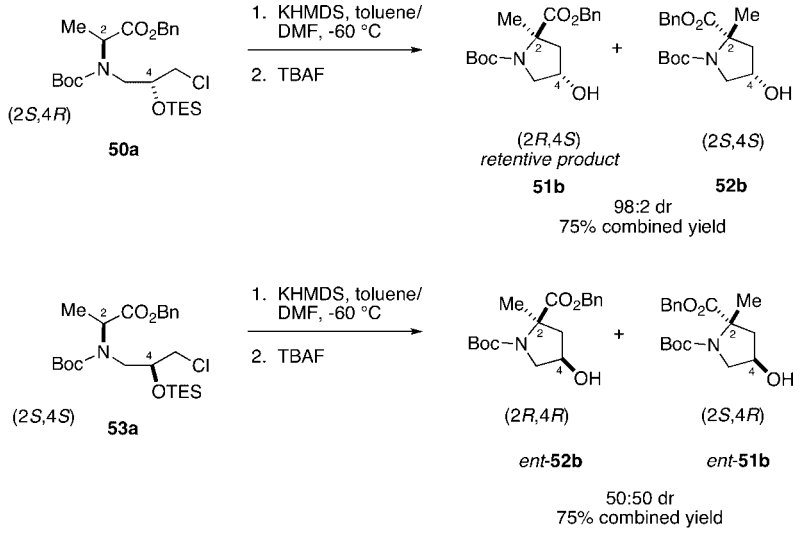
(*S*)-**46** (*R*)-**47**

Scheme 2.12.



Scheme 2.13.

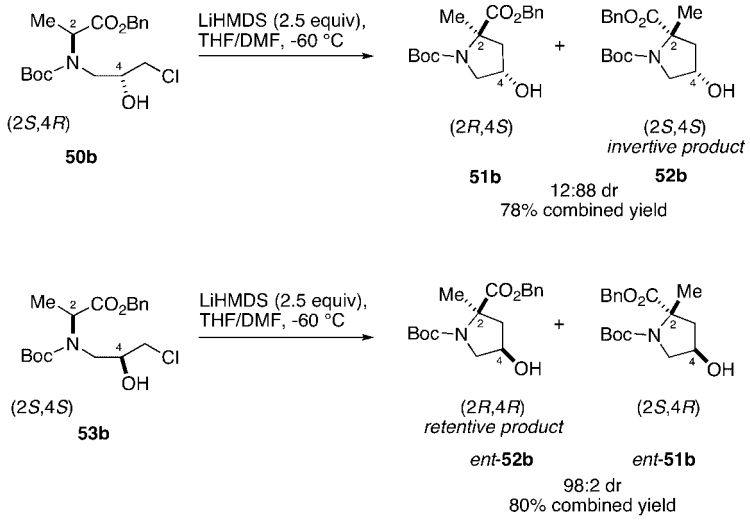
acid ester derivatives (Scheme 2.13).[40] Earlier work[41] had established that deprotonation of (*S*)-**48a**,**b** with the phosphazene base BTTP in acetonitrile afforded the corresponding β-lactams (*S*)-**49a–b** in moderate er. Although the *t*-butyl ester derivative (*S*)-**48a** gave higher enantioselectivity, they further explored homologues of methyl ester (*S*)-**48b**. Phenylglycine analogue **48c** gave higher er than that of phenylalanine derivative **48b** (85:15 vs 67:33 er), but the homophenylalanine analogue **48d** did not perform as well as **48b**. González-Muñiz and co-workers also investigated the effect of enantiopure additives (e.g. TADDOL) on the enantioselectivity of β-lactam synthesis, describing these compounds as "memory of chirality enhancers."[42] Using (–)-TADDOL, a small improvement in er is seen for *both* (*S*)- and (*R*)-**48b**, but it is not clear how the enantiopure additives exert their beneficial effect (data not shown). Referring to Figure 2.1, the enantiopure additive could alter the rates of deprotonation (k_1, $k_{1'}$), enantiomerization (k_{MP}, k_{PM}), or trapping (k_2, $k_{2'}$). However, we would note that the addition of an external chiral control element is antithetical to Fuji's original conception of "memory of chirality." Furthermore, the effect is not general, failing to improve enantioselectivity in reactions of (*S*)-**48c–d**.



Scheme 2.14.

In the vein of Kawabata's alkylation route to cyclic α-alkylated amino acids, Kolaczkowski and Barnes explored deprotonative cyclization routes to 4-hydroxy-α-methylprolines (Scheme 2.14).[43] Compounds **50a** and **53a** are obviously quite similar to the Kawabata alanine derivative (*S*)-**26** in Figure 2.2, and the authors expected retentive cyclization of both compounds to be uneventful. However, as will be seen below, the additional stereogenic center at C4 in **50a**,**b** and **53a**,**b** plays a decisive role in *some* cyclizations. Deprotonation of **50a** with KHMDS gives highly retentive cyclization, as indicated by the 98:2 ratio of **51b** and **52b**. However, application of the same protocol to the diastereomer **53a** gives an equal mixture of retention and inversion at C2. Thus SRS via stereolabile axially chiral intermediates is successfully realized in reaction of **50a**, but fails in the case of **53a**. Divergent behavior is also seen in reactions of the corresponding unprotected alcohols **50b** and **53b** (Scheme 2.15). For these substrates the use of KHMDS (excess) produced only the corresponding epoxides, which apparently did not cyclize. However, LiHMDS (2.5 equiv) successfully mediated cyclization to give the desired 4-hydroxy-α-methylproline products. Interestingly, alcohol **50b** gave predominant inversion (12:88 dr), but alcohol **53b** gave nearly exclusive retention (98:2 dr).

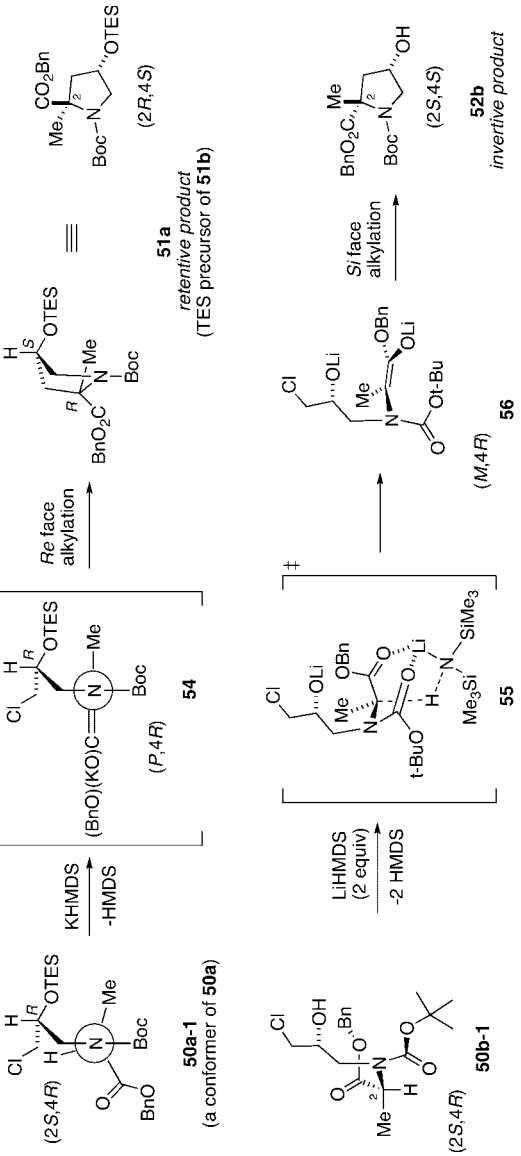
How can these diverse outcomes be rationalized? Following Kawabata's transition structure hypothesis (Scheme 2.9),[33] the authors proposed that the retentive deprotonative cyclization of **50a** with KHMDS can be rationalized by deprotonation from conformer **50a-1**, giving rise to axially-chiral enolate **54**; cyclization before C2–N bond rotation would lead to **51a**, the TES-protected version of observed major product **51b** (Scheme 2.16).



Scheme 2.15.

Note that (*P*,4*R*)-configured enolate **54** is completely analogous to enolate (*P*)-**33** in Scheme 2.9; both give the retentive product. The non-stereoselective reaction of diastereomer **53a** might be interpreted in several ways. The authors proposed that steric crowding in the alkylation step reduced diastereoselectivity, and this is possible. If cyclization was slowed to the point of competition with C2–N bond rotation, enolate epimerization could contribute to the observed 1:1 mixture of products. However, it is also possible that the 1:1 product ratio is due to poor diastereoselectivity in the deprotonation, giving both (*P*,4*S*)- and (*M*,4*S*)-configured enolates. As we have discussed previously (cf. Scheme 2.9), if C2–N bond rotation is slow compared to cyclization, deprotonation will be the enantiodetermining step.

Moving on to the free hydroxyl-bearing substrates, the predominantly invertive cyclization seen in LiHMDS deprotonation of **50b** was explained by the authors as stemming from alkoxide-directed deprotonation of the ester by LiHMDS. However we would note that Kawabata and co-workers attributed inversion in lithium amide-mediated invertive cyclization of (*S*)-**24**, **26**–**28** to Boc-directed deprotonation (cf. transition structure **32** in Scheme 2.9). Applying Kawabata's mechanism, the deprotonation of **50b** could proceed from conformation **50b-1**, to deprotonation transition structure **55**, to (*M*,4*R*)-configured enolate **56**; *Si* face alkylation would then give (2*S*,4*S*)-configured **52b** (Scheme 2.16). However, we would note that a similar mechanism cannot explain LiHMDS-mediated cyclization of diastereomer **53b**, which proceeds retentively. Furthermore, it is curious that in deprotonative cyclizations of both **50b** and **53b** the major product diastereomer features a



Scheme 2.16.

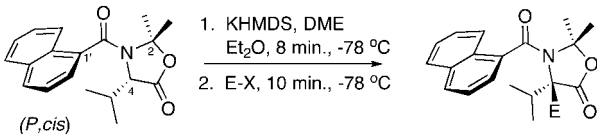
cis-relationship between the hydroxy and carbobenzyloxy groups. Thus it is possible that the hydroxyl group plays a dominant role in controlling diastereoselectivity in reactions of both **50b** and **53b**.

B. α-Amino Acid Oxazolidinone-Derived Enolates

In Section I we reviewed Seebach's development of "self-regeneration of stereocenters" (SRS) strategy, which is exemplified by deprotonation/alkylation of (2*S*,4*S*)-**13**, the *cis*-*N*-benzoyl pivalaldehyde oxazolidone of (*S*)-alanine (Scheme 2.6). In 2008, Alezra, Kouklovsky and co-workers reported synthesis of a valine-derived oxazolidinone (*S*)-**57** where the additional chiral control element is not present at C2 of the ring, but rather in the conformation of the 1-naphthoyl group (Table 2.6).[44]

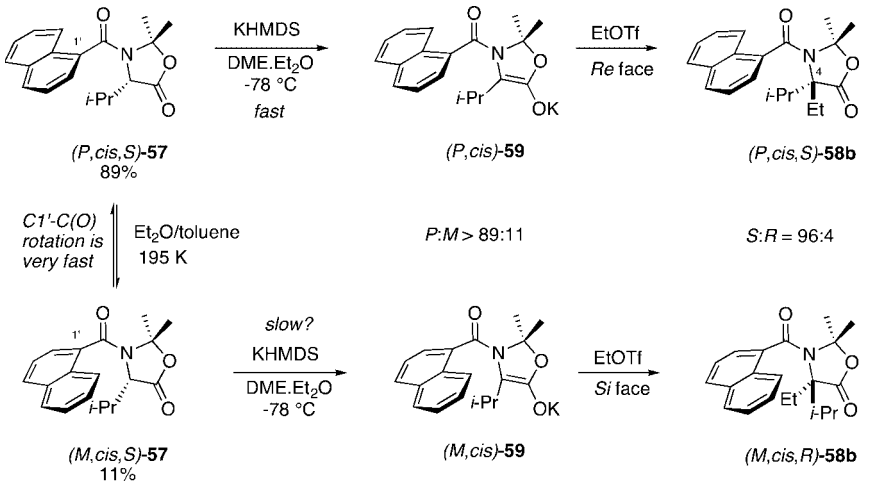
X-ray crystallography demonstrates that (*S*)-**57** adopts a (*P*,*cis*)-conformation: the 1-naphthyl group is oriented to give a (*P*)-conformation along the bond between C1′ and the amide carbonyl, and the amide carbonyl oxygen is *cis* to C2. Deprotonation of (*S*)-**57** with KHMDS in DME/Et_2O, followed by addition of a range of highly reactive electrophiles gave the desired products in good to excellent yields and 89:11 to 98:2 er. The high crystallin-

Table 2.6
Deprotonation-alkylation of valine-derived oxazolidinones.[44]



Entry	Electrophile (E-X)	E	Product	Yield (%)	er	Recrystallization Yield	er
1	MeI	Me	(*S*)-**58a**	74	89:11	N/A	N/A
2	MeOTf	Me	(*S*)-**58a**	78	91:9	60	97:3
3	EtOTf	Et	(*S*)-**58b**	59	96:4	80	>99:1
4	Allyl-I	Allyl	(*S*)-**58c**	88	94:6	67	>99:1
5	Bn-I	Bn	(*R*)-**58d**	72–98[a]	87:13–96:4[a]	85	>99:1
6	4-OMeBn-I	4-OMeBn	(*R*)-**58e**	98	93:7	83	99:1
7	Ethyl iodoacetate	CH_2CO_2Et	(*S*)-**58f**	80	98:2	89	>99:1
8	*t*-BuOD	D	(*S*)-**58g**	76	97:3	N/A	N/A

[a] The authors report that for unknown reasons, yields and er are highly variable in this case.



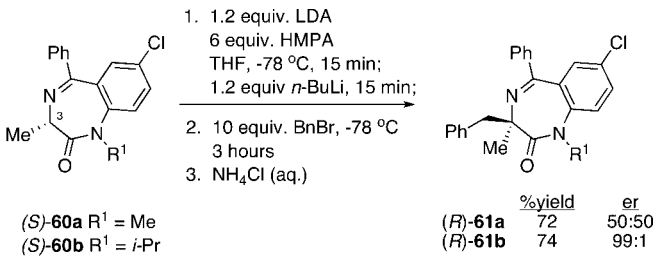
Scheme 2.17.

ity of the products made it possible in many cases to recrystallize to greater than 99:1 er.

To explain their results, the authors analyzed the conformations of (*S*)-**57** by ^{1}H NMR spectroscopy at –78 °C in Et_2O/toluene. These studies indicate that the population of *trans*-conformers is insignificant, and that the (*P*,*cis*)- and (*M*,*cis*)-conformers exist in a 89:11 ratio. As shown in Scheme 2.17, deprotonation of (*P*,*cis*,*S*)-**57** will give enolate (*P*,*cis*)-**59**. Alkylation of (*P*,*cis*)-**59** is sterically controlled by the bulky 1-naphthoyl group, favoring *Re* face attack and (4*S*)-configuration in the ethylated product **58b**. The minor (*M*,*cis*,*S*)-conformer of **57** present in solution would be expected to give the (*M*,*cis*)-configured enolate, and lead to the enantiomeric product. Since the observed er values of several products (cf. **58b**,**c**,**f**,**g**) significantly exceeds 89:11 er (before recrystallization), the authors proposed that dynamic kinetic resolution during deprotonation is responsible for preferential reaction via enolate (*P*,*cis*)-**59**.

C. α-Amino Acid-Derived 1,4-Benzodiazepine Enolates

1,4-Benzodiazepin-2-ones are among the most important scaffolds in medicinal chemistry, representing the prototypical "privileged structure."[45,46] However until 2003, 1,4-benzodiazepin-2-ones possessing a quaternary center at C3 received very little attention from synthetic or medicinal chemists, most likely due to the limited commercial availability of the most obvious starting materials (enantiopure quaternary amino acids). In 2003 Carlier and coworkers reported a deprotonation/alkylation route to such "quaternary"

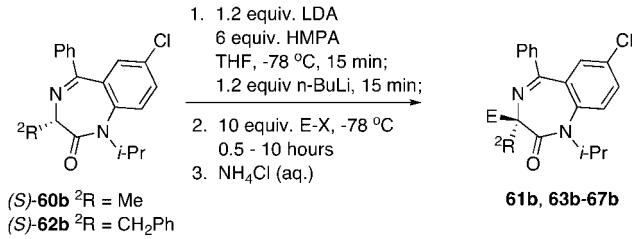


Scheme 2.18.

1,4-benzodiazepin-2-ones.[47] Whereas sequential deprotonation/benzylation of enantiopure alanine derivative (*S*)-**60a** gave racemic **61a**, application of the same protocol to the *N*-*i*-Pr analog (*S*)-**60b** gave the desired product **61b** in 99:1 er (Scheme 2.18).

The highly enantioselective deprotonation/alkylation of (*S*)-**60b** was attributed to the formation of an enantioenriched stereolabile axially chiral enolate, and stereoselective alkylation. The racemic outcome realized for (*S*)-**60a** was attributed to the smaller N1 substituent (Me vs *i*-Pr), and complete enolate racemization prior to alkylation; this hypothesis will be discussed futher below. High levels of enantioselectivity for alkylation of (*S*)-**60b** were also attained with other active electrophiles (Table 2.7).

Table 2.7
Enantioselective synthesis of quaternary 1,4-benzodiazepin-2-ones.[47]

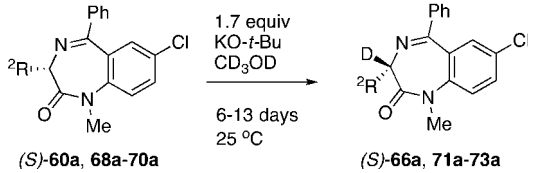


R^2	E-X	Product[a]	% yield	er
Me	BnBr	(+)-(*R*)-**61b**	74	99:1
Me	4-Me$C_6H_4CH_2$Br	(+)-(*R*)-**63b**	68	98:2
Me	2-Ph$C_6H_4CH_2$Br	(+)-**64b**	70	>99:1
Me	Allyl-Br	(+)-**65b**	76	97:3
Me	D-OTFA	(+)-(*S*)-**66b**	85[b]	>99:1
Bn	MeI	(–)-(*S*)-**61b**	64	98:2
Bn	Allyl-Br	(+)-**67b**	57	93:7

[a] Where noted, absolute configuration was determined by correlation (**61b**, **63b**), or HPLC (**66b**, see text).

[b] Extent of deuteration: 96%.

Table 2.8
Enantioselective H-D exchange of *N*-Me 1,4-benzodiazepin-2-ones.[35]



(S)-**60a**, **68a-70a** *(S)*-**66a**, **71a-73a**

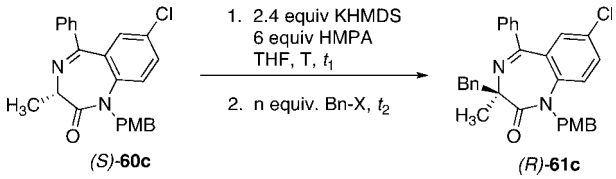
Substrate	R^2	Product	% D	er
(*S*)-**60a**	Me	(*S*)-**66a**	98	99:1
(*S*)-**68a**	Bn	(*S*)-**71a**	100	99:1
(*S*)-**69a**	CH_2CHMe_2	(*S*)-**72a**	99	98:2
(*S*)-**70a**	CH_2CH_2SMe	(*S*)-**73a**	94	99:1

Enantiomeric ratios meet or exceed 97:3, and are independent of the size of the electrophile. Methylation of the *N*-*i*-Pr phenylalanine analog (*S*)-**62b** is highly enantioselective (98:2 er), but lower selectivity is seen in allylation (93:7 er). Retentive stereochemistry was established by hydrolyzing quaternary 1,4-benzodiazepin-2-ones **61b** and **63b** to the known quaternary amino acids (8M HCl, 140 °C, 3 days, 50–62% yield), and by chiral stationary phase HPLC of deuteration product **66b**.

To test the proposal that *N*-methyl 1,4-benzodiazepin-2-one (*S*)-**60a** gave racemic **61a** due to enolate racemization prior to addition of the electrophile (cf. Scheme 2.18), four *N*-methyl-1,4-benzodiazepin-2-ones were dissolved in basic CD_3OD to effect H–D exchange (Table 2.8).[35] As can be seen in Table 2.8, highly retentive deuteration is seen in each case. To account for this success, Carlier and co-workers proposed that deprotonation leads to a stereolabile axially chiral enolate that is quickly quenched by the deuterated solvent before enolate enantiomerization could occur. These conditions differ considerably from the deprotonation/alkylation procedure of (*S*)-**60a** depicted in Scheme 2.18; which involve a 30 minute enolate preparation period at –78 °C prior to addition of the electrophile (Scheme 2.18).

To capitalize on these insights, and broaden the scope of quaternary 1,4-benzodiazepin-2-ones that could be prepared by this method, Carlier and coworkers subsequently explored deprotonation/benzylation reactions of *N*-PMB 1,4-benzodiazepin-2-one (*S*)-**60c** (Table 2.9).[35] Because of the low steric demand of the PMB group relative to isopropyl, Carlier and coworkers anticipated a low enantiomerization barrer of the enolate derived from (*S*)-**60c**. Thus optimization studies were initially conducted at –100 °C (Et_2O/CO_2 bath). Following a 5-minute deprotonation (KHMDS) period at –100 °C, addition of benzyl bromide produced nearly racemic **61c** (Table 2.9, entry 1). However, deprotonation in the presence of the electrophile ($t_1 = 0$) was found to give significantly increased enantiomeric ratio (88:12 er,

Table 2.9
Deprotonation/benzylation of *N*-PMB 1,4-Benzodiazepine-2-one at –100 to –109 °C.[35]



(S)-**60c** *(R)*-**61c**

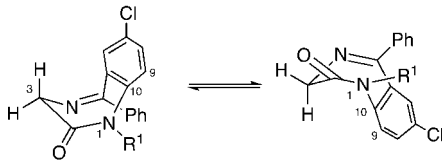
Entry	X	n	T (°C)	t_1[a]	t_2 (min)	yield (%)	er
1	Br	10	–100	5 min	120	100	58:42
2	Br	20	–100	0 min	5	78	88:12
3	Br	100	–100	0 min	1	46	90:10
4	I	20	–100	10 s	1	61	94:6
5	I	20	–109	20 min	60	93	99:1

[a] The designation $t_1 = 0$ signifies that the base was added to pre-combined mixture of (*S*)-**60c** and electrophile. All reactions run at [(*S*)-**60c**)]= 1.2 mM.

Table 2.9, entry 2). Thus near complete racemization of the stereolabile axially chiral enolate derived from **60c** occurs within 5 minutes at –100 °C. But at a substrate concentration of 1.2 mM, with 20 equivalents of an active electrophile present *during* deprotonation, retentive alkylation can be achieved in good enantiomeric ratio. To see if enantioselectivity could be further improved, the amount of benzyl bromide was raised to 100 equivalents, keeping the enolate concentration constant at 1.2 mM. As can be seen (Table 2.9, entry 3), er improved slightly to 90:10, but yield decreased, suggesting that benzylation of KHMDS competes with the intended deprotonation step. A more economical method to decrease the extent of enolate racemization involved use of benzyl iodide. The high reactivity of this electrophile toward KHMDS precluded an in situ protocol; however, use of a 10 s deprotonation prior to addition of benzyl iodide (20 equiv.) gave both improved er (94:6) and acceptable yield (61%, Table 2.9, entry 4). Thus as discussed several times in this review, competition between enolate alkylation and enantiomerization (cf. Figure 2.1) can be favorably biased by changing either the concentration or the reactivity of the electrophile.

Since the enantioselectivity achieved in reactions of (*S*)-**60c** at –100 °C was still lower than that seen in reactions of the *N*-isopropyl analogue **60b** at –78 °C, the effect of further lowering the reaction temperature was assessed. As hoped, performing the reaction at –109 °C (THF/N_2 slush) was possible and offered superior results, allowing a 20 minute deprotonation period to be employed. In this way the enantioselectivity and yield of (*R*)-**61c** were both improved (99:1 er and 93% yield, respectively). The improvement in enantioselectivity effected by a 9 °C decrease in temperature (cf. entries 1, 5

Table 2.10
Activation free energies for enantiomerization of **74a–e**.[47, 48, 50, 51]



(*M*)-**74a-e** (*P*)-**74a-e**

	R^1	$\Delta G^{\ddagger}$ (kcal/mol)[a]	T (solvent)
74a	H	12.3[48]	253 K (d_5-pyridine)
74b	Me	18.0 ± 0.3[51]	391 K (d_6-DMSO)
74c	Bn	19.5 ± 0.2[51]	416, 412 K (d_6-DMSO)
74d	*i*-Pr	21.3 ± 0.2[51]	437 K (d_6-DMSO)
74e	*t*-Bu	>24[50]	>473 K (tetramethylsulfolane)

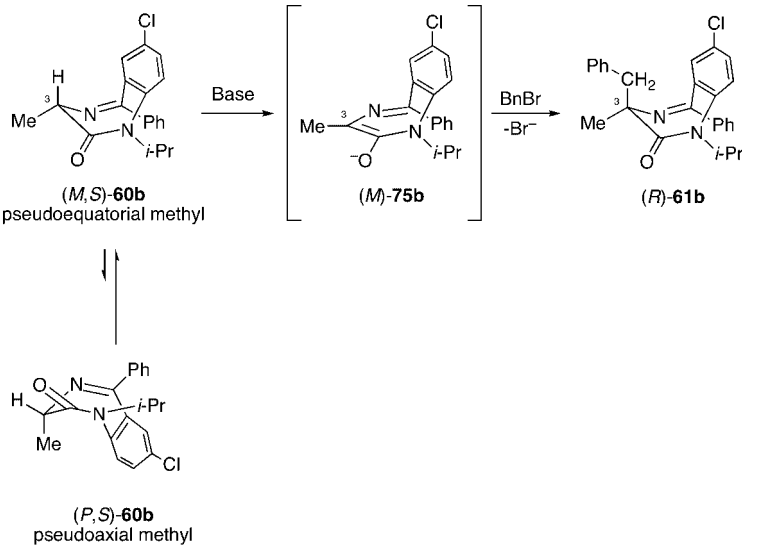
[a] Enantiomerization barriers $\Delta G^{\ddagger}$ determined by ^{1}H NMR spectroscopy.

in Table 2.9) was larger than expected, and proved successful for three other electrophiles (data not shown). It is possible that localized supercooling is partly responsible for the high enantiomer ratios seen.[35]

At this point it is appropriate to discuss the probable mechanism of stereochemical information transfer in these deprotonation/trapping reactions of 1,4-benzodiazepin-2-ones. Before considering the stereochemical dynamics of the enolates, it is instructive to examine the 1,4-benzodiazepin-2-one starting materials themselves. Despite the absence of a stereogenic center, glycine-derived 1,4-benzodiazepin-2-ones **74a–e** are chiral, existing as conformational enantiomers (Table 2.10). [48, 49]

The helical descriptors (*M*)- and (*P*)- are used to describe the sense of ring chirality, based on the sign of the R^1–N1–C10–C9 dihedral angle. Since the two hydrogens at C3 are diastereotopic and exchange via ring inversion, ^{1}H NMR spectroscopy coalescence temperature measurements can establish the rate of enantiomerization. As demonstrated in Table 2.10, the barrier to enantiomerization in these compounds depends strongly upon the size of the N1 substituent.[47, 48, 50, 51] This dependence is easily understood, since the R^1–N1–C10–C9 dihedral angle will be very nearly eclipsed in the ring inversion transition structure. Consequently, interconversion of the enantiomers of **74a–d** is fast at room temperature (cf. Table 2.1). However, the presence of the bulky *t*-butyl group at N1 allowed enantiopure **74e** to be prepared by resolution; at room temperature it racemizes slowly in the solid state, and rapidly in solution.[50]

It is also well known that when a 1,4-benzodiazepin-2-one bears a single substituent at C3 (as in **60a–c**), the pseudoequatorial conformation is strong-



Scheme 2.19.

ly preferred.[52] Thus the configuration at C3 controls the helicity of the diazepine ring of **60a–c**; (3*S*)-configured **60b** will preferentially adopt the (*M*)-conformation (Scheme 2.19).

Therefore, although deprotonation of (*S*)-**60b** would destroy the stereogenic center at C3, the resulting enolate (e.g. free ion **75b**) would remain chiral by virtue of the non-planar diazepine ring. Since the major (*M*)-conformer of (*S*)-**60b** is also stereoelectronically better disposed for deprotonation than is the minor (*P*)-conformer, deprotonation of (*S*)-**60b** should give (*M*)-**75b**. Finally, we would note that if deprotonation of (*S*)-**60b** does give an (*M*)-configured enolate (e.g. free ion (*M*)-**75b**), formation of the retentive benzylation product (*R*)-**61b** necessitates concave-face approach of the electrophile. The factors that would favor this apparently contra-steric alkylation are at present not fully understood (please see **Note added in Proof** at the end of this Chapter).

To address the issues of enolate structure and racemization, DFT calculations were carried out on **76b**, des-chloro analog of **75b** (Figure 2.3). Identical calculations were carried out on **76a**, the *N*-Me analog (structure not shown). As proposed, the equilibrium geometries of enolate free anions **76a–b** are found to be chiral, and feature essentially flat C3 carbons (sum of angles 358.5, 359.0°). Interestingly the calculated enantiomerization transition structures (**76a***–**76b***) are not perfectly flat, and thus exist as (*M*)- and (*P*)-enantiomers: R^1–N1–C10–C9 dihedral angles are +13.4° and +12.8° for (*P*)-**76a*** and (*P*)-**76b*** respectively (structure of **76a*** not shown). At 195K the calculated (B3LYP/6-31+G*//B3LYP/6-31G*) activation free energies

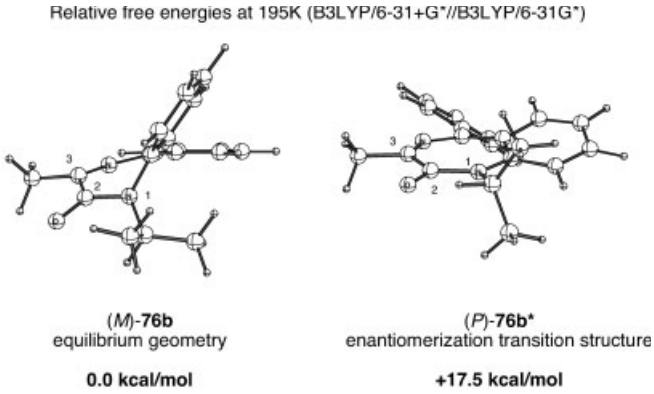


Figure 2.3.

for enantiomerization of **76a** (*N*-Me) and **76b** (*N*-*i*-Pr) are 12.4 and 17.5 kcal/mol, which correspond to $t_{1/2}(rac)$ values of 0.11 minutes and 970 hours at –78 °C respectively. Thus the nonselective benzylation of (*S*)-**60a** and the enantioselective benzylation of (*S*)-**60b** (both at –78 °C, Scheme 2.18) may be rationalized.

To experimentally measure the rate of enolate racemization, studies were performed on the *N*-benzyl analogue (*S*)-**60d**. Thus (*S*)-**60d** was subjected to deprotonation for a time *t*, followed by protic quench (Figure 2.4). The enantiomeric composition of the recovered starting material **60d** was determined by chiral stationary phase HPLC. The rate of racemization k_{rac} can be determined from equation 3:[11]

$$\ln(|2\,X(R) - 1|) = -k_{rac}t \qquad (3)$$

where X(*R*) is the mole fraction of the (*R*)-enantiomer of the **60d**. As depicted in Figure 2.4, at –100 °C, the enolate derived from (*S*)-**60d** racemizes at a rate of 5.06×10^{-3} sec^{-1}, giving a $t_{1/2}(rac)$ = 2.3 min. The need for in situ trapping of the enolate derived from *N*-PMB analogue (*S*)-**60c** at –100 °C (cf. Table 2.9) can thus be clearly understood. Applying the Eyring equation (equation 1), the $\Delta G^{\ddagger}$ for enantiomerization of the enolate of **60d** is 12.0 kcal/mol (173K).

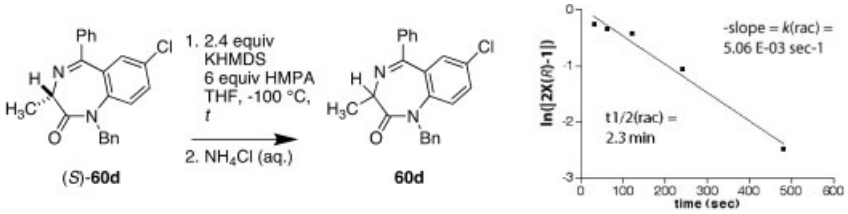
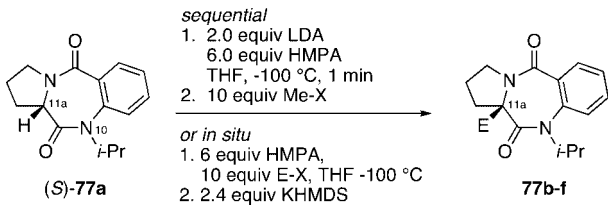


Figure 2.4.

Table 2.11
Sequential and in situ deprotonation/trapping of (*S*)-**77a** at –100 °C.[36]



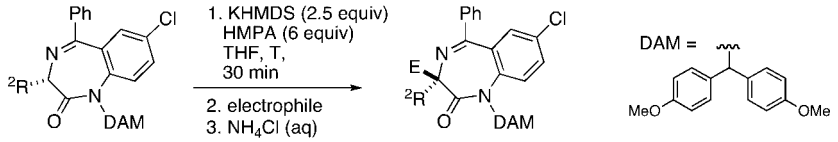
Entry	E-X	Product[a]	Sequential er (yield)	In situ er (yield)
1	MeOTf	(+)-(*S*)-**77b**	98:2 (76)	>99:1 (24)
2	Allyl-Br	(+)-**77c**	92:8 (77)	99:1 (75)
3	Allyl-I		>99:1 (89)	
4	BnBr	(+)-(*R*)-**77d**	89:1 (64)	98:2 (92)
5	BnI		97:3 (77)	
6	4-$MeC_6H_4CH_2Br$	(+)-(*R*)-**77e**[b]		>99:1 (92)
7	4-$MeC_6H_4CH_2I$		98:2 (63)	
8	2-$PhC_6H_4CH_2Br$	(+)-(*R*)-**77f**[b]		98:2 (82)
9	2-$PhC_6H_4CH_2I$		98:2 (63)	

[a] Where given, absolute configuration was determined by chemical correlation, unless otherwise indicated.
[b] Absolute configuration based on sign of rotation relative to (+)-(*R*)-**77d**.

Carlier et al. subsequently investigated deprotonation/alkylation routes to quaternary proline-derived 1,4-benzodiazepine-2,5-diones.[36] Despite the presence of an *i*-Pr group at N10 (cf. (*S*)-**60b**, Scheme 2.18), high enantioselectivity in deprotonation/alkylation of (*S*)-**77a** required reaction at –100 °C. Two protocols at –100 °C were employed: a sequential protocol involving a 1 min deprotonation with 2 equivalents of LDA, and an in situ protocol involving 2.4 equivalents of KHMDS (Table 2.11). As can be seen, the sequential protocol gives higher yields for the highly reactive electrophile MeOTf (entry 1). However, in all other cases, higher yields and enantiomeric ratios are obtained with the in situ protocol. Finally, where comparisons are possible, the use of iodide electrophiles gives higher enantiomeric ratios than bromide electrophiles (cf entries 2 & 3, 4 & 5, sequential column). These results again highlight the importance of fast electrophilic trapping to successfully compete with enolate enantiomerization (cf. Figure 2.1).

The requirement for an isopropyl group at N1 of a 1,4-benzodiazepin-2-one (e.g. (*S*)-**60b**, **62b**) or N10 of 1,4-benzodiazepin-2,5-diones (e.g. (*S*)-**77a**) clearly limits the diversity of benzodiazepines that can be prepared. Furthermore, the use of a PMB substituent at N1 of a 1,4-benzodiazepin-2-one

Table 2.12
Enantioselective deprotonation/alkylation of *N*-DAM-1,4-benzodiazepin-2-ones (*S*)-**60e**, **62e**, **78e** and **79e**.[13]



(*S*)-**60e**, **62e**, **78e**, **79e**

61e, **63e**, **65e**, **67e** **80e**-**89e**

Entry	Sub-strate	R^2	sol-vent	T (°C)	E[a]	Product[b]	% yield[c]	er[c]
1	(*S*)-**60e**	CH_3	THF	–78	Bn	(*R*)-**61e**	80 (72)	>99:1 (99:1)
2	(*S*)-**60e**	CH_3	THF	–42	Bn	**61e**	78	99:1
3	(*S*)-**60e**	CH_3	THF	–78	4-Me-$C_6H_4CH_2$-	(*R*)-**63e**	82 (76)	>99:1 (97:3)
4	(*S*)-**60e**	CH_3	THF	–78	Allyl	**65e**	88 (76)	>99:1 (97:3)
5	(*S*)-**60e**	CH_3	THF	–78	-CH_2CO_2Et	(*R*)-**80e**	86 (0)	99:1
6	(*S*)-**60e**	CH_3	THF	–78	Et	**81e**	65 (0)[d]	98:2
7	(*S*)-**60e**	CH_3	THF	–78	-CN	**82e**	95	>99:1
8	(*S*)-**60e**	CH_3	THF	–78	-N_3	**83e**	88	>99:1
9	(*S*)-**60e**	CH_3	THF	–78	-N(Boc)-NHBoc	**84e**	94	>99:1
10	(*S*)-**62e**	$PhCH_2$	DME	–42	Allyl	**67e**	58	96:4
11	(*S*)-**62e**	$PhCH_2$	DME	–42	-CN	**85e**	68	98:2
12	(*S*)-**78e**	Et	DME	–42	Bn	(*R*)-**86e**[e]	65	97:3
12	(*S*)-**78e**	Et	DME	–42	Allyl	**87e**	58	97:3
14	(*S*)-**79e**	$MeSCH_2CH_2$	DME	–42	Me	**88e**	67	94:6
15	(*S*)-**79e**	$MeSCH_2CH_2$	DME	–42	-CN	**89e**	80	94:6

[a] Electrophiles (equiv) used: BnBr (10), 4-$MeC_6H_4CH_2Br$ (10), allyl bromide (10), $BrCH_2CO_2Et$ (10), EtI (20), tosyl cyanide (2.0), 2,4,6-triisopropylsulfonylazide (2.5), BocN=NBoc (5), MeI (10).

[b] Where given, absolute configuration was determined by chemical correlation, unless otherwise stated.

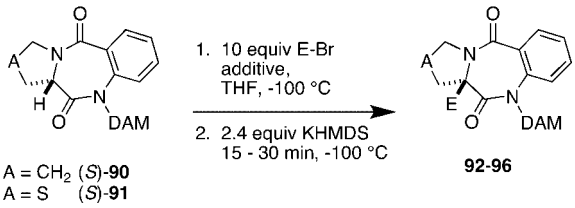
[c] Value in parenthesis corresponds to that derived from N-*i*-Pr analogue **60b**.

[d] LDA provided superior yields of **81e** and was used in place of KHMDS.

[e] Absolute configuration based on rotation and HPLC elution order relative to (*R*)-**61e**.

(e.g. (*S*)-**60c**) necessitates inconvenient cryogenic reaction temperatures to achieve adequate enantioselectivity. Thus bulky removable amide protecting groups were examined and the di-(*p*-anisyl)methyl (DAM) group was found to be ideal.[13]

Table 2.13
Enantioselective deprotonation/alkylation of *N*-DAM-1,4-benzodiazepine-2,5-diones (*S*)-**90** and (*S*)-**91** derived from proline and thioproline.[13]



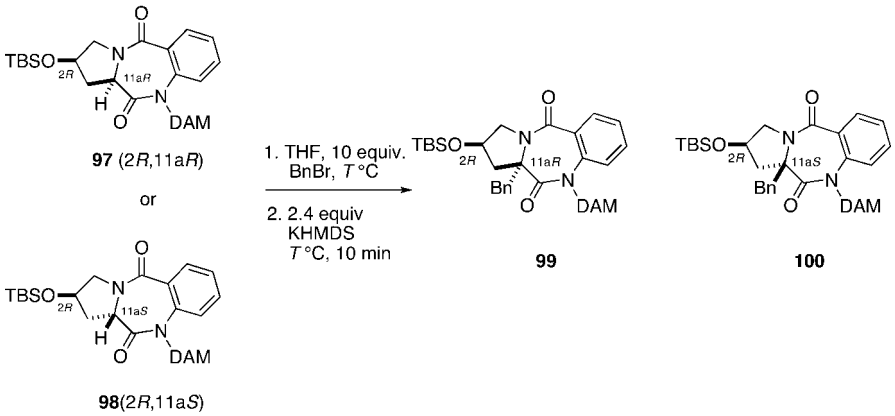
Entry	Substrate	A	Additive	E	Product[a]	% yield	er
1	(*S*)-**90**	CH_2	HMPA	Bn	(*R*)-**92**	98	99:1
2	(*S*)-**90**	CH_2	none	Bn	(*R*)-**92**	83	>99:1
3	(*S*)-**90**	CH_2	HMPA	4-$MeC_6H_4CH_2$-	(*R*)-**93**[b]	93	>99:1
4	(*S*)-**90**	CH_2	none	4-$MeC_6H_4CH_2$-	(*R*)-**93**[b]	83	>99:1
5	(*S*)-**90**	CH_2	HMPA	2-$PhC_6H_4CH_2$-	(*R*)-**94**[b]	94	>99:1
6	(*S*)-**90**	CH_2	none	2-$PhC_6H_4CH_2$-	(*R*)-**94**[b]	87	97:3
7	(*S*)-**91**	S	none	Bn	**95**	98	>99:1
8	(*S*)-**91**	S	none	Allyl	**96**	89	98:2

[a] Where given, absolute configuration was assigned by chemical correlation, unless otherwise noted.
[b] Absolute configuration based on sign of rotation relative to (+)-(*R*)-**77d**.

N-DAM protected 1,4-benzodiazepin-2-ones derived from (*S*)-alanine, phenylalanine, aminobutyric acid, and methionine were prepared and found to give high enantiomeric ratios and yields in a deprotonation/alkylation protocol at –78 and –42 °C (Table 2.12). In general yields are good and enantiomeric ratios are excellent, showing improvements in several cases relative to the *N*-isopropyl analogue **60b** (cf. entries 1,3,4). The advantages of the DAM group are especially evident in reactions with ethyl bromoacetate and ethyl iodide (entries 5–6), where the corresponding alkylations of the *N*-*i*-Pr analogue (*S*)-**60b** failed to give product. Another noteworthy feature of the *N*-DAM group is that reactions can be performed at –42 °C without significant loss of enantiomeric purity (cf. entry 1 vs 2, and entries 10–15). Finally, reactions with the sp-carbon electrophile tosyl cyanide, and with two nitrogen electrophiles are very successful (cf. entries 7, 9–11, 15).

N-DAM 1,4-benzodiazepine-2,5-diones (*S*)-**90** and (*S*)-**91** derived from proline and thioproline were also prepared. As was seen for *N*-isopropyl analogue (*S*)-**77a**, deprotonation/alkylation at –100 °C is required to achieve acceptable enantioselectivity; racemic products are formed at –78 °C. Results from an in situ protocol are given in Table 2.13. As seen in Table 2.13, yields

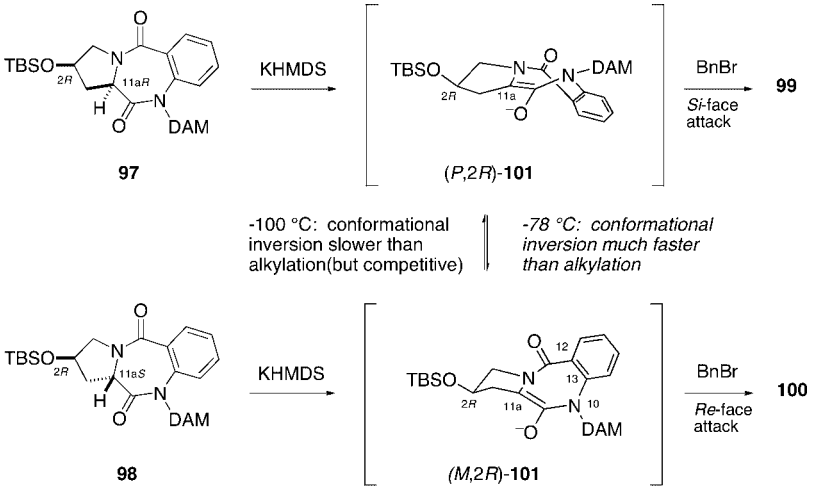
Table 2.14
Deprotonation/benzylation of diastereomeric 1,4-benzodiazepin-2,5-diones.[13]



Entry	Starting material	T (°C)	% yield (**99** + **100**)	Ratio **99**:**100**
1	**97**	–100	95	96:4
2	**98**	–100	49	8:92
3	**97**	–78	87	69:31
4	**98**	–78	82	66:34

and enantiomeric ratios are uniformly excellent. Moreover, it is important to note that addition of HMPA is not necessary to achieve high yields of the alkylated products of 1,4-benzodiazepine-2,5-diones (cf. entries 1 and 2, 3 and 4, and 5 and 6); in contrast, HMPA is required for acceptable yields in deprotonation/alkylation reactions of *N*-DAM 1,4-benzodiapin-2-ones (Table 2.12). Finally, the *N*-DAM group was easily removed in high yield by mild acidic hydrolysis (1.25–25% TFA in CH_2Cl_2); yields after chromatography range from 94–99%. Thus, this methodology may be used to prepare enantiopure quaternary benzodiazepines with diverse N1/N10-functionalization.

Inspired by Kawabata and Fuji's studies on the effect of additional stereogenic centers reactions involving stereolabile axially chiral elements,[8] Carlier and co-workers performed deprotonation/alkylation reaction on diastereomeric substrates **97** and **98** (Table 2.14). Substrates **97** and **98** have identical (*R*)-configuration at C2, but different configurations at C11a, the locus of deprotonation/alkylation. Thus retentive alkylation of **97** would give **99**, but retentive alkylation of **98** would give **100**. At –100 °C, these retentive outcomes were realized: substrate **97** gave a 96:4 ratio of products **99** and **100**, and diasteromer **98** gave a 8:92 ratio of these products (Table 2.14, entries 1–2). However at –78 °C, both **97** and **98** give essentially the same 2:1 ratio



Scheme 2.20.

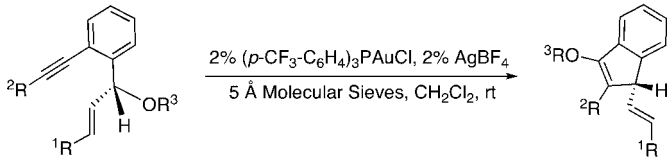
of **99** and **100**. Thus under in situ conditions at –100 °C, substrates **97** and **98** give different enolates, but at –78 °C, this difference vanishes. A likely explanation for this phenomenon is given in Scheme 2.20.

Deprotonation of (11a*R*)-configured **97** would give an enolate wherein the benzodiazepine ring adopts a (*P*)-conformation, namely (*P*,2*R*)-**101**. On the other hand deprotonation of (11a*S*)-configured **98** would give an enolate wherein the benzodiazepine ring adopts a (*M*)-conformation, namely (*M*,2*R*)-**101**. The proposed stereospecific formation of diastereomeric enolates from **97** and **98** largely accounts for the retentive outcomes observed (**99**:**100** = 96:4 and 98:2, respectively). The fact that these diastereomeric ratios are lower than the 99:1 er observed for parent compound (*S*)-**90** under identical conditions (Table 2.13, entry 2) suggests lower enantiomerization barriers for the derived enolates compared to that of **90**, leading to a small amount of enolate equilibration prior to benzylation. Extending this logic to reaction at –78 °C, conformational interconversion is much faster than in situ alkylation, to the point that both **97** and **98** give an equal mixture of diasteromeric enolates (*P*,2*R*)- and (*M*,2*R*)-**101**. Thus at –78 °C, both **97** and **98** give nearly equal 2:1 ratios of benzylation products **99** and **100**. This ratio reflects not only the relative population of the diastereomeric enolates, but their reactivity. For further discussion of reactions involving dynamic kinetic resolution, see the chapter in this volume by Coldham and Sheikh.

IV. SRS VIA STEREOLABILE AXIALLY CHIRAL ALKENYL GOLD CARBOCATION INTERMEDIATES

In 2006, Toste et al. reported a synthesis of indenyl ethers in which operation of a SRS via stereolabile axially chiral intermediate mechanism appears likely.[53] Enantioenriched alkynes **102–104** underwent enantioselective Au(I)-catalyzed intramolecular carboalkoxylation to give indenyl ethers **105–107** with inversion of configuration (Table 2.15).

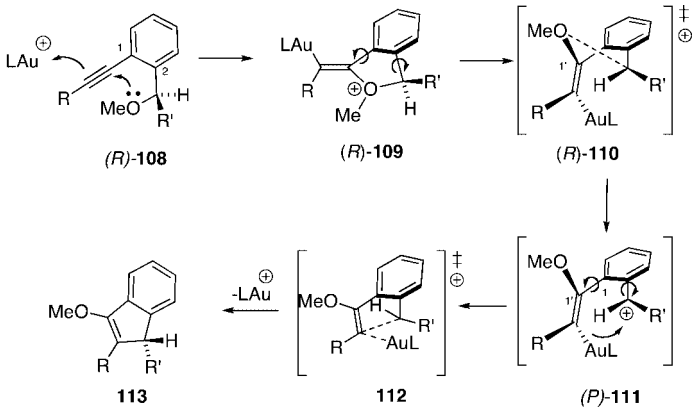
Table 2.15
Invertive Au(I)-catalyzed carboalkoxylation of alkynes



102-104 **105-107**

Substrate	R^1	R^2	R^3	Product	% yield	er
102 (91:9 er)	Ph	CO_2CH_3	CH_3	**105**	99	91:9
ent-**103** (>99:1er)	H	Ph	CH_3	*ent*-**106**	92	98:2
104 (87:13 er)	Ph	CO_2CH_3	allyl	**107**	92	80:20

Fidelity in the reactions of **102** and *ent*-**103** is nearly perfect; some degradation in er is seen in the transformation of **104**. What is the mechanism of this reaction? The imperfect stereoselectivity observed with **104** would argue against a concerted S_N2-like process. The authors proposed a mechanism involving a stereolabile axially chiral alkenyl gold benzylic carbocation intermediate (Scheme 2.21).



Scheme 2.21.

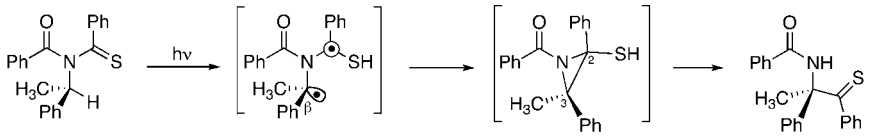
Au(I)-catalyzed intramolecular carboalkoxylation of (*R*)-**108** gives oxonium ion (*R*)-**109**, which ring opens (via transition structure (*R*)-**110**) to give the stereolabile axially chral alkenyl gold benzylic carbocation (*P*)-**111**. Intermediate (*P*)-**111** is chiral by virtue of the chirality axis along the C1′–C1 bond. Note that rotation of the carbocation out of planarity with the ring generates a second chirality axis as **111** is converted to transition structure **112**. Capture of the carbocation by the alkenyl gold requires rotation of both the C1′–C1 bond and the bond from the ring to the benzylic carbon as these two chirality axes are converted to the single chirality center in **113**.

V. SRS VIA STEREOLABILE AXIALLY CHIRAL DIRADICAL INTERMEDIATES

We have previously reviewed the work of Giese[27] and Griesbeck[54] on the enantioselective cyclization of photochemically generated diradicals. The reactivity of molecules in the excited singlet state can lead to efficient stereochemical information transfer, since the rate of intramolecular reaction is comparable to the rate of bond rotation. A recent example of this phenomenon appears in the work of Sakamoto, who reported that irradiation of enantiopure thioimide (*R*)-**114** produced α-acylamino-thioketone (*R*)-**117** (Scheme 2.22).[55]

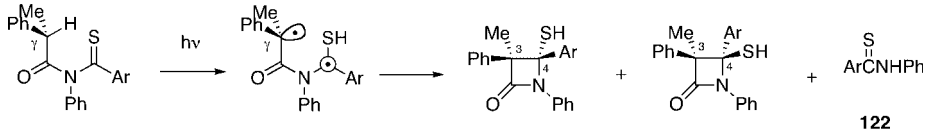
The authors proposed that intramolecular photochemical hydrogen abstraction from the reactive conformer of (*R*)-**114** depicted in Scheme 2.22 produces singlet diradical (*P*)-**115** in enantiopure form. Rapid cyclization ensues, forming (3*R*)-configured **116**, most likely as a mixture of diastereomers. Collapse of the tetrahedral intermediate **116** gives thioketone (*R*)-**117**. We would note that the author's depicted pyramidalization at C_β in (*P*)-**115** is not necessary for stereoselectivity, and is unlikely due to extensive spin delocalization into the C_β-phenyl ring. All that stereoselectivity requires is slow C_β–N bond rotation relative to the rate of radical recombination. Three other examples using substituted aryl thioimides also react with high enantioselectivity.

In 2008, Sakamoto published a similar synthetic route for γ-hydrogen abstraction of thioimides **118** to form chiral β-lactams; in this case the stereogenic center in the starting material is moved from the *N*-alkyl group to the *N*-acyl group (Table 2.16).[56]



Scheme 2.22.

Table 2.16
Photochemical γ-hydrogen abstraction route to enantioenriched β-lactams[56]



Entry	Imide	% yield **120**	er **120**	% yield **121**	er **121**	% yield **122**
1[a]	(*S*)-**118a**	50	98:2	11	98:2	21
2[a]	(*S*)-**118b**	59	97:3	10	93:7	23
3[b]	(*S*)-**118b**	56	98:2	13	97:3	15

[a] Irradiated in a 20mM toluene solution with 500 W mercury lamp.
[b] Irradiated in 50:50 solvent of *t*-BuOH and toluene.

The desired 4-mercapto-β-lactams were formed as a mixture of diastereomers (**120** & **121**) in high enantiomeric ratio (Table 2.16, entries 1–2). Sakamoto proposed that irradiation of **118** (depicted in Table 2.16 in its reactive conformation) promotes γ-hydrogen abstraction by the thiocarbonyl sulfur, leading to formation of singlet 1,4-diradical intermediate **119**. This 1,4-diradical recombines to give two diastereomeric β-lactams **120** and **121**; **122** is proposed to result from cleavage of the diradical. Note that the major enantiomers of **120** and **121** evidence retentive substitution at the stereogenic center of **118**, but differ at the newly formed stereogenic center. This result can be rationalized if photolysis of (*S*)-**118** gives (*P*)-**119**, and the rate of cyclization of **119** is faster than that of C_γ–C(O) rotation. As we noted earlier, the author's depicted pyramidalization at C_γ is not necessary to explain stereochemical information transfer. The poor diastereoselection can be rationalized by competitive clockwise and anti-clockwise rotation of the N–C(SH)Ar bond during closure of the diradical intermediate **119**. Sakamoto noted slight increases in er of **120** and **121** upon addition of *t*-BuOH to the toluene solution (Table 2.16, cf. entries 2–3). He hypothesized that in these reactions, competing back-transfer of a hydrogen atom from the diradical **119** to **118** is racemizing, and thus reduces er. The addition of *t*-BuOH is proposed to lower the rate of the back hydrogen transfer, by hydrogen bonding to the mercapto group of **119**.

VI. CONCLUDING REMARKS

SRS via stereolabile axially chiral intermediates remains a viable strategy for the synthesis of enantiomerically enriched compounds, some 18 years after Fuji's seminal publication.[1] Like Seebach's original conception of "self-regeneration of stereocenters,"[15] SRS via stereolabile axially chiral intermediates depends upon the availability of enantiopure starting materials. The wealth of amino acid-based chemistry in this field can thus be understood, and is likely to continue to grow. As in 1991, the fundamental challenge in applying this strategy is the generation of stereolabile axially chiral intermediates in highly enantioenriched form. However, as we hope this review illustrates, by appreciation of stereoelectronic effects, and careful choice of substrates and reaction conditions, this challenge can be met. Furthermore, as our understanding of stereoelectronic effects improves, it will become increasingly possible to design new enantioselective reactions that exemplify SRS via stereolabile axially chiral intermediates.

ACKNOWLEDGEMENT

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NOTE ADDED IN PROOF

Carlier and co-workers recently reported an in depth experimental and computational study of the mechanism of stereochemical information transfer in deprotonation/trapping reactions of 1,4-benzodiazepin-2-ones (see Hsu, D. C.; Lam, P. C.-H.; Slebodnick, C.; Carlier, P. R. *J. Am. Chem. Soc.* **2009**, *131*, in print, doi: 10.1021/ja907507j).

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Chapter 3

Overview of Carbanion Dynamics and Electrophilic Substitutions in Chiral Organolithium Compounds

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Stereochemical Aspects of Organolithium Compounds Edited by Robert E. Gawley

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I. INTRODUCTION

It has been noted that "organolithiums are the most widely used organometallics in contemporary organic chemistry".[1] The undeniable truth of this statement derives partly from the widespread use of commercially available butyllithium isomers as bases, but it is not an exaggeration to state that functionalized organolithiums in more complex molecules are important species in their own right, as evidenced by the large number of reviews and monographs that have appeared since 1990.[1–7] Lithium, atomic number 3, is the smallest of the metals, but the structure of organolithium compounds and their reaction chemistry can be diabolically complex. This complexity is in part due to the electrostatic nature of bonding between lithium and carbon, and the tendency of organolithium compounds to aggregate.[8,9] The possibility of homochiral and heterochiral aggregates is usually not addressed in studies of the steric course of chiral organolithium reagents. In this review, the aggregation state of the various organolithiums will not normally be considered, and for simplicity, they will be drawn as monomers.

The focus of this chapter is the dynamics, mechanism, and steric course of substitution reactions of aliphatic organolithiums whose metal-bearing carbon is stereogenic. There are four comprehensive treatises on organolithium chemistry that have been published since 2002.[7] Several topics covered briefly in this chapter are elaborated more thoroughly in accompanying chapters of this volume. Examples have been chosen to illustrate particular points, and the original literature or one of the monographs should be consulted for details on scope.

II. THE CARBON–LITHIUM BOND

What might be called the "degree of covalency" of the carbon–lithium bond varies with temperature, solvent, and structure of the organic component. Collins and Streitwieser have asserted that methyllithium is 79.7% ionic.[10] The situation is considerably more complex than that statement implies, but the view among theoreticians appears to be that the C–Li bond is best described as being ionic.[11] A recent review discusses the nature of the C–Li bond, and concludes that "the nature of the C–Li bond varies from compound to compound", [but] "the covalent components cannot be neglected".[12]

Some authors prefer to denote the carbon lithium bond as an ion pair in which the lithium and carbon are either in van der Waals contact (a contact ion pair) or separated by solvent (a solvent-separated ion pair). In such instances, scalar coupling between the lithium and carbon atoms can reveal details about structure – especially aggregation state. [13] Unless the carbanion is considerably stabilized by factors such as delocalization and the lithium ion by solvation, it is unlikely that the lithium cation strays far from the carb-

anion, so these are the two most relevant representations. The distinction between a polar covalent bond and a contact ion pair is irrelevant to the stereochemical issues under discussion in this chapter, since the species under consideration are chiral as a result of association with the lithium. Therefore for simplicity, and because it implies a specific configuration, the carbon–lithium bond will normally be drawn as covalent in the chapters of this volume.

III. CHIRAL ORGANOLITHIUMS

There are two types of chiral organolithiums commonly encountered, as illustrated in Figure 3.1: η^1 carbanion ligands associated with the lithium, and having a chirality center at the metal bearing carbon, and unsymmetric η^3 allyl carbanion ligands giving the organolithium compound planar chirality. Such species are enantiomers (isoenergetic) in the absence of any other chirality element, but become diastereomers in the presence of, for example, a ligand on lithium that is also chiral, or another chirality element in the carbanion fragment. A complicating factor in the chemistry of allylic and benzylic organolithiums is that they may be either η^1 or η^3, or equilibrating mixtures of the two. Often, the solution structure of synthetically useful organolithiums has not been determined, and it is not safe to extrapolate from similar structures.

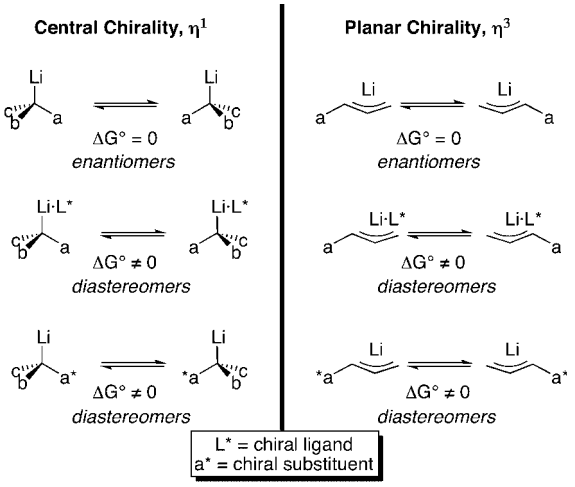

Figure 3.1. η^1 and η^3 organolithium general structures.

IV. METHODS OF GENERATION OF ORGANOLITHIUMS

Several strategies may be used to generate an organolithium, including deprotonation, reductive lithiation, and transmetalation (Figure 3.2). Deprot-

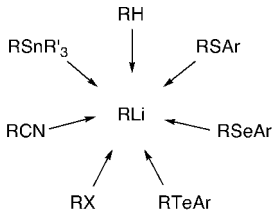

Figure 3.2. Possible sources of organolithium compounds.

onation is only useful if the conjugate acid of the carbanion is activated in some way. Protons α to a carbonyl to form enolates are the obvious example. The chapter in this volume by Simpkins and Weller reviews chiral lithium amide bases in the deprotonation of enantiotopic protons for the formation of enolates, and in several other enantioselective processes.

For deprotonation to form a lithium–carbanion pair, a proximal directing group on a heteroatom, a double bond, or an aromatic ring is usually necessary to activate the proton(s) toward removal by a strong base such as butyllithium. Recent years have seen numerous examples of butyllithium (BuLi) or *sec*-butyllithium (*s*-BuLi) complexed with a chiral ligand, to create a chiral base that is able to effect enantioselective deprotonations by distinguishing enantiotopic protons.[1,4,5,14,15] The chapter by Kizirian in this volume details the use of organolithium bases such as the alkyllithiums that are coordinated to chiral diamine ligands.

Reductive lithiations include reductions of sulfides, selenides, tellurides, or halides with lithium metal or lithium arenes.[8,16] Tertiary α-aminoorganolithiums can be made by reductive decyanation.[17] The metal most commonly exchanged for lithium is tin, via the reaction of organostannane compounds with BuLi.[18,19]

Of these, some are suitable for asymmetric synthesis of configurationally stable organolithiums. Later sections of this chapter deal with organolithiums that can interconvert due to a low inversion barrier, or be dynamically resolved with chiral ligands. More complete coverage of these issues are discussed in the chapters by Hoffmann (the Hoffmann Test for configurational stability) and Coldham and Sheikh (dynamic resolutions of chiral organolithiums). Here, two of the more common methods for preparing configurationally stable organolithiums are summarized briefly.

A. Asymmetric Deprotonations

When chiral ligands such as sparteine are complexed to *sec*-butyllithium, a chiral base is formed. The first highly selective application to stereoselective deprotonation is illustrated in Figure 3.3a.[5,20] In this example, there is no mesomeric stabilization which might lower the kinetic barrier to deproton-

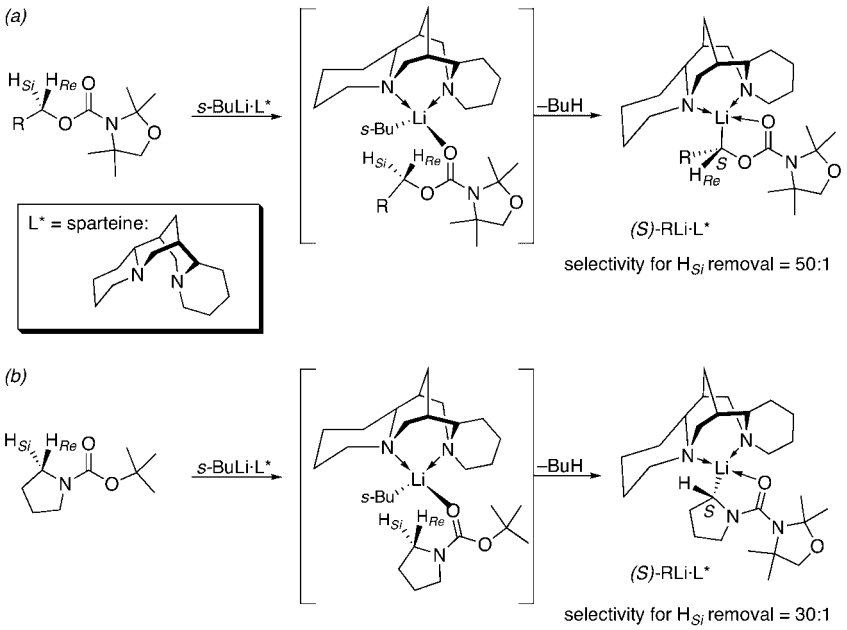

Figure 3.3. Sparteine-mediated deprotonation of carbamates: (*a*) α to oxygen in carbamates;[5,20] (*b*) α to nitrogen in pyrrolidines.[21,22]

ation, and the α-alkoxy organolithiums are configurationally stable for hours at low temperature. Shortly after this work on α-alkoxy deprotonations was disclosed, it was applied to enantioselective deprotonation of pyrrolidines, as illustrated in Figure 3.3b.[21,22] Note, however, that this deprotonation is much less successful with *N*-Boc piperidines.[23,24] Possible rationales for the steric course of the deprotonations are shown in the brackets, which assumes that the *s*-BuLi·sparteine complex is monomeric.[5,20,22,25] In both cases, the H_{Si} proton (*i.e.*, the proton that sits on the *Si* face of the triangle formed by the other 3 ligands on carbon) is removed selectively from a complex formed by coordination of the carbamate carbonyl to the lithium·sparteine chelate.[23]

B. Tin–Lithium Exchange

Virtually all tin–lithium exchange reactions occur with net retention of configuration at the metal-bearing carbon.[26] The challenge of producing enantiopure, configurationally stable organolithiums by tin–lithium exchange therefore reduces to the preparation of enantiopure organostannanes.

Enantiomerically enriched α-alkoxy stannanes can be made by the methods outlined in Figure 3.4. Asymmetric reduction of acyl stannanes can be accomplished with BINAL-H with excellent enantioselectivity (Figure

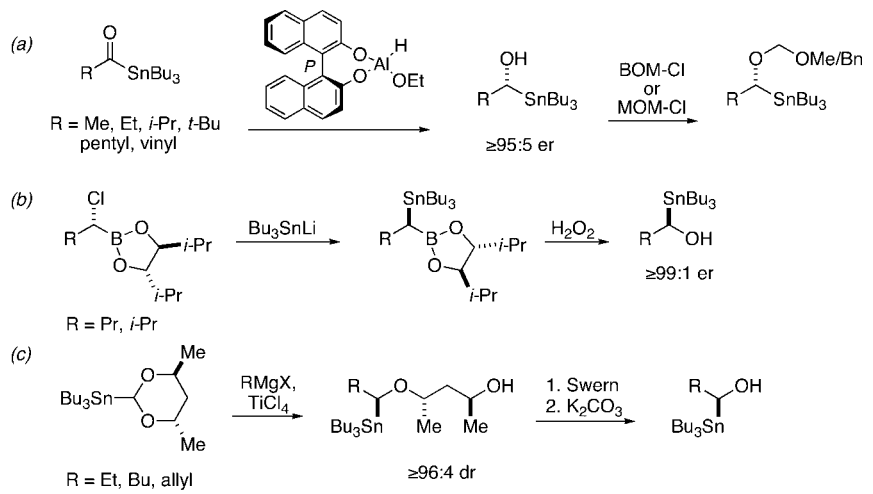

Figure 3.4. Asymmetric synthesis of α-alkoxyorganolithiums: (*a*) by reduction of acyl stannanes;[19] (*b*) from α-chloroboronates;[27] (*c*) from 2-tributylstannyldioxolanes.[28]

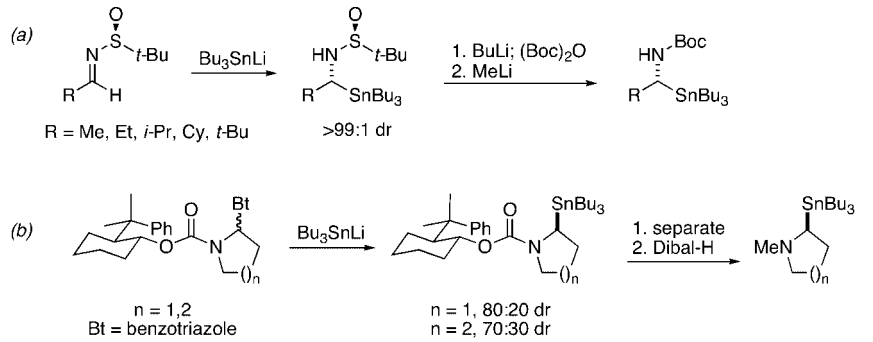

Figure 3.5. Synthesis of α-aminoorganostannanes: (*a*) by addition to acyclic sulfinimines;[29] (*b*) addition to cyclic *N*-acyliminium ions.[30]

3.4a).[19] The α-hydroxystannanes are stable to isolation and can be derivatized with either benzyloxymethyl chloride or methoxymethyl chloride easily. As shown in Figure 3.4b, chloroboronates can be treated with tributyltin lithium with inversion; subsequent oxidation affords essentially enantiopure α-hydroxystannanes.[27] Figure 3.4c illustrates the ring opening of stannyl dioxolanes with excellent diastereocontrol. Oxidation and elimination furnish the scalemic α-hydroxystannanes.[28]

Enantiopure α-aminoorganostannanes are available by the methods shown in Figure 3.5. Acyclic α-aminoorganostannanes can be prepared by diastereoselective addition of tributyltin lithium to *tert*-butyl sulfinimines, in which the tributyltin nucleophile adds to the *Si* face of the imine, when the

sulfoxide has the *(R)* configuration.[29] If the R group is unbranched, the sulfoxide can be replaced by an *N*-Boc group by the two step sequence shown. If the R group is branched, a slightly longer route is necessary. Addition of tributyltin lithium to cyclic *N*-acyl iminium ions having the *trans*-cumylcyclohexyl chiral auxiliary is only modestly selective. The reaction proceeds through a conformationally mobile iminium ion, which probably accounts for the low selectivity. Nevertheless, the diastereomers are separable. Reduction affords enantiopure *N*-methyl-2-(tributylstannyl)-pyrrolidines and -piperidines.[30]

Of course, one obvious method for making organostannanes is to treat an organolithium with a trialkylstannyl chloride. While apparently redundant, this method has advantages in certain circumstances. For example, it provides the opportunity to prepare an organolithium, by tin–lithium exchange, that is free of diamine ligands such as TMEDA or sparteine, or in a solvent different from that used for the deprotonation, or to swap the activating/directing group for another functional group.

Because the reaction of a mesomerically stabilized organolithium with tributylstannyl chloride often proceeds with inversion, while tin–lithium exchange proceeds with retention, sequential electrophilic substitutions of Li to Sn, then Sn back to Li, can invert the carbanion configuration. Two examples of this lithium–tin–lithium exchange sequence are shown in Figure 3.6. In the first example, the *(R)*-organolithium is obtained by deprotonation of the conjugate acid with *s*-BuLi·TMEDA. Electrophilic substitution proceeds with inversion to give the *(R)*-stannane. Tin–lithium exchange then affords *(S)*-organolithium.[31] The laterally lithiated pivanilides shown in Figure 3.6b are prepared by dynamic resolution of the racemic organolithium with sparteine (see later section for details).[32,33] Here again, stannylation occurs with inversion to give the *(R)*-stannane from the *(S)*-lithiopivanilide. Tin lithium exchange from the *(R)*-stannane then yields the *(R)*-organolithium.

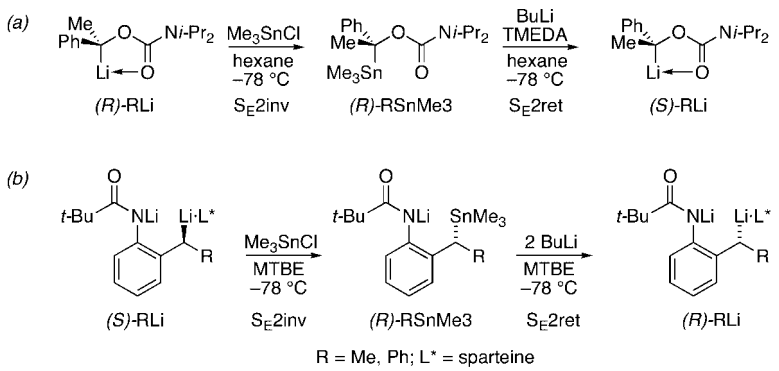

Figure 3.6. The lithium–tin–lithium exchange sequence: (*a*) α-oxyorganolithiums;[31] (*b*) laterally lithiated pivanilides.[32,33]

V. CARBANION DYNAMICS

First of all, note the distinction between enantiomerization and racemization. Enantiomerization is the conversion of one enantiomer to another, whereas racemization describes the conversion of an enantioenriched substance to a racemate. The rate constants for interconversion of two enantiomers are k_{RS} and k_{SR}, whereas the rate constant for racemization is the sum of the two: $k_{rac} = k_{RS} + k_{SR}$.

Questions of configurational stability are critical to the use of chiral organolithium compounds in asymmetric synthesis. The pertinent issue is the time frame of configurational stability. Some organolithium compounds are configurationally stable for hours, others for only seconds. The general equation for half-life toward equilibrium for two species (such as stereoisomers) is given by

$$\frac{1}{t_{1/2}} = \left(\frac{k_B \mathrm{T}}{h \ln 2}\right)\left(e^{\frac{-\Delta \mathrm{G}^{\ddagger}}{\mathrm{RT}}}\right)\left(e^{\frac{-\Delta \mathrm{G}^{0}}{\mathrm{RT}}} + 1\right),$$

where k_B is Boltzmann's constant, h is Planck's constant, and R is the universal gas constant. When $\Delta G^{\circ} = 0$ (as in conversion of enantiomers), the relationship simplifies, and can be expressed as.

$$\Delta \mathrm{G}^{\ddagger} = \mathrm{RT} \ln\left(\frac{2 k_B \mathrm{T} t_{1/2}}{h \ln 2}\right).$$

This relationship is plotted in Figure 3.7 for three temperatures (0, –40, and –80 °C). While recognizing that free energy is, itself, a function of enthalpy, entropy, and temperature, Figure 3.6 illustrates that, at a given temperature, very small differences in $\Delta G^{\ddagger}$ can have a profound effect on the lifetime of

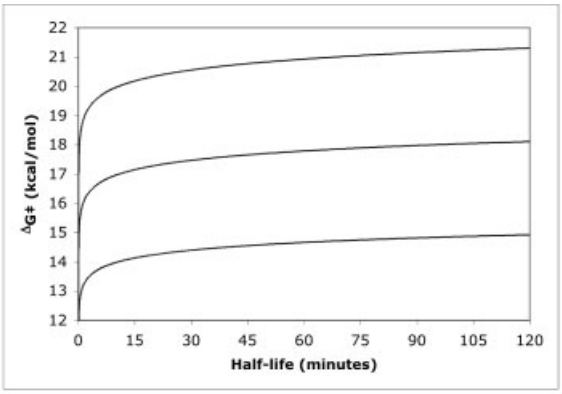

Figure 3.7. The relationship between the free energy inversion barrier and the half-life for racemization of enantiomers at three temperatures (top to bottom, 0, –40, and –80 °C).

chiral carbanions. This relationship is important, not only to the types of organolithiums discussed in this chapter, but also to the configurationally labile enolates discussed in the chapter by Carlier, Hsu, and Bryson in this volume.

VI. RELATIVE RATES: INVERSION VS. SUBSTITUTION

Unlike S_N2 reactions, in which only invertive substitution is allowed by a concerted pathway, S_E2 reactions are allowed for both retentive and invertive concerted (polar) pathways.[34] Because both are observed, the steric course is distinguished by adding the suffixes "ret" and "inv" for retentive and invertive substitutions, respectively.[35] Thus, electrophilic, aliphatic, bimolecular substitutions, abbreviated S_E2 in the Hughes-Ingold terminology,[36] may be categorized as $S_E2$ret or $S_E2$inv,[35] depending on the steric course. Single electron transfer (SET) can occur by oxidation of the carbanion to a radical, which opens new reaction manifolds that can be problematic to a synthesis plan.

The two limits for the rate of carbanion inversion are very fast and very slow – relative to the rate of reaction with an electrophile. These are considered first; subsequently, situations in which inversion and substitution compete are discussed.

A. Fast Inversion

When the rate of organolithium epimerization is fast relative to reaction with an electrophile, Curtin-Hammett kinetics[37,38] ensue. The energy profile is as shown in Figure 3.8. The relative energies of the organolithiums, *(R)*-RLi and *(S)*-RLi, are not relevant; that is, they may be enantiomers or diastereomers. In Figure 3.8, the barrier to inversion, $\Delta G^{\ddagger}_{inv}$, is low compared to

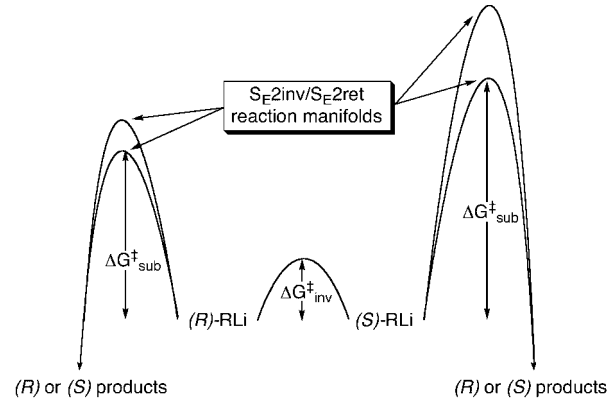

Figure 3.8. Substitution of configurationally labile organolithiums.

the energy of activation for any substitution manifold, $\Delta G^{\ddagger}_{sub}$, by whichever pathway is favored. Under these conditions, evaluating the steric course of the reaction is not a trivial matter.

B. Slow Inversion

At the other extreme are compounds that are configurationally stable for relatively long periods of time. The reaction profile for this situation is illustrated in Figure 3.9. If the configuration of the organolithium is known, then the configuration of the product(s) allows determination of the steric course. A mixture of stereoisomeric products could imply competing S_E2inv/S_E2ret reaction pathways, or competition between such polar pathways and SET. If the latter can be ruled out (*vide infra*), for example by using radical clock electrophiles,[39] the product ratio can be used to evaluate the relative rates of invertive *vs* retentive substitution using transition state theory ($\Delta\Delta G^{\ddagger}$ in Figure 3.9).

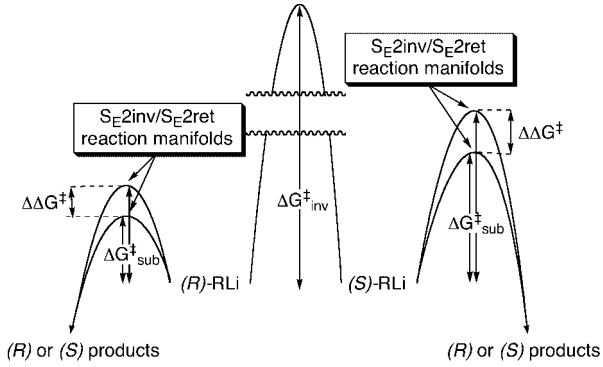

Figure 3.9. Substitution of configurationally stable organolithiums.

VII. ENANTIOMERIZATION DYNAMICS

A. Benzylic Organolithiums

Benzylic organolithium compounds usually have low configurational stability, and enantiomerization can be studied by dynamic NMR spectroscopy (DNMR). Several examples, whose thermodynamic parameters have been established, are given in Figure 3.10. The benzylic lithiohydrocarbon shown in Figure 3.10a enantiomerizes through a solvent-separated ion pair.[40] The α-thio and α-seleno compounds in Figure 3.10b/c also involve a solvent separated ion pair, but the rate determining step in these cases is rotation around the carbanion C–S or C–Se bond, as influenced by the hyperconjuga-

tion between the Li–C bond and the σ* orbital of the C–S or C–Se bond.[41–43] Enantiomerization in the examples in Figure 3.10a–c involve formation of a solvent-separated ion pair from the contact ion pair. This ion separation probably involves coordination of an additional solvent molecule to the lithium, consistent with the negative entropies of activation for these examples. Alternatively, the negative entropy of activation may be attributable to the formation of a larger dipole resulting in electrostatic restriction of the solvent.[43] The chelated α-silylbenzylic organolithium illustrated in Figure 3.10d enantiomerizes by a conducted tour mechanism,[44] that is, the lithium remains chelated by the tertiary amine as it moves from one face of the carbanion to the other.[45] Very similar dynamics were observed in an analogous allylic system in which the phenyl ring is replaced by a double bond.[46] Here again, the negative enthalpy of activation is consistent with additional solvation of the transition state. The α-aminobenzylic lithium illustrated in Figure 3.10e, which is monomeric in THF, equilibrates between η^1 and η^3 isomers. Enthalpic and entropic enantiomerization barriers were not determined for this compound, but the free energies of enantiomerization at the coalescence point were determined in THF alone, and with *N,N,N′,N′*-tetramethylethylenediamine (TMEDA) and *N,N,N′,N″,N″*-pentamethyldiethylenetriamine (PMDTA, Figure 3.10, inset).[43] Interestingly, the addition of amine additives that coordinate lithium raise the barrier slightly. Most probably, the rate determining step in this case is the formation of a solvent-separated ion pair, and the authors note that additives clearly affect the nature of the contact ion pair, but do not necessarily facilitate the formation of the solvent-separated ion

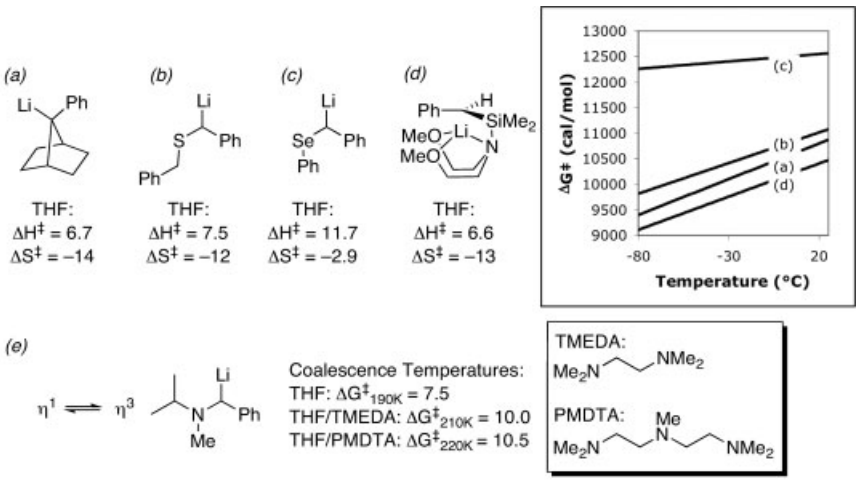

Figure 3.10. Enantiomerization barriers for representative benzylic and allylic organolithiums (ΔG and ΔH (kcal/mol); ΔS (cal/mol·K)): (*a*) benzylic lithiohydrocarbon;[40] (*b*) α-thio benzylic organolithium;[43] (*c*) α-seleno benzylic organolithium;[42] (*d*) chelated α-silyl benzylic organolithium that enantiomerizes by a conducted tour;[45] (*e*) α-amino benzylic organolithium.[43]

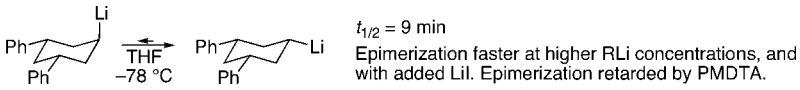

Figure 3.11. A lithiohydrocarbon that epimerizes through an aggregate.[47]

pair.[43] For the examples in Figure 3.10a–d, the free energies are plotted as a function of temperature. Note the profound effect that the negative entropy has on the free energy barriers of the examples in Figure 3.10a,b, and d. Since these compounds have $\Delta G^{\ddagger} \leq 12.5$ kcal/mol at temperatures from –80 to +25 °C, and with reference to Figure 3.7, it is clear that all of these are organolithiums configurationally labile.

B. Nonbenzylic Organolithiums

In the absence of mesomeric delocalization, the carbanion is η^1 coordinated to the lithium, but enantiomerization parameters have only been determined for a few systems. The meso organolithium shown in Figure 3.11 is an example of an organolithium which is configurationally stabile for only a few minutes at –78 °C.[47] The rate of epimerization of this lithiohydrocarbon was accelerated by lithium iodide and was strongly dependent on the total organolithium concentration, suggesting that the inversion involves a dimeric (or possibly higher) aggregate in the transition state. Consistent with this hypothesis is the fact that the tridentate ligand, PMDTA, which would be expected to inhibit aggregation, retards the rate of epimerization by a factor of 20, and increases the half life from 9 minutes to greater than two hours at –78 °C.

C. Heteroatom Stabilized Organolithiums

The dynamics of enantiomerization of heteroatom-stabilized organolithiums can vary widely, as shown by the examples in Figure 3.12. The lithiated *S,N* acetal shown in Figure 3.12a[48] is related to several acyl anion equivalents that have been developed (see below).[48–51] This organolithium is a monomer in solution, and the barrier to inversion is similar in magnitude to the examples in Figure 3.10. Two pairs of examples illustrate the difficulty in predicting the effect of chelation on enantiomerization barriers.[52] Figure 3.12b–c illustrate organolithiums stabilized by two silane groups; in the latter instance, chelation by a tertiary amine lowers the free energy barrier slightly. The authors found that the enantiomerization is unimolecular and suggest that the chelated example may invert by a conducted tour mechanism.[44–46,53] In this context, the "conducted tour" refers to a mechanism whereby the cation is "escorted"

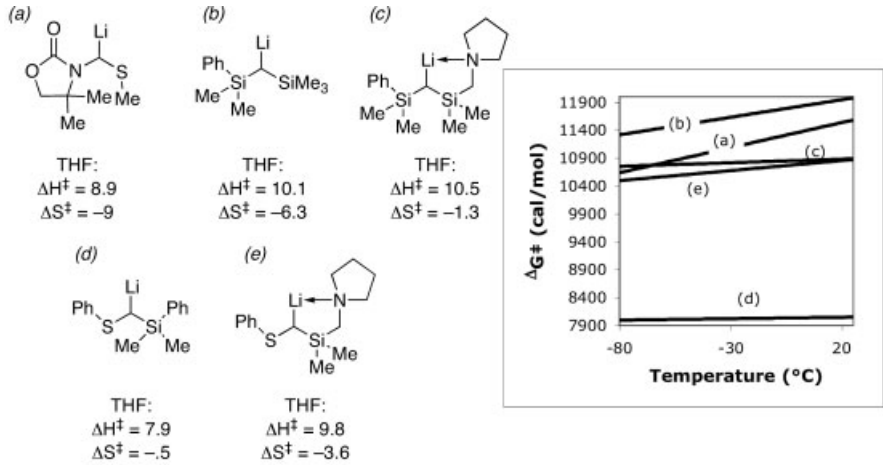

Figure 3.12. Enantiomerization barriers for nonbenzylic organolithiums: (*a*) Dipole-stabilized *S,N*-acetal;[48] (*b–e*) α-disilyl and α-thio-α-silyl organolithiums, with and without chelation.[52]

from one face of the carbanion to the other by a pendant heteroatom, to which it remains coordinated.

The effect of chelation in the two examples in Figure 3.12d–e, having one α-thio and one α-silyl group, is the opposite of that in the examples of Figure 3.12b–c.[52] Even though the enantiomerization is also unimolecular, chelation raises the free energy of activation. The small entropies of activation in these examples suggest minimal additional solvation in the transition state. Since these compounds all have $\Delta G^{\ddagger} \leq 12$ kcal/mol below +25 °C, and with reference to Figure 3.7, it is clear that none will have appreciable configurational stability.

The lithiated pyrrolidines shown in Figure 3.13a–c are much more stable, and could not be evaluated by DNMR.[54] The dynamics were evaluated in a 4:1 hexane:ether solvent mixture because similar compounds can be resolved dynamically in the presence of a chiral ligand in this solvent system.[55] All show first order kinetics for enantiomerization, but this would be observed for a monomer to monomer or a dimer to dimer inversion. The solution structures are complex,[54,56] and hypotheses about the mechanism of enantiomerization are tentative. Computational studies indicate that the lowest energy transition structures for solvated enantiomerization of all three lithiopyrrolidines are monomeric.[54,57] The *N*-methoxyethylpyrrolidine and the *N*-ethylpyrrolidine in Figure 3.13a–b have significantly larger enthalpies of activation than any of the previous examples, and negligible entropies of activation. The enantiomerization of the *N*-ethyl compound, which exists as a mixture of monomer and dimer, was accelerated by PMDTA, consistent with a lower barrier in a monomeric transition state. The enantiomerization of the *N*-methoxyethyl compound was found to be zero order in THF (*i.e.,* $[THF]^0$),

consistent with little additional solvation in the transition state. The *N*-ethyl and the *N*-Boc pyrrolidines in Figure 3.13b–c were also studied in ether because of decomposition above –80 °C in THF. The *N*-Boc pyrrolidine offered a big surprise: the very large entropy of activation, along with an enormous *positive* entropy of activation, which is in stark contrast to all the previous examples. This large, positive entropy of activation persists when the measurements were conducted in hexane ether mixtures. The authors calculated a transition structure in which the lithium is intimately bound to the carbonyl oxygen of the *N*-Boc, and concluded that the enantiomerization occurs by a conducted tour mechanism. In this scenario, the authors speculated that the bulky *O*-tert-butyl group must move through the solvent cage and force significant solvent reorganization.[54] An additional contribution to the positive entropy could be increased pseudorotation in the 5-membered ring as the C–Li bond is broken.[58] Later work showed that the diamines TMEDA and sparteine change the mechanism of carbanion inversion, whereas the diamine diisopropylbispidine (DIB), does not.[58] Sparteine and TMEDA have the interesting effect of reducing both the enthalpy of activation (C–Li bond breaking) and entropy of activation (the transition state is more organized, consistent with coordination of the additional ligand). Diisopropylbispidine

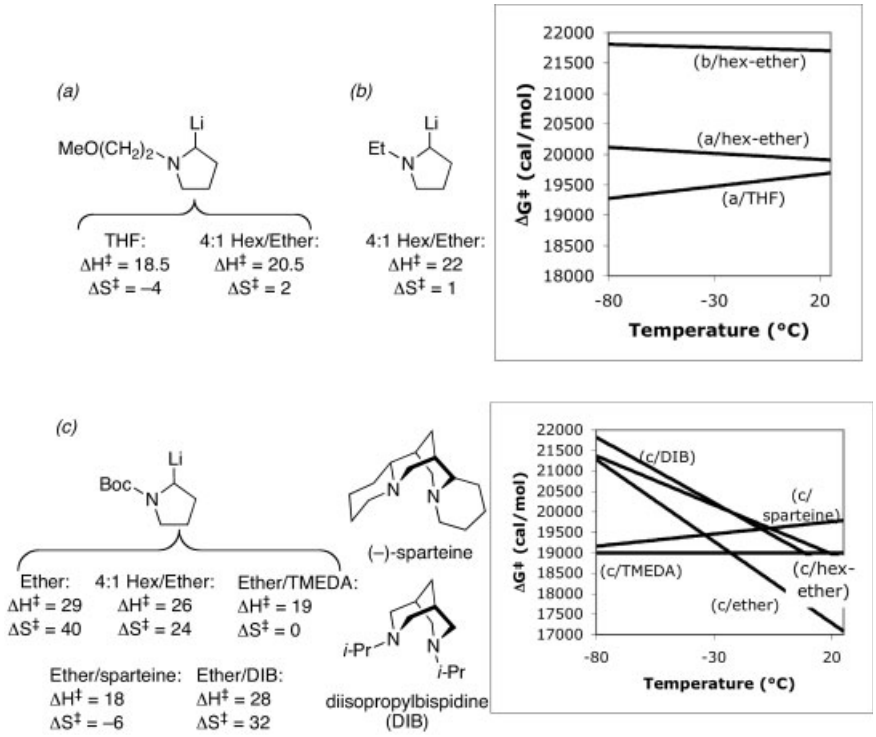

Figure 3.13. (*a–c*) Lithiated pyrrolidines.[54]

does not appear to bind the lithiums nearly as strongly, since the inversion barriers across the temperature range –80 to +25 °C is essentially the same as the barriers in hexane/ether.

D. Diastereomeric Bias

In all of the above examples, there is only one chirality element to consider. In cases of high configurational lability in a parent system, stereoelectronic factors and additional chirality elements can impart a diastereomeric bias to a system that results in a configurationally stable organolithium. An early example of presumed diastereomeric bias, inferred from the products of electrophilic substitution (and assumed to be $S_E2$ret), is shown in Figure 3.14a. The organolithium is formed by deprotonation, then quenched with methyl iodide to afford the substitution product in 98:2 dr. In this example, the more stable *(R)* organolithium diastereomer has the phenyl and the isopropyl groups trans in the bicyclic chelate.[59] Although α-thioorganolithiums are usually not configurationally stable, the *(S)* organolithium shown in Figure 3.14b, which is formed by a diastereoselective deprotonation, is configurationally stable at low temperature.[60] A particularly well-characterized organolithium, also formed by deprotonation, is shown in Figure 3.14c.[48,51,61] This lithiated *S,N*-acetal is structurally related to the achiral species depicted in Figure 3.12a. Detailed NMR and IR spectroscopic studies, and computational studies revealed the stereochemical features.[48] The geminal phenyl groups (in particular the phenyl group cis to the isopropyl group) restrict the

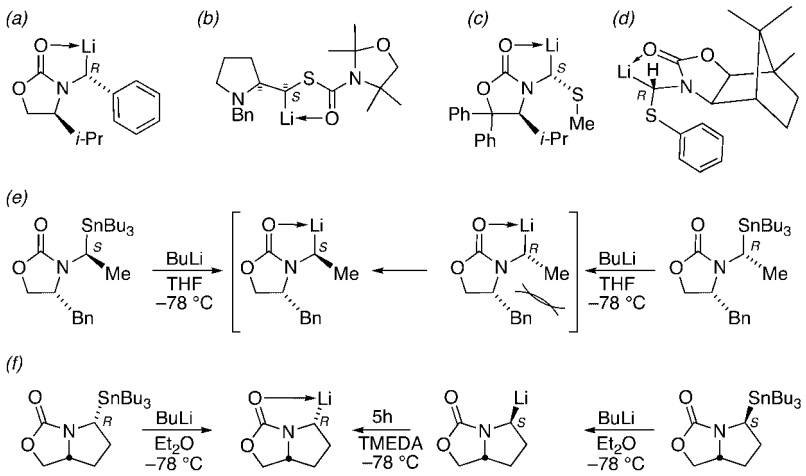

Figure 3.14. Organolithiums that are configurationally stable due to a diastereomeric bias. (*a*) α-lithio-*N*-benzyloxazolidinone;[59] (*b*) α-thioorganolithium;[60] (*c–d*) Lithiated *S,N*-acetals;[48,50] (*e*) Fast equilibration of diastereomeric organolithiums;[64] (*f*) Slow equilibration of diastereomeric organolithiums.[65]

conformational space of the adjacent isopropyl group, forcing the isopropyl methyls into a conformation that is anti to the two phenyl groups.[62] Stereoelectronic factors place the S–CH_3 bond antiperiplanar to the C–Li bond. The lithium is probably coordinated to the carbonyl oxygen,[63] (the Li–O bond is calculated to be 2.044 Å, while the Li–C bond is 2.221 Å), so the *(S)* configuration at the metal bearing carbon places the –SCH_3 group anti to the isopropyl group, or on opposite faces of the bicyclic system. Calculations at the B3LYP/6-31+G(d)//PM3 level of theory place this structure 4.3 kcal/mol lower in energy than the diastereomeric organolithium having the *(R)* configuration at the metal-bearing carbon. Similar factors control the configuration and conformation of the related organolithium in Figure 3.14d.[50] The chiral acyl anion equivalents in Figure 3.14c–d react with several electrophiles with retention at the metal-bearing carbon. Figure 3.14e illustrates the generation of each of a diastereomeric pair of organolithiums, which equilibrate rapidly at –78 °C (even more rapidly in the presence of TMEDA) to afford the less crowded diastereomer of the bicyclic chelate.[64] Figure 3.14f illustrates a similar experiment in a sterically constrained bicyclic system. In this case, the epimerization is considerably slower, but is driven by the fact that only the diastereomer having the *(R)* configuration at the metal-bearing carbon can be easily coordinated by the carbonyl oxygen in this tricyclic system.[65]

Metalated amides and amidines of tetrahydroisoquinolines are useful intermediates in alkaloid synthesis,[3,66,67] and the details of the stereoselective lithiation and electrophilic substitution are instructive. When the α-deuteriotetrahydroisoquinoline shown in Figure 3.15a was lithiated and alkylated with methyl iodide, the product was obtained with 98% diastereoselectivity *(S)*, and less than 5% of the deuterium label.[68] To account for the lack of a primary deuterium isotope effect, the authors postulated a mechanism whereby the organization of a bidentate chelate of the butyllithium as the rate determining step in the metalation. In the chelate, the butyl group is trans to the isopropyl, placing it proximal to the H_α proton (or deuterium), resulting in a stereoselective deprotonation. The authors postulated that the intermediate organolithium has the *(R)* configuration (*i.e.,* that the organolithium does not equilibrate to a mixture of diastereomers) and that alkylation with methyl iodide occurs with inversion. Deuteration with DMSO-d_6 afforded the *(R)* deuterated product. If the assumption of the configuration is correct, alkylation occurs with inversion and deuteration with retention. The chiral auxiliary is necessary to maintain configurational stability, as shown by the example in Figure 3.15b.[69] In this case, a formamidine lacking a stereocenter was used to mediate the deprotonation of an enantioenriched 1-methyltetrahydroisoquinoline at –78 °C. Quenching with benzyl chloride at –100 °C gave racemic product. These results are consistent with an inherently labile organolithium that can be stabilized in a single configuration by a chiral auxiliary. In the absence of the chiral auxiliary, enantiomerization probably occurs through a conducted tour.

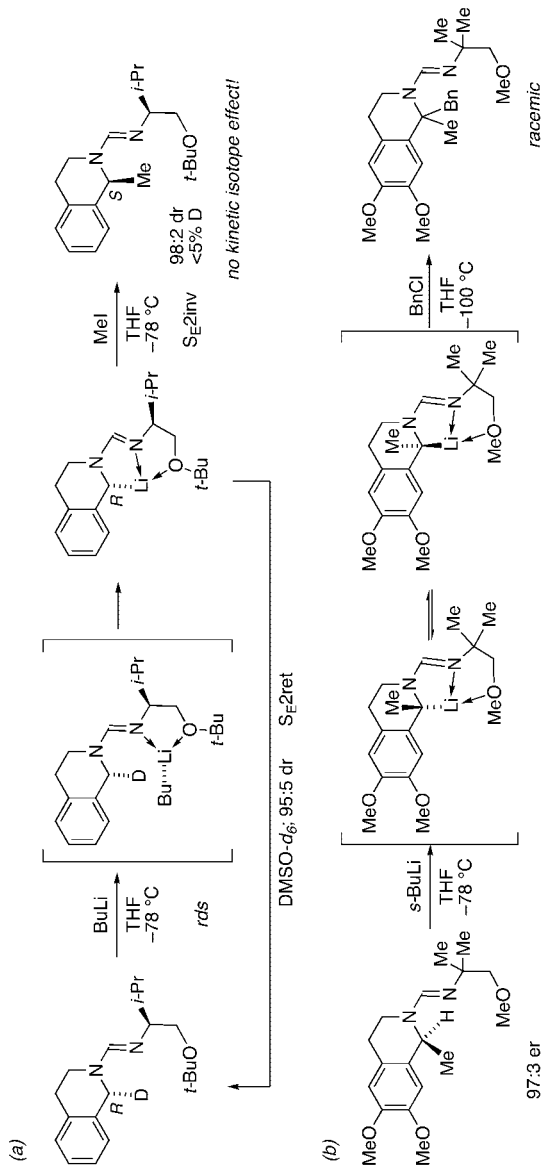

Figure 3.15. Formamidines: (*a*) Configurational stability imparted by a chiral auxiliary;[68] (*b*) Configurational lability in the absence of a chiral auxiliary.[69]

VIII. DYNAMIC RESOLUTIONS

When the ratio of a mixture of stereoisomers in solution changes for some reason, the phenomenon is called an asymmetric transformation of the first kind. Asymmetric transformations of the second kind involve a similar equilibration of stereoisomers, with concomitant separation of one of them by crystallization or chemical reaction. A subset of asymmetric transformations are called dynamic thermodynamic[1,70,71] and dynamic kinetic[1,72,73] resolutions. In organolithium chemistry, dynamic resolutions involve an external, chiral ligand on lithium. Depending on the barrier for interconversion between the two diastereomeric organolithium complexes, and the magnitude of the inversion barrier relative to the rate of reaction, the resolutions may be classified as follows:

Dynamic thermodynamic, if the barrier to organolithium inversion is relatively high compared to the rate of subsequent reaction; or
Dynamic kinetic, if the barrier to organolithium inversion is low relative to the rate of subsequent reaction (*i.e.,* Curtin-Hammett[38] conditions).

The chapter in this volume by Coldham and Sheikh cover these two topics thoroughly. The following discussion is therefore selective.

A. Dynamic Thermodynamic Resolutions

Dynamic thermodynamic resolution is distinct from classical kinetic resolutions and from dynamic kinetic resolutions (see below) in that equilibration of organolithiums and resolution by selective reaction can often be accomplished in separate steps. The energy profile for a dynamic thermodynamic resolution is shown in Figure 3.16. Enantiomeric organolithium compounds, *(R)*-RLi and *(S)*-RLi, interconvert with rate constant k_{ent} and enantiomerization barrier $\Delta G^{\ddagger}_{ent}$. Complexation with a chiral ligand, L*, affords a diastereomeric mixture of organolithium complexes, *(R)*-RLi·L* and *(S)*-RLi·L*, having an energy difference of ΔG°, and which invert with rate constant k_{inv}/k_{-inv}

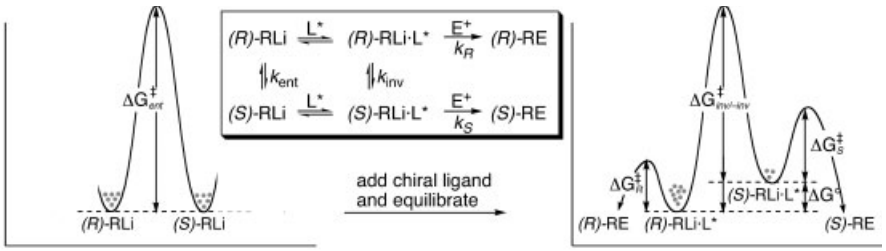

Figure 3.16. Energy profile and reaction scheme for a dynamic thermodynamic resolution.[1,70]

and epimerization barrier $\Delta G^{\ddagger}_{inv/-inv}$. Reaction with an electrophile then affords products *(R)*-RE and *(S)*-RE. The important feature of this scheme is that *(R)*-RLi·L* and *(S)*-RLi·L* can interconvert; it does not matter whether this happens by direct epimerization (rate constant $k_{inv/-inv}$) or by dissociation from L* and enantiomerization (rate constant k_{ent}, see Figure 3.16, inset). In dynamic thermodynamic resolutions, k_R, $k_S > k_{inv}$, but the relative rates, k_{inv}, k_{ent}, k_R, k_S, and the percent conversion to products can all influence the product ratio.[70] If the reaction with electrophile E^+ is taken to complete conversion, the product ratio will reflect the thermodynamic ratio of the two diastereomeric complexes, *(R)*-RLi·L* and *(S)*-RLi·L*. However, if k_R, $k_S >> k_{inv}$, the relative rates of reaction, k_R/k_S, and the relative population of the two species determine the product ratio at partial conversion, just as in classical kinetic resolutions.[70] Note that the rates of product formation depends on the quantities k_R[*(R)*-RLi·L*] and k_S[*(S)*-RLi·L*], respectively, not just k_R/k_S. Thus, for the less stable diastereomer (*(S)*-RLi·L* in this example) to provide the major product, the quantity k_S[*(S)*-RLi·L*] must be greater than k_R[*(R)*-RLi·L*]. In Figure 3.16, the more stable diastereomer has the faster rate of reaction to product, but the opposite situation can also occur.

A clear picture of a dynamic thermodynamic resolution can be found in an example where the organolithium is configurationally stable at low temperature, but labile at higher temperatures. Figure 3.17 illustrates such an example, in which the results of several experiments were used to produce an energy profile for the entire system.[74] The racemic dilithiated *ortho*-ethyl pivanilide was generated by double deprotonation at –25 °C in methyl *tert*-butyl ether (MTBE), then cooled to –78 °C for 15 minutes. A solution of sparteine in MTBE, precooled to –78 °C, was then added. This procedure should afford a 50:50 mixture of the *(S)* and *(R)* organolithium·sparteine complexes. Consistent with this is the nearly equal (56:44 ±2%) ratio of silylated products obtained when quenched with trimethylsilyl chloride (entry 1 in Figure 3.17). In contrast, quenching with 10 mol% electrophile afforded a 91:9 ratio (*R*:*S*), which was taken to indicate the difference in activation energies, $\Delta G^{\ddagger}_R - \Delta G^{\ddagger}_S = 0.81$ kcal/mol, for reaction of the diastereomeric complexes with TMS-Cl at –78 °C (entry 2). Entry 3 describes an experiment in which the *(R)* and *(S)* organolithium complexes were allowed to equilibrate at –25 °C, before being re-cooled to –78 °C and quenched. The 92:8 ratio of enantiomers (63% yield) reflects the relative population of the two organolithium diastereomers. After correcting for the unequal ratio of enantiomers obtained in entry 1, a free energy difference, $\Delta G°$, of 0.97 kcal/mol was calculated for the organolithium diastereomers. If the 92:8 thermodynamic ratio of diastereomeric organolithiums is treated with 10 mol% electrophile, the product is obtained in a 99:1 er (entry 4). This product ratio (see above) is due both to the difference in energies of activation for the two organolithium diastereomers, and to their 92:8 relative population. Since in this case, the more highly populated (more stable) diastereomer is also the most reactive ($\Delta G^{\ddagger}_R > \Delta G^{\ddagger}_S$),

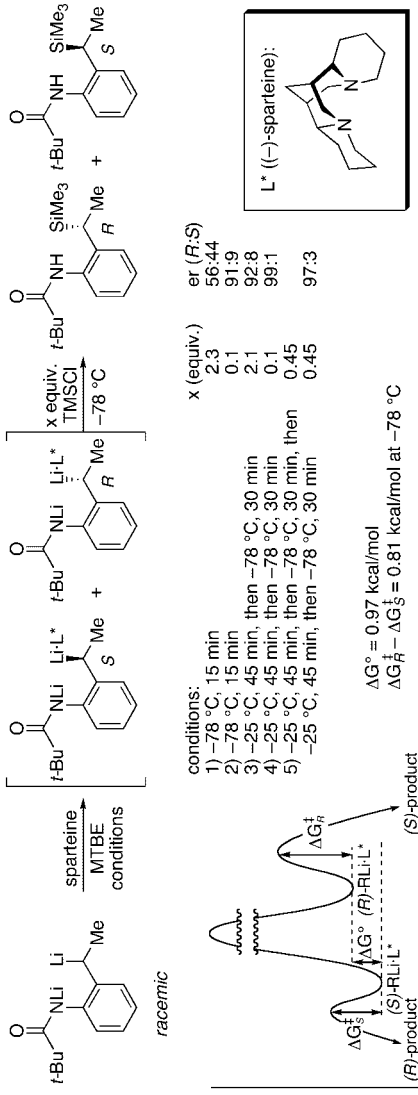

Figure 3.17. An quantitative energetic analysis of a dynamic thermodynamic resolution.[74]

the er of the product can be improved by diastereomeric recycling in the same pot, as illustrated by entry 5. After equilibration at –25 °C and cooling to –78 °C, the 92:8 ratio of organolithium diastereomers is treated with 45 mol% electrophile. In a control experiment, workup at this point afforded a 98:2 er of product. Warming the reaction mixture to –25 °C, cooling again to –78 °C, then treating with another 45 mol% electrophile, afforded silylated product in a 97:3 er and a yield of 72%.

B. Dynamic Kinetic Resolutions

A dynamic kinetic resolution[1,72,73] occurs in organolithium chemistry when diastereomeric organolithium complexes, *(R)*-RLi·L* and *(S)*-RLi·L* (L* is a chiral ligand), which epimerize with rate constant k_{inv}, are allowed to react with an electrophile (Figure 3.18). The electrophilic substitution proceeds with rate constants k_R and k_S, acting on the *(R)*-RLi·L* and *(S)*-RLi·L* complexes, respectively, to give products *(R)*-RE and *(S)*-RE. If $k_{inv} >> k_R$, k_S, the process follows Curtin-Hammett kinetics,[38] and the *(R)*-RE/*(S)*-RE product ratio depends on the difference in transition state energies, $\Delta G^{\ddagger}_{TS}$. Figure 3.18 illustrates this limiting case, in which $k_{inv} >> k_R$, k_S. Note that the product ratio depends on both ratio of rates k_R/k_S and k_{inv}/k_R since, assuming that *(R)*-RLi·L* is the faster reacting enantiomer, k_{inv} and k_R compete.[73,75] In the absence of kinetic studies on the rates of inversion *vs*. substitution, one can use deuterium labelling to deconvolute the deprotonation step from the substitution step. Alternatively, one can use the Hoffmann test. Each of these methods are discussed, in turn, below.

An example that obeys Curtin-Hammett kinetics in organolithium substitutions is found in the chemistry of tetrahydroisoquinolyl oxazolines shown in Figure 3.19.[76] This is not an example of a dynamic resolution, since it involves a chiral auxiliary in the organolithium, but it illustrates a method for determining the source of stereoselectivity in an electrophilic substitution. In these oxazolines the deprotonation is stereoselective, but the stereoselectiv-

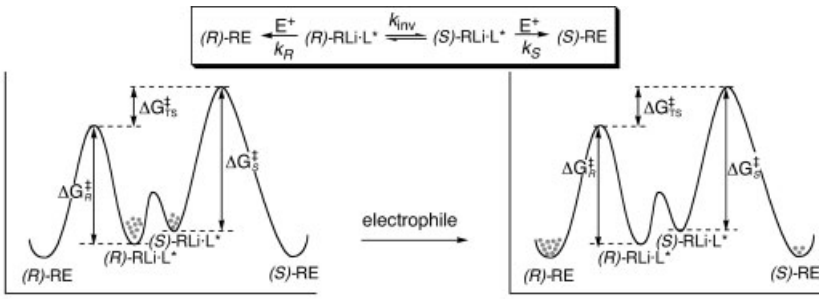

Figure 3.18. General scheme of a dynamic kinetic resolution in organolithium chemistry.[1]

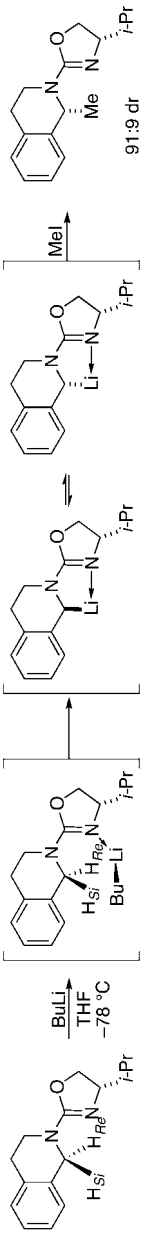

Figure 3.19. Lithiation/alkylation of tetrahydroisoquinolyloxazolines.[67,76,77]

ity in the deprotonation is not the source of the diastereoselectivity of the overall sequence. This was shown by a pair of deprotonations using diastereomeric deuterium labelled compounds. With H_{Si} replaced by deuterium, the methylated product is obtained with 50% deuterium incorporation and 92:8 dr. With deuterium in place of H_{Re}, the methylated product is obtained with 97% deuterium incorporation and 91:9 dr. From this data, the relative rate for removal of H_{Si} over H_{Re} was calculated to be 5.8:1. Prior coordination of the butyllithium to the oxazoline nitrogen was postulated to account for the selectivity in the deprotonation, similar to the coordination complex postulated for the formamidines in Figure 3.15a. However in the case of the oxazolines, there is an isotope effect of approximately 5.9, indicating that deprotonation is rate-determining in this system. The variable deuterium content in the products, coupled with the consistent diastereoselectivity in the two experiments, clearly implicate equilibration of the organolithium diastereomers shown. The initial conclusion in 1987[76] was that the stereoselectivity in the alkylation was due to a thermodynamic preference for one organolithium diastereomer, as in the formamidines of Figure 3.15,[68] but subsequent studies were less conclusive and Curtin-Hammett kinetics were also considered.[77] Later, DNMR studies placed an upper limit of 8.2 kcal/mol on the barrier to inversion, suggesting that Curtin-Hammett kinetics were the most likely explanation for the stereoselectivity in the alkylation.[67]

C. Competing Inversion and Substitution: The Hoffmann Test

It is often less obvious than in the above examples, that a dynamic kinetic resolution is operative. In between these two limiting situations are instances where the rates of inversion and substitution are similar. The energy profile is shown in Figure 3.20. The critical aspect of this situation is the configurationally stablility of the organolithium on the time scale of its reaction with an electrophile. In the continuum of relative rates, when k_{inv}, k_R, and k_S are close in value, the mathematical treatment is complex,[70] and product ratio is a function of both relative rates and percent conversion. The chapter by Hoffmann in this volume discusses the theory behind the Test that was dis-

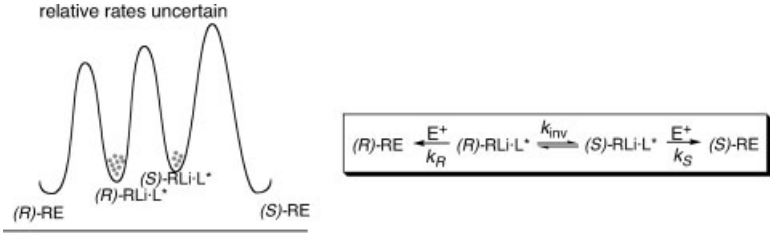

Figure 3.20. Energy profile of system where k_{inv}, k_R, and k_S are comparable.

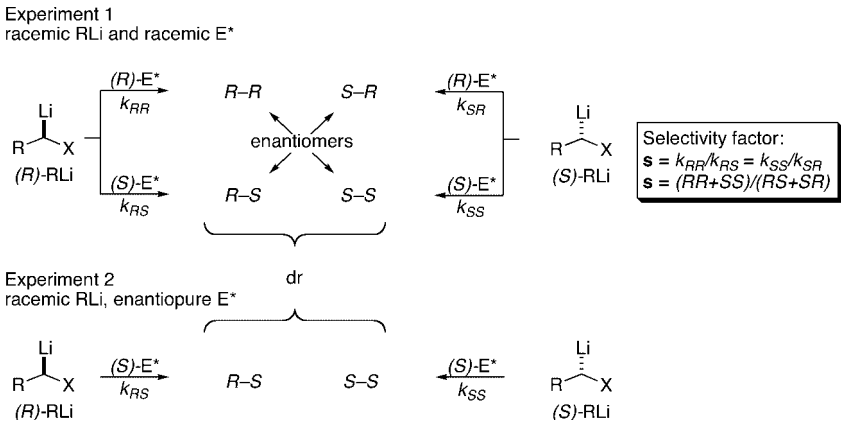

Figure 3.21. The Hoffmann test for configurational stability on the time scale of the reaction with an electrophile.[78,79]

covered in his group, and also relates the interesting story of its development. Variations on the Test are also discussed in the chapter by Kizirian in this volume.

Under some circumstances, it is possible to use mutual kinetic resolutions to evaluate relative rates of inversion and electrophilic substitution.[78,79] The Hoffmann test is based on the reaction of a chiral organolithium with a chiral electrophile, and analysis of the diasteromer ratio of the products. Two experiments are run (Figure 3.21). In experiment 1, racemic organolithium is allowed to react with racemic electrophile (*rac*-E*); the kinetic resolution selectivity factor, **s**, is evaluated by determining the diastereomer ratio of the products, which reflects the relative rates k_{RR}/k_{RS} for formation of the two products.[80] For obvious reasons, the ratio must not be unity; for practical reasons, it is best if the kinetic resolution has a low selectivity factor, $1.2 < \mathbf{s} < 3.0$ (see below). In experiment 2, the same reaction is carried out with enantiopure electrophile, and the reaction carried to 100% conversion. If the organolithium is configurationally stable, the product in experiment 2 will have a 50:50 dr. If the dr of the products of the two experiments is the same (and not 50:50), the organolithium is configurationally labile on the time scale of the reaction, and the organolithium has been kinetically resolved. If the diastereomer ratios from the two experiments are different, the organolithium is configurationally stable. In other words, comparison of the dr for the two experiments reveals the configurational stability of the organolithium on the time scale of the electrophilic substitution.

There are some limitations of the Hoffmann test that have been recognized from the beginning.[78]

1. The dr in Experiment 2 depends on the percent conversion. In order to ensure complete conversion in Experiment 2, an excess of the chiral

electrophile should be used. This will require longer reaction times than were required in Experiment 1, and the extra length of time depends on the selectivity factor, **s**. For this reason, it is prudent to employ reactions in which **s** is small (≤3.0).

2. If the rate of reaction in Experiment 2 is faster than the rate of the addition of the organolithium to the electrophile, inverse addition should be employed.
3. A 50:50 dr in Experiment 2 can only be reached if the electrophile is enantiopure. Good results are still possible if a moderate excess (1–5 equivalents) of electrophile having ≥98.5:1.5 er are used.
4. If there are side reactions that consume the organolithium, they should not exceed ten percent.

Additionally, in light of several pieces of evidence presented in this chapter, one should bear in mind some further issues that could complicate matters:

5. It is assumed that the steric course of the reaction of the chiral organometal is 100% selective, *i.e.,* that the electrophilic substitution is 100% $S_E2$ret or 100% $S_E2$inv, and that SET is not a competing mechanism.
6. It is possible that the rate of racemization changes as a reaction proceeds. Many electrophilic substitutions accumulate lithium halide or lithium alkoxide salts as the reaction proceeds. Lithium salts sometimes facilitate inversion of organolithiums.[47]
7. An asymmetric synthesis would use an enantiopure organolithium. Since the Hoffmann test uses racemic organolithium, it assumes that the aggregation state of enantiopure and racemic organolithiums are the same, and that the kinetics of reactions of electrophiles with homochiral and heterochiral aggregates (or monomers in equilibrium with them) are the same. However, aggregation can affect the rate of inversion, in either direction – depending on the system!

IX. STERIC COURSE OF ELECTROPHILIC SUBSTITUTIONS: η^1 ORGANOLITHIUMS

Electrophilic, aliphatic, bimolecular substitutions, abbreviated S_E2 in the Hughes-Ingold terminology,[36] may be categorized as $S_E2$ret or $S_E2$inv,[35] depending on the steric course. Substitution can also occur stepwise, via single electron transfer (SET) and subsequent coupling of the resultant radicals. Usually, intermolecular radical couplings are stereorandom, but advances in stereoselectivity of radical coupling reactions show significant promise.[81]

For η^1 organolithiums having central chirality at the metal-bearing carbon, possible mechanisms for electrophilic substitution are illustrated in Figure 3.22. Replacement of lithium by an electrophile can take place with inversion, designated $S_E2$inv,[35] as illustrated in Figure 3.22a. The trigonal by-

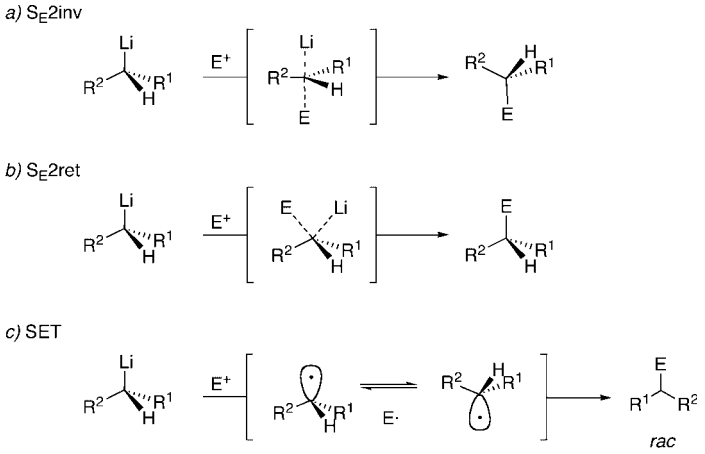

Figure 3.22.

pyramidal transition stucture can be stabilized by resonance if the groups R^1 and/or R^2 are vinyl or aryl. The invertive transition state can be destabilized by steric hindrance – especially when the electrophile is an alkyl halide that must also invert in the transition state. Substitution may also occur with retention of configuration at carbon, as shown in Figure 3.22b, and designated S_E2ret.[35] Sometimes, retentive substitutions occur when the electrophile is a carbonyl compound, and coordination to the lithium is possible. However, coordination of the halogen of an alkyl halide to the lithium, and retentive substitution through a four-membered-ring transition state, is symmetry forbidden.[34,35] The third possibility is single electron transfer, SET, shown in Figure 3.22c. In this instance, the carbanion is oxidized to a rapidly inverting radical by the electrophile; subsequent coupling affords racemic products. Radical disproportionation, dimerizations, and other undesired side reactions can also occur following SET. Various combinations of organolithiums and electrophiles may prefer one of the two polar pathways, but when a polar pathway is slowed, for example by steric crowding, SET can intervene. Examples illustrating these points follow.

A. Examples of S_E2inv

Examples of invertive electrophilic substitutions (Figure 3.22a) of organolithiums that are known to be configurationally stable under the reaction conditions are illustrated in Figure 3.23. In the first example, Figure 3.23a, double deprotonation of *ortho*-ethyl pivanilide affords an organolithium that can be dynamically resolved, with sparteine at –25 °C, to the *R* enantiomer shown. Control experiments confirmed that the organolithium is configura-

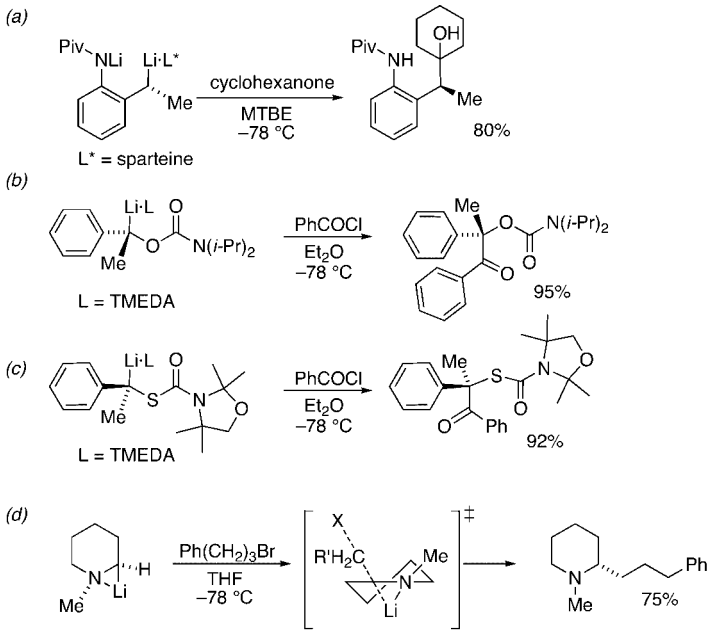

Figure 3.23. S_E2inv electrophilic substitutions of configurationally stable organolithiums. (*a*) laterally lithiated pivanilide;[32] (*b*) dipole and mesomerically stabilized α-oxyorganolithium;[31] (*c*) dipole and mesomerically stabilized α-thioorganolithium;[82] (*d*) unstabilized α-aminoorganolithium.[83,84]

tionally stable at –78 °C, and reaction with all electrophiles tested proceeds with inversion of configuration.[32] No rationale for the steric course was given, and the solution structure of the dilithio compound is not known. Possibly, a sparteine coordinates to the lithium and blocks coordination of the cyclohexanone carbonyl. The bulky sparteine could also inhibit approach of the electrophile to the carbanion from the side bearing the complexed lithium, while the benzene ring also stabilizes an sp^2-like transition structure during the carbanion inversion. Figure 3.23b shows an example of a lithiated tertiary carbamate, also configurationally stable at –78 °C.[31] Some electrophiles react with this same organolithium with retention (see below). The authors rationalize the invertive reaction by suggesting that electrophiles that are particularly reactive (having a low energy LUMO), and are weak Lewis bases (poor ligands for lithium), react preferentially with inversion when the carbanion is also mesomerically stabilized. Inversion is also seen in α-thio organolithiums that have appreciable s-character (*i.e.,* more planar carbanion) and crowding around the lithium (Figure 3.23c).[82] This α-thioorganolithium exhibits surprising configurational stability, with a half-life for enantiomerization estimated at several hours at 0 °C. In the fourth example (Figure 3.23d), alkylation of 2-lithio-*N*-methylpiperidine with primary alkyl halides proceeds

with inversion. In this case, there is no mesomeric stabilization of an invertive transition state, so the driving force for the invertive alkylation is not obvious.[83,84] Interestingly, alkylation with tributyltin chloride proceeds with retention. NMR studies revealed that the solution structure of the organolithium is a nitrogen-bridged monomer as shown.[85] In contrast, 2-lithio-*N*-methylpyrrolidines, which are homochiral dimers in solution,[85] alkylate with 80% inversion and 20% retention by a polar (*i.e.,* nonradical) mechanism.[86] It may be that steric influences are at work here, as suggested by diversion of both lithiopyrrolidines and lithiopiperidines to SET mechanisms when the rings are substituted (see below).[87,88] The alkyl group on nitrogen can affect the steric course. For example, in contrast to *N*-methyl-2-lithiopyrrolidine, *N*-2,3,3-trimethylallyl-2-lithiopyrrolidine gives products of apparently complete retention with trimethylsilyl chloride, tributyltin chloride, and carbonyl-containing electrophiles.[89]

B. Examples of S_E2ret

Figure 3.24 illustrates several examples of retentive substitution (Figure 3.22b) of configurationally stable organolithiums. The reaction of α-alkoxyorganolithiums lacking mesomeric stabilization, typified by the seminal example in Figure 3.24a, undergo retentive substitution exclusively, inde-

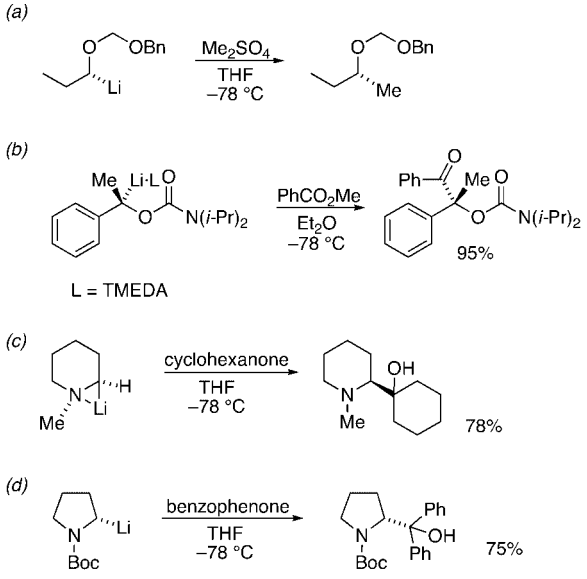

Figure 3.24. S_E2ret electrophilic substitutions for configurationally stable organolithiums. (*a*) unstabilized α-alkoxyorganolithium;[90] (*b*) dipole and mesomerically stabilized α-alkoxyorganolithium;[31] (*c*) unstabilized α-aminoorganolithium;[83,84] (*d*) dipole stabilized α-aminoorganolithium.[21,22,91,92]

pendent of the electrophile.[14,90] Figure 3.24b shows the same organolithium illustrated previously in Figure 3.23b. However in this case, acylation with an ester proceeds with retention of configuration.[31] The rationale offered for the difference in behavior is that the ester is less reactive and is a stronger Lewis base than the acid chloride, making it a better ligand for lithium, and leading to retentive substitution. In α-alkoxyorganolithiums, when coordination of a carbonyl electrophile to the lithium is likely, retentive substitution follows. Figure 3.24c illustrates the retentive substitution of 2-lithio-*N*-methylpiperidine with cyclohexanone.[83,84] In contrast to the alkylation illustrated in Figure 3.23c, reaction of this organolithium with all carbonyl compounds tested (carbon dioxide, dimethyl carbonate, methyl chloroformate, ketones, and aldehydes), proceeded with retention of configuration (except benzophenone – see below). The dipole-stabilized lithiopyrrolidine shown in Figure 3.24d reacts with trimethylsilyl chloride, tributylstannyl chloride, and carbonyl electrophiles such as ketones with complete retention.[21,22,91] These compounds do not react well with alkyl halides, probably due to the intervention of SET (see below).

C. Examples of SET

When does SET complicate synthetic schemes? For α-alkoxyorganolithiums and α-thioorganolithiums, rarely – if ever. In the case of α-aminoorganolithiums, two factors seem to be important. One is steric hindrance of an invertive electrophilic substitution, and the other is the reduction potential of the electrophile *vs* the oxidation potential of the organolithium. Eberson has extended Marcus theory to organic processes,[93] and postulated that the partitioning of SET and polar pathways is dependent in part upon the difference in oxidation potential of the nucleophile and the reduction potential of the electrophile. According to this theory, reactions whose free energies of electron transfer, ΔG_{ET}, are more endothermic than +23 kcal/mol at room temperature are unlikely to occur by SET because the rate would be too slow. Conversely, if $\Delta G_{ET} < -20$ kcal/mol, then SET will be fast. In between these extremes, other factors may come into play. Pross has suggested that both SET and polar pathways involve an initial single electron shift,[94] and if coupling of the two spins is feasible following the single electron shift, a polar pathway is followed. Moreover, Pross asserted that any factor (steric, electronic, or geometric) that operates to inhibit or hinder the coupling process will tend to favor a SET pathway over a polar one.

Invertive electrophilic substitutions involving sp^3 nucleophiles and sp^3 electrophiles are sterically demanding reactions, since both require inversion at both carbons, as shown in Figure 3.25. Tell-tale signs of SET are stereorandom couplings at the metal-bearing carbon, appearance of dimers, and formation of products of radical disproportionation. Radical probe electro-

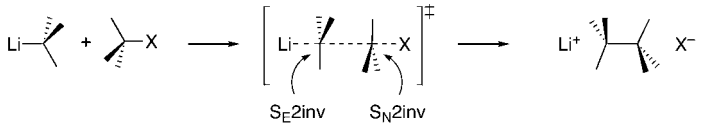

Figure 3.25. Severe crowding can result when S_E2inv and S_N2inv at sp^3 carbons are coupled.

philes can be used to confirm the presence of radicals on the reaction coordinate.[39,86,88] EPR spectroscopy has been used to detect radicals in additions of α-aminoorganolithiums to benzophenone,[84,86] but the presence of a radical in a reaction mixture does not place it on the reaction coordinate.

Figure 3.26 illustrates an example of an SET reaction that is most likely the result of steric inhibition of a preferred S_E2inv reaction pathway. Compare Figure 3.26 with Figure 3.23d. In the absence of the *tert*-butyl group (Figure 3.23d), the piperidine ring can adopt a conformation that allows invertive substitution to proceed in a relatively unhindered fashion (Figure 3.23d). On the other hand, when a *tert*-butyl group locks the ring, the axial C–H bond obstructs approach of the electrophile to the back side of the C–Li bond (Figure 3.26 inset). With invertive substitution hindered, oxidation of the carbanion to a radical ensues, producing coupling product stereorandomly and in low yield, along with a dimer and the two products of radical disproportionation.

By examining the steric course of reactions of nonracemic α-aminoorganolithiums with benzaldehyde and benzophenone, an estimate of relative oxidation potentials can been made, as shown in Figure 3.27.[6] The effect of oxidation potential of the organolithium can be seen by comparing the example in Figure 3.27a with that of Figure 3.24d, which illustrate reactions with benzophenone as electrophile.[83,84] In contrast to the *N*-Boc 2-lithiopyrrolidine, the *N*-methyl analog adds benzophenone stereorandomly. Similar comparisons of the steric course of electrophilic substitutions suggest that lithiated amidines are more prone to oxidation than lithiated *N*-methyl heterocycles,

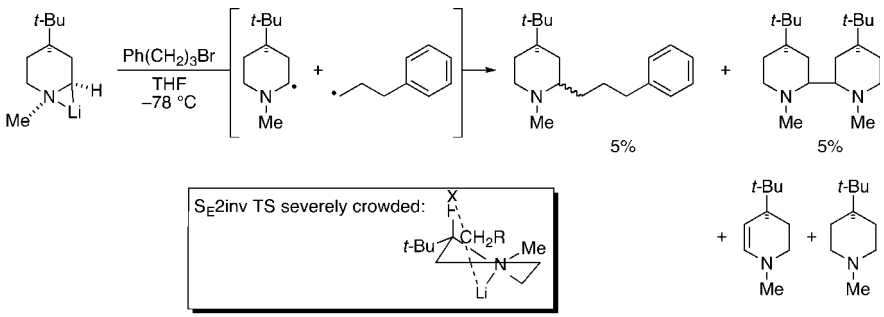

Figure 3.26. Single electron transfer can preempt electrophilic substitution when the S_E2inv transition state is crowded.[87,88]

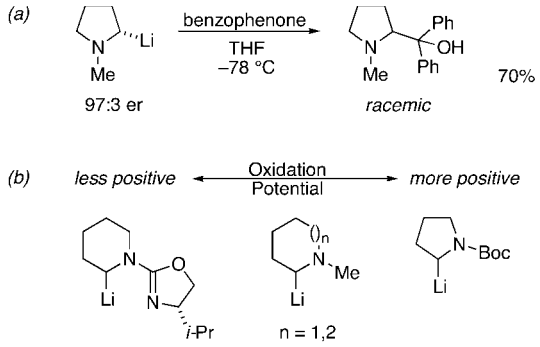

Figure 3.27. (*a*) Stereorandom addition to benzophenone attributed to SET;[86] (*b*) Approximate order of susceptibility to SET: organolithiums having less positive oxidation potentials are more easily oxidized to radicals.[6]

which are in turn more prone to oxidation than *N*-Boc compounds. It has also been noted that transmetalation from Li to MgX moves the oxidation potential to more positive values and renders SET less likely.[6,95]

D. Implicating or Eliminating SET as a Mechanism

How does one determine whether SET is operative or not? Since you can *disprove* a hypothesis, but not *prove* one, it can be a challenge. One of the more famous axioms of the fictional detective, Sherlock Holmes, states: "Eliminate all other factors, and the one which remains must be the truth."[96] Consider the reaction in Figure 3.27a;[86] racemic product is formed in good yield, and three mechanistic possibilities could be responsible:

1. $S_E2$ret and $S_E2$inv pathways compete;
2. The electrophile catalyzes the racemization of the organolithium; and
3. Radical pairs couple after SET.

The first possibility was deemed unlikely because all other carbonyl electrophiles that were examined in this system react with exclusive retention, as illustrated in Figure 3.28a.[83,84] The second possibility, catalytic racemization of the organolithium, was disproved by stirring the enantioenriched organolithium shown in Figure 3.28b with substoichiometric amounts of benzophenone. After 1h, the reaction was quenched with cyclohexanone, and analysis of the product mixture revealed that the benzophenone adduct was racemic, but the cyclohexanone adduct had the same er (within experimental error) as the starting organolithium.[86] Thus, by the Holmes axiom, SET is the most likely explanation for the stereorandom coupling.

Radical clocks can also be used to probe for single electron transfer reactions. For example, as shown in Figure 3.29a, benzyl bromide was found to couple stereorandomly with *N*-methyl-2-lithiopyrrolidine and *N*-methyl-2-

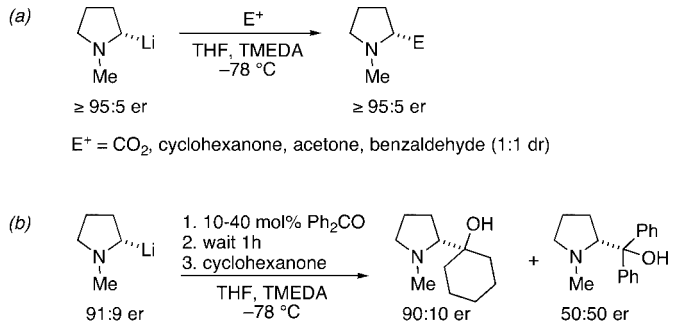

Figure 3.28. (*a*) Retentive substitution with carbonyl electrophiles;[83,84] (*b*) Evidence that benzophenone does not catalyze racemization of the organolithium.[86]

lithiopiperidine.[83,84] This activated alkyl halide is more easily reduced than an unactivated alkyl halide, so the possibility of SET was investigated using the activated halide cyclopropylmethyl bromide. Reduction of this electrophile to cyclopropylmethyl radical would be followed by fast ring opening to the butenyl radical (Figure 3.29b, inset). In the event, both pyrrolidine dimers and racemic 3-butenyl coupling products were detected. These products are consistent with an SET mechanism.

Lithiated *N*-methylpyrrolidines couple with unactivated alkyl halides to give products of lower er than the starting organolithium, as shown in Figure 3.30a.[83,84] This result could be explained by SET competing with a polar mechanism, by catalytic racemization of the organolithium, or by competing invertive and retentive pathways. The experiment illustrated in Figure 3.30b showed that radical processes are not major players in this process, since mainly hexenyl-substituted pyrrolidine was observed, with only small

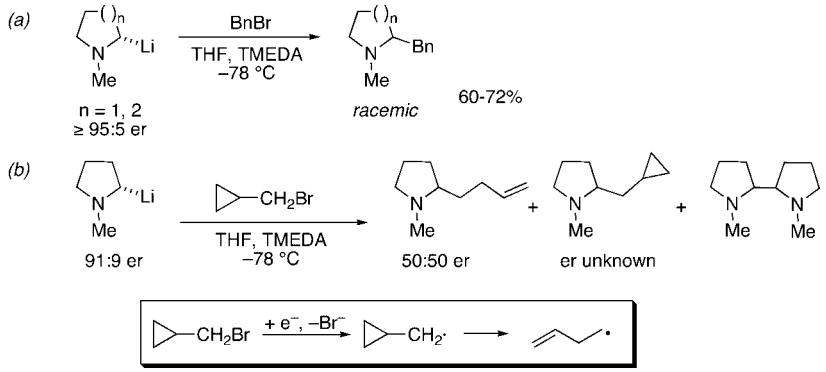

Figure 3.29. (*a*) Stereorandom coupling of benzyl bromide;[83,84] (*b*) Coupling with cyclopropylmethyl bromide affords racemic products resulting from coupling with butenyl radical, as well as dimer.[86]

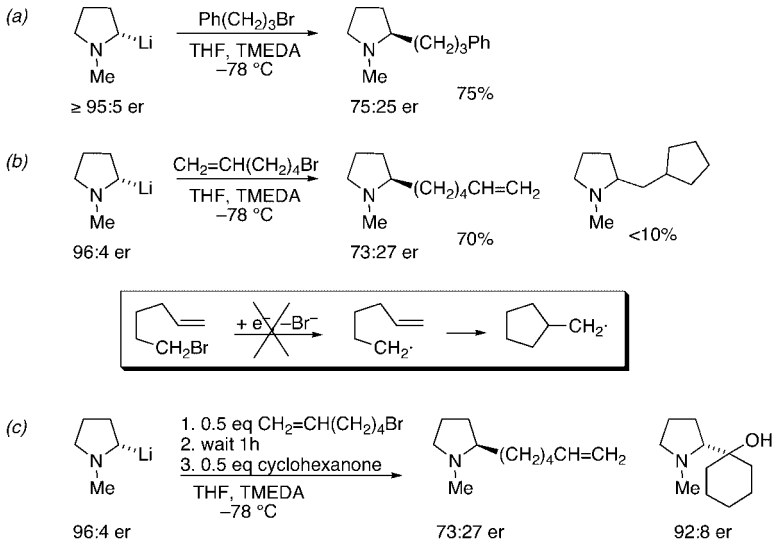

Figure 3.30. (*a*) Invertive coupling of lithiopyrrolidine with an alkyl halide, ~80% inversion and ~20% retention;[83,84] (*b*) Invertive coupling with a radical clock, giving approximately the same percentage inversion;[86] (*c*) Evidence that the electrophile is not catalyzing the racemization of the organolithium.[86]

amounts of cyclopentylmethyl-substituted product detected.[86] This experiment does not, however, completely rule out SET, since the rates of polar and radical couplings were not measured. Nevertheless, hexenyl bromide had previously been used to detect SET processes in two other types of α-aminoorganolithiums,[97] so SET seemed unlikely as a possible explanation. The possibility of catalytic racemization of the organolithium by the electrophile was disproven by the experiment shown in Figure 3.30c.[86] The conclusion was that the low er in the examples of Figure 3.30 are the result of competing $S_E2$inv and $S_E2$ret polar mechanisms. As was true of rigid 2-lithiopiperidines (Figure 3.26),[87,88] rigid 2-lithiopyrrolidines tend to suffer SET upon reaction with alkyl halide electrophiles.[88]

X. STERIC COURSE OF ELECTROPHILIC SUBSTITUTIONS: η^3 ORGANOLITHIUMS

Allylic organolithiums, either η^3 allyls or equilibrating η^1 regioisomers can add additional complications due to double bond geometry, and the site of electrophilic substitution. As shown in Figure 3.31a, invertive substitution can occur α to substituent **a** or **b** to provide two constitutional isomers. It is apparent that conjugation will stabilize the transition structure in Figure

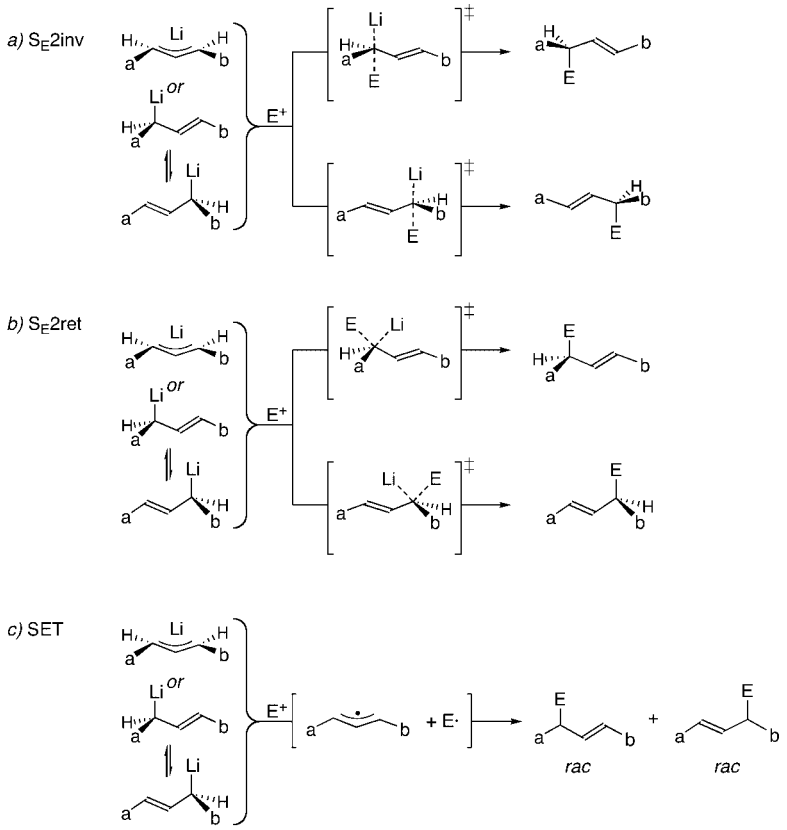

Figure 3.31. General schemes for electrophilic substitutions of η^3 organolithiums (or equilibrating η^1 regioisomers).

3.31a more so than when the carbanion is not allylic. Retentive substitution can occur at either terminus of the allyl anion, as shown in Figure 3.31b. Finally, it is possible for the electrophile to oxidize the organolithium to a radical. Stereorandom coupling following such SET would then afford the two racemic substitution products, as shown in Figure 3.31c. In all three cases, if the organolithium equilibrates between the two η^1 regioisomers in acyclic systems, the possibility of double bond isomerization arises, complicating matters further.

A. Examples of S_E2inv

Amine-substituted allyllithium compounds can serve as homoenolate equivalents, as shown in Figure 3.32. Tin–lithium exchange of a mixture of diastereomeric allyl stannanes yields an allylic organolithium which, upon

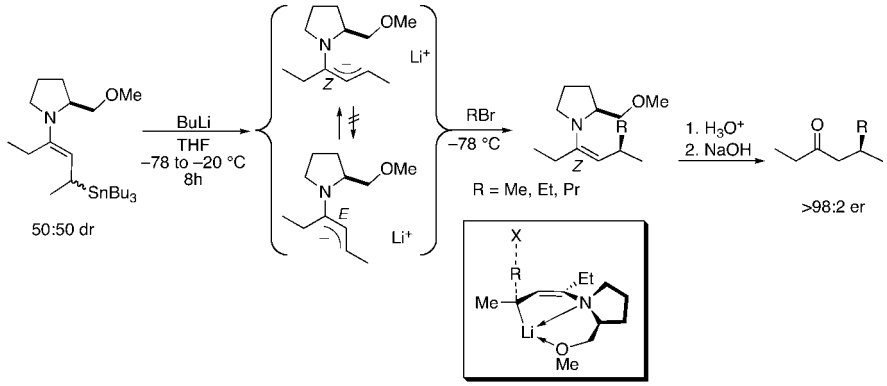

Figure 3.32. An η^3 allyllithium reagent as a homoenolate equivalent.[98]

alkylation affords only (*Z*)-configured enamines. This result was explained by equilibration to a thermodynamic mixture containing predominantly the (*Z*)-allylic organolithium. It is not clear whether the organolithium is η^1 or η^3, but the transition structure that is proposed to account for the steric course is shown in the inset. This transition structure features an enamine in which the pyrrolidine ring is twisted orthogonal to the π-system to allow coordination of the methoxy group (and perhaps the nitrogen) to coordinate the lithium, and substitution takes place with inversion. Hydrolysis gives β-substituted ketones in high enantiopurity.[98]

Lithiated *N*-Boc-*N*-aryl cinnamyl amines have been extensively studied, and several modes of substitution have been determined that depend on the conditions of the reaction.[99] The steric course of the example in Figure 3.33 is based on the solid state structure of the intermediate organolithium.[100] Stereoselective deprotonation is responsible for the enantioselective formation of the illustrated organolithium. In the solid state, the cinnamyl group is bound in an η^3 fashion, but is bound more closely to C^3 than to C^1. The Boc carbonyl oxygen is also coordinated to the lithium, and the amide bond is twisted 68° from the allyl plane to facilitate this coordination and to relieve electron

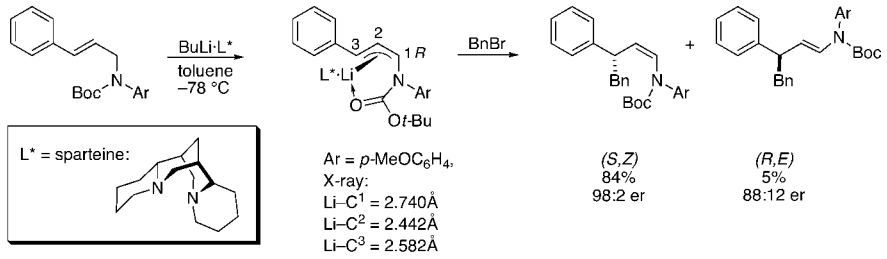

Figure 3.33. Deprotonation to a planar chiral, η^3 complexed organolithium, and invertive S_E2'inv substitution.[99,100]

repulsion between the amide π-system and the allylic anion π-system. Solution NMR studies confirmed that the η^3 structure exists as a monomer in solution.[99] Quenching the anion with benzyl bromide affords the *(S,Z)* enamide in 84% yield and 98:2 er, the product of invertive substitution. The *(R,E)* diastereomer is also formed in 5% yield and 88:12 er. If the crystals are dissolved in ether at –78 °C and quenched at that temperature with benzyl bromide, the *(S,Z)* product is obtained in 99:1 er.[100]

B. Examples of S_E2ret

The organolithium illustrated in Figure 3.33 adds to ketones with retention of configuration at the metal-bearing carbon, as shown in Figure 3.34.[99–101] In this instance, coordination of the cyclohexanone carbonyl oxygen to the lithium cation is postulated to precede electrophilic substitution. Since the organolithium is monomeric, the carbonyl addition probably proceeds through a 4-membered transition structure.

Deprotonation of indenides with butyllithium·sparteine affords η^3 organolithiums, as illustrated in Figure 3.35. The organolithium having the *(S)*

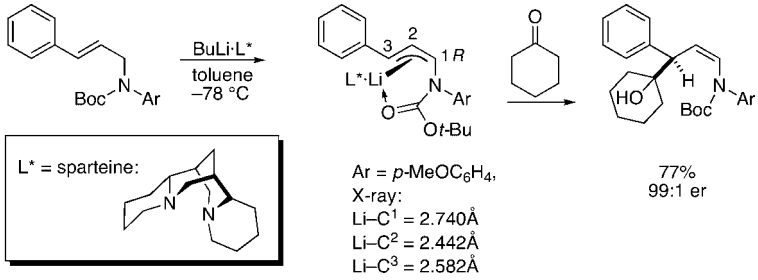

Figure 3.34. Retentive substitution with a ketone electrophile.[99–101]

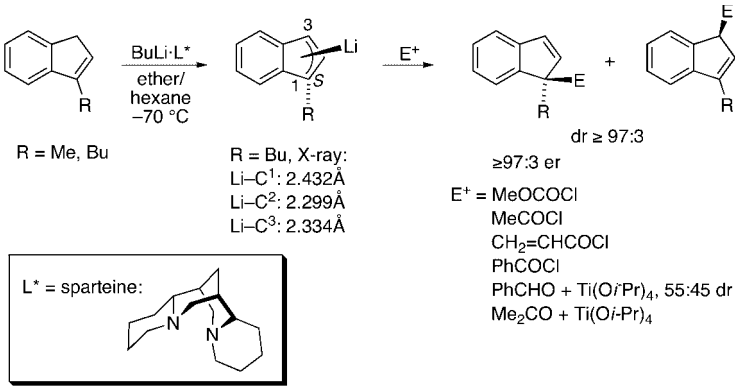

Figure 3.35. Asymmetric substitution of η^3 indenide·sparteine complexes.[102]

configuration at C^1 is the more stable diastereomer, and crystallizes preferentially. The 1-butylindenide-Li·sparteine complex was analyzed by X-ray crystallography, and revealed a shorter bond from Li to C^3 than to C^1. The products of the reaction indicate that the electrophile inserts into the longer C–Li bond, and substitutes for lithium with retention of configuration. The authors note a significant solvent effect in this system. If ether is replaced by THF, the 3-substituted indene is obtained as the major product, having a 50:50 er. X-ray crystallographic analysis of the organolithium intermediate revealed a η^1 organolithium species having the lithium bound to C^3, and coordinated to 3 THF molecules, but not sparteine.[102]

XI. SUMMARY AND CONCLUSIONS

The examples of stereoselectivity in this chapter reveal a broad array of chemical reactivity, inversion dynamics, and stereoselectivity in synthesis. Chiral, nonracemic organolithium compounds are available by a number of means, including enantioselective deprotonation, metal-exchange reactions, and asymmetric transformations such as dynamic resolutions. Particularly intriguing to the field of asymmetric synthesis is the notion that dynamic resolutions permit resolution of racemic organolithiums *in situ* by the addition of chiral ligands.[89] It now appears that both enantioselective deprotonations and dynamic resolutions can be accomplished using sub-stoichiometric amounts of chiral ligands. As of this writing, the discovery of such processes is empirical, but it is anticipated that, as knowledge of organolithium dynamics is acquired, such processes will become predictable by prior design.

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Chapter 4

Oxiranyllithiums as Chiral Synthons for Asymmetric Synthesis

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I. INTRODUCTION

Within the wide family of α-heterosubstituted organolithium compounds, α-lithiated epoxides occupy a special place. They are small-ring heterocycles carrying a peculiar polarized Li–C bond which gives them the character of "carbenoids"[1] thus exhibiting an ambiphilic behaviour, that is a nucleophilic as well as an electrophilic reactivity.

Since the beginning of the fifties of the last century, when Cope[2] postulated for the first time the intermediacy of an oxiranyllithium in the lithiation reaction of cyclooctatetraene oxide with lithium diethylamide, several synthetic strategies have been developed based on the use of oxiranyllithiums as key synthons for the synthesis of highly substituted epoxides and products that can be derived from them. Studies have also been addressed to their reactivity as documented by numerous papers, accounts and reviews includ-

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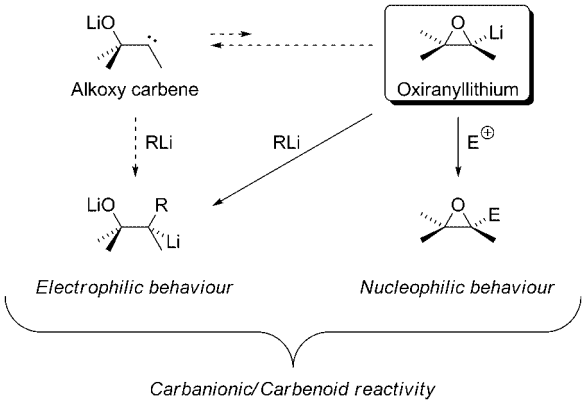


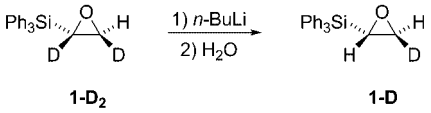
Figure 4.1. Carbanionic/Carbenoid reactivity of oxiranyllithiums.

ing the first one by Satoh in the middle of the nineties of the last century.[3] However, in spite of their widespread use in synthetic strategies, information about the reactivity and structural features of these species are still lacking. Indeed, for instance, the question of whether the oxiranyllithium is directly attacked by organolithium (RLi) or whether it converts first into an alkoxy carbene which then adds RLi, has long been debated (Figure 4.1).

Only in recent years, some structural and spectroscopic investigations[4] jointly with DFT calculations[4,5,6] on such "chameleon-like" reactive intermediates, have shown that the formation of a carbene from the carbenoid is a disfavoured process and that, most probably, it is the carbenoid itself that is directly involved in all those stereospecific rearrangement reactions which are so typical of these organometallic compounds under certain experimental conditions (*vide infra*).

A very interesting aspect of the reactivity of α-lithiated oxiranes is the stereochemical outcome of their reactions with electrophiles which, in principle, can take place with retention or inversion of configuration, or racemization. As a matter of fact, most α-lithiated oxiranyllithiums are configurationally stable so that trapping with electrophiles occurs usually with complete retention of configuration at the lithiated carbon (which is always a stereogenic center). However, racemization sometimes is observed depending upon the substitution at the oxiranyl skeleton and the employed experimental conditions. The first evidence for the configurational stability of α-lithiated oxiranes goes to the middle of the seventies when, in an elegant experiment, Eisch and Galle[7] proved that treating *cis*-dideuterioepoxyethyl(triphenyl)silane **1-D$_2$** with *n*-BuLi at –78 °C followed by deuteriolysis resulted in the formation of *trans*-deuterioepoxyethyl(triphenyl) silane **1-D** (Scheme 4.1).

Since then, the successful employment of oxiranyllithiums as powerful synthons for asymmetric reactions has grown significantly.[3] In this context,



1-D_2 **1-D**

Scheme 4.1.

efforts have been made to generate enantioenriched oxiranyllithiums either by lithiation of optically active epoxides or lithiation of racemic epoxides in the presence of chiral nonracemic ligands. This has led to an extensive use of oxiranyllithiums in asymmetric synthesis.[3e,f,h]

This chapter will focus in particular on the configurational and thermal stability of α-lithiated oxiranes generated under certain experimental conditions which vary with the temperature, solvent, ligands and so on. Emphasis will be given to the synthetic applications oxiranyllithiums currently have in stereoselective organic transformations. To this end, an overview of reactions dealing with the use of oxiranyllithiums as carbenoids and as nucleophiles will be illustrated. As the peculiar reactivity of these species depends significantly on the nature of substituents (if any) on the lithiated carbon, the following is ordered according to the different type of substituents.

II. GENERATION OF α-LITHIATED OXIRANES

α-Lithiated oxiranes can be generated under proper experimental conditions following several methods including deprotonation, desulfinylation, Li–Sn transmetalation carried out on parent epoxides commercially available or simply preparable, the deprotonation with strong bases such as alkyllithiums or lithium amides being the most convenient way.[3j] In general, an α-alkoxy group does have a substantial thermodynamic stabilizing influence upon a carbanionic center which may be attributable to a variety of effects such as an inductive effect, an optimal orientation of the heteroatom lone pair, and differences in the states of aggregation of the organolithium species.[8] However, very strong bases are required in order to bring about quantitative deprotonation of simple alkyl ethers unless an electron-withdrawing substituent is present on the carbon to be lithiated. In contrast with acyclic ethers, the epoxide moiety is prone to the H/Li exchange when treated with an organolithium. This behaviour can be explained with the enhanced acidity associated with a carbon atom incorporated into a three-membered ring: because of this, epoxides have higher energy than the acyclic ethers and thus they show an "extra" reactivity when treated with strong bases.

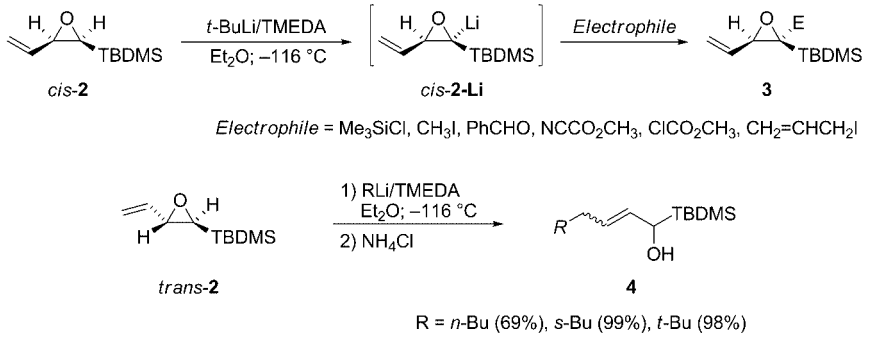
III. SILYL OXIRANYLLITHIUMS

Silyl-substituted oxiranyllithiums were the first to be investigated, particularly because of their configurational stability. Courillon and Malacria[9] demonstrated that *cis*-α,β-epoxy-γ,δ-vinylsilane **2** could be regioselectively α-lithiated with *t*-BuLi and TMEDA within 30 min in Et_2O at –116 °C and the corresponding anion *cis*-**2-Li** being trapped with external electrophiles to give trisubstituted epoxides **3** with complete retention of configuration at the oxiranyl ring (Scheme 4.2). In contrast, the *trans* epoxide **2** could not be deprotonated neither by *n*-BuLi, *s*-BuLi nor *t*-BuLi, an S_N2' reaction being observed instead with the addition of the organolithium to the double bond to give allylic alcohols **4** (Scheme 4.2).

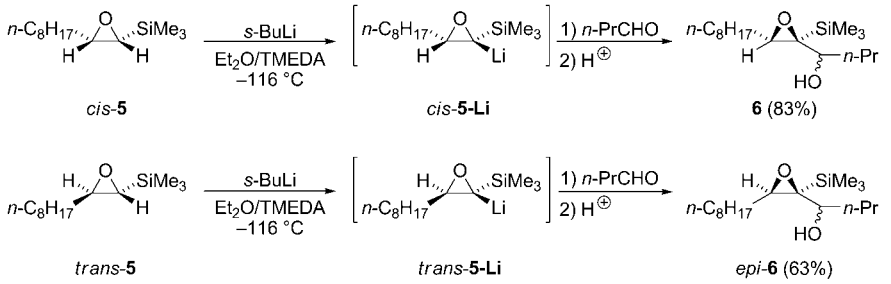
It is noteworthy that, although the *cis* configuration of the three-membered ring is thermodynamically disfavoured, the reaction occurs with complete retention of configuration at the lithiated carbon, allowing the stereoselective functionalization of the epoxide **2**. Moreover, when investigating the reactivity of the diastereomeric *trans* α,β-epoxy-γ,δ-vinylsilane **2**, the authors discovered a completely different behaviour: *trans*-**2** could not be deprotonated neither by *n*-BuLi, *s*-BuLi nor *t*-BuLi because of the nucleophilic attack of the alkyllithium to the vinylic moiety causing ring-opening of the oxirane and formation of silylated allylic alcohols **4** through an S_N2' mechanism (Scheme 4.2).

The examples above clearly support the hypothesis that the relative configuration at the epoxide stereogenic carbons may be playing a role in controlling the regioselectivity and the rate of the deprotonation reaction. A plausible explanation likely resides in the formation of competitive prelithiation complexes between alkyllithiums and the oxirane oxygen having different thermodynamic stabilities.[10]

Similar results were previously obtained by Molander,[10] who studied the direct deprotonation of several *cis*- and *trans*-epoxysilanes. Lithiation of *cis*-α,β-epoxysilane **5** with *s*-BuLi and TMEDA was complete after just 10 min-



Scheme 4.2.



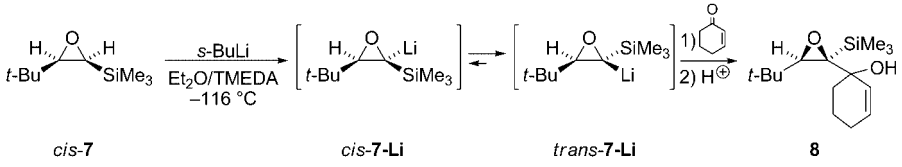
Scheme 4.3.

utes despite the very low temperature (–116 °C), whereas deprotonation of *trans*-α,β-epoxysilane **5**, under the same conditions, proved to be much slower requiring 4 h for completion (Scheme 4.3). Both the corresponding oxiranyl anions *cis*-**5-Li** and *trans*-**5-Li** are stable from minutes to hours at –116 °C in Et_2O and can be trapped with propionaldehyde to give epoxyalcohols **6** and *epi*-**6** in good yields and with retention of configuration at the lithiated carbon.

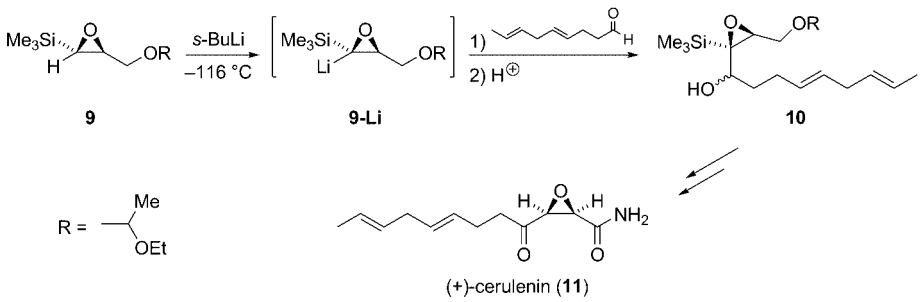
An exception was represented by *cis*-oxirane **7**: once lithiated and then treated with 2-cyclohexen-1-one, the major product was the epoxyalcohol **8** whose relative configuration was opposite with respect to the starting oxirane. An isomerization from *cis*-**7-Li** to *trans*-**7-Li** is likely to occur prior to carbonyl addition (Scheme 4.4). This behaviour could be due to the strain created in forcing the *t*-butyl and the trimethylsilyl groups on the same side of the oxirane ring so facilitating the isomerization process.

The importance of silicon-stabilized oxiranyl anions as key intermediates in stereoselective synthesis was substantiated by Townsend who used a chiral lithiated epoxysilane in the asymmetric synthesis of a potent natural antimicrobial agent: (+)-cerulenin **11**.[11] Optically pure oxirane **9** (er = 99.5:0.5) was metalated by *s*-BuLi and the lithiated intermediate **9-Li** subsequently trapped with (4*E*,7*E*)-nonadienal to give the product **10** in 77% yield. Further elaboration led to the target product **11** highly enantiomerically enriched in 12 steps and 26% overall yield (Scheme 4.5).

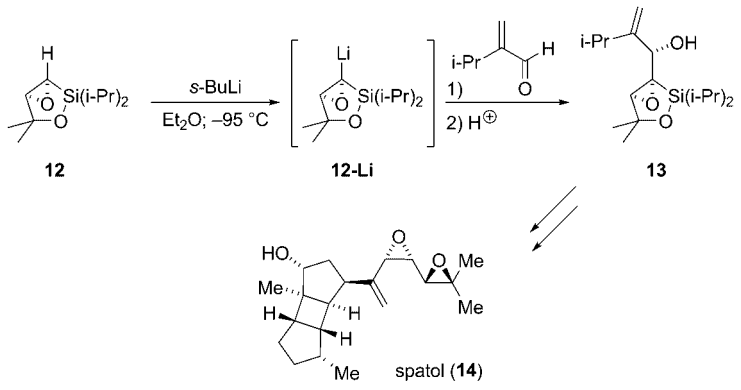
In the course of the stereoselective synthesis of spatol **14**, a temporary tether was used as a trick by Salomon and Murthi[12] to circumvent the configurational instability of α-silylated epoxide **12-Li**, obtained deprotonating the precursor **12** with *s*-BuLi (Scheme 4.6). Further elaboration of **13** leads to the target natural product **14**.



Scheme 4.4.



Scheme 4.5.



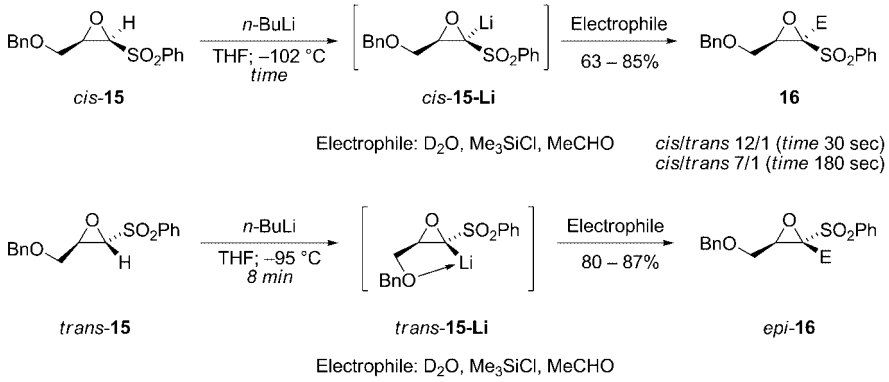
Scheme 4.6.

At the end, one may conclude that, in the major part of cases, lithiated epoxysilanes tend to react with electrophiles with retention of configuration thus transferring their "chirality" to the final products. Additional studies on the structural features of such lithiated intermediates are needed for the comprehension of the observed configurational stability and a proper rationalization of the known exceptions.

IV. SULFONYL OXIRANYLLITHIUMS

The reactivity as well as the chemical and configurational stability of sulfonyloxiranyllithiums (obtainable from the corresponding sulfonyl epoxides by treatment with alkyllithiums at a temperature lower than –90 °C), are strongly dependent upon the stereoelectronic nature of the substrate as well as upon the reaction conditions, as demonstrated by Jackson[13] in the metalation studies of diastereomeric epoxides *cis*- and *trans*-**15**.

Deprotonation of *cis*-**15** with *n*-BuLi at –102 °C to give *cis*-**15-Li** was extremely rapid since just 30 seconds were enough for the completion of the



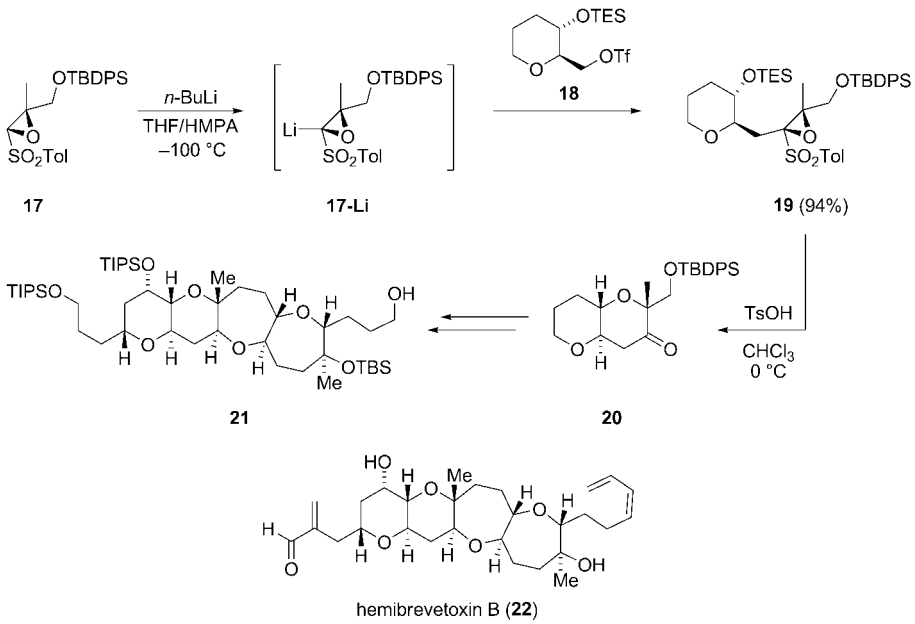
Scheme 4.7.

reaction (Scheme 4.7). Subsequent addition of several electrophiles gave the corresponding *cis*-adducts **16** together with a small quantity of the epimers *epi*-**16** (ratio *cis*/*trans* 12/1), the epimerization process being influenced by the lithiation time. In fact, treatment of epoxide *cis*-**15** with *n*-BuLi for 3 minutes and subsequent quenching with D_2O resulted in a reduced overall yield in deuterated product together with a decreased diastereomeric ratio (*cis*/*trans* 7/1) (Scheme 4.7).

These results imply that the sulfonyl group makes the oxirane moiety quite acidic since deprotonation occurs very fast at –102 °C, but the corresponding oxiranyllithium is configurationally unstable, the reason being at present unexplained.

When *trans*-**15** was deprotonated with *n*-BuLi, longer reaction times and higher temperatures were necessary to complete the metalation: 8 minutes at –95 °C. Intermediate *trans*-**15-Li** was subsequently coupled with several electrophiles in a retentive stereospecific manner (Scheme 4.7). The configurational stability of the oxiranyllithium *trans*-**15-Li** could be ascribed to an internal coordination of the lithium atom by the benzyloxy group, although this may not be the only contributing factor.

An attractive application which exploits reactivity of lithiated epoxysulfones was discovered by Mori[14] who employed such oxiranyllithiums as key intermediates for the construction of cyclic ethers and, in particular, for the total synthesis of natural polycyclic ethers such as marine toxins.[15] Since lithiated epoxysulfones such as **17-Li** are known to be configurationally unstable even at a temperature around –100 °C, optically pure oxirane **17**, once lithiated, was straightforwardly coupled with triflate **18** by an *in situ* trapping strategy. Thus, a mixture of **17** and **18** in THF at –100 °C treated with *n*-BuLi in the presence of HMPA afforded functionalized epoxide **19** in a stereospecific way (Scheme 4.8). Treatment of **19** with TsOH at 0 °C resulted first in the removal of the triethylsilyl-group (TES) and subsequently in an intramolecular epoxide ring-opening. It is noteworthy that epoxy sulfone **19** might



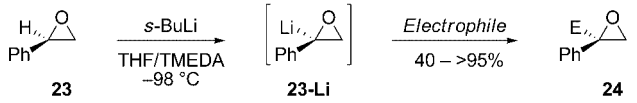
Scheme 4.8.

give a tetrahydrofuran or a tetrahydropyran system via a 5-*exo* or 6-*endo* mode of cyclization, respectively; however, the presence of a sulfonyl group, due to its electron-withdrawing ability, favors the *endo* mode pathway, thus leading to the *six*-membered ketone **20**. The sequence involving the coupling of lithiated epoxysulfones with triflates and subsequent oxirane-ring opening was iterated three times leading first to the stereoselective construction of the tetracyclic core of hemibrevetoxin B **21** and finally to the total synthesis of this marine toxine **22** (Scheme 4.8).[16]

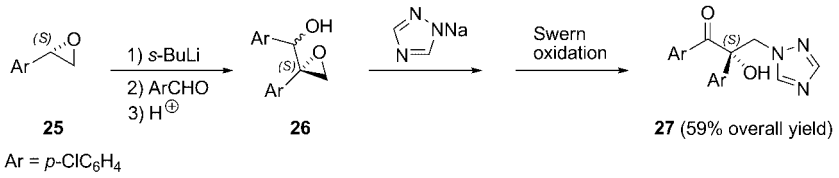
In conclusion, lithiated epoxysulfones, although known to be configurationally unstable, can be stereospecifically trapped with electrophiles if their coupling reactions are fun under appropriate experimental conditions such as *in situ* trapping.

V. α-LITHIATED ARYLOXIRANES

α-Lithiated aryloxiranes have been rather extensively investigated over the last thirty years. The role of the phenyl ring as anion-stabilizing group was for the first time investigated by Eisch and Galle in 1976. As successively demonstrated by Florio[17] and coworkers, optically active (*R*)- or (*S*)-styrene oxide **23** can be smoothly lithiated at –98 °C to give **23-Li** and functionalized with a wide range of electrophiles to give more substituted arylepoxides **24**,



Scheme 4.9.



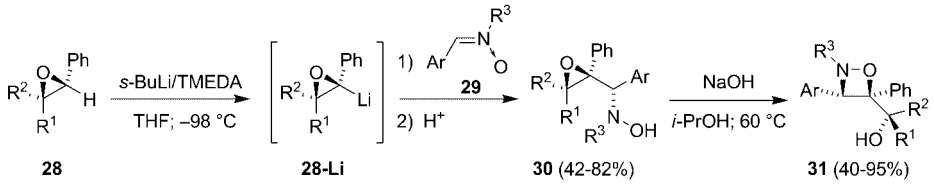
Scheme 4.10.

the absolute configuration of the benzylic carbon remaining completely unaffected (Scheme 4.9).

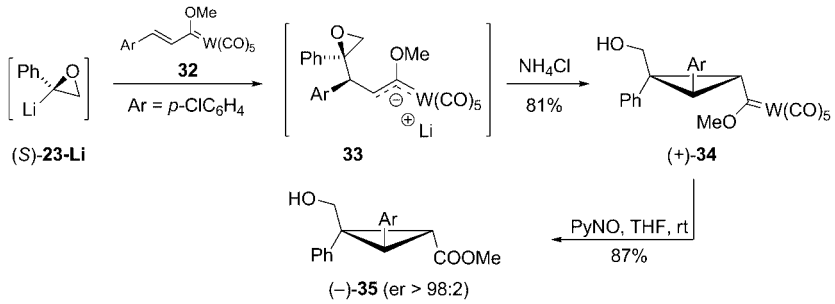
The styrene oxide anion-strategy was successfully exploited for the stereospecific synthesis of the antifungal agent **27** (Scheme 4.10). To this end, (*S*)-**25** was first lithiated and coupled with *p*-chlorobenzaldehyde to give a diastereomeric mixture of epoxy alcohols **26** (dr = 66/34); subsequent ring-opening with triazole and Swern-oxidation furnished α-hydroxy ketone **27** as a single enantiomer in 59% overall yield.

An additional useful application of this methodology is represented by the highly stereospecific synthesis of the 1,2-oxazetidine system (Scheme 4.11),[18] based on the coupling of enantiopure α-lithiated aryloxiranes **28-Li**, generated from **28**, with aromatic nitrones **29** to give epoxyhydroxylamines **30** which could be smoothly cyclized to the corresponding 1,2-oxazetidines **31**.

It is noteworthy that the coupling reaction takes place with complete retention of configuration at the lithiated carbon and with very high asymmetric induction at the newly formed stereogenic center. This behavior is quite intriguing considering that addition of lithiated aryloxiranes to aldehydes and non-symmetric ketones often results in nearly equimolar mixtures of



Scheme 4.11.



Scheme 4.12.

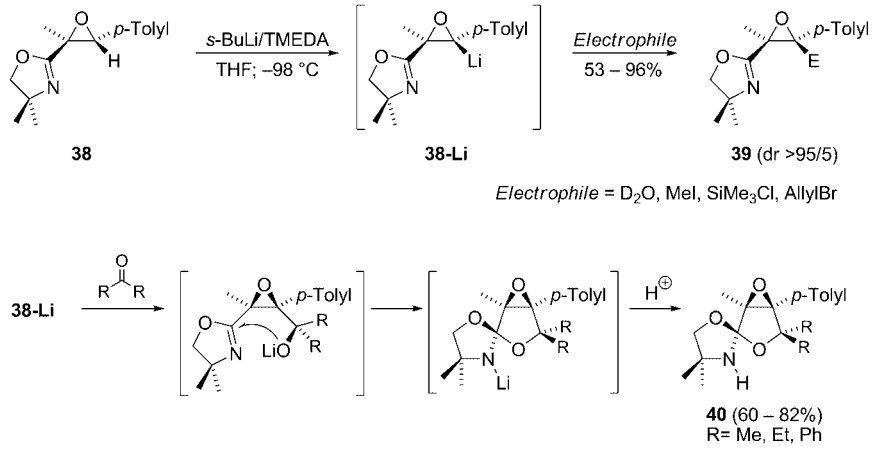
diastereoisomers. A possible reaction mechanism has been proposed by the authors,[18] explaining the observed diastereoselectivity with two five-membered cyclic transition states, having different energy because of a different steric repulsion. The above strategy has been also applied to the enantioselective synthesis of both epoxyhydroxylamines **30** and hydroxyalkyl-1,2-oxazetidines **31** (98/2 er) starting from enantioenriched aryloxiranes **28**.

The addition of enantiomerically enriched lithiated styrene oxide (*S*)-**23-Li** to α,β-unsaturated Fischer carbene complexes **32** affords, through a conjugate addition, intermediate **33** which cyclizes into functionalized cyclopropanes **34** in enantiopure form (Scheme 4.12).[19] The process is remarkable either for its high diastereoselectivity (> 98/2 dr) or considering that lithiated carbanions usually tend to give 1,2-additions. The organometallic moiety can finally be oxidized with pyridine *N*-oxide to the corresponding methyl carboxylate **35**.

It is interesting to note that, analogously to styrene oxide, *N*-Bus-phenylaziridine **36** (Figure 4.2) can be lithiated at the benzylic carbon and functionalized in a stereospecific manner with retention of configuration.[20] In contrast, α-lithiated phenyl-substituted cyclopropane **37** shows an increased sp^2 character at the carbanionic carbon atom and undergoes a fast racemization at a temperature above –45 °C.[21]

Benzylic deprotonation of α-oxazolinyl-β-aryl-substituted oxiranes results in the formation of oxiranyllithiums with a higher kinetic stability at –98 °C if compared to that of lithiated styrene oxide. One example is represented by the oxazolinyloxirane **38**[22] that can be easily functionalized, in a stereospecific manner, upon lithiation of the benzylic carbon and trapping with electrophiles.

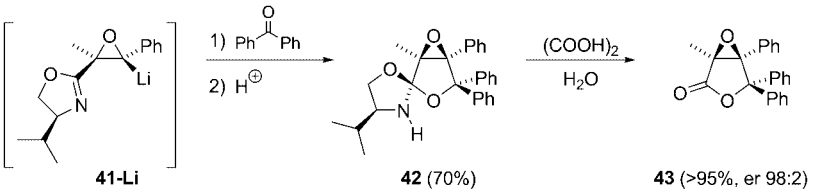
Figure 4.2.



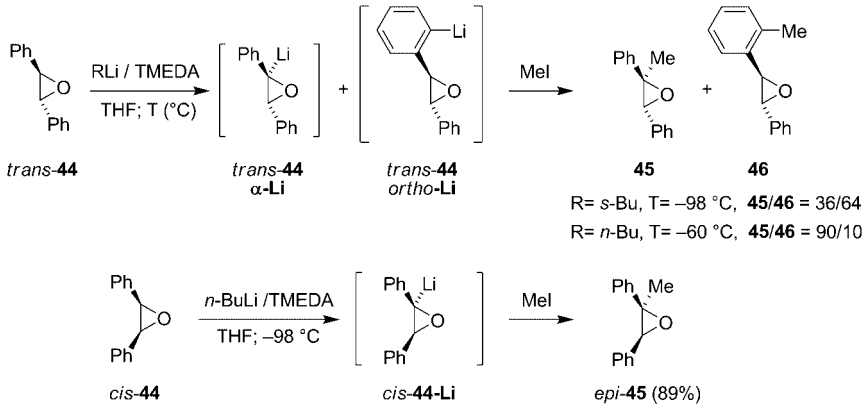
Scheme 4.13.

Oxiranyllithium **38-Li**, generated by treating oxazolinyloxirane **38** with *s*-BuLi/TMEDA at –98 °C, proved to be stable for several hours without decomposition. Upon treatment with alkyl halides or TMSCl, it was transformed into the corresponding tetrasubstituted epoxide **39** with complete retention of configuration (Scheme 4.13). Interestingly, the reaction of **38-Li** with aliphatic and aromatic ketones afforded spirocyclic compounds **40** with high diastereoselectivity, most likely resulting from an intramolecular nucleophilic addition of the incipient lithium alkoxide to the oxazoline C–N double bond (Scheme 4.13).

The oxazoline moiety proved to be crucial not only in the stabilization of the intermediate oxiranyllithium, but also for the role played as chiral auxiliary in the asymmetric version of the above reaction. In fact, starting from the enantiomerically enriched lithiated epoxide **41-Li** and performing hydroxyakylation, spirocyclic compound **42** was obtained as a single diastereoisomer and in high enantiopurity (Scheme 4.14). Such oxazolidine spirocyclic architectures can be easily hydrolyzed to the corresponding α,β-epoxy-γ-butyrolactones (such as **43**) which are useful synthons for the synthesis of biologically active compounds such as (+)-cerulenine,[11] epolactaene[23] or in general α-methylenebis-γ-butyrolactones.[24]



Scheme 4.14.

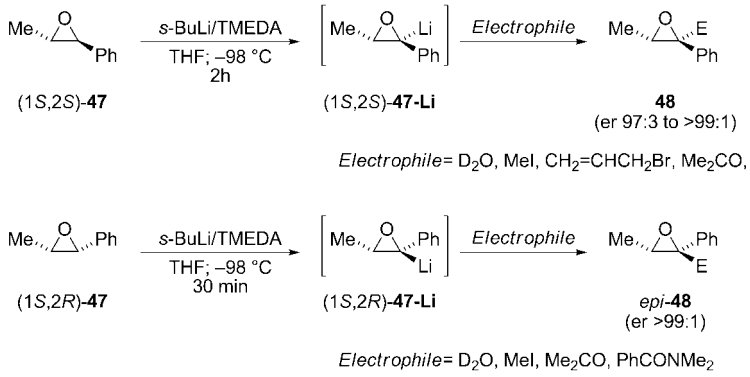


Scheme 4.15.

Investigating the lithiation of 1,2-disubstituted aryloxiranes, Florio and Aggarwal found that both *cis*- and *trans*-stilbene oxides **44** are characterized by an unusual acidity representing the first case of aryloxiranes that can be lithiated by *n*-BuLi (Scheme 4.15).[25] In particular, it was ascertained that treatment of *trans*-**44** with alkyllithiums (*s*-BuLi or *n*-BuLi) followed by quenching with MeI gave not only the expected α-methylated epoxide **45** from *trans*-**44-α-Li** but also the *ortho*-substituted epoxide **46** from *trans*-**44-*ortho*-Li**, the regioselectivity of the metalation being strongly dependent upon the temperature and the base used: the employment of 1.5 equiv *n*-BuLi and 3 equiv TMEDA at –60 °C in THF for 2 h favours α-lithiation. Under the latter conditions, the benzylic position of *trans*-**44** could be regioselectively functionalized with many electrophiles.

Such behaviour was not observed in the lithiation reaction of the *cis*-stilbene oxide **44** since it was always regioselectively metalated at the benzylic position (Scheme 4.15); in the coupling reaction of *cis*-**44-Li** with MeI *epi*-**45** formed as the sole product. Moreover, once again, the *cis* isomer undergoes a faster deprotonation than the *trans* stilbene oxide, which was complete in just 30 min at –98 °C vs 2 hours required by the *trans* isomer at –60 °C and with only 85 % conversion. Optically active *trans*-(*R*,*R*)-**44** has also been lithiated under conditions which favor α-deprotonation (*vide supra*) and trapped with EtI to give the corresponding trisubstituted highly enantiomerically enriched derivative.[25]

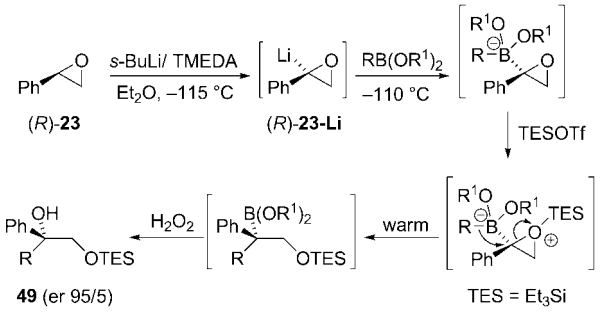
The lithiation reaction of *cis*- and *trans*-phenylpropylene oxides **47** has been also studied.[26] Treatment of (1*S*,2*S*)-**47** with *s*-BuLi and TMEDA at –98 °C furnished the expected oxiranyllithium (1*S*,2*S*)-**47-Li** which was stereospecifically trapped with electrophiles with retention of configuration, thus allowing the synthesis of trisubstituted epoxides **48** with the same enantiomeric purity as the starting oxirane (Scheme 4.16).



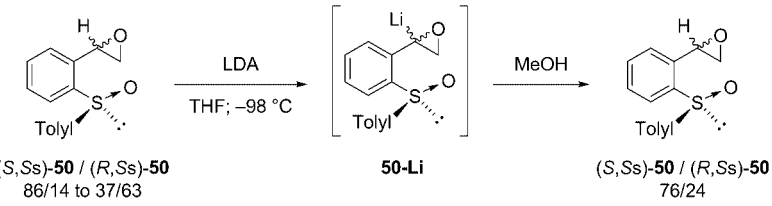
Scheme 4.16.

A similar reactivity was also found for the epimeric *cis*-(1*S*,2*R*)-**47** which could be smoothly lithiated at –98 °C and the corresponding (1*S*,2*R*)-**47-Li** trapped with electrophiles to give highly enantiomerically enriched epoxides retaining the configuration at the benzylic carbon. As in the case of other *cis*-epoxides (*vide supra*), *cis*-(1*S*,2*R*)-**47** was metalated four times faster than the diastereomer *trans*-(1*S*,2*S*)-**47**.

Despite α-lithiated styrene oxide (*R*)-**23-Li** retains its absolute configuration when coupled with a large number of electrophiles, it loses its stereochemical integrity during the reaction with boronic esters leading to racemic diols, as recently reported by Aggarwal (Scheme 4.17).[27] However, changing the solvent from THF to Et_2O, lowering the temperature up to –115 °C, and using a less hindered and more reactive neopentyl boronic ester, diols **49** were obtained in a very good enantiomeric ratio (up to 95/5) after a final work-up under oxidative conditions through the mechanism depicted in Scheme 4.17 which represents a useful homologation of boronic esters with lithiated epoxides. This is the first experimental evidence that the configurational integrity of the lithiated styrene oxide was found to depend remarkably upon the solvent used, the temperature, and the nature of the electrophile in the trapping step.



Scheme 4.17.



(*S*,*S*s)-**50** / (*R*,*S*s)-**50**
86/14 to 37/63

50-Li

(*S*,*S*s)-**50** / (*R*,*S*s)-**50**
76/24

Scheme 4.18.

The effect of the substitution at the aryl group on the configurational stability of α-lithiated aryloxiranes is currently being investigated. Indeed, it has been recently reported by Florio and Ruano,[28] that the *ortho*-positioned *p*-tolylsulfinyl group of α-lithiated styrene oxide induces epimerization. Treatment of **50** with alkyllithiums (*n*-BuLi, *s*-BuLi) leads to desulfinylation of the aromatic ring, whereas a smooth lithiation of the benzylic position occurs with lithium amides such as LDA. In particular, deprotonation–reprotonation reactions, run employing different diastereomeric mixtures of (*S*,*S*s)-**50** and (*R*,*S*s)-**50** ranging from 37/63 to 86/14, always lead to the same final ratio [dr (*S*,*S*s)-**50**/(*R*,*S*s)-**50** = 76/24] regardless of the diastereoisomeric composition of the starting mixture (Scheme 4.18).

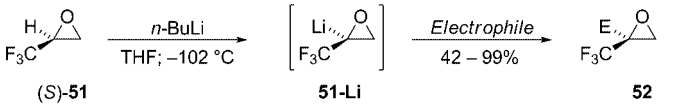
This result is consistent with a configurational instability of such substituted oxiranyllithium **50-Li** and has been rationalized by considering an equilibrium between the starting epoxides and the lithiated intermediates in the presence of LDA. To confirm such a hypothesis the authors used an excess of *N*-deuterated DIPA as source of LDA and the amount of deuterium incorporation was checked into the final diastereomeric mixture. As expected, about 59% of the benzylic carbons were deuterated after quenching the reaction with MeOH.

The influence of the sulfinyl group is remarkable not only from a stereochemical point of view but also considering the enhancement of the acidity of the oxirane ring hydrogen, since LDA is not effective in the lithiation of phenyloxiranes.

Recently, lithiated aryloxiranes have been the subject of a paper in which the oxiranyl anion methodology has been exploited to synthesize substituted styrene oxides on a large scale, taking advantage of microflow systems.[29] The employment of such a technology also represents a powerful tool for starting mechanistic studies. The intriguing dichotomy (carbanionic/carbenoid character) of α-lithiated styrene oxide has been deeply investigated by means of NMR measurements and DFT calculations and related, for the first time, to the different aggregation states this very reactive intermediate does have in solution.[30]

VI. α-TRIFLUOROMETHYL- AND ESTER-STABILIZED OXIRANYLLITHIUMS

The lithiation reaction of simple trifluoromethyl oxiranes has been investigated by Uneyama,[31a] who developed a useful methodology for the α-functionalization of epoxide (*S*)-**51** with a wide range of electrophiles in a completely stereospecific manner (Scheme 4.19).



Electrophile = RCHO, R_2CO, PhCONMe(OMe), Ph_3SiCl, Ph_3SnCl, $(EtO)_2POCl$

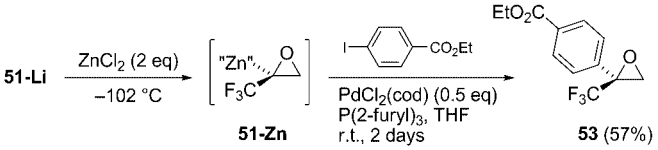
Scheme 4.19.

The metalation was performed using *n*-BuLi at –102 °C and resulted in the formation of functionalized organolithium **51-Li** that showed a surprising chemical and configurational stability; the coupling with electrophiles led to the synthesis of optically active fluorinated epoxides **52** with the stereospecific formation of C–C, C–Si, C-Sn and C–P bonds.

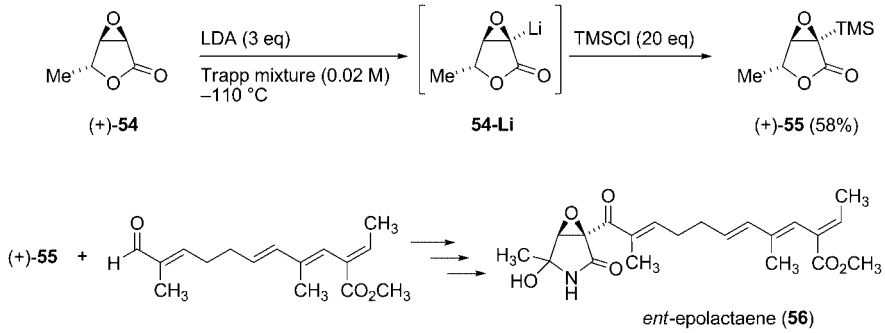
The configurational stability of enantiopure **51-Li** is remarkable since it is well-known that α-trifluoromethyl-substituted carbanions have an sp^2 structure and their reactions lead to racemic mixtures.[31b] Moreover, it was proved that α-lithiated trifluoromethyloxirane **51-Li** retains its absolute configuration even at –78 °C for 1 hour.

The possibility of using oxiranyllithiums as precursors of zinc-oxiranes to be successfully employed in Negishi cross-coupling reactions (in order to gain a direct functionalization of the parent epoxide with aryl moieties)[32] has been explored by Uneyama (Scheme 4.20).[31a] In particular, lithiated epoxide **51-Li**, once generated as above described, was treated at –102 °C with $ZnCl_2$ to give the thermally stable zinc-species **51-Zn** whose structure, however, still remains unclear. The zinc-oxirane **51-Zn** was then coupled with an aryl iodide in the presence of a sub-stoichiometric amount of a Pd catalyst to give the styrene oxide derivative **53** with retention of configuration at the metalated carbon.

β-Angelica lactone epoxide (+)-**54** has been successfully lithiated and stereospecifically silylated at the oxirane ring by Kobayashi[23] to give (+)-**55**



Scheme 4.20.



Scheme 4.21.

(Scheme 4.21). This functionalization represents one of the few examples employing an ester-stabilized oxiranyllithium as key intermediate.[33] The reaction requires peculiar experimental conditions: an excess of base and the Trapp mixture (THF/ether/pentane) as the preferred solvent. Moreover, the *in situ* quenching technique and a low concentration of **54** (0.02 M) avoids undesired transformations (such as dimerization) of the very reactive oxiranyl anion **54-Li**.

This new synthetic approach provides the first example of the formation and reaction of a bridgehead oxiranyllithium. Furthermore, α-silylated epoxylactone (+)-**55** also represents an oxiranyl anion precursor; indeed, after being treated with a fluoride source, it has been successfully employed for the total synthesis of *ent*-epolactaene **56** and its substituted analogs (Scheme 4.21).[23]

VII. ALKYL-SUBSTITUTED OXIRANYLLITHIUMS

In the oxiranyl anion methodology the presence of a stabilizing group on the epoxide ring is not strictly necessary for the lithiation to occur. A protocol for the lithiation-trapping reaction with electrophiles of terminal epoxides has been recently developed by Hodgson and coworkers.[34] Transient oxiranyllithium **57-Li**, obtained by treating commercially available (*S*)-propylene oxide **57** with an excess *s*-BuLi (2.5 equiv) at –90 °C and in the presence of *N,N'*-dibutylbispidine (DBB) (Figure 4.3), reacts with Bu_3SnCl to furnish the *trans*-stannylated product (*S*,*S*)-**58** in 54% yield and as a sole enantiomer

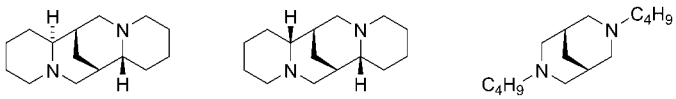
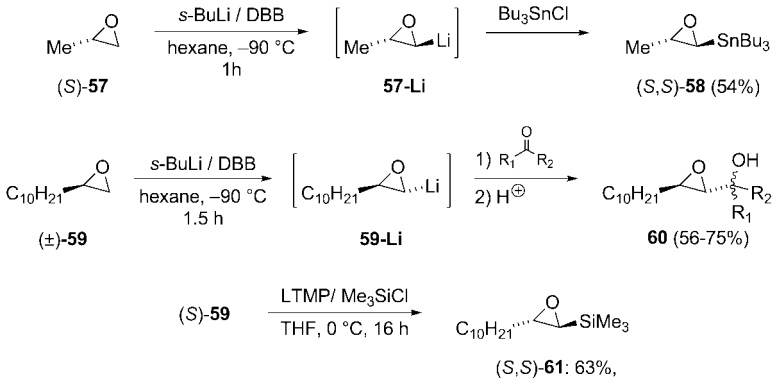


Figure 4.3.



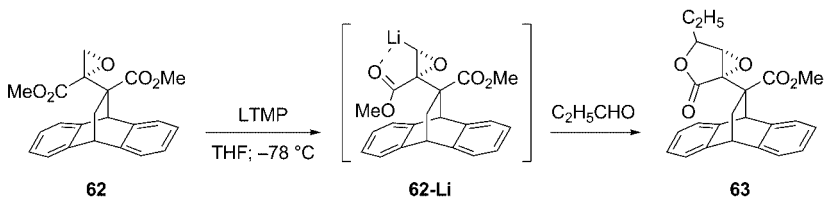
Scheme 4.22.

(Scheme 4.22). Noteworthy is the regio- and the stereoselective abstraction by the base of the proton in the *trans*-position with respect to the methyl group.

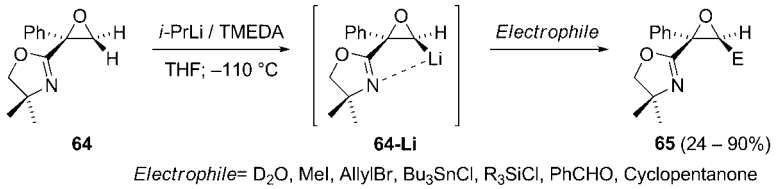
The life-time of β-lithiated 1,2-epoxydodecane **59-Li**, obtained treating **59** with *s*-BuLi and DBB at –90 °C in hexane, is remarkable since it survives long enough, at low temperature, to allow the trapping with external electrophiles. The methodology proved to be successful for the preparation of epoxyalcohols by the reaction of **59-Li** with aldehydes and ketones (Scheme 4.22).[34]

Addition of enantiopure (*S*)**-59** to a mixture of LTMP and trimethylsilyl chloride at 0 °C in THF gave the expected α,β-epoxysilane (*S*,*S*)-**61** in 63% yield, as a single enantiomer (Scheme 4.22).[35] The protocol is limited to the trapping with Me_3SiCl and needs the simultaneous presence of the base and the electrophile (*in-situ* quenching conditions).

Some terminal epoxides can be readily lithiated due to a "remote" coordination carried out by some heteroatoms. One example is represented by the oxirane **62** that, once treated with LTMP at –78 °C in THF, leads to the stereoselective generation of **62-Li**, most probably stabilized by an intramolecular coordination by the ester oxygen on lithium through a five-membered ring (Scheme 4.23).[24] It is interesting to note that an internal stabilization through a six-membered ring provided alternatively by the other ester group has not been observed. The reaction of **62-Li** with propionaldehyde gave access to epoxylactone **63**, which represents a useful intermediate in the stereoselective synthesis of naturally occurring α-methylene bis-γ-butyrolactones.[36]



Scheme 4.23.

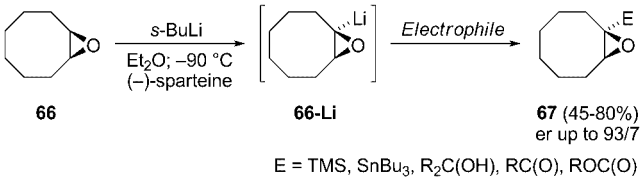


Scheme 4.24.

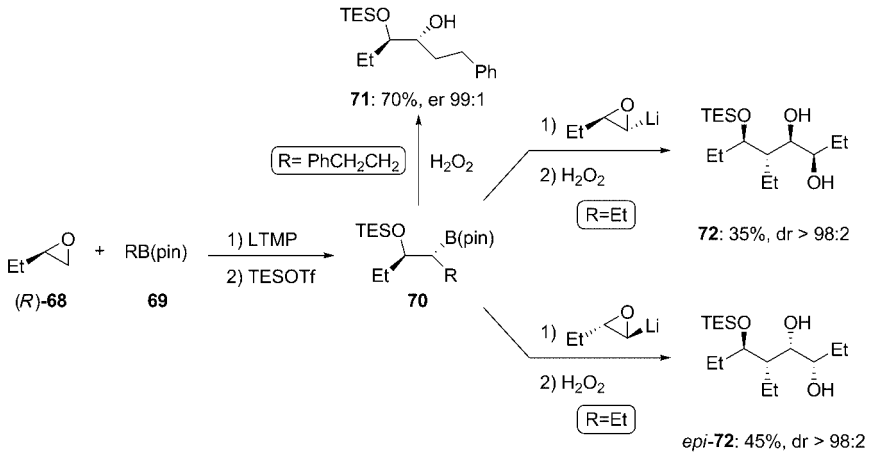
Another example of a "remote" stabilized oxiranyl anion is represented by a β-lithiated-oxazolinyloxirane such as **64-Li**, generated by treatment of **64** with *i*-PrLi and TMEDA at very low temperature (–110 °C), in which the oxazoline group directs the deprotonation of a terminal epoxide to the *cis* hydrogen (Scheme 4.24).[37] Oxiranyllithium **64-Li** could be trapped with electrophiles to give stereoselectively trisubstituted epoxides **65**.

More functionalized chiral alkyl-substituted epoxides have been obtained by pursuing a different strategy. This starts from meso epoxides and uses chiral bases. In the asymmetric deprotonation of *meso*-cycloalkene oxides, chiral non-racemic bicyclic diamines containing the diazabicyclononane structural motif have been used (Figure 4.3). Treatment of cyclooctene oxide **66** with *s*-BuLi at –90 °C in the presence of (–)-sparteine furnishes the chiral non-racemic oxiranyllithium **66-Li**: its coupling with electrophiles results in the synthesis of enantioenriched functionalized epoxides **67** with enantiomeric ratios up to 93/7 (Scheme 4.25).[38]

The use of α-lithiated oxiranes as nucleophiles is particularly advantageous as it allows the incorporation of the three-membered ring in a molecule and, subsequently, the epoxide moiety can be synthetically elaborated. This idea has been used by Aggarwal,[27] who recently reported a stereospecific reaction of lithiated epoxides with boronic esters aimed at obtaining polyoxygenated derivatives, which are an important class of bioactive compounds. A mixture of (*R*)-1-butene oxide **68** and boronate **69** was treated with LTMP according to the Hodgson protocol (*in-situ* quenching conditions);[35] the addition of triethylsilyl triflate (TESOTf) (necessary to avoid a boron-Wittig elimination) followed by a final oxidative work-up leads, through **70**, to the *syn*-O-silylated diol **71** in a highly enantiomerically enriched form (Scheme 4.26). A mechanism involving a 1,2-metalate migration with a simultaneous ring-opening reaction has been proposed.[27]



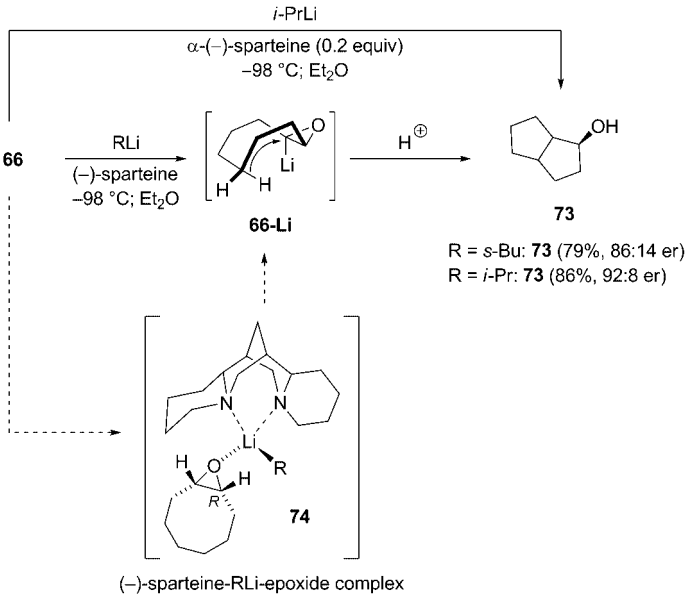
Scheme 4.25.



Scheme 4.26.

It is noteworthy that the reaction can be stereospecifically iterated: by adding an additional enantiomerically enriched oxiranyllithium to the intermediate **70** before the oxidative work-up, the entire process ends with the formation of the 1,2,4-triols **72** or *epi*-**72**, regarding to the chirality of the employed oxiranyllithium, under complete stereochemical control of four stereogenic centers (Scheme 4.26).

An alternative use of alkyl-substituted oxiranyllithiums exploits their carbenoid reactivity. Desymmetrization of *meso*-epoxides performed with alkyllithiums and enantiopure ligands in the absence of external electrophiles gave stereodefined bicyclic alcohols as the final products. This interesting approach proved to be particularly efficient in the isomerization of medium-sized cycloalkene oxides because of the peculiar spatial arrangement of the cyclic carbon skeleton of the epoxides and the orientation of the nucleophilic C–H orbitals in which the carbenoid itself inserts. The first enantioselective α-deprotonation of cyclooctene oxide **66** in the presence of (–)-sparteine, followed by a stereospecific transanular C–H insertion within **66-Li** in absence of electrophiles, has been reported by Hodgson and coworkers in 1996;[39] it allowed the asymmetric synthesis of bicyclo[3.3.0]octanol **73** in 79% yield and 86:14 er (Scheme 4.27). The same reaction carried out with *i*-PrLi results in the formation of **73** with an improved yield (86%) and 92:8 er. Surprisingly, the alternative use of *n*-BuLi or *t*-BuLi gave poor or no enantioselectivity. The observed enantioselectivity has been rationalized speculating the formation of a (–)-sparteine-RLi-epoxide complex **74** (Scheme 4.27) in which RLi approaches preferentially the *R* proton of the epoxide for steric reasons. A similar marked discrimination between enantiotopic protons was also observed in the enantioselective α-lithiation of **66** upon treatment with *i*-PrLi in the presence of a *sub*-stoichiometric amount of (–)-α-isosparteine (86%, er 92:8) (Figure 4.3 and Scheme 4.27).[40] This result would encourage

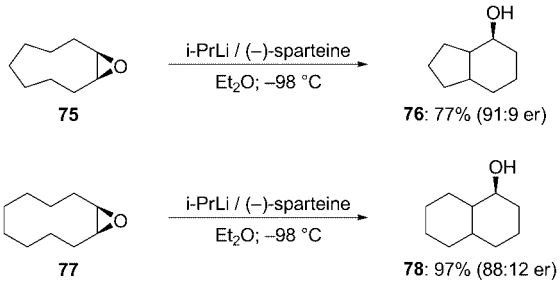


Scheme 4.27.

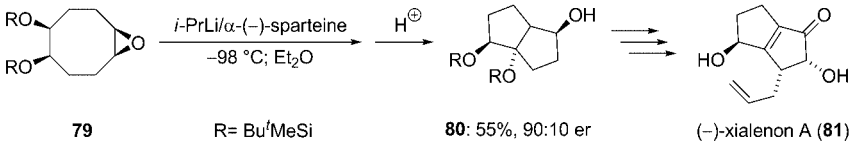
the deprotonation of *meso*-epoxides in a so far unreported catalytic asymmetric version.

Such a strategy has also been applied to cyclononene and cyclodecene oxides **75** and **77** whose asymmetric deprotonation with *i*-PrLi/(–)-sparteine leads to bicyclic alcohols **76** and **78** in both good yield and enantioselectivities (Scheme 4.28).[39]

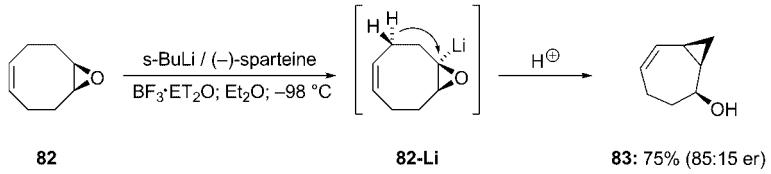
The importance of oxiranyllithiums as key intermediates in the synthesis of target natural compounds can be once more appreciated by considering the total synthesis of (–)-xialenon A.[41] A crucial step concerned lithiation of a doubly functionalized achiral cyclooctene oxide **79** with *i*-PrLi and α-(–)-isosparteine aimed at promoting a transanular desymmetrization; the process gave the bicyclic alcohol **80** in 55% yield and 90:10 er (Scheme 4.29).



Scheme 4.28.



Scheme 4.29.

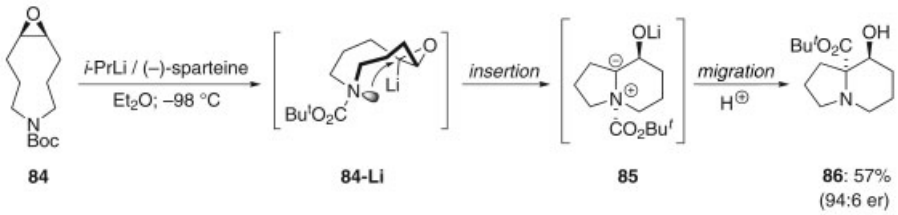


Scheme 4.30.

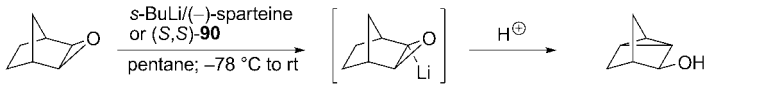
Once constructed, the bicyclo[3.3.0]octane skeleton, with the desired configuration, was further elaborated to (–)-xialenon A **81** in 12 steps. This study constitutes the first application of an epoxide transanular desymmetrization in the total synthesis of a natural product.

C–H insertion reactions on α-lithiated epoxides can be dramatically affected by Lewis acids, as demonstrated by Alexakis[42] who reported an enantioselective preparation of cyclopropyl alcohols starting from cycloalkene oxides (Scheme 4.30). Treatment of epoxide **82** with *s*-BuLi and (–)-sparteine, in the presence of $BF_3{\cdot}Et_2O$ resulted in the insertion of the carbenoidic lithiated α-carbon into the allylic C–H bond, within the intermediate **82-Li**, with the formation of the cyclopropane derivative **83** as chiral non-racemic compound (75% yield and 85/15 er).

Desymmetrization of *meso*-epoxides also allows the construction of nitrogen-containing heterocyclic compounds. When epoxide **84** is deprotonated with *i*-PrLi/(–)-sparteine (18 h at –98 °C), the indolizine derivative **86** is isolated in 57% yield and 94:6 er (Scheme 4.31).[43] A possible mechanistic explanation is that the lithiation of **84** leads to the carbenoidic oxiranyllithium **84-Li** which readily evolves through a transannular insertion of the lithiated carbon into the nitrogen lone pair to give the ammonium ylide **85**; further [1,2]-migration of the exocyclic *N*-substituent should afford the indolizine **86**.



Scheme 4.31.

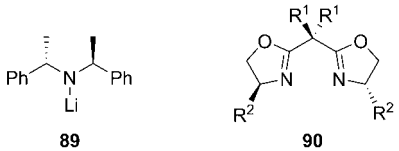


87 **87-Li** **88**: 73%, up to 76:24 er

Scheme 4.32.

The indolizine synthesis was also tested in its catalytic version by performing the reaction with 0.24 equiv of α-(–)-isosparteine, as the asymmetric inductor. The process showed the same enantioselectivity, even though the reaction was very slow, as 40 hours were needed to convert 75% of the starting epoxide **84**.

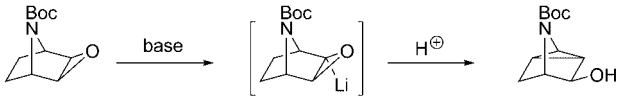
Transannular reactions involving enantioenriched oxiranyllithiums can also be performed on tricyclic systems as in the case of lithiation of *exo*-norbornene oxide (Scheme 4.32).[44] Deprotonation of epoxide **87**, carried out with *s*-BuLi and (–)-sparteine from –78 °C to room temperature in pentane, results in the formation of nortricyclanol **88** through oxiranyllithium **87-Li** in good yield (73%) and moderate enantioselectivity (76:24 er). Comparable results in the synthesis of **88** (73% yield, 75:25 er) are obtained employing the chiral non-racemic lithium amide (*S*,*S*)-bis(1-phenyl)ethylamide **89** (Figure 4.4).



89 **90**

Figure 4.4.

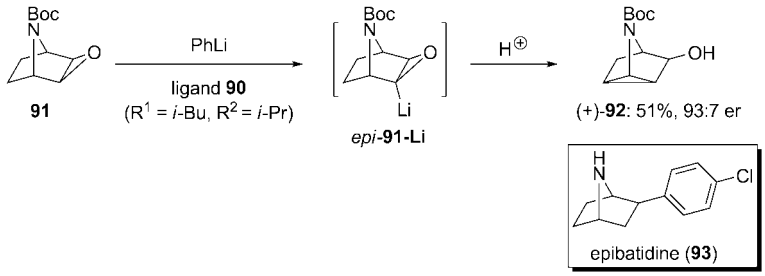
An interesting development of the above methodology is the rearrangement of azanorbornene **91** to the alcohol (–)-**92**, through the oxiranyllithium **91-Li**, performed with different base-ligand systems as depicted in Scheme 4.33.[45] The use of lithium amide **89** was almost ineffective [(–)-**92**: 20%, 54:46



91 **91-Li** (–)-**92**

base	(–)-**92**
(*S*,*S*)-**89**	20%, 54:46 er
(–)-sparteine/*s*-BuLi	12%, 82:18 er
(–)-sparteine/ MeO–Li, Me	60%, 88:12 er

Scheme 4.33.

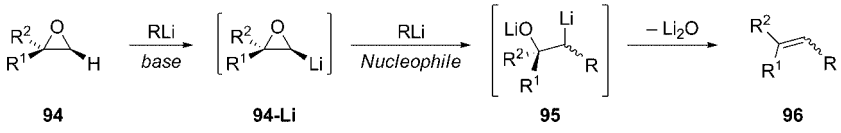


Scheme 4.34.

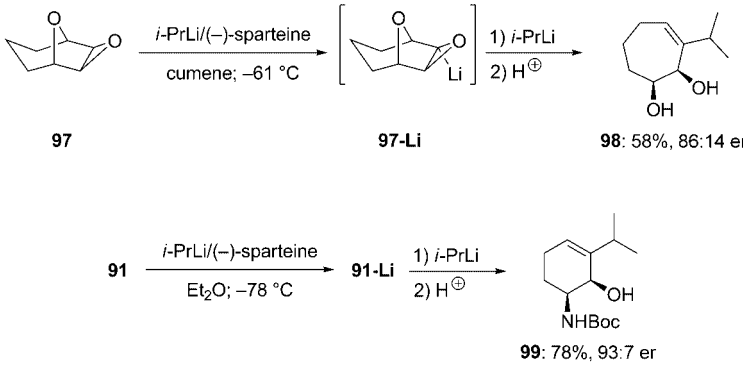
er] whereas using the mixture *s*-BuLi/(–)-sparteine, the desired product was obtained in only 12% yield and moderate enantiopurity (82:18 er). A remarkable improvement came from the use of an aryllithium as the base: the combination 2-methyl-4-anisyllithium/(–)-sparteine furnished the azanortricyclanol (–)-**92** in both good yield (60%) and enantioselectivity (88:12 er). This example represents the first case of *meso*-epoxide desymmetrization mediated by aryllithiums complexed to chiral ligands.

However, the use of (–)-sparteine in enantioselective deprotonations can also be a limit because of the lack of availability of both the enantiomers which might allow, in principle, the obtention of the two enantiomeric forms of a certain chiral product. To this end, many efforts have been made in order to find or synthesize single chiral enantiopure ligands with a high structural variability and in both enantiomeric forms. Among the most successful asymmetric inductors, a special role has been played by *bis*-oxazolines such as **90** (Figure 4.4). Treatment of epoxide **91** with PhLi in the presence of a variety of oxazoline-based ligands results in enantioselective synthesis of alcohol (+)-**92**, through the chiral intermediate *epi*-**91-Li**, with a substantial improvement in the optical purity (93:7 er using ligand **90**, R^1= *i*-Bu, R^2= *i*-Pr) (Scheme 4.34). Such a strategy opened new routes to the synthesis of analogs of epibatidine **93**, a potent non-opioid analgesic.[46]

The "reductive alkylation" reaction is another carbenoid-like reaction of α-lithiated epoxides which converts an oxirane such as **94** into an alkene **96**.[38,47] The proposed mechanism is based on a preliminary deprotonation to give oxiranyllithium **94-Li** which undergoes a nucleophilic addition at the lithiated carbon affording the dilithium compound **95** which finally furnishes alkene **96** by the loss of Li_2O (Scheme 4.35).



Scheme 4.35.



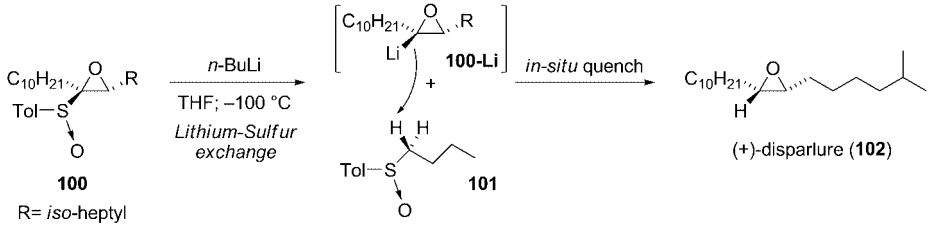
Scheme 4.36.

This type of reaction has been exploited for the synthesis of enantioenriched diols and aminoalcohols. Treatment of epoxide **97** with an excess *i*-PrLi in the presence of (–)-sparteine at –61 °C gives the alkylated diol **98,** trough intermediate **97-Li**, in moderate yield (58%) and good enantioselectivity (86:14 er).[48] Similarly, lithiation of azanorbornene oxide **91** with *i*-PrLi/(–)-sparteine in Et_2O at –78 °C furnishes bifunctionalized cyclohexene **99**, thorough **91-Li**, in improved yield (78%) and enantiomeric enrichment (93:7 er) (Scheme 4.36).[49]

The reductive alkylation suffers, however, from one major drawback: the base and the nucleophile are always the same molecule. Therefore, only simple alkyl and aryl units can be incorporated in the starting epoxide.

VIII. OXIRANYLLITHIUMS BY DESULFINYLATION

Enantiopure oxiranyllithiums can be generated from the corresponding sulfinyl epoxides by treatment with alkyllithiums. The method constitutes an important asymmetric tool for the synthesis of simple 1,2-disubstituted epoxides as demonstrated by Satoh[50] in the total synthesis of (+)-disparlure, a pheromone of the female gypsy moth. Treated with *n*-BuLi at –100 °C, enantiomerically enriched sulfoxide **100** gives the oxiranylanion **100-Li** as tran-



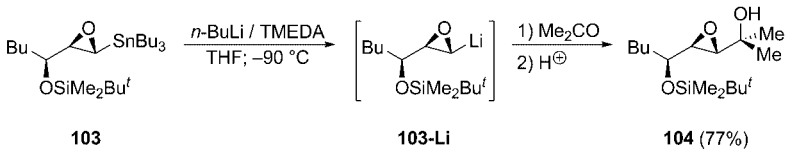
Scheme 4.37.

sient intermediate; the fast *in situ* quenching with *n*-butyl-*p*-tolylsulfoxide **101** leads to the *cis*-disubstituted epoxide (+)-disparlure **102** (Scheme 4.37).

It is reasonable to guess that the unexpected chemical and configurational stability of lithiated oxirane **100-Li** was due to the *in-situ* quenching by the corresponding sulfoxide α-hydrogens, since the absence of a stabilizing group often causes an epoxide ring-opening reaction. For this reason, the methodology is limited to the stereospecific protio-desulfinylation of epoxysulfoxides.

IX. OXIRANYLLITHIUMS BY TRANSMETALATION

In 1991, Pfaltz[51] and coworkers reported that tributylstannyl epoxide **103** could be lithiated in only 5 minutes by treatment with *n*-BuLi at –90 °C in the presence of TMEDA to give **103-Li**. Subsequent quenching of **103-Li** with acetone gave the hydroxyalkylated epoxide **104** in 77% yield as a single diastereoisomer, the entire process being highly stereoselective (Scheme 4.38). Moreover, the authors set up an asymmetric version of the above reaction since the epoxide **103** can be prepared in enantiopure form by Sharpless epoxidation of the corresponding allylic alcohol.



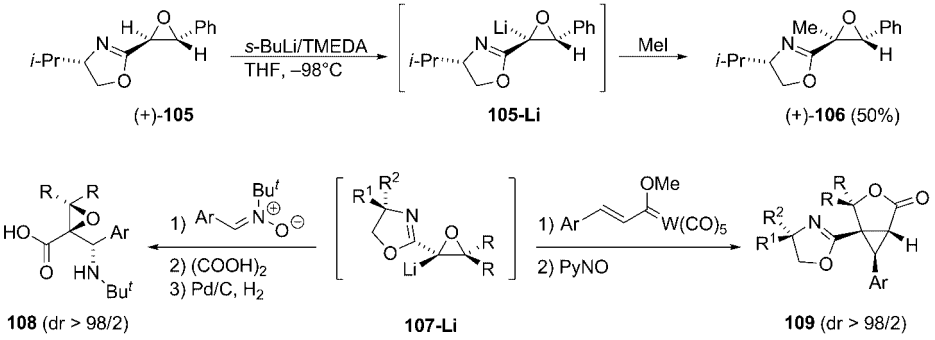
103 **103-Li** **104** (77%)

Scheme 4.38.

X. α-LITHIATED OXAZOLINYLOXIRANES

α-Lithiated oxazolinyloxiranes can be easily generated by deprotonation and reacted with many electrophiles. They are, generally, configurationally unstable on the macroscopic time scale at low temperature[52a,b] even if some of them seem to be, apparently, configurationally stable: oxazolinyloxirane **105-Li**, obtained by Li–H exchange from optically active oxirane (+)-**105**, was indeed methylated with retention of configuration to afford the epoxide (+)-**106** (Scheme 4.39).[22] The synthetic utility of oxazolinyloxiranyllithiums can be appreciated by considering that **107-Li** has been successfully coupled with nitrones and Fischer carbene complexes for the highly stereoselective synthesis of α-epoxy-β-amino acids **108**[52c] and cyclopropane-γ-butyrolactones **109**,[52d] respectively (Scheme 4.39).

In order to get more detailed information about the configurational stability of α-lithiated oxazolinyloxiranes, a multinuclear magnetic resonance

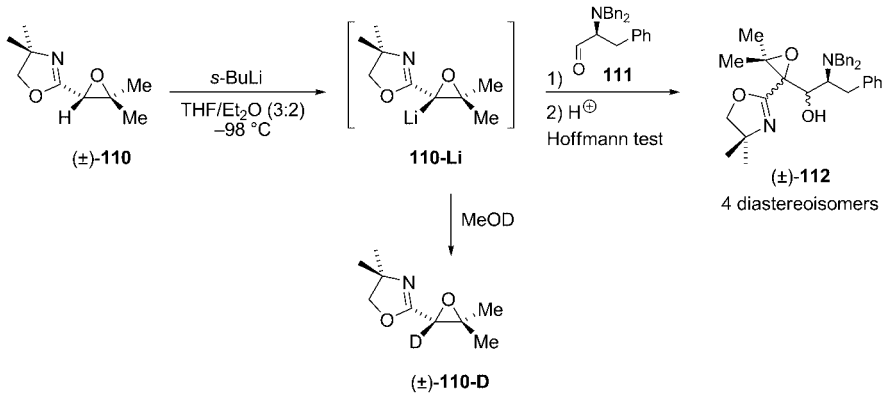


Scheme 4.39.

study on **110-Li**, jointly with an in situ IR investigation,[53] has been recently reported. Such an intermediate was generated in THF upon treatment of **110** with *s*-BuLi at –98 °C. At this temperature, **110-Li** proved to be chemically stable for several hours and could be quantitatively trapped with a deuterium source to give **110-D** (Scheme 4.40).

Preliminary information about the configurational stability of **110-Li** were gathered by the Hoffman test (see Chapter 5 in this volume) employing racemic **110** and a chiral aldehyde such as **111**: oxiranyllithium **110-Li** underwent enantiomer equilibration at –98 °C with a rate comparable to that of its addition to aldehyde **111** (Scheme 4.40). However, an enantiopure sample of (–)-**110**, once deprotonated, was found to racemize within 1 min at –130 °C in THF/Et_2O (3:2) ($t_{1/2}$ = 6.05 s). The application of the Eyring equation suggested a barrier to inversion for **110-Li** of 8.8 kcal/mol at –130 °C in THF/Et_2O (Figure 4.5).

IR spectroscopic studies *in situ* showed that lithiation of **110** at –98 °C in THF is accompanied by a decrease of the C=N wavenumbers by only 60 cm^{-1},



Scheme 4.40.

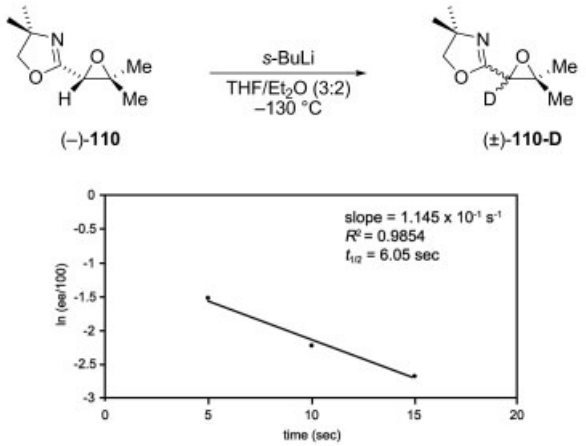
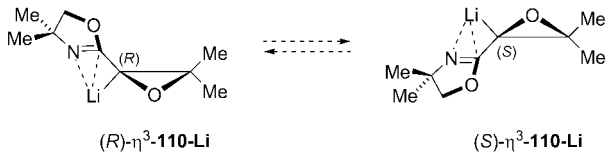


Figure 4.5.

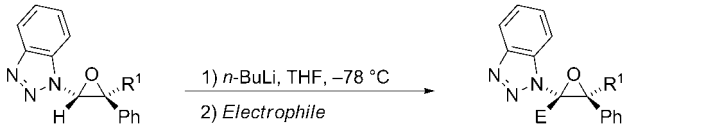
thus supporting the idea that **110-Li**, under the above conditions, mainly exists as a true organolithium and not as an azaenolate. Finally, a multinuclear magnetic resonance study suggested that several η^3-aza-allylic coordinated species might be involved in dynamic equilibria in a THF solution at 170 K. An indirect dynamic interconversion between two lithiated η^3-aza-allyl enantiomeric monomers, namely (*R*)-η^3-**110-Li** and (*S*)-η^3-**110-Li**, mediated by a complex mixture of diastereomeric oxazoline-bridged dimeric species variously intra-aggregated, has been proposed as a possible mechanism responsible for the fast racemization **110-Li** undergoes (Scheme 4.41).



Scheme 4.41.

XI. α-LITHIATED BENZOTRIAZOLYLOXIRANES

The benzotriazolyl moiety represents a useful heteroaromatic anion-stabilizing group for lithiated epoxides, as recently demonstrated by Katritzky.[54] While arylepoxides are often generated and trapped at very low temperatures (T ≤ –98 °C), benzotriazolyl oxirane **113** can be deprotonated at –78 °C with *n*-BuLi and trapped successfully with electrophiles to give tetrasubstituted oxiranes **114**. In one case, the lithiation on the (*E*)-configured epoxide **115** (R^1= Et) and the subsequent trapping with ethyl benzoate proceeds stereoselectively, leading to the α-benzoylated epoxide **116** (Scheme 4.42).



113 (R^1=Ph)
115 (R^1=Et)

114 (72 – 92%, R^1=Ph)
116 (68%, R^1=Et, E=PhCO)

Electrophile= MeI, BuBr, PhCHO, Et_2CO, $PhCO_2Et$

Scheme 4.42.

XII. CONCLUSIONS

α-Lithiated epoxides represent an important class of functionalized organolithiums that can be used for many synthetic purposes: their high nucleophilicity can be exploited for the formation of C–C, C–Si, C–B, C–Sn and C-P bonds. On the other hand, the rearrangement of carbenoidic metalated epoxides opens a wide range of transformations into complex structures such as polycyclic hydrocarbons and highly strained molecules whose preparation would, otherwise, be difficult. Therefore, oxiranyllithiums constitute a peculiar category of organometallic species since they can be "tuned" as nucleophiles or electrophiles depending upon the experimental conditions.

Last but not least, putting a C–Li on a rigid three-membered cycle, such as that of epoxides and aziridines, has a precise consequence: the obtainment of functionalized organolithiums that can be generated as enantiopure intermediates and employed in asymmetric synthesis.

Further studies are, however, needed for the comprehension of their stereochemical properties with subsequent practical applications in synthesis, as well as of their reactivity.

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Chapter 5

Test on the Configurational Stability/Lability of Organolithium Compounds

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I. INTRODUCTION

Organometallic reagents, especially organolithium[1] and Grignard reagents[2] are indispensable carbon nucleophiles in organic synthesis. When stereoselective synthesis became the major frontier in organic synthesis,[3] it was obvious that attention turned to chiral enantiomerically pure organometallic reagents. As with any chiral reagent, useful application in synthesis is possible, when the reagent is either configurationally stable under the reaction conditions, or when it racemizes rapidly under these conditions opening the application of dynamic kinetic resolution.[4] For a review of dynamic kinetic and dynamic thermodynamic resolutions of chiral organolithiums, see the chapter by Coldham and Sheikh in this volume. For a concise summary of several variations of the Test, see the chapter by Kizirian in this volume. Hence, information on the configurational stability of organolithium compounds and Grignard reagents became a key prerequisite to their application in stereoselective synthesis.

Stereochemical Aspects of Organolithium Compounds Edited by Robert E. Gawley

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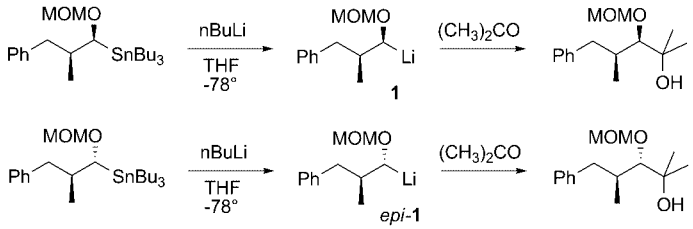
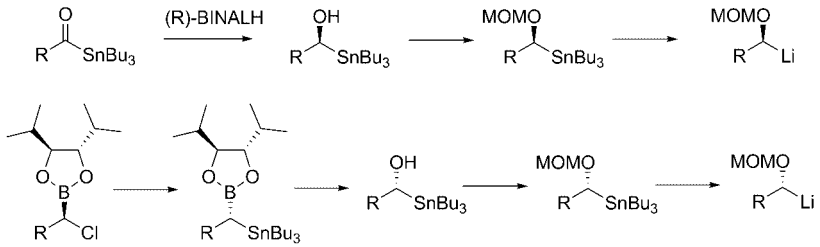


Scheme 5.1.

In this respect, a landmark experiment by Still and Sreekumar[5] (Scheme 5.1) demonstrated the configurational stability of the diastereomeric α-alkoxyisobutyllithium reagents **1** under the reaction conditions. In due course routes to enantiopure α-alkoxyalkyllithium reagents were developed (Scheme 5.2).[6]

Obviously, considerable effort was invested in the development of these routes,[7] effort that could not have been justified without the precedent from the Still-Sreekumar study.[5] Hence, before starting to develop routes to enantiopure organolithium reagents, information on their configurational stability is mandatory.



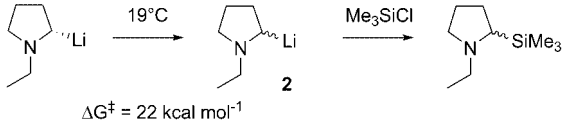
Scheme 5.2.

II. CONFIGURATIONAL STABILITY

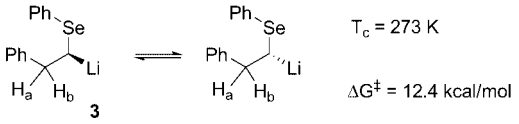
Traditionally the configurational stability of a chiral entity is assessed by following the rate of racemization of an enantiomerically enriched sample. An example is given for *N*-ethyl-2-lithiopyrrolidine (**2**)[8] in 4:1 hexanes/Et_2O, whereby the racemization was followed by trapping with Me_3SiCl and subsequent analysis by chiral HPLC (Scheme 5.3).

While this experiment provided the desired information on the configurational stability of the lithium compound **2**, this approach required routes to access enantiomerically enriched **2** to be developed beforehand.

It would be by far preferable, if such information could be accessed by simply using the racemic organolithium compound. This is accomplished us-



Scheme 5.3.



(*Scheme 5.4.*)

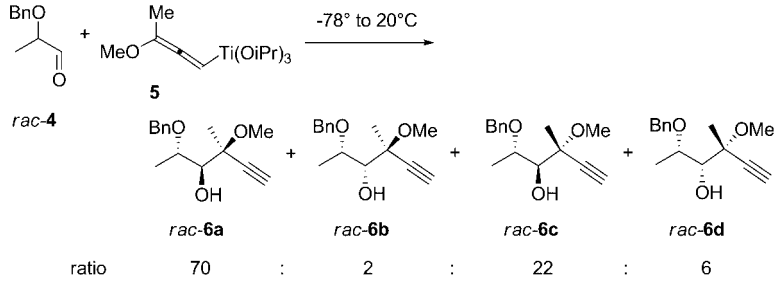
ing NMR-methods that rely on the topomerisation of diastereotopic nuclei. An example is given by 1-phenylseleno-2-phenyl-ethyllithium (**3**), in which the ^{1}H-NMR signals of H_a and H_b coalesced at 273 K (Scheme 5.4).[9]

The low barrier to enantiomerisation for **3** indicated that any attempts to generate enantiomerically pure **3** would be doomed with failure, whereas the lithium compound **2** can safely be generated and handled as an enantiomerically enriched species.

When activation barriers for racemization of organolithium compounds have to be determined that fall in between those of compounds **2** and **3**, NMR-methods soon reach their limits, because the coalescence temperature of the signals of diastereotopic nuclei will soon exceed the temperature for the thermal decomposition of the organolithium compound of interest. Hence, there was a lack of methodology to determine racemization rates of compounds that are less configurationally stable than compound **2**, but more than compound **3**, for example. This gap was filled by a Test developed in our group in 1992.[10]

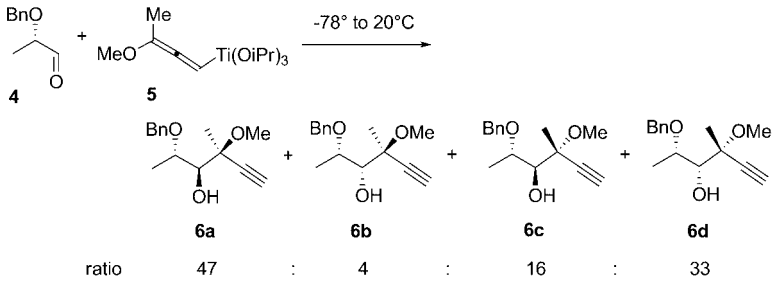
III. THE TEST, HISTORIC DEVELOPMENT

The Test for assessing the configurational stability of organolithium compounds was in no way rationally developed. It rather arose by serendipitous observation of (at that time) unexpected chemical results. We had been engaged in a project to generate 2,6-dideoxy-(L)-hexoses by addition of allyl- and allenyl-metal reagents to *(S)*-2-benzyloxypropionaldehyde (**4**) (Scheme 5.5). Thus, in an experiment to explore the reaction conditions the allenyl-titanium reagent **5** was added to racemic **4.** This led in a 88% yield to the four diastereomeric adducts in a 70 : 2 : 22 : 6 ratio determined by gas chromatography.[11,12]



Scheme 5.5.

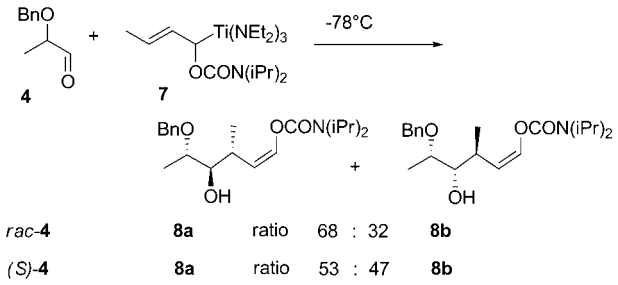
When the experiment was repeated with optically pure **4** the same four diastereomeric products were obtained in 78% yield, but in a different diastereomer ratio (Scheme 5.6):



Scheme 5.6.

This discrepancy surprised us for a moment until we realized that the titanium reagent **5** is chiral, of course a racemate. Thus, on reaction of enantiomerically pure aldehyde **4** the products **6a,b** derive from one enantiomer of **5**, compounds **6c,d** from the other. The product ratio **6a,b** to **6c,d** of 51 : 49 reflects the enantiomer ratio of (racemic) **5.** On reaction with the racemic aldehyde **4** a different situation prevailed, as in reactions between two racemates a situation of mutual kinetic resolution is given. The product ratio *rac*-**6a,b** to *rac*-**6c,d** of 72 : 28 reflects the relative rates, by which the two enantiomer pairings of the reactands react, the selectivity factor **s**.[14] We noted on a sideline that this set of experiments demonstrated that the enantiomers of the chiral titanium reagent **5** did not interconvert on the timescale of their addition to the aldehyde **4**. Had the former equilibrated (racemized) more rapidly than they added to the aldehyde **4**, the diastereomer ratios in the two experiments should have been identical! But this insight was buried under the disappointment that reaction of enantiomerically pure aldehyde **4** with the reagent **5** didn't open a diastereoselective route to the desired 3-methyl-2,6-dideoxyhexoses.

A similar observation on varying diastereomer ratios had been made concurrently by Hoppe and Tarara (Scheme 5.7):[13]



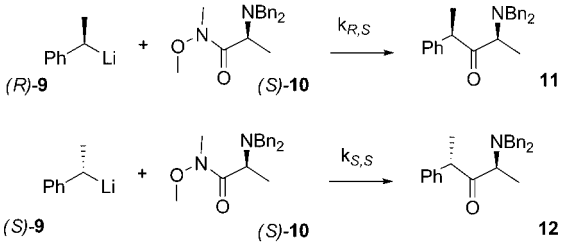
Scheme 5.7.

Again, it was the reaction of a racemic organotitanium species, once with a racemic and once with an enantiomerically pure aldehyde. Actually, this finding was not novel, since related observations on varying diastereomer ratios had been recorded on other occasions where a racemic substrate was reacted with another chiral partner.[15] Yet, all these observations were seemingly useless until the moment when the irrevocable thought crossed the mind, that the principles underlying these observations constituted a Test on the configurational stability of the organometallic intermediates **5** or **7**, a test that could be carried out with the racemate, not requiring any enantiomer enrichment on the side of the organometallic substrate! From that very moment, the "Test" became the objective of research and the conditions to carry it out in an optimal manner were rationally developed.[10] The Test and its implications have been reviewed several times.[1,16,17] For concise summaries of the Test, including of several variations, see the chapters by Gawley and Kizirian in this volume.

IV. THE TEST

The reaction system should be composed of the racemic substrate and a chiral partner that combine to form configurationally and chemically stable[18] products that retain the stereochemical information from both the substrate and the partner. In this manner, the reaction leads to two diastereomeric products (Scheme 5.8).

Thus, on addition of compound **9** to the Weinreb-amide **10** the resulting ketones (**11** and **12**) contain one stereogenic centre derived from **9** and another one derived from **10**.[19] Diastereomer **11** can be seen to come from *(R)*-**9** and *(S)*-**10**, diastereomer **12** from *(S)*-**9** and *(S)*-**10**. It is the ratio of these two diastereomeric products that has to be determined by a suitable



Scheme 5.8.

analytical method. Hence, these products should be identified, but it is not necessary to assign their relative configuration.

Let us consider first the situation, that organolithium compound **9** were configurationally stable on the time scale of its addition to **10**; more precisely, that *(R)*-**9** and *(S)*-**9** interconvert at a slower rate (if at all) than they add to **10**. In this case we have, on reaction of the racemate, two independent parallel reactions [*(R)*-**9** giving **11**, and *(S)*-**9** giving **12**]. As racemic **9** contains equal amounts of *(R)*-**9** and *(S)*-**9,** the products **11** and **12** should arise after complete conversion in a 1 : 1 ratio. However, when $k_{R,S}$ and $k_{S,S}$ differ (they relate to diastereomeric transition states!), the product ratio **11**/**12** varies over time as it depends on the amount of conversion as shown with the bold lines in Figure 5.1. Initially the two products are formed in a ratio that corresponds to the kinetic resolution $k_{R,S} / k_{S,S}$, the selectivity factor "**s**". Figure 5.1. shows the calculated development of the product ratio (ratio of diastereomeric products) along the progress of the reaction (conversion) for a choice of selectivity factors **s** (from **s** = 1.5 to **s** = 20).[10,20,21]

If the two enantiomers of **9** were to interconvert more rapidly than they add to **10**, then the product ratio would correspond at all times to the selectivity factor **s**, because the 1 : 1 ratio of *(R)*-**9** and *(S)*-**9** is maintained through rapid racemization, irrespective of which enantiomer is reacting faster. In this situation the product ratio would be independent on the amount of conversion, as illustrated by the dashed horizontal lines in Figure 5.1.

In order to arrive at a statement, whether the substrate is configurationally labile or stable on the time scale of the addition to the chiral partner (**10**), one has to carry out two experiments to ascertain, whether the given situation corresponds to the solid lines or that of the dashed lines in Figure 5.1. Inspecting Figure 5.1, it is immediately apparent that a distinction will be difficult, if not impossible in the case when the kinetic resolution $\mathbf{s} = k_{R,S} / k_{S,S}$ is smaller than 1.5. Other practical considerations reveal[10] that **s** should be optimally in the range between 1.5 and 3. Hence, to evaluate the test system one should first determine the prevailing selectivity factor **s**. This can be done in a twofold manner: Figure 5.1. suggests to run the reaction between the racemic substrate and the enantiomerically pure electrophile to low (< 20%)

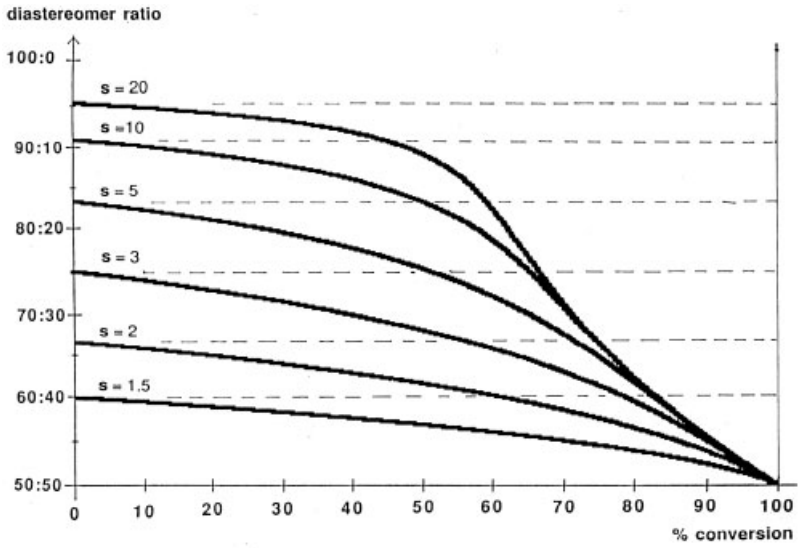


Figure 5.1. Ratio of the diastereomeric products as a function of the amount of conversion.

conversion. This leads to a product ratio which will approximate that resulting from kinetic resolution. Another way, as originally proposed,[10] is to run a reaction between the racemic substrate and the *racemic* electrophile. In this case of a reaction between two racemates, the product ratio is independent on conversion and is equal to the selectivity factor **s**.[14] On reaction of racemic **9** with racemic **10** the selectivity factor was found in this manner to be 1.70,[19] *i.e.* in the optimal range. In case the system investigated shows a selectivity factor **s** < 1.5 or > 4, one should choose another reaction partner, *i.e.* to turn to another system.

Once the reaction system possesses a suitable selectivity factor, the crucial experiment is to be carried out, in order to recognize whether the system at hand corresponds to the boldface or the dashed lines in Figure 5.1. In the case of **9** and **10**, racemic **9** and enantiomerically pure **10** were allowed to react to high (76%) conversion. The products **11** and **12** were obtained in a 63 : 37 ratio, matching the **s**-value of 1.70. This shows that the system corresponds to the dashed lines in Figure 5.1. In consequence, the benzyllithium species **9** enantiomerizes more rapidly than it adds to the Weinreb-amide **10**.

The statement regarding configurational lability or stability refers to a time-scale set by the rate of addition to the chiral partner chosen. This time scale could be quantified by determining the reaction rate between the partners (**9** and **10**). More information on the rate of enantiomerization could be obtained, when a set of chiral reaction partners is tested, which react over a wide range of reaction rates (which would have to be determined).

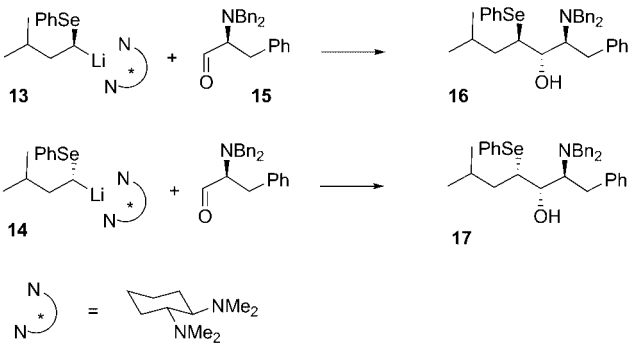
The Test thus comprises two experiments: first racemic substrate + racemic partner determining the ratio "p" of the diastereomeric products, which corresponds to the selectivity factor **s**. If **s** is in the optimal range, 1.5 – 3.0, go to the second experiment: racemic substrate + enantiomerically pure partner run to high conversion giving the product ratio "q". If q is equal to p, the substrate enantiomerizes rapidly on the time scale of the reaction rate between the two partners. If q is (in an analytically significant manner!) smaller than p, approaching unity on complete conversion, the substrate is configurationally stable on the time scale of the reaction rate between the two partners.

The attraction of the Test is due to the fact that the substrate in question can be used as a racemate. The two diastereomeric products have only to be identified as such and their ratio has to be determined. It is not necessary to secure the relative configuration of the diastereomers. This convenient simplicity may be lost, when additional stereogenic centers are created in the reaction between the substrate and the chiral reaction partner; cf. the reaction between **4** and **5**. In this case four diastereomeric products were generated and it became necessary to assign the relative configuration to each of the diastereomers. It only then became possible to group the diastereomers, **6a** and **6b** to come from one enantiomer of the substrate **5**, and **6c** and **6d** to come from the other enantiomer of **5**. That means, in situations in which more than two diastereomers are produced, the Test is still possible and valid, but more laborious.

V. VARIANTS OF THE TEST

The Test cannot only be applied to racemic chiral organolithium compounds, it may become of interest to determine the configurational stability of organolithium species complexed to a chiral ligand. When one starts from a racemic organolithium compound, the complexes with a chiral ligand may be present in a 1 : 1 ratio or in a different ratio controlled by thermodynamics, if the complexes had equilibrated prior to the Test reactions (Scheme 5.9).

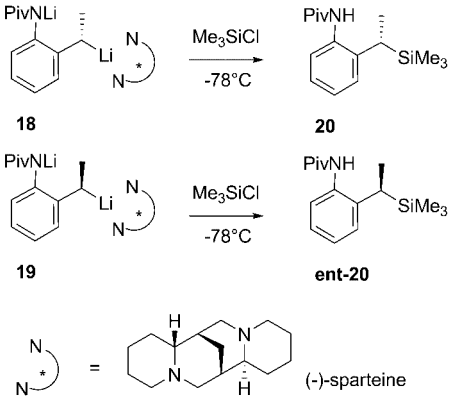
When the diastereomeric complexes **13** and **14** were to be studied, ^{77}Se-NMR-spectroscopy showed that the diastereomeric starting complexes were present in a 70 : 30 ratio. The mixture of complexes was first allowed to react with a deficiency (0.1 equivalents) of the enantiomerically pure aldehyde **15** to give **16** and **17** in a 78 : 22 ratio. In order to determine the selectivity factor **s** in this system, the ratio of the diastereomeric products **16** and **17** had to be corrected for the ratio of the starting complexes leading to a **s**-value of 78 : 22/70 : 30 = 1.5, which falls into the optimal range. The follow-up experiment with an excess of the enantiomerically pure aldehyde **15** gave a different ratio (71 : 29) of the diastereomeric products, indicating that the complexes **13**, **14** are configurationally stable on the time scale of their addition to the aldehyde **15**.[22]



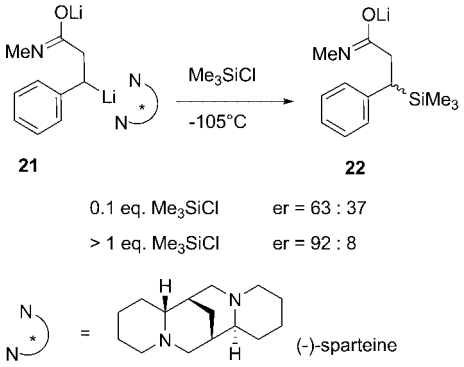
Scheme 5.9.

The fact that in the above system the starting substrate is a mixture of diastereomers (rather than enantiomers) allows for a further simplification of the Test. It is no longer required that the reaction partner is chiral. Any achiral partner can be used, that reacts at different rates (selectivity factor **s**) with the equilibrating or non-equilibrating diastereomeric substrate complexes. This variant of the Test has been demonstrated and propagated by Beak.[23]

In this case (Scheme 5.10), the diastereomeric complexes **18** and **19** were generated in a ≈1 : 1 ratio at –78 °C. On reaction with a deficiency (0.1 equivalents) of Me_3SiCl the product 20 was obtained in an 91 : 9 enantiomer ratio. This corresponds to a selectivity factor **s** of 10. In the second experiment, the mixture of the complexes **18** and **19** were allowed to react with an excess (1.5 equivalents) of Me_3SiCl. The enantiomer ratio of the resulting **20** was found to be 56 : 44, approaching the ratio of the initial complexes. This should result when **18** and **19** do not interconvert on the timescale of their reaction with Me_3SiCl.[23] Complete conversion of **18** and **19** into **20** may probably not



Scheme 5.10.



Scheme 5.11.

have been reached even with a larger excess of Me_3SiCl on account of the high (>3) **s**-value.

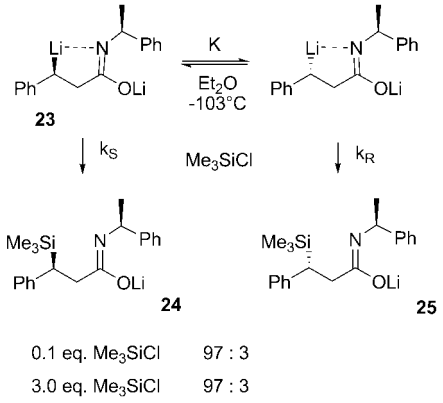
A similar case was reported (Scheme 5.11),[24] in which differing enantiomer ratios of **22** on trapping with a deficiency and an excess of trimethylchlorosilane prove the configurational stability of the complexed benzyllithium species **21** on the time scale of their reaction with trimethylchlorosilane.

In this case the diastereomeric complexes are present in a ratio of ~92 : 8 and it is the minor complex that is the faster reacting one (with trimethylchlorosilane). With a very similar scenario it could be shown[25] that α-trifluoromethylsulfonyl-benzyllithium is trapped by aromatic aldehydes faster than it racemizes.

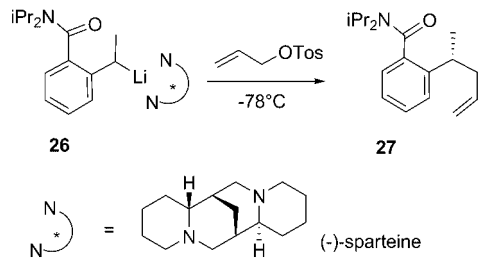
However, such a reaction scheme is only conclusive when it delivers different product ratios in the two experiments. Once the product ratios remain the same in the two experiments an ambiguous situation arises, such as the one encountered when the diastereomeric benzyllithium compounds **23** were trapped with a deficiency and an excess of trimethylchlorosilane (Scheme 5.12).[26]

In this case the congruent diastereoselectivity of 97 : 3 suggests that the benzyllithium compounds **23** are trapped more slowly than they equilibrate. However, the diastereomer ratio **24** : **25** (97 : 3) is equal to the product of equilibrium constant K and the selectivity factor **s**, K × **s**, and hence, does not provide evidence of the presence of sufficient kinetic resolution, *i.e.* that $\mathbf{s} = k_S/k_R > 1.5$.[26] Beak reported another similar observation in ref.[20], see footnote 10.

Likewise an ambiguous situation was encountered, when the complexes of the lithium compound **26** with sparteine were trapped with allyl tosylate (Scheme 5.13).[27] Here, the enantiomer ratio of the product **27** remained constant with varying conversion, suggesting a configurational lability of the organolithium species with respect to the time scale of trapping by the allyl tosylate. However, the range of conversions studied (13–35%) was in the low



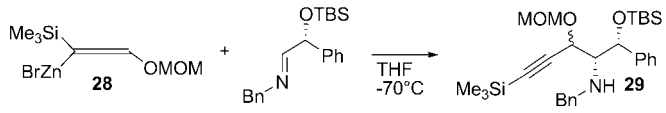
Scheme 5.12.



Scheme 5.13.

conversion regime, in which, according to Figure 5.1, only very small changes in the stereoisomer ratio are to be expected for configurationally stable entities, rendering the conclusions highly tentative.

There is a further variant of the Test, which may be applicable when the rates of enantiomerization of the substrate and the rate of trapping are of the same order of magnitude. Enantiomerization is usually a first order reaction, trapping is a second order process, the rate of which depends on the concentration of the trapping agent. Hence, on high concentration of the trapping agent, trapping may be faster than enantiomerization, on low concentration of the trapping agent enantiomerization may become faster than trapping. A method to visualize such a situation, is to add the trapping agent in one experiment very slowly (to maintain a rather low concentration), and in another experiment, to add the substrate into an excess of trapping reagent (to maintain a high concentration). As Norton has shown these two experiments may lead in a diagnostic manner to differences in the ratios of the diastereomeric products.[28] This variant was independently discovered and used by Normant[29] to characterize the reaction between the racemic allenylzinc **28** and an enantiomerically pure imine as trapping reagent (Scheme 5.14).



Experiment 1	slow addition of imine	diastereomer ratio = 75 : 25
Experiment 2	inverse addition to imine	diastereomer ratio = 50 : 50

Scheme 5.14.

Experiment 1 maintains a low concentration of the trapping agent such that the allenylzinc species may enantiomerize after each increment of the imine has reacted. The diastereomer ratio of the products **29** then reflects the selectivity factor **s**. Since **s** is in the optimal range (**s** = 3), the second experiment is carried out as usual. The resulting diastereomer ratio reaches the 50 : 50 value, expected when the substrate **28** is trapped more rapidly than it enantiomerizes. In case the diastereomer ratios in experiments 1 and 2 would have been found to be the same, this would have indicated that in both experiments enantiomerization is faster than trapping, provided **s** is in the appropriate range.

This Norton variant of the Test requires only the enantiomerically enriched trapping agent and not, in addition, the racemic trapping agent as in the classical Test. There is a fundamental difference between experiment 1 in this variant and experiment 1 in the classical Test. In the latter, the situation with regard to "configurational stability/lability" is the same in experiment 1 and experiment 2. In the Norton variant described above, the situation is intentionally sought, that in experiment 1 trapping becomes slower than enantiomerization. This then allows an estimation of the magnitude of the selectivity factor **s**.

In the Norton variant of the Test, the inherent reference time scale is different than in the classical Test. In the Norton variant it is the physical rate of addition of the trapping agent to the reaction mixture, whereas in the classical Test the time scale is the reaction rate of addition of the substrate to the trapping agent. Realizing this difference, one understands why for the classical Test it is recommended to carry out experiment 2 by inverse addition.[10] The reader is referred to the apparatus described in ref.[30] in order to carry out inverse addition of thermally labile organometallic species at low temperatures.

VI. APPLICATION OF THE TEST TO THE CONFIGURATIONAL STABILITY OF ORGANOMETALLIC SPECIES

The Test has mainly be applied to gain quick information on the behavior of chiral organolithium and Grignard reagents. The aim was to find out whether, upon reaction with electrophiles, a Curtin-Hammett situation[31] exists or not.

The results have been compiled in Table 5.1. Aldehydes have been mostly used as electrophiles, because that models closest the reactions of the organometallic species of preparative interest. The term "configurationally stable" or "labile" in the heading of the table refers to the time scale set by the reaction rate of addition of the organometallic species to the electrophile shown.

The discussion of these results is beyond the topic of this chapter, but one recognizes that benzyl lithium compounds have a much higher tendency to racemize than do their aliphatic counterparts. Chelation in turn reduces the tendency to racemize.

Table 5.1
Configurational stability or lability of organometallic species on the time scale of their reaction with electrophiles.

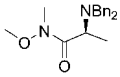
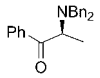
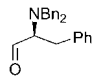
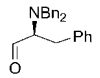
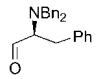
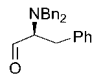
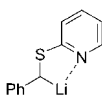
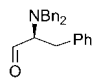
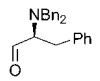
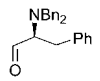
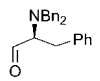
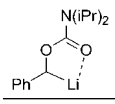
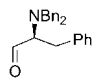
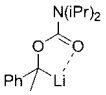
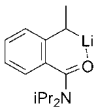
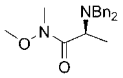
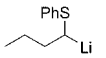
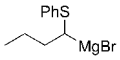
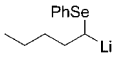
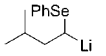
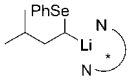
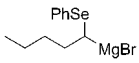
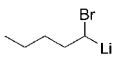
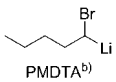
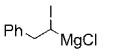
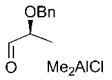
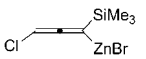
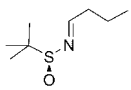
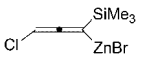
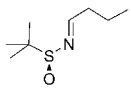
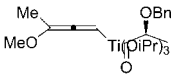
R–M	Electrophile	Solvent	Temp.	Conf. stable	Conf. labile	Reference
		THF	–78 °C		+	19
		THF	–78 °C		+	19
		THF	–78 °C		+	19
		THF	–78 °C		+	32
		THF	–78 °C		+	32
		Cumene	–78 °C		+	33
		Cumene	–78 °C	+		33
		THF	–78 °C		+	32
		THF	–78 °C	+		32
		THF	–78 °C		+	18
		THF	–78 °C	+		32

Table 5.1 (continued)

R–M	Electrophile	Solvent	Temp.	Conf. stable	Conf. labile	Reference
		THF	–78 °C	+		32
		THF	–78 °C		+	20
		MeTHF	–120 °C	+		34
		Et_2O	0 °C	+		34
		Et_2O	–105 °C	+		34
		Et_2O	–60 °C	+		22
		Et_2O	–60 °C	+		22
		CH_2Cl_2	–20 °C	+		35
		Trapp[a]	–110 °C	+		34
		Trapp[a]	–110 °C	+		17
		THF	–78 to 20 °C	+		36
		Et_2O	20 °C	+		37
		Et_2O/ HMPT	–15 to 20 °C	+		38
		THF	–78 to 20 °C	+		11

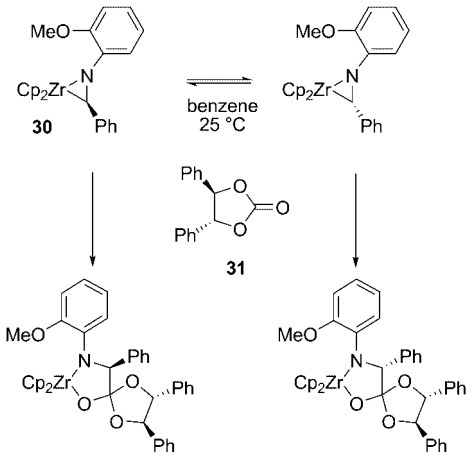
[a] Trapp refers to the Trapp solvent mixture (THF/ether/pentane).[39]
[b] PMDTA = pentamethyldiethylenetriamine.

VII. APPLICATION OF THE TEST TO OTHER MECHANISTIC PROBLEMS

It has been noted that zirconia-aziridines, *e.g.* **30**, are not configurationally stable.[40] Application in stereoselective synthesis to form α-amino-acids therefore required information regarding the relative rates of racemization and trapping with the chiral ethylene carbonate *(R,R)*-**31**. The following experiments revealed that trapping and racemization occurred at about the same rate (Scheme 5.15).[41] In a related study, Norton developed the variant of the Test that relies on the slow versus fast addition of the trapping agent (Scheme 5.16).[28,42]

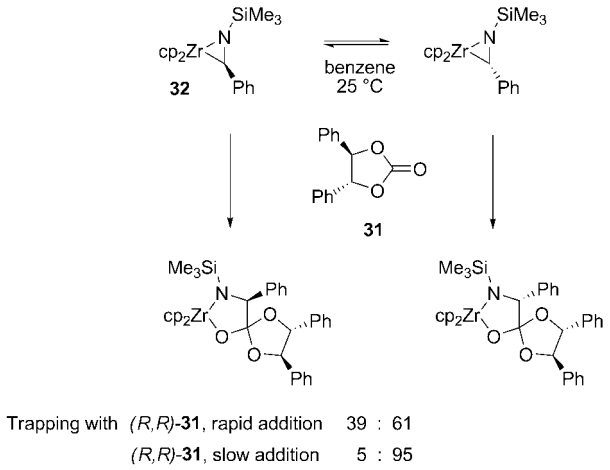
By these two experiments he established that trapping of **32** by **31** and enantiomerization of **32** are competitive processes, the relative rate of which can be controlled by the concentration of the trapping agent **31**.

A mechanistic problem of considerable scope in stereoselective synthesis is posed by the addition of η^1-crotyl metal compounds to aldehydes.[43] The reaction may lead to four different isomeric homoallyl alcohols (the product set B) (Scheme 5.17). The crotylmetal species in turn, may be present as either of the isomeric species **33**–**35** in set A, with a marked tendency to equilibrate by a 1,3-metallotropic shift. In order to find the mechanistic connectivities between individual members of set A with distinct members of the product set B, it is imperative to know whether addition of the crotyl metal species to an aldehyde is faster or slower than the interconversion of



Trapping with *rac*-**31**	14 : 86
(R,R)-**31**, low conversion	15 : 85
(R,R)-**31**, high conversion	30 : 70

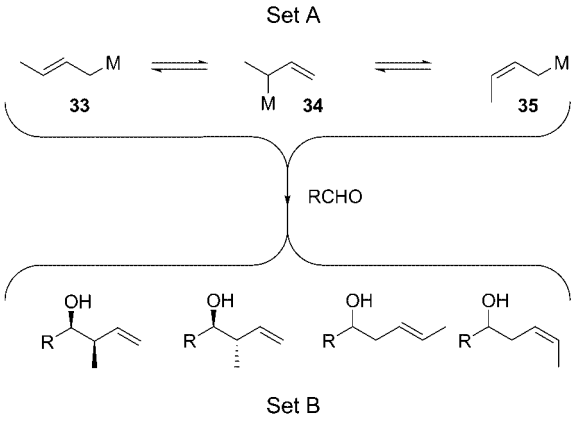
Scheme 5.15.



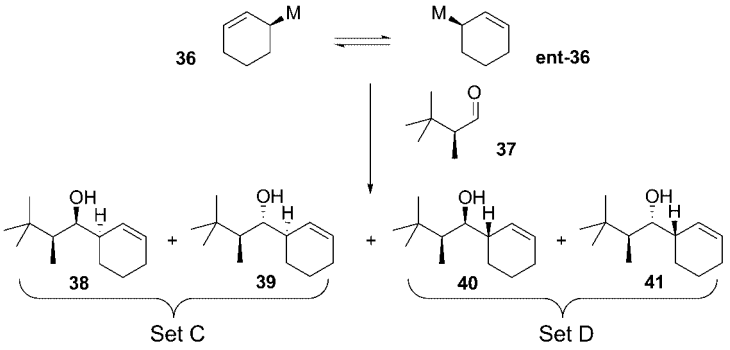
Scheme 5.16.

the crotyl metal compounds in set A. This question falls right into the scope of the Test discussed in this chapter.

The applicability of the Test becomes obvious, when one considers η^1-cyclohexenyl metal compounds **36** as models for the η^1-crotyl metal compounds. As the metallotropic shift in **36** causes enantiomer interconversion of **36**, the task is to check whether enantiomer interconversion of **36** is faster or slower than addition to an aldehyde.[44] Of various chiral aldehydes tested, aldehyde **37** best fulfilled the requirements of the Test. Four diastereomeric adducts **38** – **41** may result on addition of the cyclohexenyl metal compounds to the aldehyde **37**. Hence, the relative configuration of the adducts had to be secured in order to assign the product diastereomers to set C and set D, the ratio of which reflects the kinetic resolution inherent in the system (Scheme 5.18).



Scheme 5.17.



Scheme 5.18.

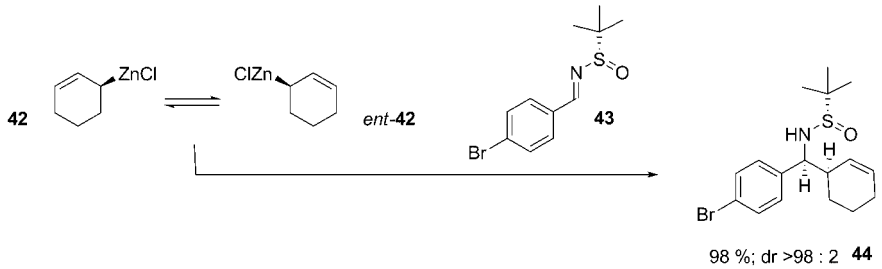
The results are summarized in Table 5.2.

The data of "experiment 1", reaction of the racemic cyclohexenyl metal compounds with racemic aldehyde **37**, show that kinetic resolution is present albeit with the selectivity factors **s** of the first two entries on the low side (**s** ≈ 1.2). In order to compensate for this deficiency, the conversion in "experiment 2" had to be ≥80% in these cases. Sufficiently high yields could be realized in all cases. Hence, clear cut answers became available: for the lithium, magnesium, and titanium compounds the metallotropic rearrangement was faster than the trapping by the aldehyde **37**. In contrast, the cyclohexenyl boron compounds added more rapidly to aldehyde **37** than the competing metallotropic enantiomer interconversion.[44] While we were interested as well in the properties of the corresponding allylic zinc reagents, their reaction with the aldehyde **37** was not clean enough for the Test. Recently, though, the cyclohexenyl-zinc chloride **42** has been added to an enantiomerically pure sulfininylimine **43**.[45]

Table 5.2
Set C / Set D product ratios on reaction of cyclohexenyl-metal compounds **36** with racemic and enantiomerically pure aldehyde **37**

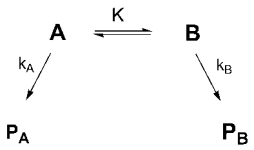
M	*rac*-**37**		(*S*)-**37**	
	Set C / set D	yield	Set C / set D	yield
Li	57 : 43	83	56 : 44	85
MgCl	55 : 45	81	54 : 46	76
$B(OR)_2$	29 : 71	84	47 : 53	79
BEt_2	31 : 69	86	50 : 50	83
$Ti(OiPr)_3$	77 : 23	70	75 : 25	73
$Ti(OiPr)_4^-$	63 : 37	75	61 : 39	69

Since the product **44** was obtained in > 50% yield and diastereomerically pure, this single experiment suggests that metallotropic equilibration of the cyclohexenyl-zinc compounds **42** is faster than the reaction with the sulfinamide. The validity of this statement depends on the prevalence of kinetic control in the formation of the product, a fact that was not proven (Scheme 5.19).



Scheme 5.19.

Here one should finally point out the generality of the Test, which allows conclusions regarding the relative rates of an equilibration and a follow-up reaction in the following scenario (Scheme 5.20):

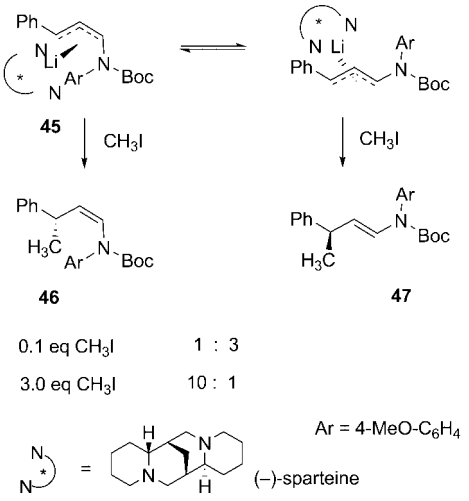


Scheme 5.20.

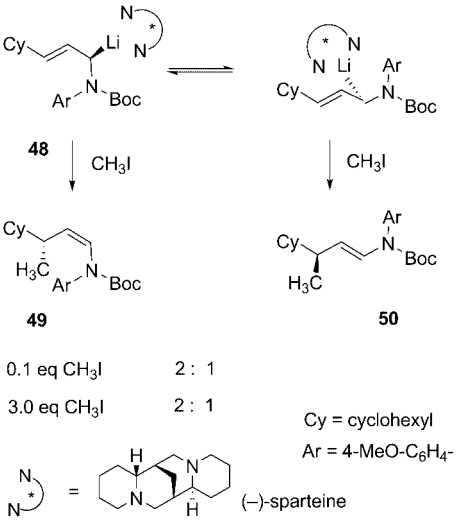
First of all, **A** and **B** do not have to be symmetry related (enantiomers). They can be diastereomers or any chemical entity. It is not required that the equilibrium constant K is unity (as with enantiomers). The products $\mathbf{P_A}$ and $\mathbf{P_B}$ should be constitutionally and configurationally stable and should manifest a structural signature that marks their origin as from **A** or **B**. All that is required is that the conversion of **A** and of **B** into the products **P** is irreversible and that the rates k_A and k_B are sufficiently different ($k_A / k_B \approx 1.5$ to 3), which has to be proven!

Hence, the Test could be applied as well to the rotamer interconversion of allyllithium compounds **45** (Scheme 5.21).[46]

The difference in the *E*/*Z*-ratio of the trapping products **46**/**47** between the two experiments proves both the existence of kinetic resolution and the fact that trapping is faster than rotamer interconversion in **45**. The presence of sparteine in the system is in this case not necessary for the Test, but originated from other aspects of the study. The study has also been extended to the corresponding cyclohexyl derivatives (Scheme 5.22).[47] In compounds **48**



Scheme 5.21.



Scheme 5.22.

the lithium is no longer η^3-, but rather η^1-bound. This should facilitate the rotation about the allylic bond.

In the case of the cyclohexyl derivatives **48** the diastereomer ratios **49**/**50** on trapping with a deficiency and an excess of methyl iodide remained the same. While this is consistent with the notion that rotamer interconversion in **48** is faster than trapping, this remains unproven in as much that the prevalence of kinetic resolution has not been established.

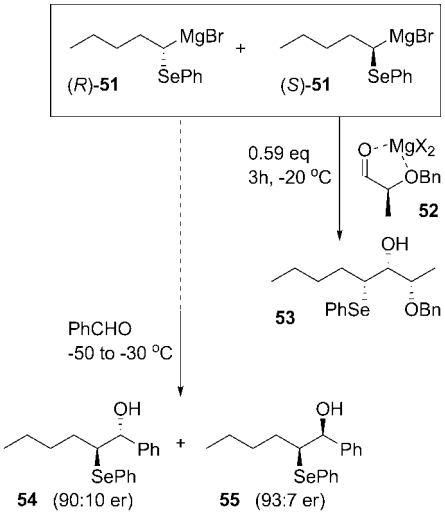
VIII. ALTERNATIVE APPROACHES

When one wants quick information on the configurational stability of chiral organometallic species, such as **2** or **3**, the classical approach would be to generate enantioenriched samples of the organometallic species, lets say by kinetic resolution, and to follow its rate of racemization. This is exemplified by a study of the α-phenylseleno-alkyl-magnesium reagent **51** (Scheme 5.23).[35]

The racemic Grignard reagent **51** was allowed to react for 3h with a deficiency of the "resolving agent", the aldehyde **52**, to give the alcohol **53**. This should leave the remainder of **51** enantiomerically enriched. At this point, benzaldehyde was added to trap the remaining **51** to give the seleno-alcohols **54** and **55**. These showed substantial enantiomeric enrichment.

In order for this approach to be successful, the "resolving agent" should have a high selectivity factor ($\mathbf{s} > 10$). This may require trial and error testing of a number of resolving agents! In the present case, **s** was determined by reaction between the racemates of **51** and **52** to be 20. Knowing the selectivity factor **s** and the level of conversion (59%), an enantiomer enrichment of ca. 97 : 3 er in the products **54**/**55** is to be expected.[48] The fact that the er values of **54**/**55** were found to be somewhat lower, indicates that the Grignard reagents **51** are only marginally configurationally stable under the reactions conditions (3h, –20 °C, CH_2Cl_2).[35]

This set of experiments referred to a macroscopic time scale (period between addition of the resolving agent and addition of the benzaldehyde) of configurational stability. When the configurational lability of the organometallic species is faster, trapping would have resulted in only racemic products **54**, **55**! A change to a microscopic time scale in this sort of experiments is pos-

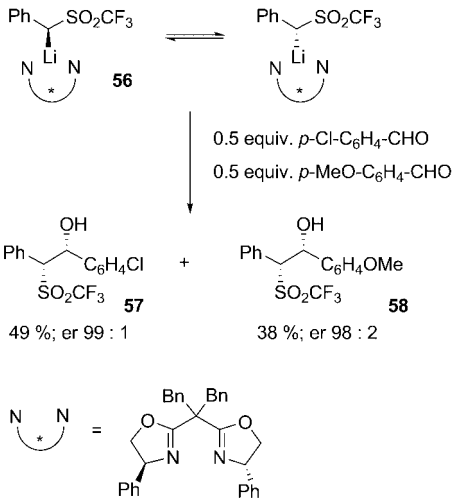


Scheme 5.23.

sible, when the organometallic substrate is added into a mixture of the trapping agent and the resolving agent. In this case, the resolving agent should react more rapidly with the substrate than the trapping agent. A rate factor of 100 would seem sufficient. That means, a limited amount of a resolving agent would attain an enantiomer enrichment in the remaining substrate, which is revealed by the slower follow-up reaction with the trapping agent (being present in situ) to deliver configurationally stable products. I am not aware of such an experiment having been carried out to evaluate the microscopic configurational stability of an (organometallic) substrate.

However, there is a report[25] on the reaction of the complexes **56** of lithiated benzyl-trifluormethylsulfone having a chiral bisoxazoline ligand (Scheme 5.24). These (configurationally stable) complexes appear to be present in a 92 : 8 ratio, as evidenced by trapping with an excess of *p*-chlorobenzaldehyde. When the reaction was carried out with a deficiency of *p*-chlorobenzaldehyde the product **57** displayed an enantiomer ratio of 99 : 1, indicating the prevalence of kinetic resolution ($\mathbf{s} \approx 9$).

In a subsequent experiment, the complexes were allowed to react with a mixture of 0.5 equiv. each of *p*-chlorobenzaldehyde and *p*-methoxybenzaldehyde, the latter reacting (somewhat) more slowly. Hence, the faster reacting *p*-chlorobenzaldehyde should effect kinetic resolution, *i.e.* shifting the ratio of the diastereomeric complexes; and it does so as evidenced from the er of 99 : 1 of the trapping products **57**. The slower reacting *p*-methoxybenzaldehyde should then find a biased diastereomer ratio of the organolithium complexes, which should be reflected in the enantiomer ratio of its trapping products **58**. In case the diastereomeric complexes are configurationally stable on the time scale of this *in situ* trapping experiment, this ratio should be



Scheme 5.24.

lower than that expected on the basis of the **s**-value of *p*-methoxybenzaldehyde. The results reported[25] correspond to these predictions, but the diagnostic features are hardly outside the experimental uncertainties. In case of configurational lability of the complexes **56**, the enantiomer ratios of the *p*-methoxybenzaldehyde trapping products **58** should have corresponded to the **s**-value of *p*-methoxybenzaldehyde. One should add that these experiments have been carried out with a different aim and, thus, are not necessarily optimal to serve as an alternative test on the configurational stability of **56**; because the rate difference between *p*-chlorobenzaldehyde and *p*-methoxybenzaldehyde may be (too) small, and the chiral ligand was present only in substoichiometric amounts. Hence, the mechanistic setting is more complex than represented above. Nevertheless, this study showcases experiments which come close to an alternative test of configurational stability.

IX. CONCLUDING REMARKS

The Test and its variants presented in this chapter provide mechanistic information regarding reactions of equilibrating systems. It establishes whether a Curtin-Hammett situation[31] is given, in which equilibration is faster than the follow-up reaction, or not. This allows the proper design of subsequent diastereoselective or enantioselective transformations via dynamic kinetic resolution[4] or via dynamic thermodynamic resolution.[49, see also Coldham & Sheikh chapter in this volume] As is the nature of a test, it allows fairly quick access to limited information required, but it can never replace a thorough mechanistic investigation.

ACKNOWLEDGEMENT

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Chapter 6

Mechanism and Stereochemical Features in Asymmetric Deprotonation Using RLi/(–)-Sparteine Bases

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I. INTRODUCTION

The chemistry of organolithium compounds is one of the most versatile in synthetic organic chemistry and its use has been widely reported in the literature.[1] Asymmetric transformations based on deprotonation have become a

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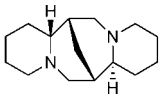
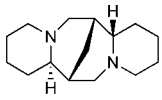
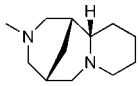


(-)-sparteine **1**



(+)-sparteine **2**



(+)-sparteine surrogate **3**

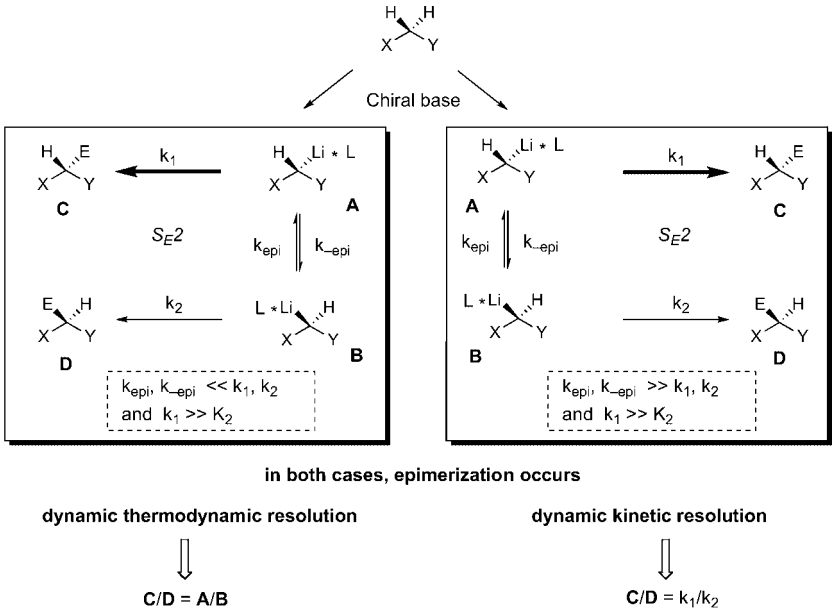
Scheme 6.1.

powerful tool in synthesis. However, these transformations are not as simple as they may appear. A very large number of chiral bases have been studied. They usually involve amides or organometallic species (RLi, RMgX, etc...) combined with a chiral ligand. Moreover, efficient processes based on the use of chiral auxiliaries are also available. Amongst all these methods, one particular system that uses the combination of an organolithium base RLi (usually *n*-BuLi or *s*-BuLi) and (–)-sparteine stands out from the others. Some substrates having enantiotopic protons fitted particularly well when using these deprotonation conditions. After a thorough study, no better ligand than (–)-sparteine could be found in terms of chiral inducer, highlighting at the same time its major drawback as only the levorotatory enantiomer is available (Scheme 6.1). Its enantiomer, (+)-sparteine, has to be synthesized and this prohibits any use of this method in view of the complexity of the structure. One challenge for many years was to find a sparteine surrogate available in both enantiomeric forms. The solution eventually came from the discovery that the whole structure is not essential. Indeed, the (+)-sparteine surrogate can be obtained in a few synthetic steps from (–)-cytisin, which is isolated from *Laburnum anagyroids* seeds.

While particularly efficient and general, this deprotonating system has to be used with suitable substrates of a particular structure. It allows the formation of a chiral anionic species, where the metal is bonded to a sp^3 stereogenic carbon. The configurational stability of these species is then the issue because it is a key element for determination of the origin of the selectivity. Two extreme situations may occur:

1. *The anion is configurationally stable*: the selectivity may come from either the deprotonation, or the electrophilic substitution (S_E) if there is a kinetic resolution.
2. *Epimerization takes place* (which does not mean that it is configurationally unstable because epimerization may be required before S_E (see warm–cool procedure)): the selectivity comes from the subsequent electrophilic substitution because of either a dynamic kinetic resolution (DKR) or a dynamic thermodynamic resolution (DTR) (Scheme 6.2).

In the former (DKR), epimerization is faster than the S_E which involves transforming the whole product through one single stereoisomer of the carbanion. The **C**/**D** product ratio depends upon the relative rates k_1 and k_2. In

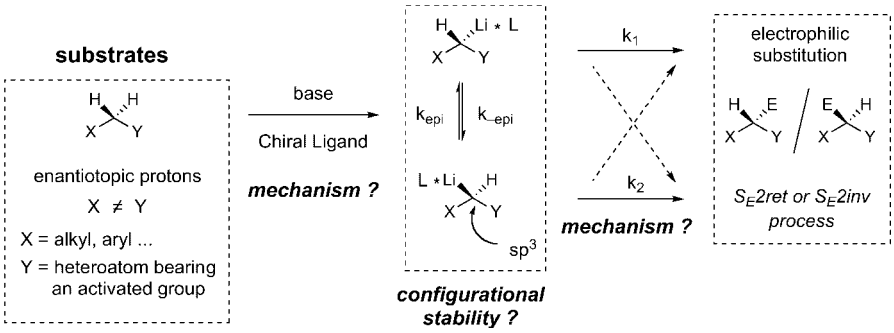


Scheme 6.2.

the latter (DTR), the S_E reaction occurs rapidly after epimerization takes place so that the **C**/**D** ratio is identical to that of **A**/**B**. For a review of dynamic resolutions of chiral organolithium compounds, see the chapter by Coldham and Sheikh in this volume.

The concept of configurational stability has always to be considered with notions of time and temperature or in relation to another reaction (the electrophilic substitution). For example, in the case of dynamic thermodynamic resolution, S_E is faster than epimerization, which means that the organolithium species may keep its configuration for a short time (it can thus be classified as configurationally stable) but definitely needs to be epimerizable. Moreover, thermodynamic equilibrium must be obtained before introducing the electrophile. Lithiated species are classified as configurationally stable or unstable on the basis of the rate of epimerization, but the type of dynamic resolution (kinetic or thermodynamic) considers only the relative value between k_{epi}/k_{-epi} and k_1/k_2. The question of the origin of the selectivity is not at all obvious and predictions are impossible with an unknown system as it depends upon various factors such as the structure of the organometallic species, ligands, solvents, temperature, etc, and specific mechanistic experiments have to be performed to resolve the question (Scheme 6.3).

In the following section, we discuss the mechanism of the deprotonation step using RLi/(–)-sparteine as the base, and the configurational stability of the lithiated species. The subsequent electrophilic substitution is not covered.



Scheme 6.3.

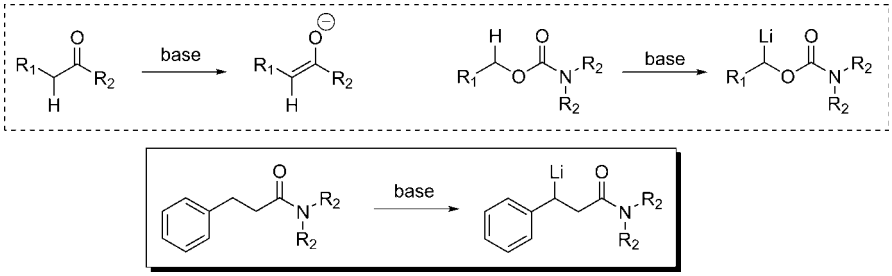
This second step of the reaction is indeed complex, as lithiated compounds can react with retention or inversion of stereochemistry. The mechanisms of this S_E reaction have been studied thoroughly.[2] For a review of electrophilic substitutions of chiral organolithiums, see the chapter by Gawley in this volume.

We first present the substrates studied and detail the basics of the regioselectivity of the deprotonation (complex-induced proximity effect). The question of the configurational stability of the lithiated species will therefore be dealt with generally. Each group of substrates will subsequently be considered according to the nature of the α-heteroatom (C, N, O, S, Se, Si, P) when reacting using RLi/(–)-sparteine as chiral base. Discussion will be restricted to the synthesis of lithiated species borne by a sp^3 carbon atom.

II. DEPROTONATION: REGIOSELECTIVITY AND MECHANISM

Regioselectivity of the Deprotonation

When a substrate is deprotonated, the resulting metallic cation can be located either on the carbon that bore the proton or on a heteroatom, as for instance in the case of enolates (Scheme 6.4). In the former case, deprotonation is more difficult as the metal stays on a sp^3 carbon atom. On the other hand, deprotonation that leads to mesomerically stabilized organolithium compounds seems easier. For carbonyl derivatives, the proton is removed from a sp^3 carbon but the metal is borne by an oxygen atom. Acid-Base reactions are usually predicted using the pKa value of both reacting partners. These values are thermodynamic properties. It therefore follows that, from comparison of all pKa of acidic protons, the smaller value corresponds to the most acidic, that should be removed first. However, it is not always that simple. Indeed, in addition to thermodynamic acidity, the kinetic acidity has



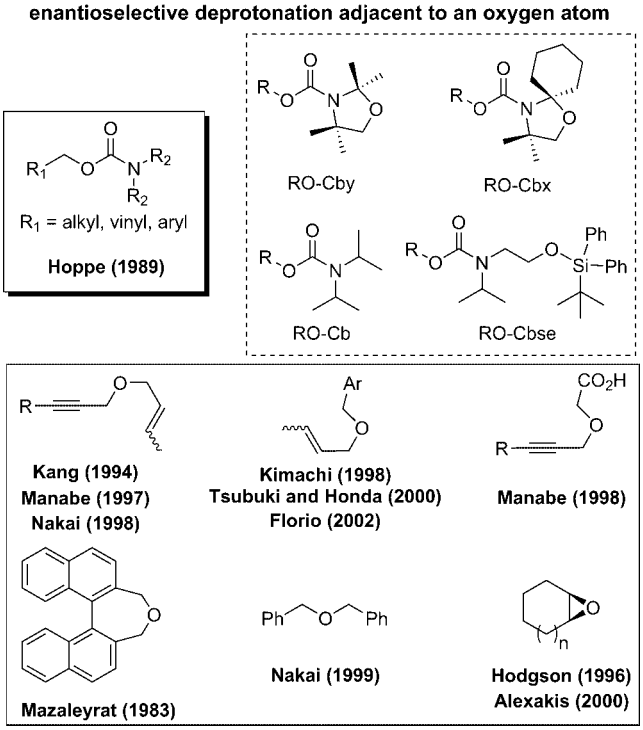
Scheme 6.4.

to be considered. This means that, because of the structure of the molecule, a less acidic proton can be removed first. Such situations usually arise when an activating group (also known as directing group) is present in the neighborhood. An example is given in Scheme 6.4. The lithiation occurs at the benzylic β position, while the α hydrogen is thermodynamically several units more acidic (more than 10 units considering pKa (toluene) = 41 and pKa (dimethylacetamide) = 30).[3] The regioselectivity of the reaction is kinetically directed.

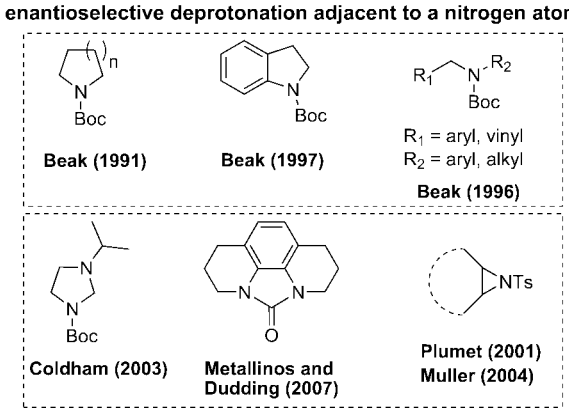
In most cases, the deprotonation of a substrate that retains the metal on a sp^3 carbon atom leads to a chiral lithiated species. This situation is of particular interest because of its possibilities in synthesis. The control of the configuration of the intermediate may be important to control the configuration of the final product. However, this is not always necessary because either the lithiated species epimerizes rapidly, or because selective electrophilic substitution can subsequently occur (Scheme 6.2). In order to retain the metal on a carbon atom in an organolithium species, the deprotonation site must be away from a mesomerically stabilizing group possessing a heteroatom that could potentially receive the metal. Deprotonation often occurs because of the presence of an activating group borne by a heteroatom. The acidity of such protons is very weak, sometimes weaker than that of others in the same molecule. This regioselectivity comes from an orientation of the base induced by the directing group that brings it closer to a particular proton. This behavior, called the complex-induced proximity effect (CIPE), accounts for the selectivity observed and is explained below.[3,4,5]

Substrates Studied

Substrates that fulfill requirements for such transformations have been grouped together using two main criteria. First, we choose to consider the position of the deprotonation: α to an oxygen atom (Scheme 6.5), to a nitrogen atom (Scheme 6.6), to a sulfur or a phosphorus atom (Scheme 6.7),

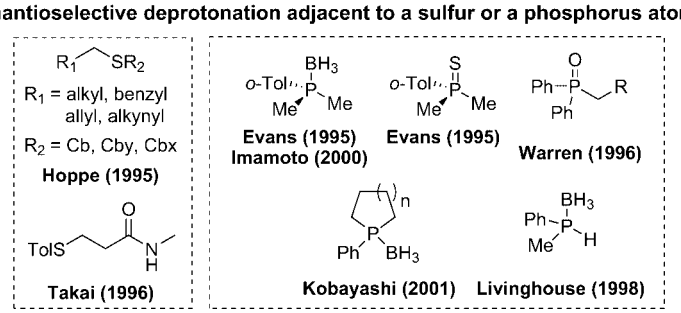


Scheme 6.5.

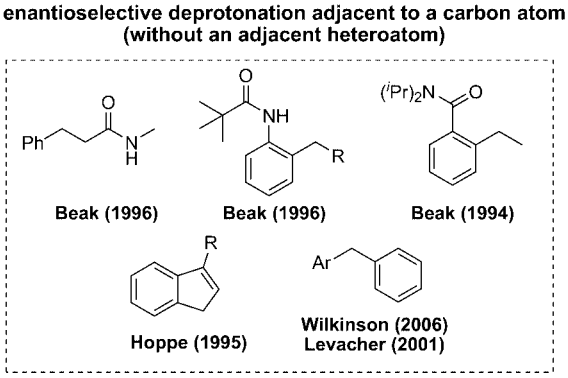


Scheme 6.6.

and to a carbon atom (Scheme 6.8). In the latter case, this means that no heteroatom is in the α position. The second criterion, *i.e.* the stabilization of the lithiated intermediate (dipole stabilized, mesomerically ...), will be considered later.

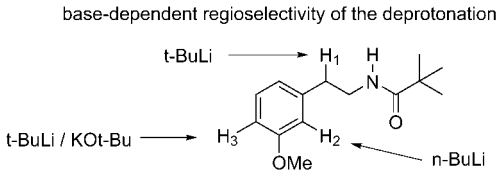


Scheme 6.7.



Scheme 6.8.

The deprotonation of these substrates always leads to a stabilized organolithium species because of an interaction with the adjacent functionalization. Except for the substrates in Scheme 6.8, all the deprotonation occurs next to a heteroatom. However, in all cases there is a stabilization that may be mesomeric (benzyl, allyl, propargyl), or dipolar (with a carbamate). Therefore, the effectiveness of the deprotonation comes not only from the orientation of the directing group, but also from the subsequent stabilization provided. In other words, deprotonation is oriented towards a site where the directing group still complexes the metal.

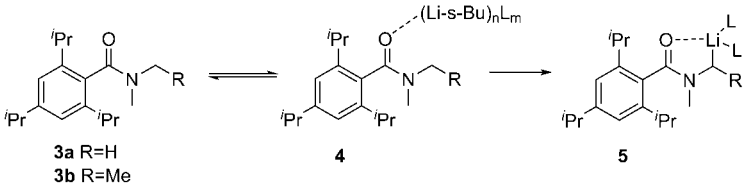


Scheme 6.9.

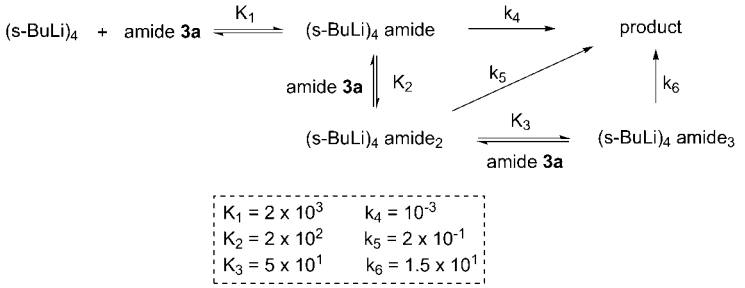
Again, it is not simply that only the substrate has to be considered to predict the deprotonation site. Indeed, although several deprotonating positions have been determined, the regioselectivity may vary from one base to another (Scheme 6.9).[6] Obviously, the mechanism of deprotonation may also differ from one base to another. In the example given in Scheme 6.9, organolithium bases complex the directing group that enhances abstraction of H_1 or H_2. On the other hand, the superbase *t*-BuLi/KO*t*-BuLi is weakly affected by the complexation and removes H_3.

Deprotonation Mechanism

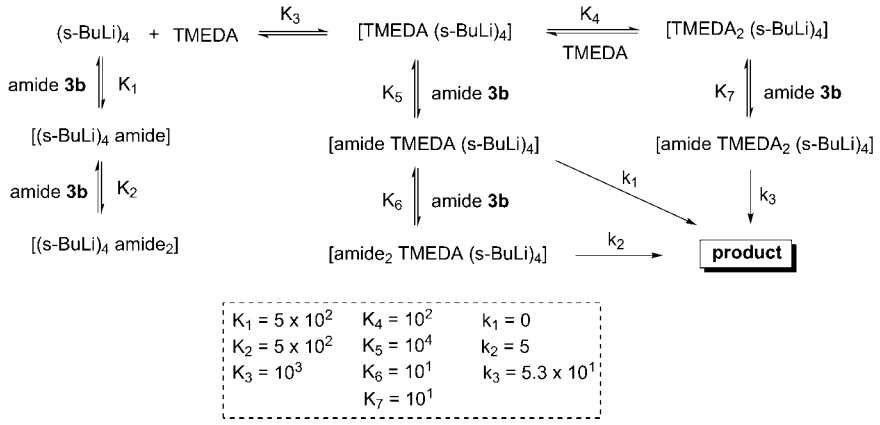
In the system we are discussing, we consider deprotonation using only a base that is a combination of an organolithium reagent RLi and (–)-sparteine. Such bases are prone to complex the directing group prior to abstracting a proton. These prelithiation complexes have been recognized since the earliest report of this reaction but experimental proof was provided much later. Beak et al showed in 1988 in a kinetics study performed on *N*,*N*-dimethyl-2,4,6-triisopropylbenzamide **3** that deprotonation occurs from complex **4** formed between the substrate RLi in an aggregated state and the ligand (Scheme 6.10).[7] The simpler mechanism drawn in Scheme 6.10 can only be viewed as a simplification of reality. The mechanistic Scheme that was found to fit the kinetics data involves three different complexes in which only (*s*-BuLi)$_4$ is considered as an aggregated state (Scheme 6.11). It is indeed the



Scheme 6.10.



Scheme 6.11.

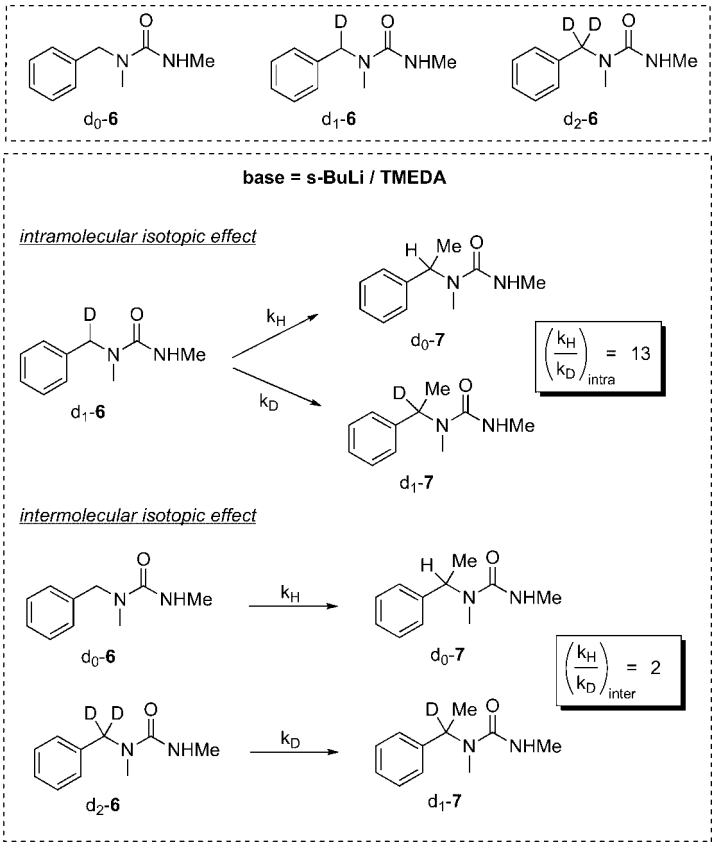


Scheme 6.12.

major aggregated state of *s*-BuLi in cyclohexane solvent. The mechanism that involves TMEDA is depicted in Scheme 6.12. Obviously, these particular mechanisms are specific to the reactions studied and cannot be generalized to other substrates. The exact mechanism is dependent upon various factors that may evolve differently from one situation to another (substrate, base, solvent, additive, concentration, temperature, etc...). The important fundamental information is that deprotonation involves a complex intermediate that combines the substrate, the ligand and the base (such as **4**), giving experimental support to the complex-induced proximity effect proposed.

Kinetic isotopic effect (KIE) experiments were performed for the benzylic lithiation of **6** (Scheme 6.13).[5] Two sets of experiments were performed, *i.e.* the intramolecular isotope effect and the intermolecular isotope effect. In the former, deprotonation of d_1-**6** led to a mixture of d_0-**7** and d_1-**7**. In the latter, deprotonation was performed with a mixture of d_0-**6** and d_2-**6**, producing d_0-**7** and d_1-**7**. Two very different values were found for the KIE, suggesting more than one step for the deprotonation mechanism. The hypothesis that a complexation occurs prior to lithiation is consistent with the KIE observed.

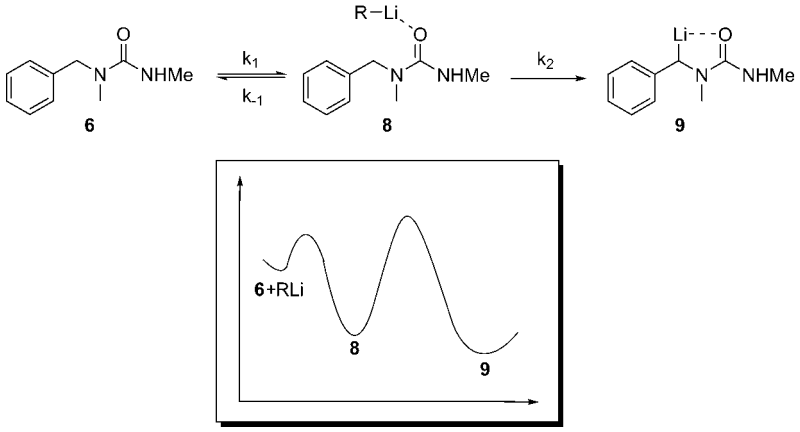
Several energy diagrams were considered, depending on the relative rates of complexation, decomplexation and deprotonation (Scheme 6.14).[4b] From the KIE value, a profile that considers interconversion between **6** and **8** followed by slow deprotonation can be ruled out, because otherwise an identical value would have been obtained. On the other hand, the pre-lithiated complex must be formed rapidly and irreversibly, followed by a slower deprotonation step. The corresponding energy diagram is given in Scheme 6.14. Indeed, such experiments have the advantage of avoiding the discussion of the nature of the lithiating reagent, which can be complicated. However,



Scheme 6.13.

only qualitative conclusions can be drawn, and evaluation of the relative magnitudes of k_1, k_{-1} and k_2 cannot be determined in such a way. This means that the mechanism is still not fully characterized and may arise from other possible pathways that have different energy diagrams (relative value of k_1, k_{-1} and k_2 and different nature of the reactive species involved in its aggregated state).

Deprotonation occurs from an intermediate in which the lithium is complexing the lone pair of the carbonyl oxygen atom. A variation in the structure of the substrate therefore influences the rate of deprotonation by changing the orientation of the carbonyl group. In the benzamide series, rate variations with factors up to 32,000 have been recorded because of a dihedral angle between the aromatic ring and the carbonyl moiety.[8] Such structural effects have been applied to carbamate substrates[9] and will be discussed in section V.A.

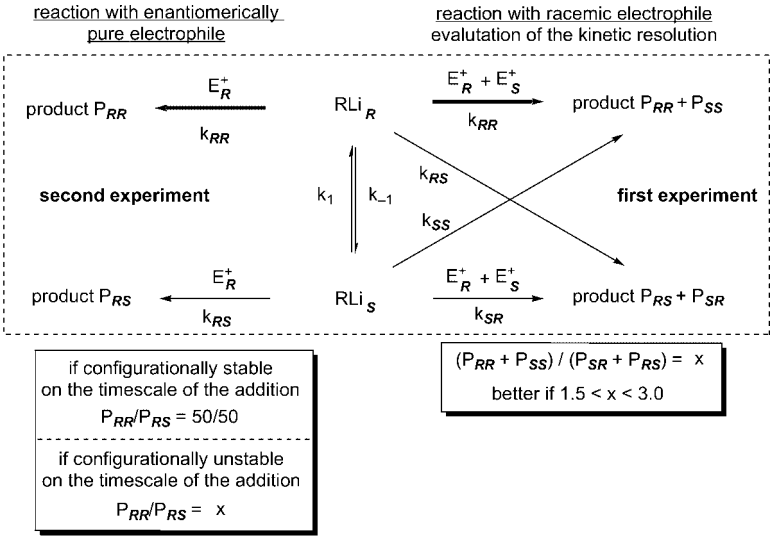


Scheme 6.14.

III. CONFIGURATIONAL STABILITY OF LITHIATED SPECIES

The deprotonation of the methylene group of substrates described in Scheme 6.5, Scheme 6.6, Scheme 6.7 and Scheme 6.8 with a lithiated base led to a chiral organolithium intermediate. (–)-Sparteine has been used to induce enantioselectivity in either the deprotonation step or the electrophilic substitution. The origin of the selectivity is dependent on the configurational stability of the intermediate. Indeed, questions regarding this topic were asked years ago,[10] and we briefly present the methods that have been used to address this problem. Undoubtedly, Hoffmann's seminal work provided effective methodology to obtain relevant information upon the inversion rate.[11] For a review of Hoffmann's test, see the chapter by Hoffmann in this volume. A number of modifications of Hoffmann's methodology have appeared. To simplify subsequent discussions, they are called configurational stability tests (CSTs).

1) Test Using an Enantiomerically Pure Organometallic Reagent (CST1): The conceptually simplest method consists of producing the enantiomerically pure organometallic compounds, then allowing them to react with an electrophile, and measuring the enantiomeric purity of the product.[12] For a configurationally stable organometallic compound, the product obtained is enantiomerically pure. Any racemization is detected with the enantiomeric purity of the product. Obviously, synthesis problems arise from the preparation of an enantiomerically pure precursor of the organometallic compounds. If several stereogenic centers are present, it may be sufficient in a specific case to work with a diastereoisomerically pure substrate.[13] Care must be taken that when synthesized this enantiomerically pure organometallic compound is in a different environment than that of the asymmetric deprot-



Scheme 6.15.

onation, which may alter its behavior. The presence of a diamine ligand can either increase or decrease its configurational stability.

2) Test Using an Enantiomerically Pure and Racemic Electrophile (CST2): Developed by Hoffmann et al, the method consists of making the racemic organometallic compound react with an enantiopure electrophile and the same racemic electrophile (Scheme 6.15).[11] The electrophile of choice must lead to diastereoisomeric products with high stereoselectivity, usually a chiral α-aminoaldehyde or α-aminoamide. In the first experiment, the degree of kinetic resolution has to be evaluated with a racemic aldehyde, which must be in the range of 1.5–3.0 to obtain relevant information. Both enantiomers of the organometallic compound react with the matched electrophile partner. A racemic mixture of diastereoisomer is obtained in a ratio determined by NMR spectroscopy or another analytical technique, without the need for identification of the diastereosiomers. In the second experiment, the reaction is performed with the enantiomerically pure electrophile. Both enantiomers react with their own k_{RR} and k_{SR} rates. If the organometallic compound is configurationally stable, the reaction leads eventually to a product ratio of 50/50. If the ratio is the same as that of the first experiment, the organometallic compound is configurationally labile. Because both enantiomers react at different rates, one disappears faster than the other, and is regenerated as a result of the fast equilibrium between RLi_R and RLi_S. The reaction ends in an enantiomerically pure mixture of diastereoisomer for which the ratio follows the Curtin-Hammett principle.[14]

3) Test Using Enantiomerically Pure Electrophile Alone (CST3): Hoffmann et al proposed an alternative test when only the enantiomerically

pure electrophile is available.[11b] The first experiment is performed with only 0.1–0.2 equiv. of electrophile that gives the k_{SS}/k_{RR} ratio at low conversion. The second experiment is allowed to reach full conversion. If both ratios are equal, the organometallic compound is configurationally labile, if the ratio is 50/50, it is stable (on the timescale of the reaction).

4) Test Using Organometallic Compound in the Presence of a Chiral Ligand (CST4): The tests presented above use racemic or enantiomerically pure organometallic compounds in the absence of ligand. Another has been set up that uses the organometallic compound in the presence of the chiral ligand.

a) Reaction with Stoichiometric and Substoichiometric Amounts of Achiral Electrophile (CST4a): The organometallic compound is made to react with either substoichiometric amounts of electrophile, or an excess.[15] With an excess of electrophile and a configurationally stable organometallic compound, two products can be obtained in a ratio that reflects that of the diastereoisomeric complexes. On the other hand, with an insufficient amount of electrophile, the ratio reflects the reaction rate of each organometallic complex, *i.e.* $\Delta\Delta G^{\ddagger}$. When both ratios are different, this demonstrates a degree of stability of the organometallic complexes. When both ratios are equal, no conclusion can be drawn because two totally different situations can account for this result: either the organometallic compound is labile, or it is stable but with accidentally equal reaction rates ($\Delta\Delta G^{\ddagger} = 0$). This method can therefore only establish configurational stability, but not configurational lability.

b) Warm–Cool Cycle (CST4b): The organometallic complexes prepared in the presence of the chiral ligand are made to react with an achiral electrophile in two different reactions: a) the reaction is performed at a low temperature (usually –78 °C); b) complexes formed at –78 °C are warmed to a temperature that equilibrates the diastereoisomeric complexes (–25 °C), then the temperature is cooled down to –78 °C to perform the reaction with the electrophile.[15a,16] The conclusion is drawn from the comparison of the enantiomer ratio of the product. The organometallic compound is configurationally stable if different ratios are obtained.

c) In situ Quenching Procedure (ISQ) (CST4c): A mixture of the substrate and TMSCl is allowed to react with the chiral base. The intermediate organometallic compound reacts with TMSCl before epimerizing and gives the product in an enantiomeric ratio er_1. On the other hand, the external quenching procedure (EQ) yields the product in an enantiomeric ratio er_2. The ISQ procedure is a very useful technique to determine the most kinetically acidic proton. In addition, any differences between er_1 and er_2 indicate that epimerization has occurred.

5) Test Using Deuterated Substrate (CST5): The deprotonation rate is influenced by an isotopic effect. When the deprotonation is the rate determining step, a wide difference between the abstraction rates of a deuteron and a proton is observed.[17] When the reaction site is a methylene, information

about the mechanism is obtained by studying the behavior of racemic or enantiomerically enriched monodeuterated derivatives. This technique is often used to determine whether asymmetric deprotonation occurs, whatever the configurational stability of the organometallic compound.

a) Use of an Enantiomerically Pure Monodeuterated Substrate(CST5a): If asymmetric deprotonation occurs, a large KIE (kinetic isotopic effect) may operate. The chiral base, which selects one of the two enantiotopic protons, extracts a proton but may not remove the deuteron because of the KIE. Instead, an achiral base (RLi/TMEDA) selectively removes the proton, leading to an enantiomerically pure lithiated species as intermediate. At the end of the reaction, if the product has retained its enantiomeric purity, it can be concluded that the intermediate is configurationally stable.[18,19]

b) Use of a Racemic Monodeuterated Substrate (CST5b): If there is a large KIE, and the deprotonation performed with the chiral base leads to good yields and enantioselectivities for the deuterated product, then asymmetric deprotonation is not dominating the process (KIE is the dominating factor), and the lithiated intermediate epimerizes.

Such experiments may be used only to find the enantiodetermining step. Configurational stability is often known from other experiments (see above). This method can then highlight asymmetric deprotonation, or differentiate a dynamic kinetic resolution from a dynamic thermodynamic resolution.

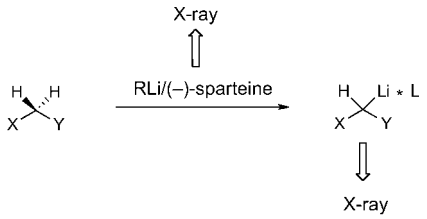
A wide range of techniques has been developed to verify the configurational stability of an organometallic species, and the complete energy profile of the reaction can be determined using these experiments. Generally, several tests have to be performed to obtain an unequivocal conclusion. The first information required is the relative equilibrium rate compared to the electrophilic substitution rate (configurational stability on the time-scale of the reaction), and the second important information is the origin of the selectivity (asymmetric deprotonation, dynamic kinetic resolution, or dynamic thermodynamic resolution). One has to be careful when reaching conclusions because the tests presented above give information about only one of the two steps, but do not resolve the problem in only one experiment. In the case of a configurationally labile organometallic compound, the configuration of the carbon that bears the metal is lost, but it can be formed from asymmetric deprotonation.[16a,19] On the other hand, a configurationally stable organometallic compound can be formed after non-selective deprotonation.[15a] Obviously, in both cases the selectivity obtained in the final product comes from the second step. The general situation described in this section is developed in greater detail in section V with RLi/(–)-sparteine as the chiral base.

IV. X-RAY STRUCTURE OF RLi/(–)-SPARTEINE COMPLEXES

This section groups together the RLi/(–)-sparteine complexes for which X-ray structures have been studied. The few studies where data obtained with (+)-sparteine surrogate have been reported will be mentioned. Two types of complexes are considered, those involving the bases used for the deprotonating step, and those involving the lithiated species obtained after deprotonation (Scheme 6.16). The former may clarify the reactivity and selectivity obtained with a given base; the latter may provide insight into the selectivity of the electrophilic substitution step. Discussion of the X-ray structure of the deprotonated product will help in determining which of the enantiotopic protons is removed. This information, together with features of configurational stability will be discussed in section V.

X-Ray Structure of Chiral Bases

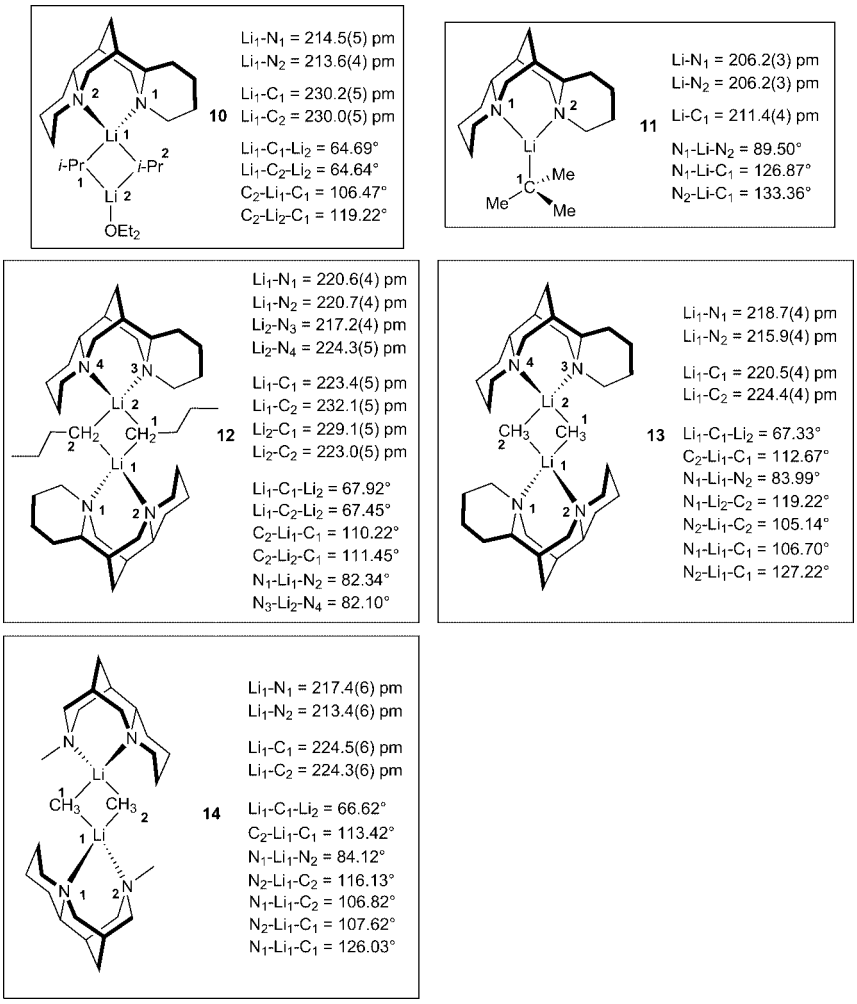
In most deprotonating systems, the organolithium used is a derivative of butyllithium, particularly *n*-BuLi and *s*-BuLi. It is interesting to compare the structures of such reagents in solution and in the solid state. Indeed, their chemical structures have to be determined to understand their reactivity. NMR studies and X-ray analysis are the most convenient methods; the former providing information about the structure in solution and the latter in the solid state. Obviously, when undertaking a reaction, the organolithium reagent is in solution but its structure is not known accurately because reaction conditions may differ from the conditions of the NMR experiments. Furthermore, the aggregated states depend on the equivalent number of additives. In some cases, they are used stoichiometrically, and in others catalytically. On the other hand, X-ray analysis provides a very accurate picture of the structure. Unfortunately, this may differ between the solid state and the solution state. Comparison of these two analyses, in solution and in the solid state, provides information about whether or not the structure is the same in both situations. If it is the same, then the accurate solid state structure can be used as a good starting point for mechanistic studies.



Scheme 6.16.

It is known from cryoscopic and NMR spectroscopic studies that *n*-butyllithium is a mixture of tetrasolvated tetrameric and dimeric aggregates in THF solutions.[20] In Et_2O solution, only the tetramer exists. However, with both solvents, when one equivalent of TMEDA is added, the dimeric structure is formed exclusively.[21] Chiral diamines such as (–)-sparteine and TMCDA[22] also lead to a dimeric structure when complexed with $(RLi)_n$ aggregates.[21a,b] Indeed, many of the asymmetric deprotonations are performed using *s*-butyllithium. The only structure study reported to date showed that *s*-BuLi exists as a mixture of dimer (minor), tetramer and hexamer in hydrocarbon media[23]. One important drawback is the presence of a stereogenic center that creates diastereomeric complexes. To avoid this, *i*-PrLi has been studied instead. The 1:1 mixture of *i*-PrLi and (–)-sparteine provides the nonsymmetrical dimer complex **10** (Scheme 6.17)[24].

X-ray of the structure of RLi/(–)-sparteine complexes (R = *t*-Bu, *n*-Bu, *i*-Pr) confirms the structure predicted by NMR studies. In addition, it provides very accurate information such as bond lengths and angle values. The X-ray structure of the corresponding complexes with TMEDA is given as a comparison. [*t*-BuLi·(–)-sparteine] **11** was the first complex obtained.[25] The lithium atom is trivalent and with a slightly pyramidalized environment (angle sum at Li = 349.7°). With isopropyllithium, which is still hindered, only one sparteine is incorporated in the complex **10** because of steric interactions.[26] There are two strikingly different lithium atoms. One lithium atom is tetracoordinated in a distorted tetrahedral environment, the other lithium atom is trivalent and nearly planar. The sum of angles at Li_2 is 355°. When changing isopropyllithium to *n*-butyllithium, an important part of the steric interaction is removed. Both of the lithium atoms are coordinated by the diamine, leading to a symmetric dimer **12**.[26] The complex is C_2 symmetric with two distorted tetrahedral lithium atoms and a slightly deformed four membered ring Li–C–Li–C with a sum angle of 357.0° (envelope conformation). Methyllithium forms two C_2 symmetric dimers **13** and **14** with (–)-sparteine and the (+)-sparteine surrogate ((1*R*,2*S*,9*S*)-11-methyl-7,11-diazatricyclo[7.3.1.$0^{2,7}$]tridecane), respectively.[27] In complex **14**, both methyl substituents are pointing to the same side of the Li–C–Li–C ring. As a consquence, the C_2 symmetric axis is orthogonal to the four membered ring plane. Indeed, the similarity between structures **13** and **14** is consistent with the similar stereoselectivities obtained in asymmetric deprotonations (see below). In contrast, with either (–)-sparteine or (+)-sparteine surrogate, phenyllithium leads to two 4:2 complexes of different structures. Both have an internal ladder framework, the former being C_2 symmetric. In this case, there are no available data to compare their reactivity or selectivity that could be related to their particular structure. It is interesting to note that while [PhLi·(–)-sparteine]$_2$ cannot be formed, the mixed aggregate [PhLi·PhOLi·(–)-sparteine]$_2$ is obtained because the alkoxide moved a bulky substituent away from the hindered diamine ligand.[28]



Scheme 6.17.

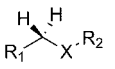
Two other diamines are frequently studied, TMEDA as the most simple model representative of diamine ligands, and TMCDA (*trans*-tetramethylcyclohexane diamine) that is frequently used in asymmetric synthesis.[29] Several complexes combining TMEDA with organolithium species have been characterized by X-ray analysis, in particular with *n*-butyllithium, methyllithium, or phenyllithium.[30] In the case of TMCDA, there is a clear relationship between the steric hindrance of the organolithium and the aggregated state of the complexes. With methyllithium, the dimer $[MeLi\cdot(R,R)\text{-TMCDA}]_2$ is formed,[31] while with *n*-butyllithium, dimer $[n\text{-BuLi}\cdot(R,R)\text{-TMCDA}]_2$ and aggregate $[(n\text{-BuLi})_2\cdot(R,R)\text{-TMCDA}]_2$ are obtained, depending on the con-

centration of the lithium compound.[32] By changing to *i*-PrLi, the steric hindrance is increased but, in contrast to what is observed with (–)-sparteine (Scheme 6.17)[26], the complex still retains the dimer structure [*i*-BuLi·(*R*,*R*)-TMCDA]$_2$.[31] The TMCDA ligand is much less hindered than (–)-sparteine and steric interactions occurring in the TMCDA complex are less unfavorable than those occurring in the (–)-sparteine complex. The adduct formed with *s*-BuLi is a diastereoisomeric mixture of monomeric complexes [(*R*)-*s*-BuLi·(*R*,*R*)-TMCDA] and [(*S*)-*s*-BuLi·(*R*,*R*)-TMCDA] in a 55:45 ratio. It is the only known example of crystal structure between *s*-BuLi and a diamine ligand. The lithium atom is tricoordinated, offering a free coordination site for a possible substrate. This monomeric structure accounts for the high reactivity of *s*-BuLi/diamine as a base. Unfortunately, the crystal structure of the famous *s*-BuLi/(–)-sparteine combination is still lacking. There is a general trend in overcrowded complexes that an increase in Li–N interactions occur. In monomeric complexes, the strain released leads to remarkably short Li–C and Li–N bond lengths. Comparison of the structures assists the understanding of the difference in reactivity and selectivity obtained in a given reaction. One striking example is the asymmetric deprotonation of ferrocenyl derivatives, for which *n*-BuLi/(–)-sparteine and *s*-BuLi/(–)-sparteine provide opposite enantiomers.[33]

V. DEPROTONATION USING RLi/(–)-SPARTEINE AS BASE

Generally, whatever the nature of the heteroatom present in the α position of the deprotonation site, identical classification is made regarding the nature of the R_1 group, that can be an alkyl, vinyl or aryl group. For unsaturated systems, the mesomeric stabilization of the organometallic species has important consequences on the configurational stability and on reactivity. The orbital overlap tends to flatten the carbon and facilitate its isomerization. In addition, dipolar stabilization with the XR_2 group may occur. Depending on these structural features, a configurationally stable or labile lithiated species is produced.

A good understanding of a particular system can lead to the development of selective processes by choosing the most appropriate experimental conditions. In some cases, studies have only considered the final result, *i.e.* the enantiomeric purity of the product, without paying attention to the intermediate.[34] In order to discuss the stereochemical aspects of these transformations, we only consider systems that have been fully studied.



X=O, N, S, P...
R_1= alkyl, allyl, aryl
R_2=activating group

Scheme 6.18.

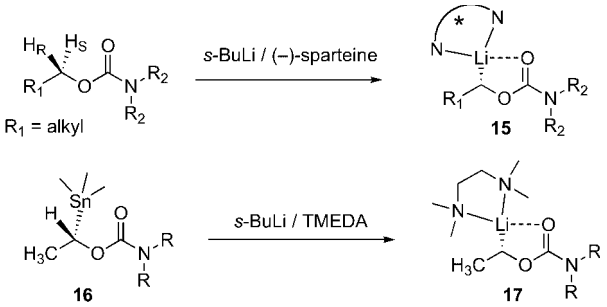
A. Deprotonation α to an Oxygen Atom

1. Hoppe's Alkyl Carbamates

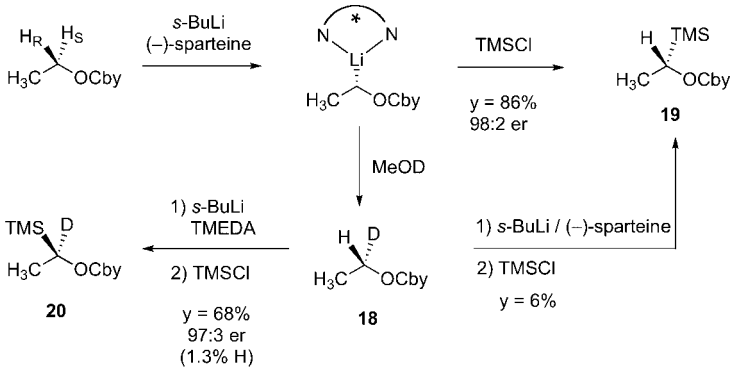
Carbamates are very selectively deprotonated by the chiral base *s*-BuLi/(–)-sparteine. Several types of carbamates can be used. They serve at the same time as protecting group for the alcohol (they need to be removed easily) and as activating group for the deprotonation (Scheme 6.5). Those derived from 2,2,4,4-tetraalkyl-1,3-oxazoline (Cbx, Cby) or *O*-silylated-1,2-aminoethanol (Cbse) are easier to deprotect compared to *N*,*N*-diisopropylcarbamate OCb.[35]

The (–)-sparteine ligand is selective for the pro-*S* hydrogen (Scheme 6.19). The diastereomerically pure organolithium intermediate **15** is configurationally stable at –70 °C. Starting from the enantiomerically pure α-stannylated carbamates **16**, the enantiomerically pure organolithium **17** is generated with *n*-BuLi/TMEDA and reacts with electrophiles without loss of enantioselectivity (CST1, section III).[36] When R_1 is methyl or isopropyl, enantioselectivities greater than 97% are recorded, while in the case of *t*-Bu no deprotonation occurs. For hindered alkyl carbamates, it has been found that TMCHD is an effective ligand that can replace (–)-sparteine.[37] The enantiomerically pure monodeuterated carbamate **18** is easily prepared by deuteration with MeOD (Scheme 6.20).[18] Deprotonation of **18** is very effective in the presence of TMEDA while almost no reaction occurs with (–)-sparteine. Because of a large kinetic isotopic effect, *s*-BuLi/TMEDA removes only the proton, leading to a configurationally stable intermediate that reacts with the trimethylsilyl chloride (CST5a). In contrast, (–)-sparteine, a specific pro-*S* hydrogen remover, encounters a deuteron at the pro-*S* position which cannot be removed because of a strong KIE. As a result, the asymmetric deprotonation cannot occur and product **19** is obtained in only 6% yield.

Theoretical investigations of the reaction provide insight into the mechanism of deprotonation. To simplify the study, *i*-PrLi and 2,2,5,5-tetramethylpyrrolidine carbamates are considered for the theoretical model.[38] The real



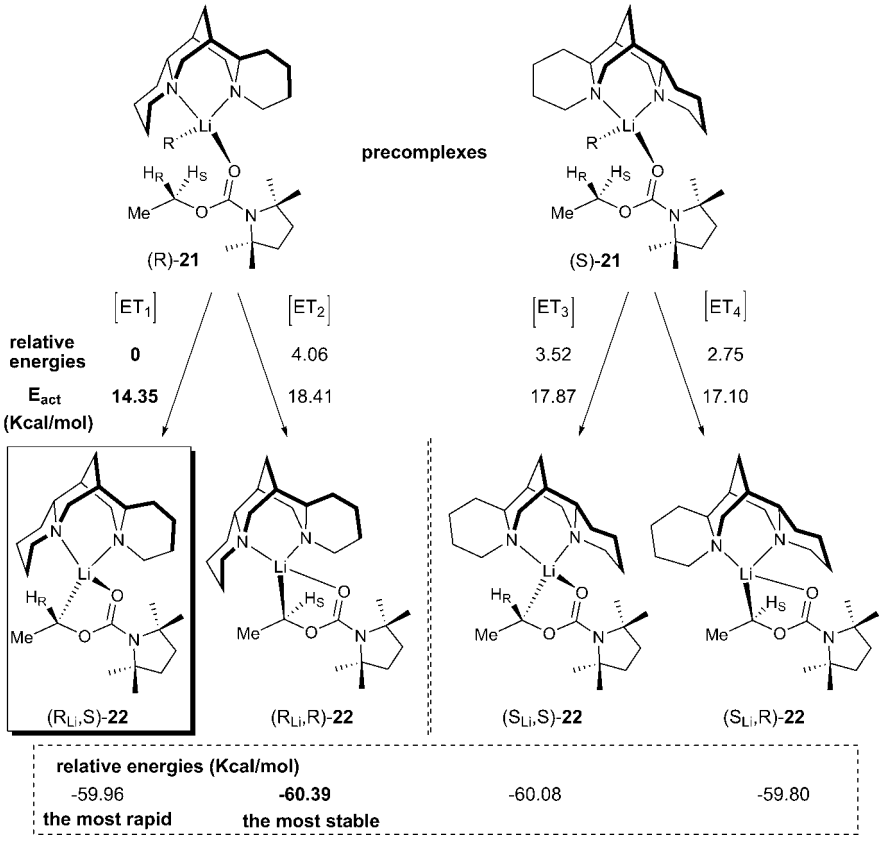
Scheme 6.19.



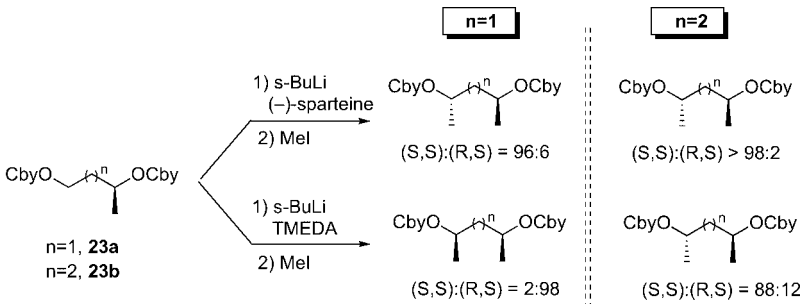
Scheme 6.20.

system is more complicated to imitate theoretically because it uses non-symmetrical base (*s*-BuLi) and carbamate moieties (OCby, OCbx). In addition, even with these simplifications, because (–)-sparteine has a C_1 symmetry, two enantiomeric precomplexes (*S*)-**21** and (*R*)-**21** are formed, followed by two diasteroisomers of each lithiated intermediate (Scheme 6.21). Eventually, four possible diastereoisomers are considered, the two stereogenic centers being the carbon and the lithium atoms. The result is that the complex formed (R_{Li},*S*)-**22** is not the most stable but is the most rapidly formed. Amongst the four possible complexes, the most stable have the same absolute configuration at the lithium atom, but the opposite at the carbon. The stability calculated for the precomplexed species displays a similar trend to that of the transition states. The reasons for the formation of the particular intermediate (R_{Li},*S*)-**22** are indeed already contained in the precomplex (*R*)-**21**. It has been calculated that, in the transition state, the proton is closer to the base than to the carbamate, indicating a late transition state. Furthermore, the short lithium–hydrogen distance is evidence that the lithium ion may be actively involved in the proton transfer.

Substrates that already bear one or more stereogenic centers give rise to more complicated situations. The alkylated product obtained with *n*-BuLi/TMEDA has a diastereomeric ratio influenced by the already existing stereogenic center. On the other hand, in such substrates, (–)-sparteine is still selective to pro-*S* hydrogen and this preference is not influenced by the nearby stereogenic center. Obviously, two classical situations occur: the stereogenic center induces the deprotonation towards H_S (match situation), or towards H_R (mismatch situation). In the alkylation described in Scheme 6.22, both these situations occur. Interestingly, the asymmetric deprotonation is a match situation for **23b**, and a mismatch situation for **23a**. In the latter case, both diastereoisomers can be prepared selectively depending on the base used.[39] The stereogenic center in carbamate **24** induces very selective deprotonation in favor of **25**. Using (*R*)-**24**, deprotonation of the pro-*S* hydrogen is preferred, in the



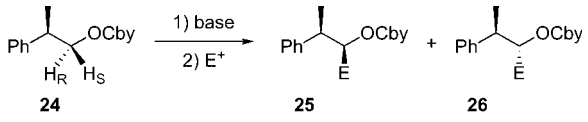
Scheme 6.21.



Scheme 6.22.

same way as (–)-sparteine. Very high selectivity is achieved with (*R*)-**24** (up to 250:1) while (*S*)-**24** affords products in much lower yields and selectivity.[40]

This methodology has been applied to the synthesis of natural products,[41] aminoalcohols (Scheme 6.24),[42] desymmetrisation of meso compounds,[43] and

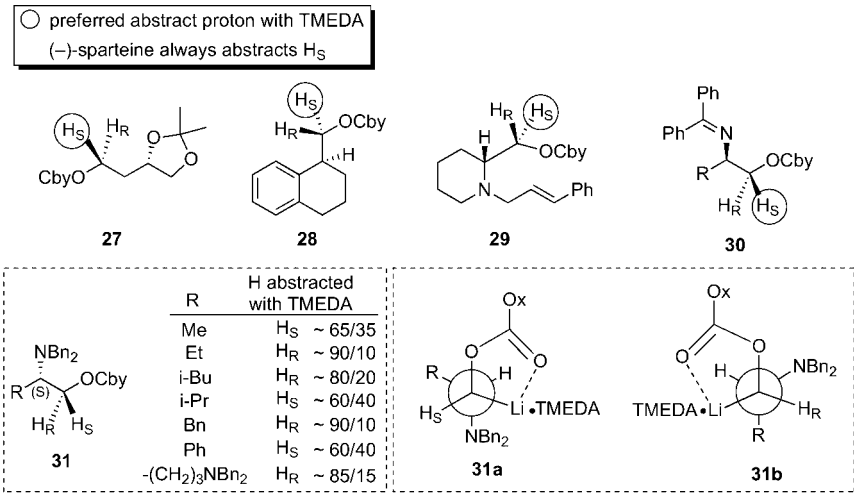


24 **25** **26**

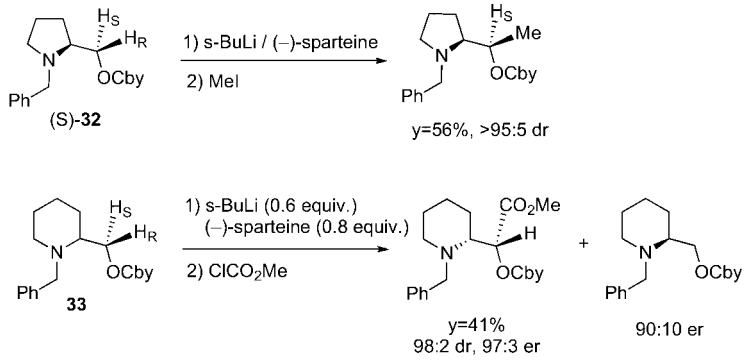
base	E^+	**25:26**
s-BuLi / (–)-sparteine	MeI	250:1
	CO_2	150:1
s-BuLi / TMEDA	MeI	24:1
	CO_2	20:1

Scheme 6.23.

with substrates that bear a remote functionality that react subsequently in a cyclization reaction.[44] Several other substrates with more complex structures that can influence the selectivity of the deprotonation have been studied. Although (–)-sparteine always selectively removes the pro-*S* hydrogen, the deprotonation of the mismatched enantiomer may be much less selective. The matched enantiomers are grouped together in Scheme 6.24.[45] The selectivity of the deprotonation of (*S*)-**31** depends upon the R substituent. When R is Et, *i*-Bu, Bn, and $-(CH_2)_3NBn_2$, preferential deprotonation of H_S occurs, implying that (*S*)-**31** is the matched enantiomer in the deprotonation with (–)-sparteine. On the other hand, it is (*R*)-**31** when R is Me, i-Pr and Ph. In the favored transition state **31a**, both electronegative moieties, OCby and NBn_2, are antiperiplanar to each other. The transition state **31b** is favored with the bulkier R substituent, with the exception that it occurs even when R=Me.



Scheme 6.24.



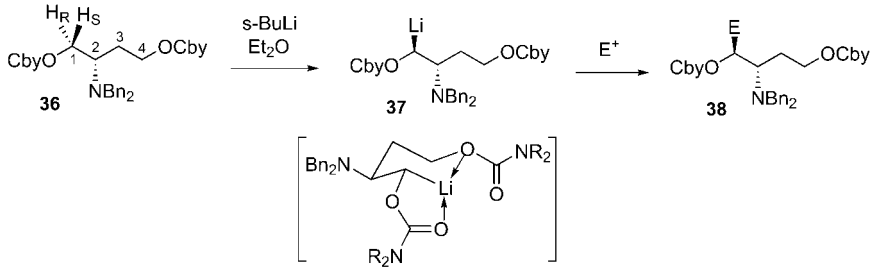
Scheme 6.25.

For aminoalcohol **32** derived from proline, the deprotonation of the pro-*R* hydrogen occurs selectively in the presence or absence of diamine (Scheme 6.25).[46] Even with (–)-sparteine, the selectivity is imposed by the substrate. The alkylation product is obtained with high selectivity. On the other hand, when the homolog aminoalcohol **33** derived from pipecolic acid is used, the deprotonation of pro-*S* occurs in the presence or absence of TMEDA. In asymmetric deprotonation conditions with *s*-BuLi/(–)-sparteine, **33** is resolved efficiently (Scheme 6.25).

Anomalous behavior is observed with *O*-carbamates of *N,N*-dimethylaminoethanol **34** and **35** (Scheme 6.26).[42a] While **34** is deprotonated rapidly using *s*-BuLi in ether without additives, carbamate **35** is unreactive under the same reaction conditions. Furthermore, when the reaction is performed in the presence of (–)-sparteine, products of methylation with MeI are isolated in good yields but in racemic form from **34** and nearly enantiopure (99:1 er) from **35**. The dimethylamino moiety complexes the lithium atom efficiently impeding the (–)-sparteine complexation. In contrast, the dibenzylamino moiety has poor complexing ability and asymmetric deprotonation is conducted efficiently.

The amino dicarbamate **36** is prepared from (*S*)-aspartic acid. It reacts very selectively under deprotonation conditions (*s*-BuLi, Et_2O) at the C_1 position (Scheme 6.27).[47] Formation of the bicyclic chelate accounts for this stereoselective deprotonation. In the presence of TMEDA, a non-selective process occurs that leads to a mixture of equal amounts of the four possible deprotonated products. The asymmetric deprotonation with *s*-BuLi/

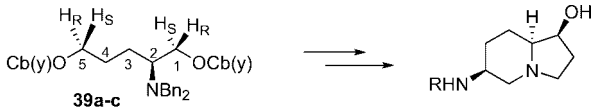
Scheme 6.26.



Scheme 6.27.

(–)-sparteine is not as selective as expected. Although only one product is obtained with MeOD or CO_2 as electrophile, a mixture of diastereoisomers is obtained with Me_3SnCl. The removed proton is always 1-H_S. Removal of 1-H_R leads to the minor diastereomer obtained. A second deprotonation is possible at the less crowded C_4 position. Deprotonation of 4-H_S is favored in the presence of (–)-sparteine. No reaction occurs in the absence of diamine.

The bis-carbamate **39** prepared from (*S*)-glutamic acid, and homolog of **36**, is deprotonated with different regioselectivity depending on the type of carbamate moiety and the reaction conditions (Scheme 6.28).[48] In the absence of diamine, the proton 1-H_S of bis-OCby carbamate **39a** is deprotonated, while *s*-BuLi/(–)-sparteine removes 5-H_S very selectively. Both bis-carbamates **39b** and **39c** are deprotonated with the same selectivity, the reverse of **39a** in the same reaction conditions. In these substrates, both carbamates have important complexation roles that compete with (–)-sparteine. Indeed, (–)-sparteine is not required to achieve high regio- and diastereoselectivity, although it enhances the rate of lithiation.

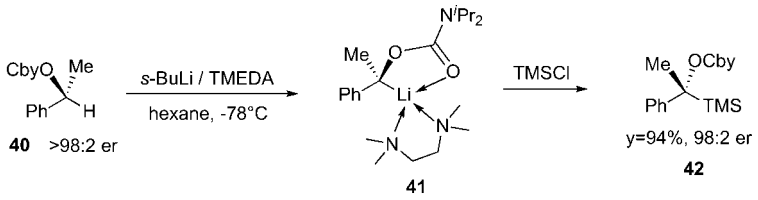


carbamate		base	H abstracted	yield
1-OCby / 5-OCby	**39a**	s-BuLi	1-H_S	87%
		s-BuLi / (–)-sparteine	5-H_S	80%
1-OCb / 5-OCb	**39b**	s-BuLi / (–)-sparteine	1-H_S	70%
1-OCby / 5-OCb	**39c**	s-BuLi / (–)-sparteine	1-H_S	87%

Scheme 6.28.

2. Hoppe's Aryl Carbamates

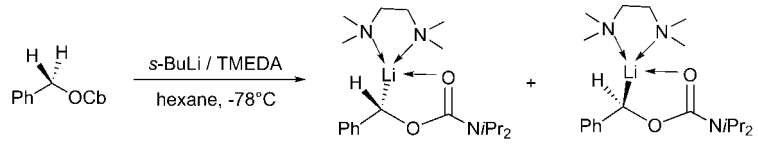
The deprotonation of aryl carbamates leads to benzylic lithiated intermediates. In such species, enhancement of the stability of the carbanion by resonance increases the planarization of the carbanionic center and its capacity



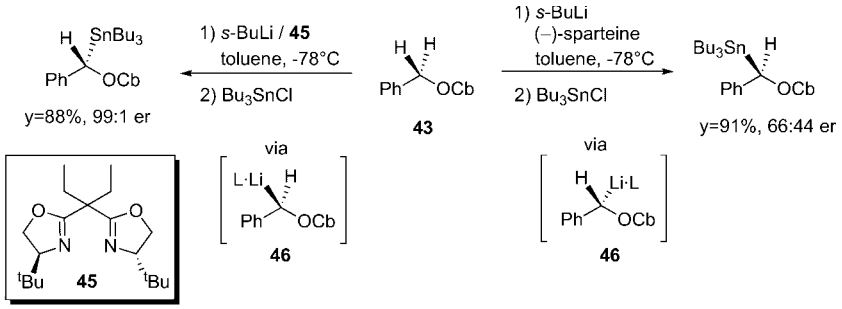
Scheme 6.29.

for configurational inversion. However, in the presence of an α-heteroatom bearing a chelating group, intramolecular coordination takes place, forming a cyclic chelate that stabilizes the organolithium. The deprotonation of **40** with *s*-BuLi/TMEDA led to an enantiomerically pure benzylic lithiated complex that retained its configuration at low temperatures in hexane solution.[49] In contrast, in THF solution, only the racemic product was obtained, indicating that tetrahydrofuran is basic enough to replace TMEDA, producing a configurationally labile complex.[50] A few studies have been performed using enantiomerically pure secondary benzylic carbamates that take advantage of the configurational stability of **41** or its derivatives.[35,51]

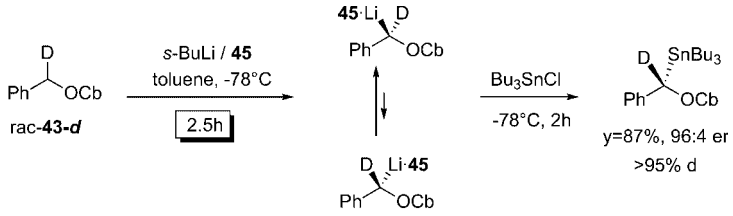
On the other hand, examples of enantioselective deprotonation of achiral benzylic carbamates such as **43** is rare. The lithiated product was found to be chemically unstable after a few minutes at –78 °C, but more stable in the presence of TMEDA. The configurational stability of **44**·TMEDA was established by Hoffmann et al. using the test he developed (CST2) (Scheme 6.30).[52] It was reported in 1997 that enantiomerically enriched secondary alcohol with er up to 95:5 (reaction in hexane with the crystallized complex separated from the solution) can be synthesized using (–)-sparteine as ligand.[53] However, no detailed studies were reported on this subject. In 2008, deprotonation of **43** was reported in the presence of (–)-sparteine or bis(oxazoline) ligands (Scheme 6.31).[54] Secondary alcohols with moderate enantioselectivities (64:36 to 77:23 er) were produced with (–)-sparteine in toluene. In addition, bis(oxazolines) were also used on the basis of the successful examples reported by Nakai[55] and Toru.[56] Bis(oxazolines) are the ligands of choice for carbamate **43**. Secondary alcohols with er's consistently greater than 97:3 were obtained. Study of the origin of the selectivity revealed that carbamate **43** has a strikingly different behavior to the secondary derivatives such as



Scheme 6.30.



Scheme 6.31.



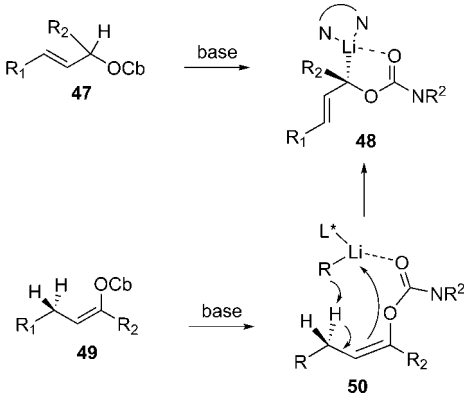
Scheme 6.32.

40. An *in situ* trapping experiment with TMSCl produced secondary carbamates with increased er in the case of (–)-sparteine (77:23 instead of 63:37), and decreased enantioselectivity in the case of bis(oxazoline) (54:46 instead of 99:1), compared to the external quenching conditions. This means that during the period of time before the addition of the electrophile, the organolithium intermediate epimerizes at –78 °C. Although asymmetric deprotonation occurs, the diastereomeric ratio of **46** changes to the thermodynamic ratio, leading to a dynamic thermodynamic resolution (Scheme 6.2). In that situation, it is necessary to study the deuterated substrate to check the stereoselectivity of the deprotonation (Scheme 6.32). The deprotonation of *rac*-**43-*d*** in the presence of **45** leads to the product containing 95% deuterium in 87% yield. This means that the base removes only the proton because of a strong KIE, but with no enantioselectivity. Both diastereomeric lithiated complexes are produced in a 1:1 mixture (racemic starting material) that equilibrate in the presence of the chiral ligand to the more stable complex. The origin of the selectivity is not in contradiction with the configurational stability of **44** as this stability is relative to the rate of electrophilic substitution.

3. Hoppe's Vinyl Carbamates

A wide range of vinyl carbamates have been studied.[57] For these systems, there are two methods that can produce the alkenyllithium carbamate (Scheme 6.33):

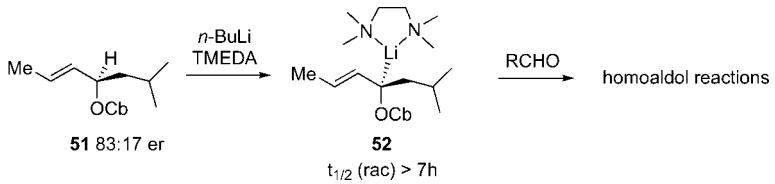
1) α-deprotonation of allylic carbamate **47** that produces the dipole stabilized complex **48**.
2) γ-deprotonation of (*Z*)-vinylic carbamate **49** that produces complex **48** through a nine-membered transition state **50**.



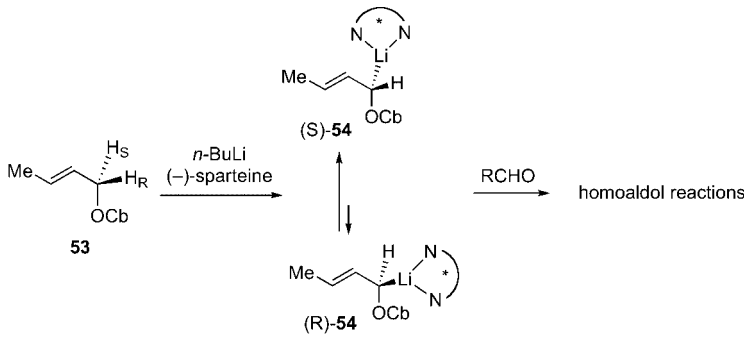
Scheme 6.33.

The configurational stability of these compounds follows the identical trend as that of aryllithium derivatives. Secondary alkenyllithiums are configurationally stable while primary alkenyllithiums are configurationally labile. Furthermore, in most cases deprotonation using *n*-BuLi/(–)-sparteine is selective for removal of pro-*S*, to a certain extent.

This has been proved by using an enantiomerically enriched secondary allylic carbamate **51**. Under deprotonation conditions using *n*-BuLi/TMEDA, the configurationally stable complex **52** was produced and found to racemize only slowly at temperatures below –70 °C (Scheme 6.34).[58] This peculiar be-



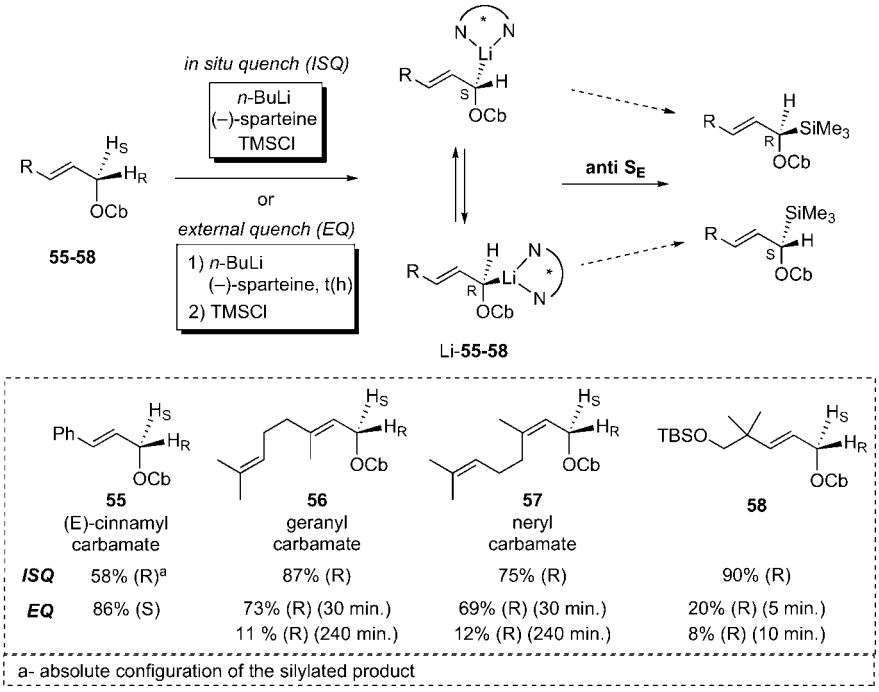
Scheme 6.34.



Scheme 6.35.

havior is due to the strong Li–O coordination that fixed the lithium atom at the C1 position. It was used for the kinetic resolution of secondary alkenyl carbamates.[59] On the other hand, primary alkenyl carbamates are configurationally labile even at temperatures below –78 °C. However, in the case of crotylcarbamate **53**, one of the diastereomeric complexes crystallizes in the presence of a certain amount of hexane, shifting the equilibrium almost totally to (*S*)-**54** (dynamic thermodynamic resolution – Scheme 6.35). The selective reaction that ensues is the result of careful optimization of the process.[60] During this study, the configuration of the major diastereomeric complex was corrected and attributed to (*S*)-**54**.[61]

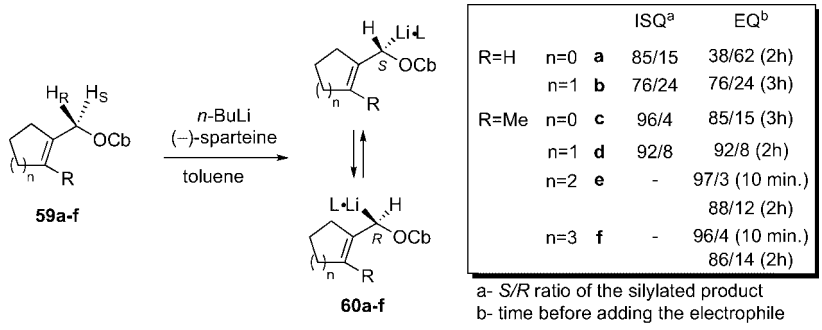
The stereochemical outcome of the deprotonation step was studied by using the *in situ* quenching (ISQ) technique. As the electrophile is in the reaction mixture before the addition of the base, the lithiated intermediate is trapped as soon as it is formed (Scheme 6.36). In a general manner, the H_S proton is removed more rapidly than the H_R proton, leading to an intermediate that shows variable configurational stability. Carbamates **56** and **57**, when lithiated, epimerize slowly at the carbanion center.[62] In contrast, carbamate **58** reaches the thermodynamic ratio only 10 minutes after lithiation. However, the enantiomerically enriched organolithium intermediate is synthetically useful when a cyclization reaction is possible in the case of substrates that have a leaving group (Cl, Br) instead of the OTBS moiety.[63] (*E*)-cinnamyl carbamate **55** is kinetically deprotonated at the H_S position, as indicated by the *in situ* quenching experiment, but it epimerizes moderately rapidly to the more stable epimer (*R*)-Li-**55**.[64] Equilibration is complete in 0.5h. Furthermore, experiments with shortage of methyliodide have demonstrated that a dynamic kinetic resolution occurs between both intermediates (*R*)-Li-**55** and (*S*)-Li-**55**. Indeed, high conversion is an important factor to obtain good levels of selectivity: the lower the equivalent of MeI, the lower the enantiomeric ratio. It then follows that (*S*)-Li-**55** is kinetically formed, less thermodynamically stable that its epimer (*R*)-Li-**55**, but more reactive. In this "negative dynamic kinetic resolution", the higher reactivity of the minor isomer only



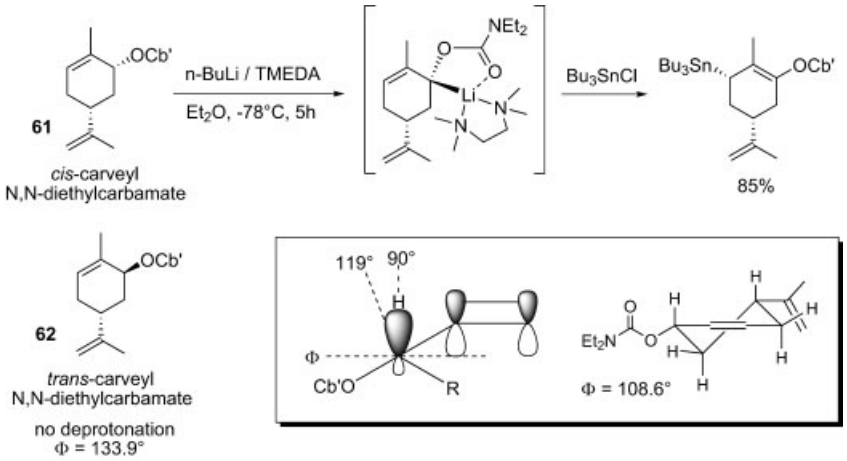
Scheme 6.36.

decreases the stereoselectivity of the overall process because the differences in rates are not great enough.

In situ quenching experiments performed with substrates **59a–f** show that *n*-BuLi/(–)-sparteine preferentially removes the pro-*S* proton (Scheme 6.37).[65] However, there are dramatic differences in the configurational stability of the intermediates **60a–f**. For 6, 7, and 8 membered rings, as well as for tetrasubstituted olefins, good configurational stability is observed. However,



Scheme 6.37.



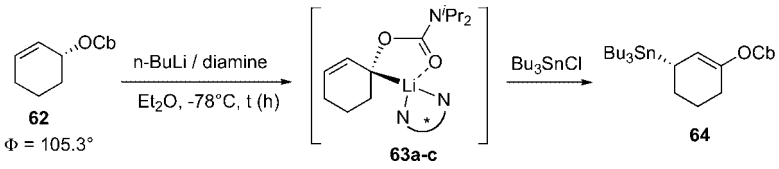
Scheme 6.38.

carbamate **59a** is kinetically deprotonated into (*S*)-**60a** that epimerizes almost completely in only 40 minutes into the most stable complex (*R*)-**60a**. For other carbamates **59b–f**, the kinetically formed complex (*S*)-**60b–f** retains the same absolute configuration with only a small loss of enantiomeric purity after a few hours at a low temperature.

The deprotonation of cyclic substrates derived from cyclohex-2-enols such as *cis*-carveol provide further information about the mechanisms of deprotonation (Scheme 6.38).[66] Indeed, the particular conformation of the molecule, due to ring strain, imposes a well-defined spatial position of the carbamate and the acidic proton. Stereoelectronic effects have an important role in the deprotonation of the cyclic system and guide the deprotonation towards the axial or equatorial proton. While *cis*-carveyl carbamate **61** is deprotonated with *n*-BuLi/TMEDA, the *trans* isomer **62** is unchanged. This difference in reactivity correlates with the α angle formed between the CH bond and the π system (Scheme 6.38). It has been confirmed by calculation that deprotonation is possible when this angle is in the range [90°–119°].

The deprotonation of carbamate **62** with *n*-BuLi associated with diamines such as TMEDA, TMCDA,[22] or (–)-sparteine leads to the complex **63a–c** that reacts in an *anti*-$S_{E'}$ fashion to give stannane **64** (Scheme 6.39).[67] Its enantiomeric purity is identical to that of the starting material only in the case of (–)-sparteine, which indicates that the intermediate **63c** is configurationally stable (*CST1*). By contrast, complexes **63a** and **63b** epimerize after 1h at –78 °C. This transformation has been applied in the kinetic resolution of *rac*-**62** and for the synthesis of hexahydroisobenzofuran-4(1H)-ones derivatives.[67,68]

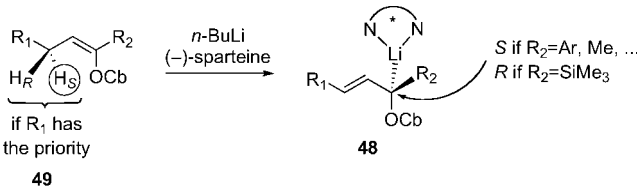
As mentioned above, another way to produce alkenyllithium reagents is to use alkenyl carbamates such as **49** that undergo γ-deprotonation. In this way, an asymmetric deprotonation transforms the whole substrate into **48**



starting material (er)	ligand	t (h)	Y(%)	er
(S)-**62** (95:5)	TMEDA (**a**)	1	54	72:28
(R)-**62** (98:2)	rac-TMCDA (**b**)	1	64	95:5
		5	42	86:14
(R)-**62** (>99:1)	(–)-sparteine (**c**)	1	61	98:2

Scheme 6.39.

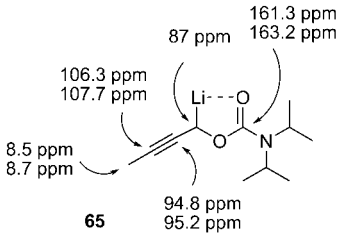
with high enantiomeric purity. Starting from *rac*-**47**, only a kinetic resolution can produce **48** in an enantiomerically enriched form. The deprotonation occurs with (–)-sparteine at the γ-pro-*S* hydrogen (referred to as pro-*S* when R_1 has priority over the vinyl moiety, otherwise, this proton is pro-*R*) leading to complex **48**.[69]



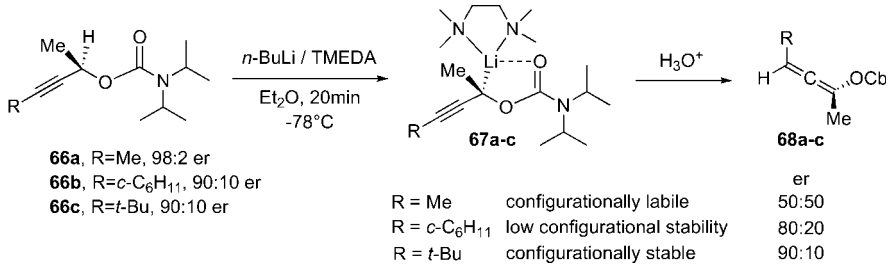
Scheme 6.40.

4. *Hoppe's Propargylic Carbamates*

The deprotonation of propargylic carbamates leads to lithiated intermediates that can have either the propargylic or the allenic structure. It has been proven by NMR studies that **65** exists as a mixture of two diastereomeric dimers having a propargylic structure (Scheme 6.41).[70]



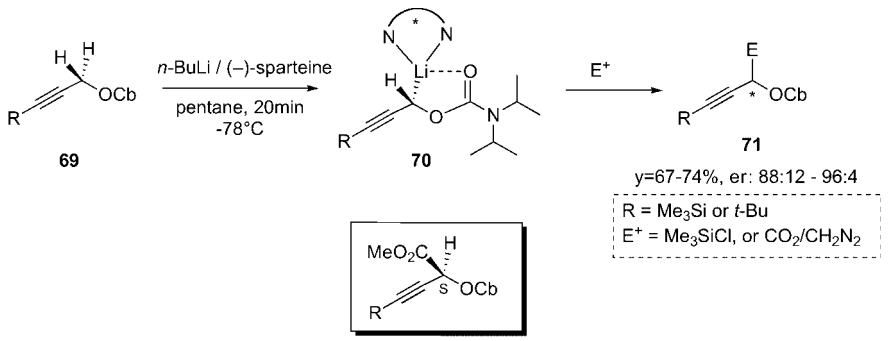
Scheme 6.41.



Scheme 6.42.

The use of enantiomerically enriched secondary propargylic carbamates **66a–c** has demonstrated the dependence of the configurational stability of the propargylic organolithium **67a–c** with the substituent R bearing the alkyne moiety (Scheme 6.42). There is a considerable influence that induces drastic differences in the configurational stability between **67a** and **67c**.[71]

The deprotonation of primary propargylic carbamates **69** has been studied in the presence of (–)-sparteine (Scheme 6.43).[72] It is necessary to perform the reaction in pentane to obtain a very selective process. Indeed, the intermediate (*S*)-**70** crystallizes in pentane, displacing the equilibrium that exists between both diastereomeric complexes. The electrophilic substitution occurs at the α position with TMSCl and carbon dioxide in a very selective manner. On the other hand, when the reaction is performed in toluene, no crystallization takes place and products are obtained with low enantiomeric ratios. This methodology has been used for the synthesis of several highly enantiomerically enriched allenes.[73]

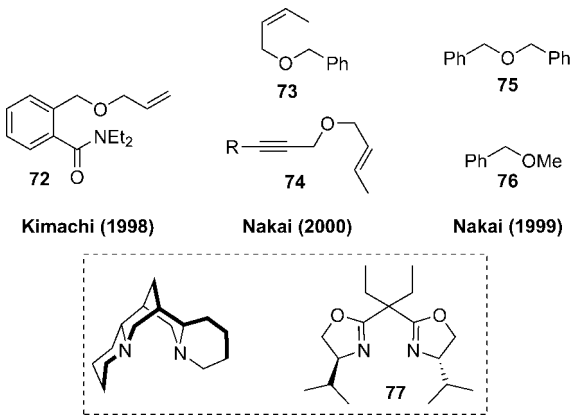


Scheme 6.43.

5. *Benzylic, Allylic and Propargylic Ethers*

Unsaturated ethers are useful substrates that undergo the Wittig rearrangement after deprotonation in the allylic or benzylic position.[74] Chiral bases using *n*-BuLi associated with (–)-sparteine have been used by Kimachi et *al*. on substrate **72** (Scheme 6.44).[75] The rearranged product is obtained in 83% yield and in 80:20 er in favor of the (*S*) enantiomer. The rearrangement performed on the monodeuterated substrate *rac*-**72-d** leads to the deuterated product (98% d-content) in 60% yield and 67:33 er. There is a strong KIE and a significant decrease in enantioselectivity, indicating that the stereoselectivity is obtained by asymmetric deprotonation (*CST5b*).

Nakai et al. have studied the Wittig rearrangement of **73** and **74** in the presence of (–)-sparteine and bis(oxazoline) **77** (Scheme 6.44).[76] Only moderate enantioselectivity was obtained with (–)-sparteine, while **77** led to the rearranged products in 70:30 er and 94:6 er, respectively. The origin of the selectivity was studied by using the monodeuterated substrate *rac*-**73-d**. The product was obtained in 70% yield and 57:43 er (86% erythro) with 98% d-content. There was a significant decrease in enantioselectivity and a strong KIE, indicating that the origin of the selectivity is predominantly the deprotonation step (*CST5b*). On the other hand, it was suggested that the selectivity of the Wittig rearrangement of dibenzylether **75** with *t*-BuLi/**77** occurs at the second step.[77] The methylbenzylether **76** has been deprotonated using either *t*-BuLi/**77** or *t*-BuLi/(–)-sparteine, leading to an intermediate that was allowed to react with carbon dioxide, aldehydes and alkyl halides.[78] In the particular case of carboxylation, the use of (–)-sparteine induced no selectivity, while **77** led to the product in 97:3 er in favor of the *R* enantiomer. The origin of the selectivity was determined with *rac*-**76-d** that led to the carboxylic acid in 73% yield, 87:13 er and 96% d-content. This result was consistent with a selective electrophilic substitution step. Furthermore, by varying the amount of carbon



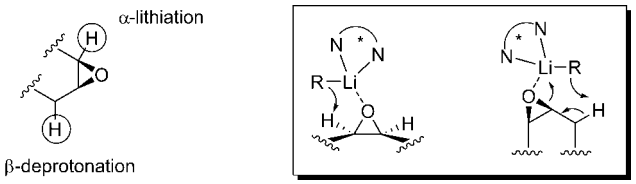
Scheme 6.44.

dioxide from 4 equivalents to 0.5 equivalents, and to 0.1 equivalents, the product was isolated in er's *(R:S)* of 87:13, 74:26, and 72:28, respectively. The variation in the enantioselectivity observed indicates that the reaction proceeds through a dynamic thermodynamic resolution. This means that both epimeric intermediate complexes are in slow equilibrium compared to the carboxylation reaction. It has been suggested that the S_E step occurs with retention, which means that the major complex has the (*S*) absolute configuration.

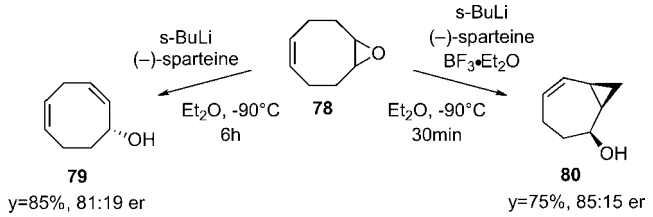
6. *Epoxides*

The reactions of epoxides under basic conditions have been widely studied and reviewed.[1,79] For a review of lithiated oxiranes, see the chapter by Capriati, Florio, and Salamone, in this volume. Depending on the structure of the epoxide and the base used, α-lithiation or β-deprotonation takes place. In both cases, the hydrogen abstraction occurs in a ternary complex that involves the ligand, the base, and the epoxide (Scheme 6.45). The sole β-deprotonation product is an allylic alcohol, while α-deprotonation can lead to several different products including the allylic alcohol. The reaction conditions (temperature and additives) can preferentially induce the formation of a given product (Scheme 6.46). Cyclooctene oxide **78** leads to the allylic alcohol **79** in the presence of *s*-BuLi/(–)-sparteine. However, in the presence of $BF_3{\cdot}Et_2O$ as additive, the chemoselectivity changes and cycloheptene derivative **80** is isolated in good yield.[80]

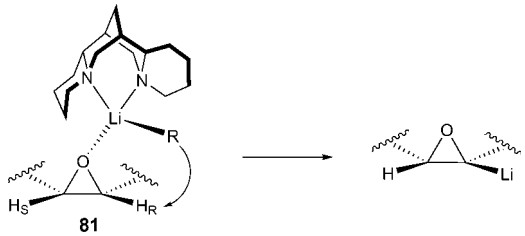
In the reactions that involve α-lithiation, the chiral base *n*-BuLi/(–)-sparteine selectively removes the pro-*R* hydrogen. In the transition state of the de-



Scheme 6.45.

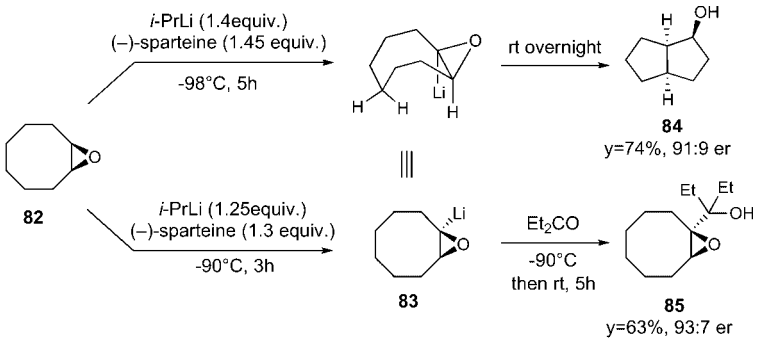


Scheme 6.46.



Scheme 6.47.

protonation that comes from the ternary complex **81** the base RLi is oriented closer to pro-*R* because of the steric interactions between (–)-sparteine and the epoxide (Scheme 6.47). The stereochemistry of the bicyclic alcohol **84** can be explained by considering the oxiranyl anion **83** and its rearrangement through a conformation that allows a transannular C–H insertion (Scheme 6.48).[81] When the intermediate oxiranyl anion is trapped, the absolute configuration at the carbon center is preserved. It can react with a wide variety of electrophiles and lead to alcohol **85** by reaction with 3-pentanone.[82]

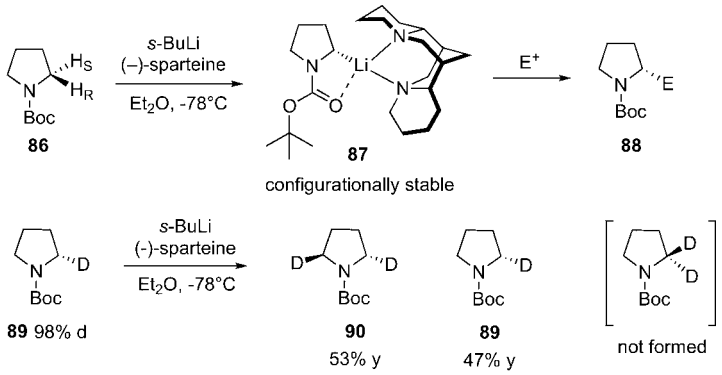


Scheme 6.48.

B. Deprotonation α to a Nitrogen Atom

1. Heterocyclic Substrates

Beak et al. applied asymmetric alkylation to *N*-Boc-pyrrolidine **86** very successfully (Scheme 6.49).[83] The mechanism of the deprotonation proceeds through the ternary complex *i*-PrLi/(–)-sparteine/*N*-Boc-pyrrolidine obtained from the unsymmetric dimer[24] (–)-sparteine/i-PrLi$_2$/$(Et_2O)_n$ and the substrate. This equilibrium is followed by the rate determining step which is the deprotonation. The kinetic data are consistent with a high value of the equilibrium constant of the reaction between the unsymmetric dimer (–)-sparteine/i-PrLi$_2$/$(Et_2O)_n$ and the substrate that lead to ternary complex i-PrLi/(–)-sparteine/N-



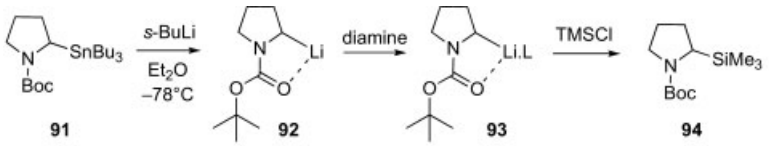
Scheme 6.49.

Boc-pyrrolidine and a rapid equilibrium compared to the deprotonation step. The reaction is zero order in the organolithium reagent and the intermolecular isotope effect (k_H/k_D) was calculated to be >30.[84]

Computational study has revealed that the most stable ternary pre-complex is also the most reactive, which means that it produces (*S*)-**87**.[85] The energy difference between the pre-complexes that lead to (*S*)-**87** and (*R*)-**87** is 3.1 Kcal mol^{-1} and the corresponding difference in transition-state free energy is 3.2 Kcal mol^{-1}. These differences are due to non-bonding interactions in the pre-complexes that persist in the less favored transition state. In concrete terms, these interactions are marked by several short atom distances within the range of 2–3 Å between hydrogens of (–)-sparteine and the *tert*-butyl moeity. The enantioselectivity of the reaction is due to steric interactions, and molecular mechanics calculations are consistent with the observed results. The deprotonation of enantiomerically pure monodeuterated *N*-Boc-pyrrolidine **89** led to a mixture of starting material and the dideuterated product **90**-d_2. These experiments confirm the stereochemical pathway of the reaction that follows asymmetric deprotonation with abstraction of H_s, leading to the configurationally stable intermediate **87**. If (–)-sparteine is added after the formation of the racemic organolithium species, either by deprotonation or tin–lithium exchange, the product is isolated in less than 55:45 er.

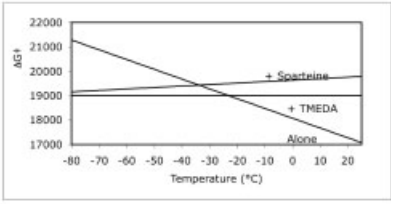
The dynamics of this system have been studied in detail (Scheme 6.50).[86] The thermodynamic parameters for the carbanion inversion, measured in ether, are listed in Scheme 6.50, along with a plot of the free energy barriers as a function of temperature. The configurational stability of **92/93** as function of temperature and added diamine is not straightforward, and entropy can contribute significantly to the free energy barrier. These studies reconcile the conflicting reports regarding the effect of racemization in the presence of TMEDA.[84,88]

The case of *N*-Boc-piperidine **95** is dramatically different. The main reaction that occurs is the addition of the base to the carbamate function.[87] The



diamine	$\Delta H^{\ddagger}$ [a]	$\Delta S^{\ddagger}$ [b]
none	29±2	40±8
TMEDA	19±1	0±2
(–)-sparteine	18±1	–6±2

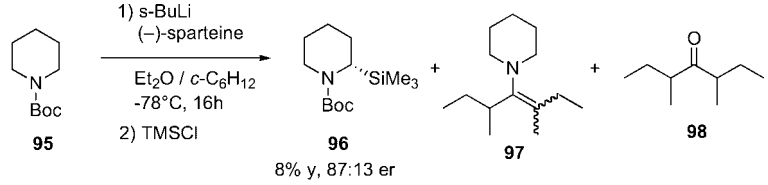
a) kcal/mol; b) cal/mol·K

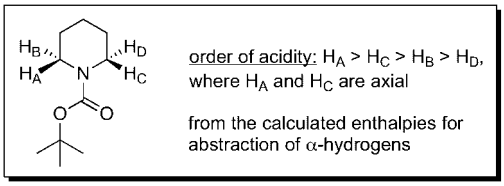


Scheme 6.50.

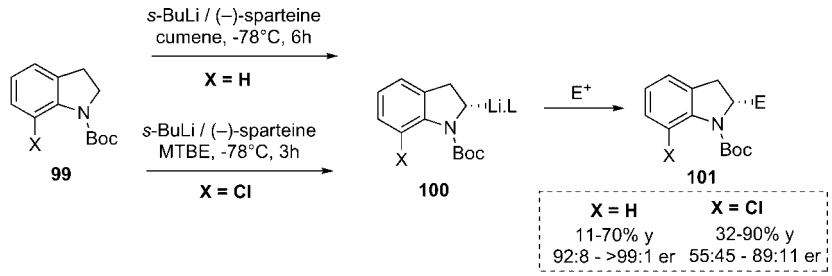
product of silylation that arises from deprotonation is isolated in 8% yield (87:13 er). The calculated acidity of the 4 hydrogens depends upon their axial or equatorial position, with respect also to the carbamate function (Scheme 6.51). The hydrogen that has to be removed in the reaction is the equatorial pro-*S* hydrogen, selected by (–)-sparteine. This hydrogen is placed at the side of the carbonyl moiety because of the CIPE that directs the base towards this site. Unfortunately, this hydrogen is the least acidic of the four, which drastically impedes deprotonation, and the main pathway is a totally non-interesting reaction, i.e. the nucleophilic addition of the base to the carbonyl. These calculations also determined a small difference between the transition state energies that would favor the *R* enantiomer. This error is attributed to the large structures involved. Experimentally, the *S* enantiomer is formed in 87:13 er.

Several conformationally restricted bicyclic substrates have provided insights into the factors determining the selectivity in this alkylation sequence.[88] In such substrates, the dihedral angle between the carbonyl group and the





Scheme 6.51.

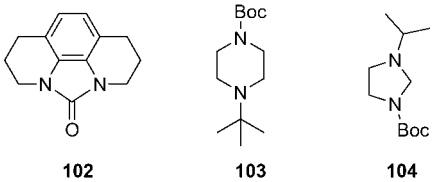


Scheme 6.52.

proton to be removed is substrate-controlled. The stereoselectivity in the deprotonation of several bicyclic and monocyclic substrates has highlighted the importance of this geometric feature. The orientation of the base by the carbonyl group through CIPE results in the removal of the proton on the same side. Furthermore, depending on the neighborhood of the carbamate, the distance between the oxygen of the carbonyl group and the hydrogen to be removed may vary. The most efficient reactions occur when this distance is about 2.78Å.

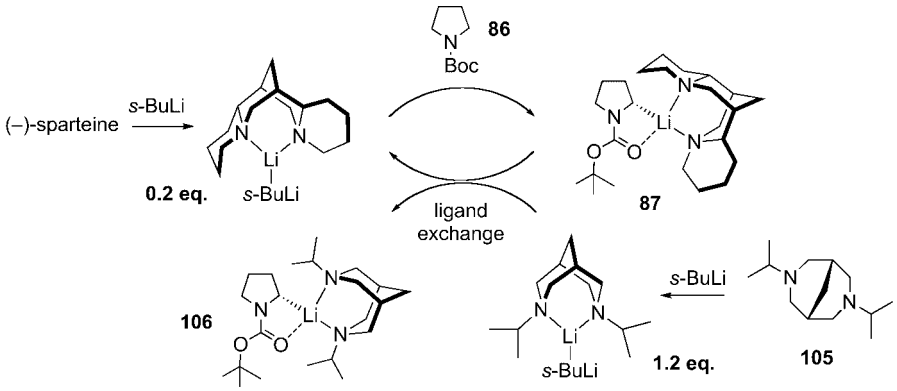
The case of *N*-(*tert*-Butoxycarbonyl)indoline **99** is in fact very similar (Scheme 6.52).[89] After deprotonation, it leads to an enantiomerically enriched intermediate **100** that retains its configuration. Starting from enantiomerically enriched **100**, obtained from the enantiomerically pure organostannane, an alkylated product is isolated of equal enantiomeric purity (*CST1*). Furthermore, racemic **100** mixed with (–)-sparteine produces a racemic final product. The selectivity is introduced at the first step, during asymmetric deprotonation. The regioselectivity of the deprotonation in **100** is a real problem. There are two removable protons, α to the nitrogen atom and in the ortho position. The use of deuterated substrates shows that this regioselectivity is kinetically controlled, rather than thermodynamically. When X is a chlorine atom, suppressing the regioselectivity problem, lower levels of enantioselectivity are obtained.

Substrates **102**,[90] **103**[91] and **104**[92] have been successfully subjected to asymmetric deprotonation in the presence of (–)-sparteine. The reaction pathway and the direction of induction are similar to those described with *N*-Boc-pyrrolidine. It is noteworthy that the piperazine derivatives are efficiently transformed in terms of yield and selectivity.



102 **103** **104**

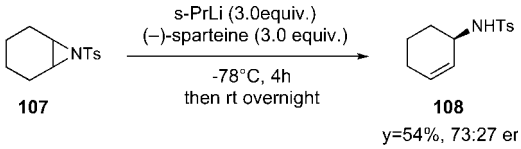
Scheme 6.53.



Scheme 6.54.

Application of the successful (+)-sparteine surrogate **3** in these reactions has allowed the synthesis of enantiomers with similar enantioselectivity. Furthermore, a catalytic version is possible using *N,N*-diisopropyl-bispidine **105**, which liberates (–)-sparteine from the complex **87** after deprotonation (Scheme 6.54).[93] This produces complex **106** and the base *s*-BuLi/(–)-sparteine that can deprotonate the substrate in another catalytic cycle. In contrast, the complex **105**/*s*-BuLi is not an efficient base, it removes the α-hydrogen only slowly.

The desymmetrisation of sulfonylated aziridine is a reaction analogous to that of epoxides. In the case of aziridine **107**, the mechanistic pathway studied with the dideuterated meso derivatives is more likely to be α-deprotonation. However, the stereochemical outcome of the reaction is the opposite to that of the corresponding epoxide (Scheme 6.55).[94] The differences in the mechanism may occur at the complexation stage, that could take place with the sulfone moiety. This would induce a different orientation of the base and favor the removal of the other enantiotopic hydrogen.

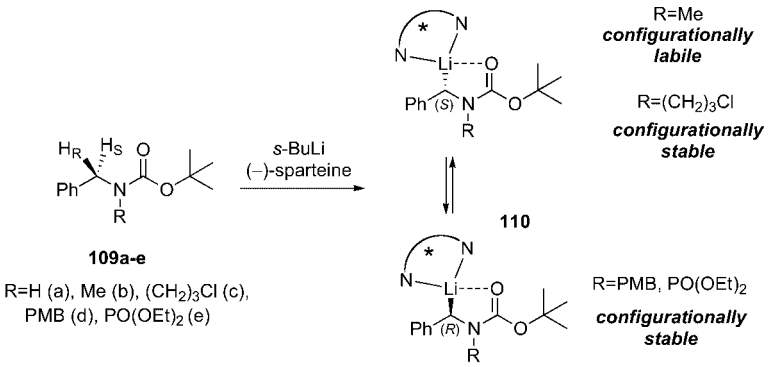


Scheme 6.55.

2. Acyclic Substrates

Benzylic carbamate derivatives show important differences in the mechanism of the deprotonation–alkylation sequence, depending on the nitrogen substituent. The efficiency of the result is also drastically altered from one

substrate to another, and that can be taken as a clue to different operative mechanistic pathways (Scheme 6.56). Carbamates **109a** and **109e** are transformed with low selectivities (~54:46 er).[95] The intermediate **110e** is not quenched by an electrophile, but rearranged with a 1,2-migration of the phosphorylated group that produces a *N*-protected α-aminophosphonate. Changing the R substituent to the methyl enhances the enantioselectivity of the process. The carbonylation reaction is 81% (*R*) in hexane, and 85% (*S*) in THF. In the latter solvent, precipitation of the intermediate is observed, accounting for the reversal of selectivity.[19] The deprotonation of **109b** with s-BuLi/(–)-sparteine produces (*S*)-**110b** in a very selective deprotonation, followed by a rapid epimerization. The final selectivity is obtained through a selective electrophilic substitution. Evidence of such asymmetric deprotonation is obtained directly from experiments with (*S*)-**109b–d** (94:6 er). Its deprotonation is impossible with *s*-BuLi/(–)-sparteine because of the strong KIE that impedes the removal of the deuterium. Furthermore, deprotonation with *s*-BuLi/TMEDA in 2h at –78 °C followed by carbonylation leads to the racemic carboxylic acid. This means that the organolithium complexed by TMEDA is configurationally labile. On the other hand, if the deprotonation occurs first with *s*-BuLi alone, followed by addition of (–)-sparteine, two epimeric complexes are formed in a ratio of 1:1. The carbonylation that follows produces the carboxylic acid in 91:9 er (*S:R*). The intermediate **110b** is also labile when complexed by (–)-sparteine, which implies that the electrophilic substitution is necessarily the stereodetermining step of the process.[96] In a general manner, enantioselectivity (sense and value) is very solvent and electrophile-dependent. Determination of the absolute configuration of the final product revealed the retentive or invertive pathway of the electrophilic substitution. However, the equilibration in a short period of time suggested the existence of both complexes in the presence of the electrophile. Determination of relative rates of equilibrium and electrophilic substitution, as well as the position of the equilibrium, would provide a better insight into

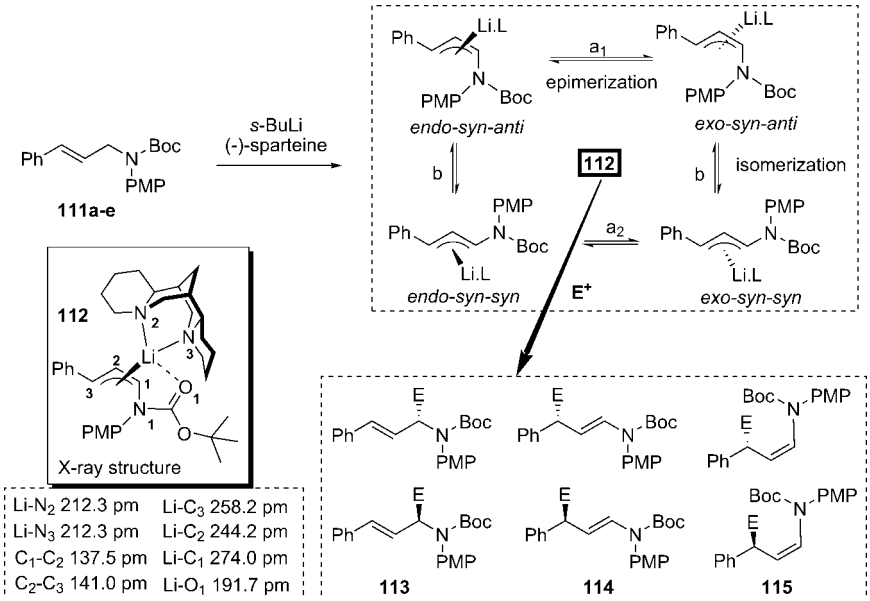


Scheme 6.56.

the mechanism of the electrophilic substitution. The phosphorylated analog of **109b** ($POPh_2$ instead of Boc) probably reacts in an asymmetric deprotonation with a configurationally stable intermediate.[97]

A similar substrate, **109c**, that contains an alkyl nitrogen substituent, undergoes a cyclization reaction after deprotonation.[98] Reaction of the racemic lithiated species complexed to (–)-sparteine led to the racemic product. On the other hand, monodeuterated (*rac*)-**109c**-d_1 (96% d_1) led to a deuterated cyclized product (88% d_1) in much lower er and yield than for **109c**. The enantiomer (*R*)-**109c**-d_1 has similar behavior to that of **109c**; but (*S*)-**109c**-d_1 is deprotonated much more slowly because of the strong KIE that dominates the process, resulting in an overall decrease in enantioselectivity of the final product. The stereochemical pathway is described as an asymmetric deprotonation of pro-*S*, and a subsequent stereospecific (although non-selective) cyclization.

The use of an aromatic amine substituent, in particular *p*-methoxyphenyl (PMP), is of synthetic importance because of its function as protecting group. The stereochemical outcome of the reaction is the result of enantioselective deprotonation, leading to a configurationally stable intermediate.[99] However, in contrast to the *N*-alkyl substrates, the preferred hydrogen for removal is pro-*R*. The best solvent for this reaction is toluene, but no reversal of selectivity is observed by changing the solvent but only a reduction of enantioselectivity. Evidence of a mechanism pathway is obtained by using stannylated or monodeuterated derivatives. The racemic lithiated intermediate, produced from the racemic stannylated derivative and complexed with (–)-sparteine, produces the racemic product. However, starting from the enantiomerically enriched stannane (95:5 er), the same enantiopurity is measured in the product. In this case also, the use of (–)-sparteine is needed because an almost racemic product (56:44 er) is obtained by using TMEDA after 10 hours. The configurational stability measured on a timescale at a determined temperature is better described on the timescale of the electrophilic substitution. Using a modified version of Hoffmann's test, the configurational stability of the intermediate can be highlighted, which means that the epimerization is slow compared to the electrophilic substitution. These results (that indicate a non-selective electrophilic substitution) are associated with experiments that give information about the first step. The deprotonation of the racemic monodeuterated substrate leads to the methylated product with 89% d content and 88% yield, but low enantioselectivity compared to the normal reaction. This comes from a process dominated by the KIE that retards deuterium removal. The chiral base with a strong preference for the removal of pro-*R* is obliged to remove the pro-*S* hydrogen, due to the presence of the less acidic deuterium atom. The configurational stability increases from primary to secondary substrates. Indeed, in the latter case, the secondary carbamate is deprotonated with the achiral base *s*-BuLi/TMEDA that produces a configurationally stable intermediate.



Scheme 6.57.

The situation encountered with allylic carbamate **111** after the deprotonation step is more complex. Four allylic complex diastereomers have to be considered in the mechanism, each with specific stereochemical features (Scheme 6.57).[100] They are in equilibrium through two different isomerization processes, *i.e.* an epimerization that reverses the configuration of the planar-chiral allylic fragment (equilibrium a), and an *E*,*Z*-isomerization of the allyl group (equilibrium b). The deprotonation step produces *endo* and *exo syn-anti* isomers which are configurationally stable at –78 °C. The ratio is determined by the kinetic factors of this step. The silylated products (*E*,*S*)-**113** and (*Z*,*S*)-**115** are isolated in 46% and 34% yields, respectively, and 98:2 and 97:3 er, respectively. The pro-*R* hydrogen is preferentially removed, leading to the η^3 allyllithium *endo-syn-anti* complex that crystallizes in the reaction mixture.[101] The same enantiomers are obtained from the reaction mixture and from the pure isolated crystalline **112**. Although some silylation and stannylation occurs at the α position, most electrophiles react at the γ position. Reactions that use racemic (followed by addition of (–)-sparteine) or enantiomerically pure stannane derivatives lead to products (*Z*)-**115** in enantiomer ratios identical to those of the starting materials. During these experiments, starting from racemic stannane derivative, 15% of the (*E*,*R*)-**114** (E = Bn) is obtained in 84:16 er. In the presence of *n*-BuLi/(–)-sparteine, the reaction of (*E*,*S*)-**113** (E = $SnMe_3$, 97:3 er) produces the complex *exo-syn-anti*-**112** (97:3 er) that reacts with BnBr to give (*E*,*R*)-**114** (13% yield) and (*Z*,*R*)-**115** (56% yield) in 90:10 and 88:12 er, respectively. However, in

the presence of TMEDA, or without diamine ligand, a racemic product is obtained. These experiments are consistent with an asymmetric deprotonation pathway for the *syn-anti* complexes, while an asymmetric substitution operates for the *syn-syn* complexes. The situation at –78 °C is the following: the *E*,*Z*-isomerization (equilibrium b) is frozen; the *endo-syn-anti/exo-syn-anti* complexes are configurationally stable (equilibrium a_1); and the *endo-syn-syn/exo-syn-syn* complexes are configurationally labile (equilibrium a_2).

When the racemic complex *syn-anti*-**112** is produced at –78 °C, then warmed up to –25 °C, and finally allowed to react with methyl iodide at –78 °C, (*Z*,*S*)-**115** is obtained in 57% yield and 87:13 er. However, only 53:47 er is obtained when the reaction is performed entirely at –78 °C. Thus, *endo-syn-anti/exo-syn-anti* complexes equilibrate at –25 °C (equilibrium a_1). Equilibrium (b) also takes place at this temperature. When the electrophile is TMSCl, the product obtained at –25 °C is (*E*,*R*)-**114**. In this case, the reaction is likely to proceed through a dynamic kinetic resolution to provide the *E* isomer. The evaluation of the configurational stability of **112** using a variation of the Hoffmann test (*CST4a*) highlights the configurational stability on the time scale of the reaction with TMSCl. The reaction with the electrophile occurs through a dynamic thermodynamic resolution with a smaller activation energy for the reaction of the minor diastereomeric complex *endo-syn-syn*. It thus follows that the reaction at –25 °C is controlled by both dynamic kinetic and thermodynamic resolution. The *Z*/*E* ratio is controlled by kinetic factors (*E* favored), while the enantiomeric ratio (of diastereomer *E*) is controlled by thermodynamic factors (*endo-syn-anti* + *exo-syn-syn* / *exo-syn-anti* + *endo-syn-syn*).

The allylic carbamate that bears a $(CH_2)_3Cl$ group instead of the PMP protecting group reacts in an asymmetric deprotonation that produces an enantiomerically enriched intermediate. However, rapid epimerization occurs, and the subsequent cyclization takes place in a highly selective manner through an asymmetric substitution.[102]

C. Deprotonation α to a Sulfur or a Phosphorus Atom

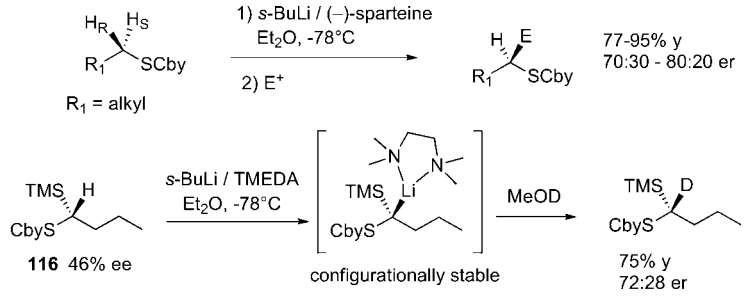
1. Deprotonation in α-Position to a Sulfur Atom

Alkyl Thiocarbamates

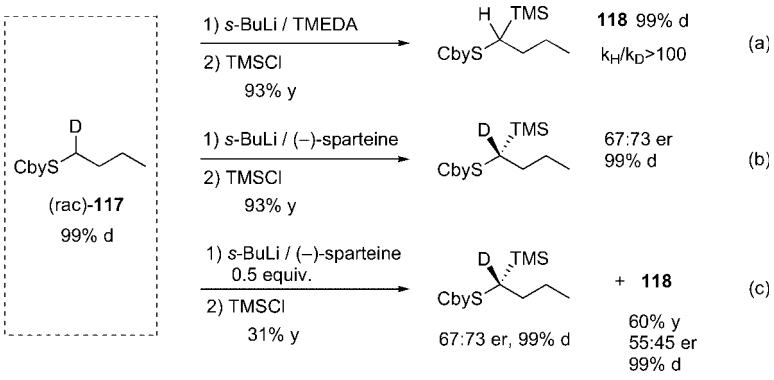
The deprotonation of primary alkyl thiocarbamates leads to much lower selectivity than the oxygenated derivatives (Scheme 6.58).[103] This indicates a significantly different behavior of the lithiated intermediate, either in its reactions (deprotonation and electrophilic substitution selectivity) or in its stability. Indeed, reactions performed on the deuterated substrate indicate

that there is no asymmetric deprotonation (strong KIE and good yield of silylation, Scheme 6.59, reaction a). There is only a very small preference in the hydrogen abstraction step (reaction c). Furthermore, both epimeric complexes equilibrate rapidly at –78 °C. However, the deprotonation of enantiomerically enriched **116** leads to the deuterated product with the same enantiomeric excess (*CST1*, Scheme 6.58). Secondary alkyl thiocarbamates are configurationally stable.

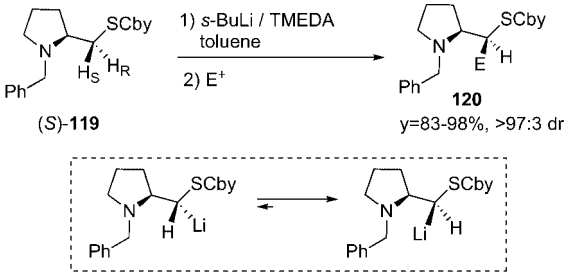
The deprotonation of pyrrolidine **119** performed in the presence of *s*-BuLi/TMEDA leads to the alkylated product with very high selectivity (Scheme 6.60).[104] In situ quenching experiments (ISQ) and reactions with enantiomerically pure monodeuterated substrate allow the determination of the stereochemical pathway of the reaction, meaning that H_s is removed kinetically. In addition, starting from monodeuterated substrate (D at the H_s position), the equilibration of complexes occurs rapidly to give only one diastereomer under *in situ* quench or external quench (EQ) conditions. The product obtained is favored for both kinetic and thermodynamic reasons. Interestingly, the selectivity of the deprotonation is the opposite to that obtained with the oxygenated derivatives (*S*)-**32** (Scheme 6.25).



Scheme 6.58.



Scheme 6.59.

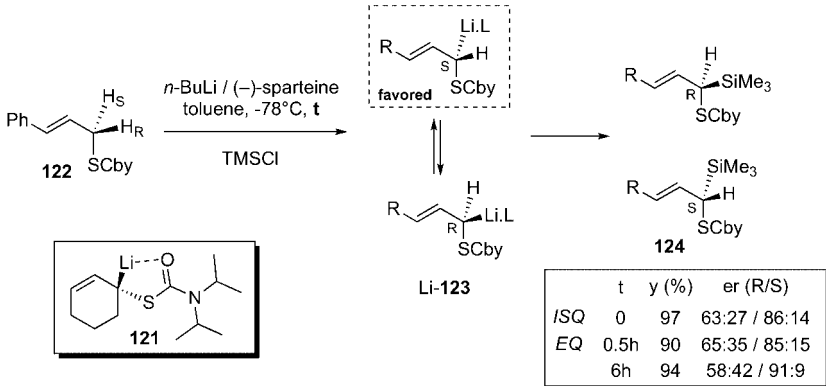


Scheme 6.60.

Allyl Thiocarbamates

Similar to secondary alkyl thiocarbamate **116**, the secondary allyl thiocarbamate in the cyclic system **121** is highly configurationally stable. Starting from enantiomerically pure starting material and using *s*-BuLi/TMEDA as the base, enantiomerically pure α- or γ-alkylated products are obtained (Scheme 6.61).[105]

The deprotonation of primary allyl thiocarbamate has been performed with (–)-sparteine and bis(oxazoline) (Scheme 6.61).[106] (–)-Sparteine showed poor selectivity as a ligand in an *in situ* quench (ISQ) experiment. Furthermore, when formed, the **123** complexes equilibrate slowly at –78 °C, increasing the enantiomeric ratio of the product. The process goes through a dynamic thermodynamic resolution, with (*S*)-**123** as the more stable complex. On the other hand, bis(oxazoline) ligand leads to the alkylated products with very high selectivity, up to 98%. Further experiments performed with bis(oxazoline) have also corroborated this stereochemical pathway.



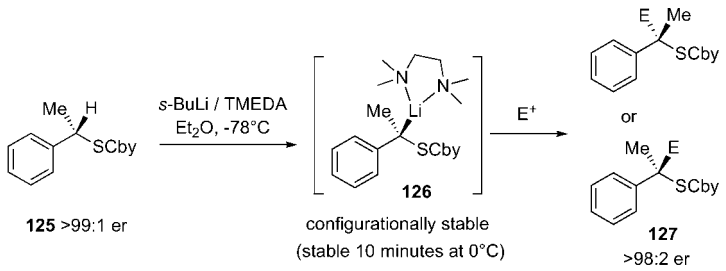
	t	y (%)	er (R/S)
ISQ	0	97	63:27 / 86:14
EQ	0.5h	90	65:35 / 85:15
	6h	94	58:42 / 91:9

Scheme 6.61.

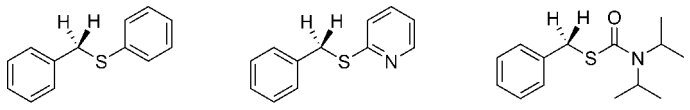
Aryl Thiocarbamates

Secondary benzyl thiocarbamate is highly configurationally stable. Starting from enantiomerically pure (*S*)-**125**, enantiomerically pure **127** is produced through the stable intermediate complex (*S*)-**126**.[107]

The stereochemical pathway of primary benzylic thiol derivatives depends upon the substituent placed on the sulfur atom. Three compounds have been studied, *i.e.* benzyl thiocarbamate **128**,[108] benzyl phenyl sulfide **129**, and benzyl 2-pyridyl sulfide **130** (Scheme 6.63).[109] The selectivity obtained with (–)-sparteine is rather low, while bis(oxazoline) leads to highly enantiomerically enriched products. The presence of a chelating moiety is important because it enhances the configurational stability of the lithiated intermediates. For sulfides **128** and **129**, high selectivity is obtained starting from the racemic α-stannylated derivatives. This clearly indicates that the selectivity is introduced during the second step, but it does not mean that the deprotonation is non-selective. On the other hand, *in situ* quenching experiments (ISQ) performed on thiocarbamate **130** with either (–)-sparteine or bis(oxazoline) result in very low selectivity, whereas the latter ligand induces 97:3 er in external quenching experiments (EQ). The selectivity is introduced during the second step. When (–)-sparteine is used, both ISQ and EQ experiments lead to 58:42 er at –78 °C (ISQ with TMSCl, EQ with MeOTf). However, when the reaction is performed at –30 °C, the other enantiomer is isolated in 58:42 er (with MeOTf). Further reactions performed with bis(oxazoline) ligand have indicated the same feature of the intermediate. The stereochemical pathway for substrate **130** is a non-selective deprotonation, followed by a dynamic thermodynamic resolution in which (*R*)-Li-**130** complexed by bis(oxazoline) is the favored complex. The question that arises is whether complexes **128** and **129** are configurationally stable or not, which may differentiate the dynamic kinetic resolution pathway from the dynamic thermodynamic resolution pathway. Using Hoffmann's test (*CST2*) and Beak's modification (*CST4a,b*), it can be determined that **128** is configurationally labile, and **129** is configurationally stable. It then follows that **128** reacts through a dynamic kinetic resolution while **129** reacts through a dynamic thermodynamic resolution.



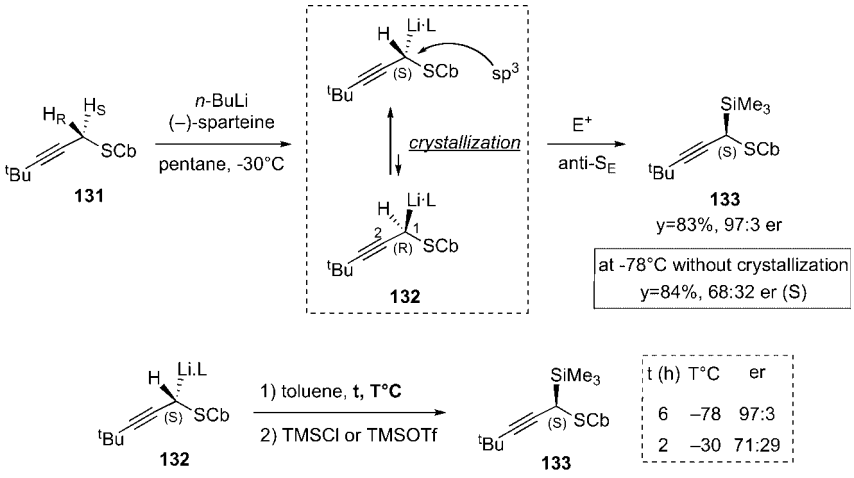
Scheme 6.62.



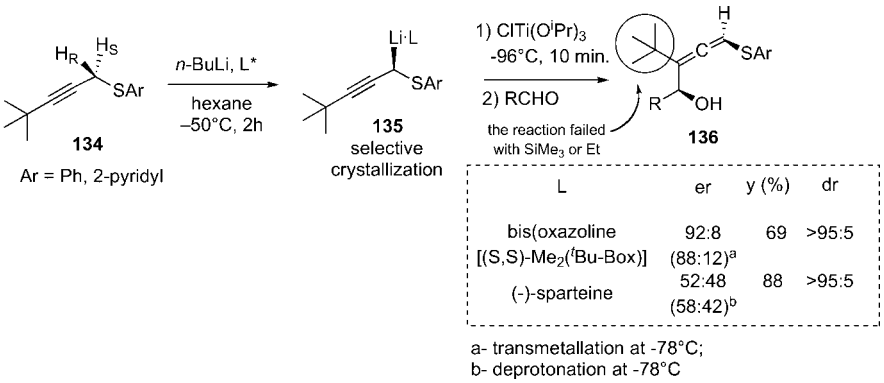
Scheme 6.63.

Alkynyl Thiocarbamates

The alkynyl thiocarbamate **131** is deprotonated at –78 °C in the presence of (–)-sparteine with a small preference for abstraction of pro-*S* (36%, Scheme 6.55). However, at –30 °C a selective crystallization of (*S*)-**132** occurs that shifts the equilibrium.[110] The electrophilic substitution leads to the alkylated products with high enantiomeric ratios. The X-ray structure obtained for (*S*)-**132** confirms its absolute configuration and the propargylic structure. Indeed, the propargylic stereogenic carbon has a sum of angles of 323.5° (sum of angles Li–C_1–S, Li–C_1–C_2 and S–C_1–C_2; the ideal values for sp^3 and sp^2 hybridation are 328.4° and 300.0°, respectively). Furthermore, bond lengths are characteristic (119.8 pm and 141.7 pm for the C≡C bond and C–C bond on the sulfur side, respectively). In solution, the thermodynamic ratio of diastereomeric complexes is 71:29, but it equilibrates rapidly to shift the equilibrium through crystallization. The product is obtained through a stereochemical pathway close to the dynamic thermodynamic resolution, better referred to as asymmetric transformation of a second kind. Enantiomerically enriched allenes are also obtained by transmetallation from Li to Ti, and then reaction with aldehydes.



Scheme 6.64.



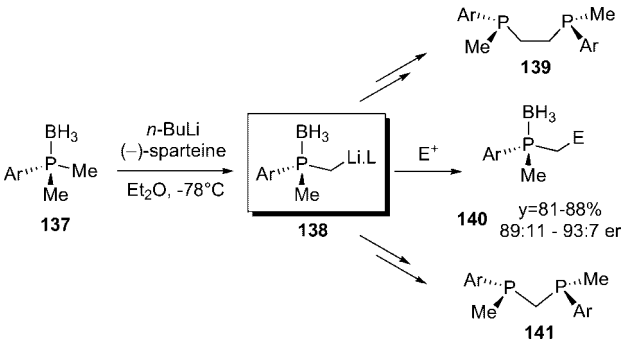
Scheme 6.65.

Alkynyl aryl sulfide leads to highly selective transformation with bis(oxazoline) as ligand and *tert*-butyl as substituent at the alkyne terminus.[111] An asymmetric transformation of a second kind also occurs, only with a particular bis(oxazoline) ligand. Another kind of bis(oxazoline) or (–)-sparteine has led to much lower selectivity because no selective crystallization could be achieved.

2. *Deprotonation in α-Position to a Phosphorus Atom*

The asymmetric deprotonation–alkylation sequence has aroused much interest because of the importance of *P*-chiral diphosphine and other chiral phosphorinated derivatives in asymmetric synthesis.[112] The deprotonation always occurs on activated phosphine forms such as phosphine-boranes, phosphine-sulfides and phosphine-oxides. The mechanisms in such systems have not been discussed and little information is available on the stereochemical pathway as it is for oxygen, nitrogen, or sulfur derivatives. It has been determined using the Hoffmann test, that α-lithiated diphenylphosphine oxide does not maintain its configuration, but equilibrates on the timescale of the reaction.[113] An attempt at enantioselective silylation with *n*-BuLi/(–)-sparteine as chiral base performed on a similar substrate led to the silylated product in 55:45 er.[114]

Phosphine-borane **137** is deprotonated by *n*-BuLi/(–)-sparteine that selectively removes the hydrogen of one of the two enantiotopic methyl groups (Scheme 6.66).[115] When **138** is formed, there is no exchange of the lithium atom to the other methyl group, and **138** is configurationally stable. The absolute configuration of the product is determined at the deprotonation step. This intermediate is very useful to prepare enantiomerically pure mono- and diphosphine. Enantiomeric mono- and diphosphines are accessible by using

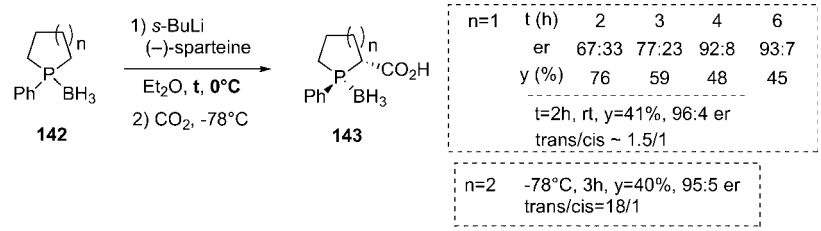


Scheme 6.66.

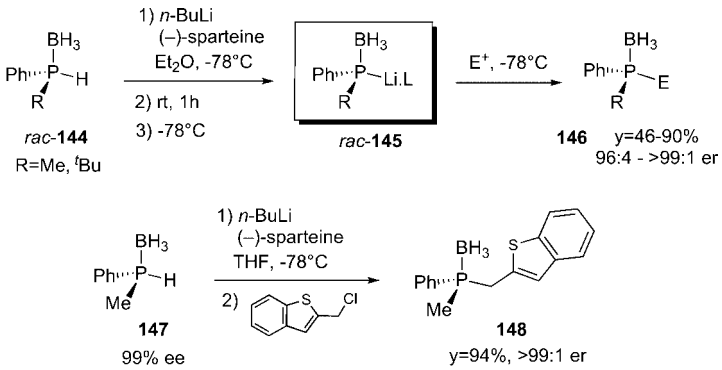
the (+)-sparteine surrogate **3**.[116] Furthermore, a catalytic version of the reaction was set up, performed on phosphine-sulfide, in such a way that only 5 mol% of ligand (**1** or **3**) was sufficient to obtain products in equal enantioselectivities (88:12 er under stoichiometric conditions and 85:15 er with 5 mol% of ligand).[116a,b]

Cyclic phosphine-borane has also been studied as starting material in the synthesis of proline and pipecolic acid phosphorous analogs (Scheme 6.67).[117] No specific studies have been performed to determine the selectivity of the deprotonation or the stability of the lithiated species. However, a hypothesis can be formulated on the stereochemical pathway of the proline analog. Indeed, the deprotonation step needs to take place at a high temperature, and the enantiomeric enrichment is time and temperature dependent. In this case, the stereochemical pathway is likely to be a dynamic thermodynamic resolution.

The removal of a hydrogen directly linked to a phosphorous atom of a phosphine-borane molecule leads to an organometallic species with a P–Li bond.[118] In the case of a stereogenic P-atom, such as in **144**, the question of the configurational stability arises (Scheme 6.68). It has been reported that when warmed to 0 °C after deprotonation had occurred at –78 °C, a precipitate formed that was subsequently alkylated selectively at –78 °C. Starting from enantiomerically pure substrate **147**, the alkylated product **148** can be



Scheme 6.67.



Scheme 6.68.

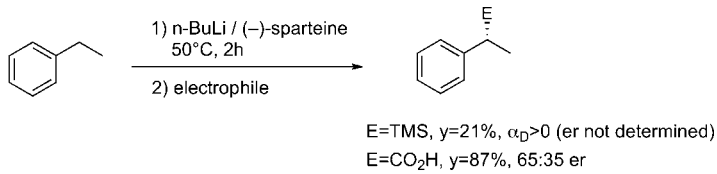
obtained with the same enantiomeric purity. However, highly enantiomerically enriched products are also obtained from racemic substrate **144**, which indicates that intermediate **145** has to epimerize. The reaction is likely to proceed through an asymmetric transformation of the second kind.

D. Deprotonation α to a Carbon Atom

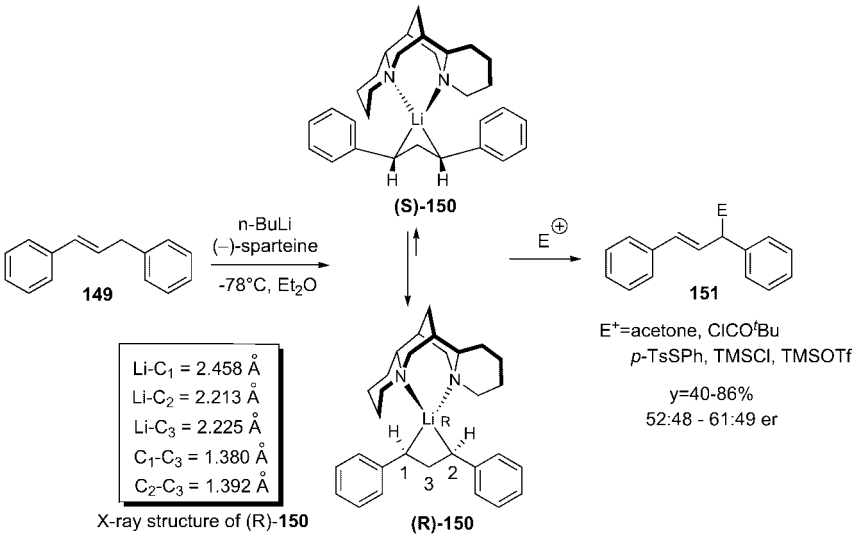
1. Without Remote Coordinating Moiety

The acidity of a proton placed on a carbon atom is always very low, except when an activating group is nearby. As seen in the previous sections, the presence of a functionalized heteroatom helps the deprotonation by stabilizing the lithiated species through a cyclic chelate. Another possibility is the presence of a mesomerically stabilizing group such as aryl and alkenyl moieties. In this section, all the substrates considered undergo benzylic deprotonation. Indeed, as no α-heteroatoms are involved, the sole carbonylated moiety that is sufficiently stabilizing is an aryl group.

Nozaki et al. were the first to report the asymmetric deprotonation–alkylation process using the RLi/(–)-sparteine base system.[119] The products of silylation and carbonylation of ethylbenzene were isolated with the same (*R*) absolute configuration (Scheme 6.69).[120]

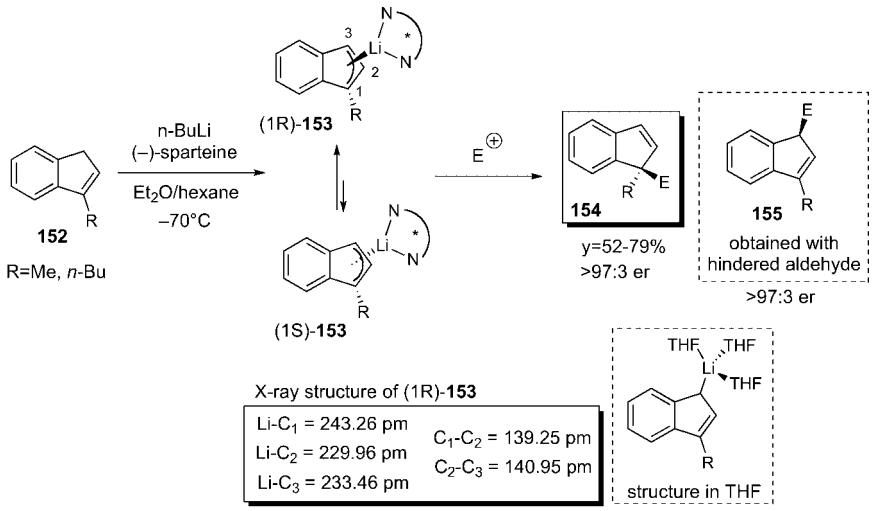


Scheme 6.69.



Scheme 6.70.

Hoppe reported the asymmetric deprotonation–alkylation study of substrates **149** and **152**. In both cases, X-ray structures were obtained for the intermediate lithiated complexes (*R*)-**150** and (1*R*)-**153**. The complex (*R*)-**150** crystallized, along with 3 other molecules contained in the unit cell. The calculation showed that the energy difference between (*R*)-**150** and (*S*)-**150** was very small (< 1 KJ mol^{-1}), suggesting that both epimeric complexes were in equilibrium (Scheme 6.70).[121] The subsequent alkylation reaction

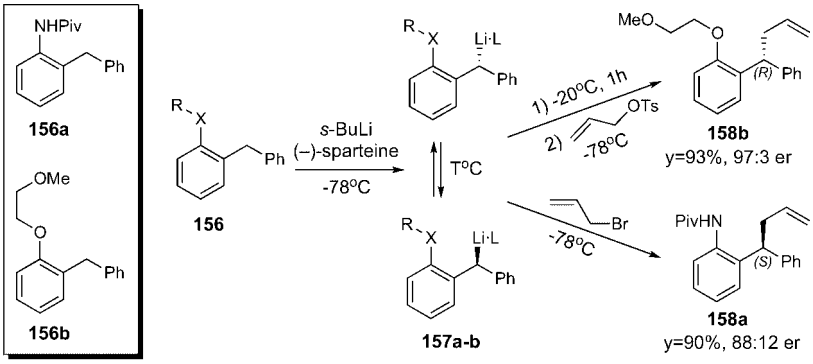


Scheme 6.71.

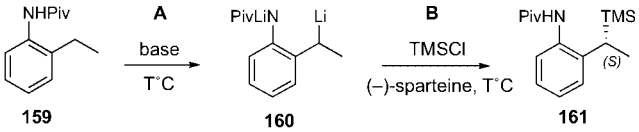
occurred with low enantioselectivity. Similarly, the deprotonation of 1-alkylindene derivatives **152** at –70 °C was followed by a selective crystallization that displaced the equilibrium towards (1*R*)-**153**. However, in this case, a very selective reaction took place with aldehydes and acylchlorides (Scheme 6.71).[122] Interestingly, the complex had a η^1 structure in THF, with the lithium atom coordinated with three solvent molecules. Under these reaction conditions, the adduct **154** was obtained as a racemic mixture of diastereomers.

2. With a Remote Coordinating Moiety

An intramolecular coordination that forms a cyclic complex is possible with remote functions such as ethers, carbamates or amides. Substrates **156a–b** are deprotonated with *s*-BuLi/(–)-sparteine, giving the allylated product in good yields and enantioselectivity (Scheme 6.72).[123] It is interesting to note that **156a** and **156b** lead to opposite enantiomers, but the same absolute configuration is obtained using either allyl bromide or allyl tosylate. The reaction conditions used are somewhat different. The ether **156b** needs two cycles of a warm–cool procedure to give high selectivity. If the whole process is performed at –78 °C, the product is obtained in only 72:28 er. On the other hand, in the case of amide **156a**, warming the reaction mixture does not improve the selectivity. The configurational stability has been tested with enantiomerically enriched trimethyltin derivatives. When the lithiated species was generated in the absence of (–)-sparteine, only a racemic product was isolated. However, in its presence, an identical level of enantiopurity in the final product was measured. In both cases, the (+)-sparteine surrogate was as efficient as (–)-sparteine (90:10 er for **156a** and 96:4 er for **156b**). Considering the experimental results available, the steric course for **156a** remains uncertain, although it is likely to be a dynamic thermodynamic resolution for **156b**.



Scheme 6.72.



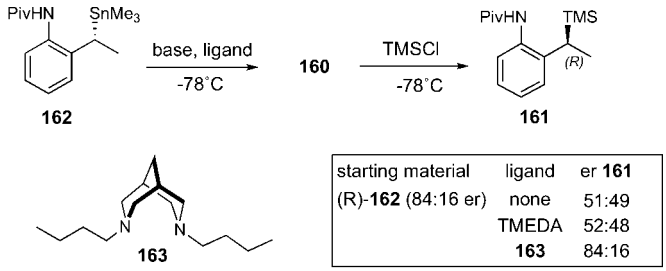
159 160 161

A	B	y (%)	er
s-BuLi, -25°C	**-78°C**, (–)-sparteine then TMSCl	88	56:44
s-BuLi, -25°C	**-78°C**, (–)-sparteine then TMSCl (**0.1 equiv**)	-	91:9
s-BuLi, -25°C	(–)-sparteine, **-25°C, 45 min.** then -78°C, TMSCl (**0.1 equiv**)	-	99:1
s-BuLi, -25°C	(–)-sparteine, **-25°C**, 45min then **-78°C**,TMSCl	63	91:9
s-BuLi, -25°C	(–)-sparteine, **-25°C**, 45min then TMSCl	95	93:7
s-BuLi, -25°C	(–)-sparteine, -25°C, 45 min. then -78°C, TMSCl (**2 x 0.45 equiv**)[a]	72	97:3

a- 2 cycles, a second warm-cool cycle is applied after the first addition of TMSCl

Scheme 6.73.

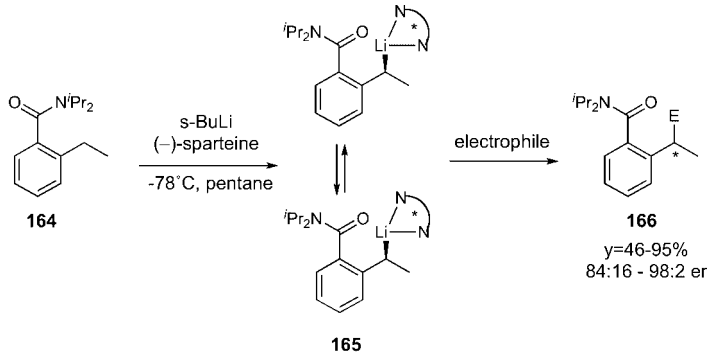
The nature of the coordinating functions is of major importance for the stereochemical behavior of the lithiated intermediate. Small changes in the substrate also induce significant behavior changes. Amide **159** differs from **156a** by the lateral group: it bears an ethyl group instead of a benzyl group. The lateral deprotonation occurs in the presence of (–)-sparteine at –78 °C but with very low selectivity (Scheme 6.73).[15a,16a,124] However, there are wide differences in reactivity between the diastereomeric complexes. Using 0.1 equivalent of electrophile, the product **161** is obtained with high selectivity. When (–)-sparteine is pre-mixed with **160** at –25 °C prior to adding the electrophile at –78 °C, an er of 99:1 is achieved at the beginning of the reaction. The best procedure uses a step that mixes (–)-sparteine and **160** at –25 °C over 45 minutes. Addition of the electrophile is then performed at –78 °C in two steps with two warm–cool cycles. These results suggest that the deprotonation is not involved in the stereochemically determining step. Organolithium **160**, formed as a racemic mixture, is complexed by the ligand, and equilibration between diastereomeric complexes is necessary before the addition of the electrophile. The configurational stability of **160** has also been checked by lithiodestannylation of enantiomerically enriched stannane **162** (*CST1*) (Scheme 6.74). When **160** is formed in the absence of a ligand or with TMEDA, **161** is obtained as a racemic mixture. However, the configuration is retained with dibutylbispidine **163** that is structurally similar to (–)-sparteine. The stereochemical pathway is then as follows: deprotonation at –25 °C produces a racemic mixture of **160** that becomes an epimeric mixture upon



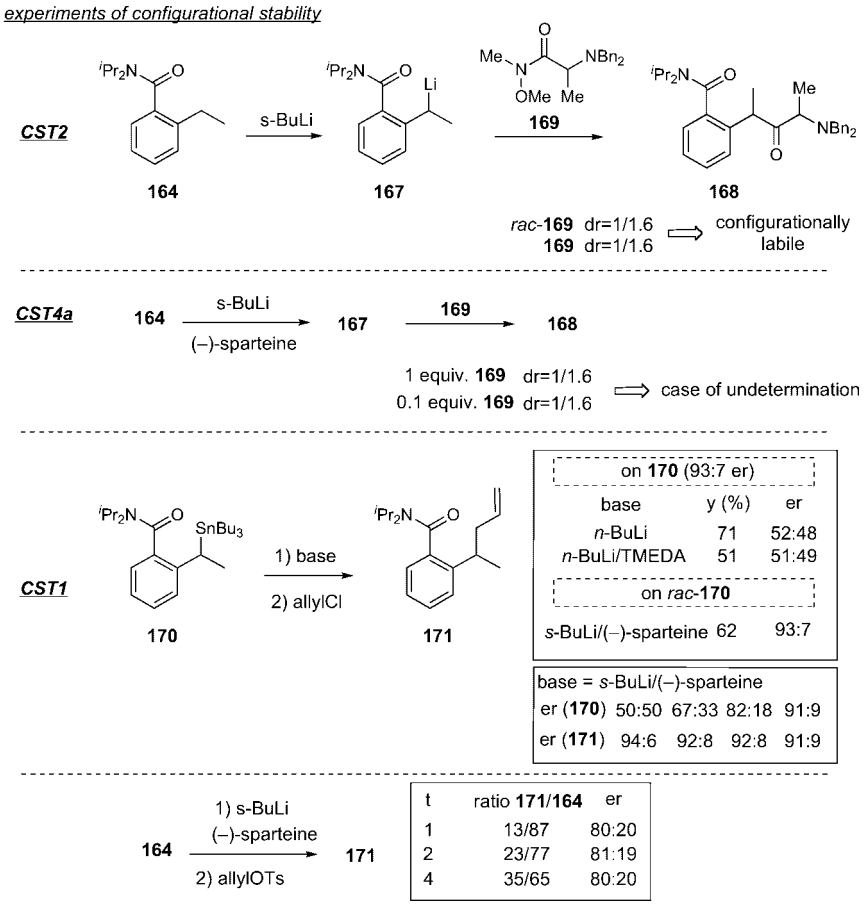
Scheme 6.74.

exposure to (–)-sparteine. After equilibration to the thermodynamic ratio, the temperature is cooled down to –78 °C, at which point the equilibrium is frozen. The asymmetric induction is obtained through a dynamic thermodynamic resolution. The configuration of the final product may be controlled by either the experimental procedure or the nature of the electrophile. From stannane **162**, both enantiomers of the same product can be reached by allowing the equilibration of epimeric complex **160** or not. Another possibility offered by this system is to choose the adequate electrophile; allyl tosylate and allyl bromide lead to opposite enantiomers in 91:9 and 86:14 er, respectively.

Despite the structural similarity with the previous substrates, amide **164** follows a different mechanistic pathway. For this substrate, the whole process is performed at –78 °C.[16a,125] The configuration of the final product is dependent upon the electrophile. For instance, allyl tosylate leads to (*S*)-**166** in 94:6 er while allyl chloride leads to (*R*)-**166** in 96:4 er. Testing configurational stability using Hoffmann's method, Beak's method, and enantiomerically enriched stannane has led to the conclusion that **165** or **167** are configurationally labile (Scheme 6.76). In the procedure used to obtain enantiomerically enriched products, the substrate is added to a mixture of the base and the ligand. However, identical results are obtained when (–)-sparteine is added



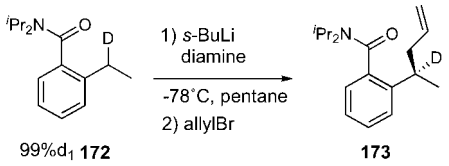
Scheme 6.75.



Scheme 6.76.

to racemic **167**, followed by the addition of the electrophile. The selectivity is established after the deprotonation step. The reactions performed with various enantiomerically enriched stannanes have all led to the identical enantiomerically enriched product **171**. Furthermore, the enantiomeric excess of the product is independent of the extent of conversion. The product is obtained through a dynamic kinetic resolution.

Although deprotonation does not determine the configuration, this does not mean that the hydrogen removal is not a selective process. Deprotonation of the racemic monodeuterated amide *rac*-**172**-d leads to the allylated product with 94% d content (Scheme 6.77). This corresponds to a KIE of 19. Using (–)-sparteine, 22% of deuterium is removed despite this high KIE value. If we suppose that this KIE value is identical for the reaction with (–)-sparteine, the facial selectivity for the deprotonation can be estimated



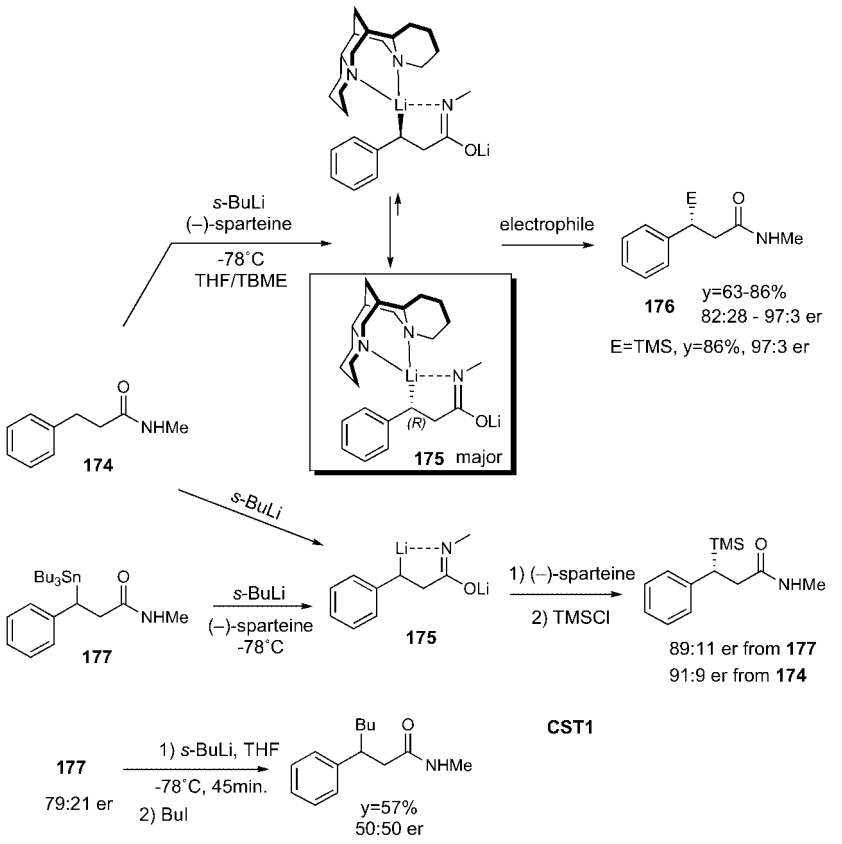
99%d_1 **172** **173**

	diamine	ratio **173**/**172**	%d	er
99%d_1	TMEDA	62/38	94	-
0% d	(–)-sparteine	90/10	-	74:26
99%d_1	(–)-sparteine	76/24	77	73:27

Scheme 6.77.

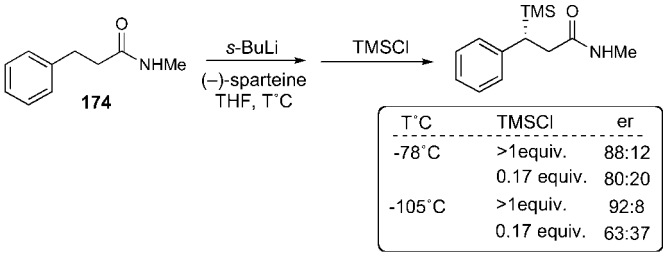
to be 96/4. The stereochemical pathway of the deprotonation–alkylation sequence for **164** follows a highly enantioselective deprotonation that leads to an enantiomerically enriched organolithium that racemizes because it is configurationally labile, and an asymmetric substitution by dynamic kinetic resolution.

In phenylpropiolic amide **174**, the coordinating moiety is located on the lateral chain. After deprotonation, a cyclic chelate **175** is obtained in which the lithium atom is coordinated with the nitrogen atom. The nitrogen–lithium coupling is visible in NMR studies.[15b] The stereochemically determining step is the electrophilic substitution. If **175** is first produced as a racemic mixture followed by addition of (–)-sparteine, a high level of selectivity is obtained (Scheme 6.78). On the other hand, starting from an enantiomerically enriched stannane that with *s*-BuLi produces an enantiomerically enriched uncomplexed intermediate **175**, a racemic alkylated product is obtained. This means that both complexed and uncomplexed lithiated **175** epimerize rapidly (*CST1*).[15b,126] However, the rate of this epimerization has to be compared with the rate of the electrophilic substitution. Using *CST4a*, the configurational stability is directly compared on the timescale of the reaction. The difference in ratio using either 1 equivalent or 0.17 equivalent of electrophile indicates that **175** is configurationally stable on the timescale of the reaction; *i.e.* that the electrophilic substitution is faster than epimerization (Scheme 6.79). It follows that the stereochemical information is transferred through a dynamic thermodynamic resolution. At the end of the reaction, the enantiomeric ratio obtained represents the population of both diastereomeric complexes. At the beginning of the reaction, the lower value of this ratio measured using a shortage of electrophile is explained by lower activation energy of the minor complex. The minor complex reacts faster than the major complex. The difference in activation energy of the two complexes is 0.24 and 0.64 Kcal mol^{-1} at –78 °C and –105 °C, respectively. These energy differences should be similar. It is suggested that competition between a dynamic thermodynamic resolution and a dynamic kinetic resolution occurs at

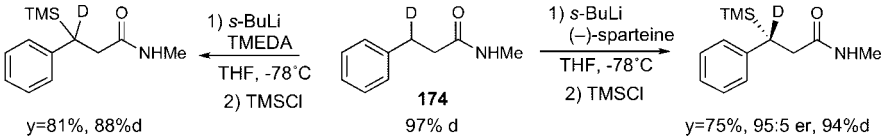


Scheme 6.78.

–78 °C because of the small difference between the equilibration rate and the electrophilic substitution. The formation of complex **175** during the deprotonation step is studied by using the monodeuterated substrate *rac*-**174**-d_1 (Scheme 6.80). The final products are formed in similar yields and retain the deuterium atom that indicates a strong kinetic isotopic effect. If an asym-



Scheme 6.79.



Scheme 6.80.

metric deprotonation were operative, one enantiomer of *rac*-**174**-d_1 would require removal of the deuterium atom. A lower yield would be expected because of the high KIE value. On the other hand, a non-selective deprotonation removes the β-hydrogen of both enantiomers at similar rates, leading to good yields of the product and high percent deuterium content. The whole deprotonation–alkylation process involves a non-selective deprotonation, followed by a selective electrophilic substitution that occurs in a dynamic thermodynamic resolution with the minor complex reacting faster. A certain degree of dynamic kinetic resolution is probably operative at –78 °C.

VI. CONCLUSIONS

The exact determination of the mechanistic pathway of an asymmetric deprotonation–alkylation process is a delicate task. However, it helps to understand the reaction conditions and the optimization of yields and selectivities. There are several techniques that have been developed for that purpose. The best ligand remains (–)-sparteine because of its wide range of use and efficiency. Furthermore, the discovery of (+)-sparteine surrogate has enhanced its importance in the field of asymmetric synthesis.

We chose to organize this chapter according to the nature of the atom in α position to the deprotonation site (oxygen, nitrogen, sulfur, phosphorus, carbon), and then the structure of the lithiated species (alkyl, aryl, alkenyl, alkynyl). However, an interesting comparison can be made with structurally similar lithiated species having a different α-heteroatom. Throughout this overview of the stereochemical implications in asymmetric deprotonation reactions, we encountered systems for which the nature of the α-heteroatom dramatically influences the behavior of the corresponding lithiated species. Those that are configurationally stable with oxygen are not obviously stable with nitrogen or sulfur atoms. In some cases, even small changes in the structures induce a totally different stereochemical outcome and mechanistic pathway. The extraordinary complexity of such systems should lead to extreme caution in the extrapolation of results.

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Chapter 7

Dynamic Resolutions of Chiral Organolithiums

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I. INTRODUCTION

Organolithiums are ubiquitous in synthetic chemistry. Almost all research groups use organolithiums at some point, particularly as bases or nucleophiles. The importance of organolithiums to synthetic chemistry has resulted in a number of reviews of these species,[1–11] plus recent reviews focusing on their enantioselective formation and transformations.[12–21] This review aims to focus on one aspect of organolithium chemistry, namely the ability of chiral organolithiums to undergo dynamic resolution. Previous reviews that describe chiral organolithiums have normally encompassed their structure, stereoselective formation (particularly by asymmetric deprotonation), the possibility of enantiomerization (leading to asymmetric substitution) and their stereoselective reaction. It is our aim in this review to pull together the theory and examples of asymmetric substitutions of chiral organolithiums, in which the organolithium can undergo dynamic equilibration. The focus will be on organolithiums that are attached to a stereogenic carbon center (Scheme 7.1 – the organolithiums in this review are drawn for simplicity as

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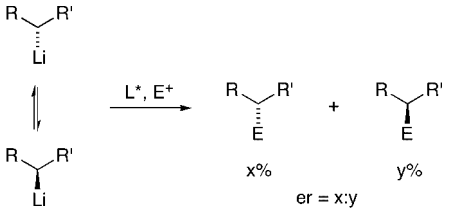
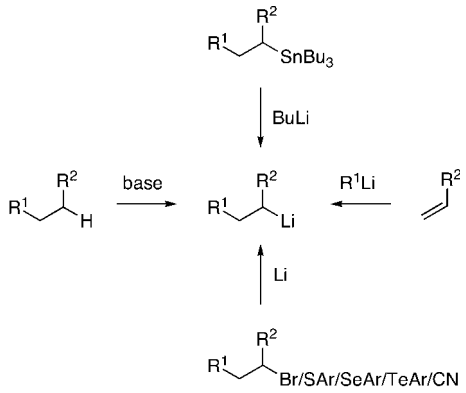
monomers, although often dimers or higher aggregates are present in solution). In this chemistry the enantiomer ratio (er = x:y in Scheme 7.1) (or diastereomeric ratio, dr) of the product after electrophilic quench is influenced by the rate of interconversion of the enantiomeric (or epimeric) organolithiums. Since 1990, there have been many important developments in this area that have led to a greater understanding of how to promote highly stereoselective reaction with chiral organolithiums. In particular, the use of non-covalently attached chiral ligands (L*) has provided, after electrophilic quench, highly enantiomerically enriched products using a range of substrates. This review will discuss first the theory behind dynamic resolutions of organolithiums and will then describe examples of different types of substrates, which we have categorized depending on the lack or type of heteroatom attached to the carbanion carbon. We will also describe examples in which another stereocentre is present in the molecule (covalently attached). We hope that, by outlining the principles of this chemistry and giving specific applications, the reader will gain an appreciation of the merits of this methodology and how to apply it to their own substrates.

Chiral organolithium compounds can be formed by a number of methods, including deprotonation, tin–lithium exchange, carbolithiation or reductive lithiation (Scheme 7.2). These methods complement each other and provide access to many different types of organolithium species. Enantiomerically enriched organolithiums can be prepared from enantiomerically enriched organostannanes, since tin–lithium exchange is stereoselective (proceeding with retention of configuration). Asymmetric deprotonation provides an alternative method, as long as the kinetic barrier to deprotonation is sufficiently low. By using tin–lithium exchange or asymmetric deprotonation, followed by electrophilic quench at low temperature (to avoid racemization of the intermediate organolithium), enantiomerically enriched products can be obtained. In contrast, reductive lithiation is non selective as it proceeds by single electron transfer (SET) and carbolithiation normally gives racemic (or epimeric) organolithiums. However, the formation of enantiomerically enriched products does not require the formation of an enantiomerically enriched organolithium, but can occur by an asymmetric substitution reaction. In contrast to asymmetric deprotonation (or stereospecific tin–lithium exchange), asymmetric substitution benefits from the enantiomerization (or



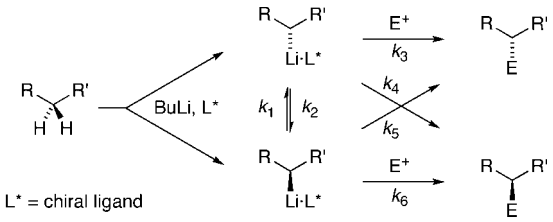
Scheme 7.1.



Scheme 7.2.

epimerization) of the intermediate organolithium. One of the advantages that asymmetric substitution has is that any method to prepare the racemic organolithium can be used. This avoids the need to prepare enantiomerically enriched tin compounds or to choose a substrate for which asymmetric deprotonation is possible. In addition, low temperatures can sometimes be avoided, as (for a dynamic resolution) it is necessary to promote interconversion of the organolithiums.

Asymmetric deprotonation and asymmetric substitution are significantly different from one another as methods for asymmetric induction (Scheme 7.3). In asymmetric deprotonation, the chiral base abstracts preferentially one enantiotopic proton, such that one chiral organolithium is formed predominantly. This organolithium species must be configurationally stable at the temperature used during its formation so as not to lose enantiopurity. At low temperatures (–78 °C or below) many organolithium species maintain their stereochemical integrity (i.e. the kinetic barrier to inversion is relatively high in comparison to reaction with the electrophile, such that $k_{3-6}>k_{1-2}$). Reaction with the electrophile must occur stereospecifically (with retention or inversion). In a resolution, however, a racemic organolithium is typically prepared and ideally the organolithium will be configurationally labile (k_1,k_2>0),



Scheme 7.3.

such that, under the influence of a chiral ligand, a dynamic resolution takes place, thereby allowing (in theory) up to 100% yield of the product. The diastereomeric organolithiums (in which the organolithium is complexed with a chiral ligand or bears more than one stereocentre) will have different thermodynamic stabilities and different reactivities. Either of these aspects can be exploited to promote asymmetric induction in the product.

II. RATES OF INTERCONVERSION OF CHIRAL ORGANOLITHIUMS

The rate of interconversion (between the two enantiomers) of the organolithium is critical to asymmetric substitution chemistry. Knowledge of the barrier to inversion of the chiral organolithium (or at least its relative rate in comparison with electrophilic quench) aids the understanding of how to promote asymmetric substitution. Despite this, there are as yet little quantitative data on the barriers to inversion of chiral organolithiums. Where such data are lacking it is possible to use the Hoffmann test as a qualitative guide to the relative configurational stability of the organolithium in comparison to the rate of reaction with an electrophile.[22,23] This involves comparing the ratio of diastereomers of the product obtained on reaction of the racemic organolithium with a chiral, racemic electrophile and with its enantioenriched form, and is discussed further in a separate Chapter in this volume.[24]

Some quantitative data for the barrier to inversion of several acyclic and cyclic chiral organolithiums are shown in Figures 7.1 and 7.2 respectively. These values were measured either by dynamic NMR studies (line shape analysis on coalescence of diastereotopic signals) or by using polarimetry or by determination of the enantiomer ratios after electrophilic quench on aging the enantioenriched organolithium for different times at different temperatures. The barriers depend on the solvent. In general, more polar solvents lower the barrier to inversion, although this is not always the case. Ethereal solvents, such as Et_2O, which are more polar than hydrocarbons such as hexane, could aid the formation of solvent-separated ion pairs by coordination to the lithium atom; this should promote enantiomerization, a process that is thought to involve the formation of the discreet (solvated) Li^+ cation, inversion of the free carbanion, and re-attachment of the cation.

Acyclic chiral benzylic organolithiums tend to have low barriers to inversion (typically 8–10 kcal/mol, Figure 7.1a–c).[25–28] The lithium atom can bridge the *ipso* and *ortho* positions of the benzene ring and this may facilitate enantiomerization. Acyclic alkyllithiums have slightly higher barriers to inversion (compare Figure 7.1b–c with g–j). The benzylic α-amino-organolithium (Figure 7.1a) has a slightly higher barrier in the presence of the additive *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) than in pure THF. This may be a result of a slightly higher barrier to the formation of the solvent-

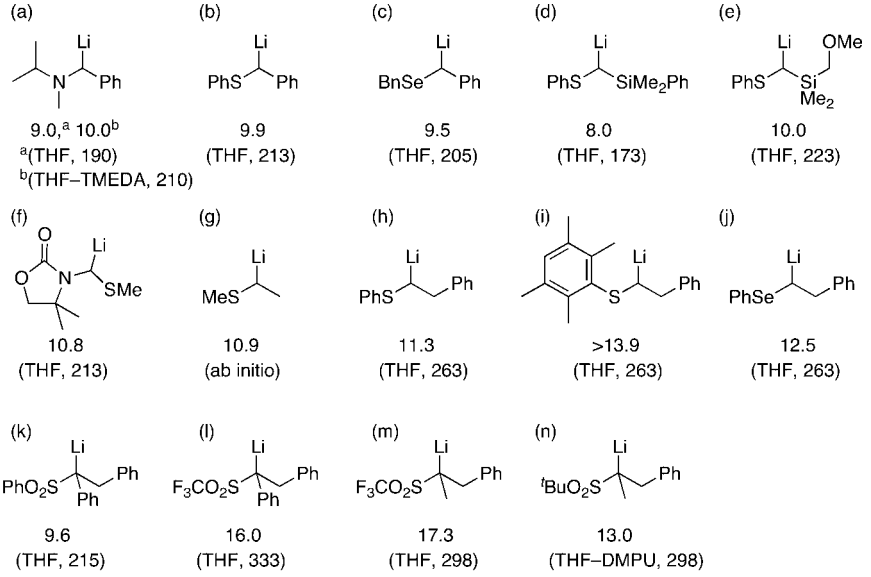


Figure 7.1. Inversion barriers of some acyclic chiral organolithiums, $\Delta G^{\ddagger}$ in kcal/mol (solvent, temperature in K).

separated ion pair when coordinated to TMEDA. Acyclic alkyllithiums with α-oxygen or α-amino substituents are thought to have even higher barriers to inversion, although as yet no quantitative data are available. Internal coordination can influence the barrier for interconversion, although it is not always obvious whether interconversion will become faster or slower. For the organolithium shown in Figure 7.1e, with α-thio and silyl groups, chelation with the internal methoxy group raises the barrier in comparison with the organolithium in Figure 7.1d.[29,30] The interconversion is believed to be unimolecular and there is little change in entropy of activation, suggesting little solvent effect. The barrier for the monomeric organolithium in Figure 7.1f has been determined to be about 11 kcal/mol.[31] Interestingly, the rate-determining step in the enantiomerization of α-thio and α-seleno organolithiums is not the transfer of the lithium atom from one face to the other, but rather the rotation around the S–R (or Se–R) bond. Thus, more bulky R substituents increase the barrier to inversion. This is illustrated by the higher barrier to inversion for the organolithium in Figure 7.1i compared to Figure 7.1g–h.[27,32] The same trend was observed for the selenides (Figure 7.1j).[33] It is likely that α-sulfonyl organolithiums (Figure 7.1k–n) exist as carbanions with the lithium atom more closely associated with the oxygen atoms of the sulfone. Despite this, the barrier to inversion can be relatively high, particularly when an electron-withdrawing group such as trifluoromethyl is attached to the sulfone.[34,35]

The barriers to inversion for several cyclic α-amino-organolithiums have been determined (Figure 7.2). These barriers are too high to measure using dynamic NMR methods, but can be determined by electrophilic quench and enantiomer ratio (er) measurement of the product, which is then assumed to correlate with the er of the organolithium. The α-amino-organolithiums bearing a further (oxygen) heteroatom (*N*-Boc or *N*-methoxyethyl, Figure 7.2a–b) have slightly lower barriers to inversion in comparison with the *N*-alkyl derivatives (Figure 7.2c).[36] The solution structures of these organolithiums have not been determined or are not well defined (mixtures of monomer and dimers).[37,38] It is possible that the heteroatom is involved in promoting a conducted tour type mechanism for enantiomerization.[39,40]

Although not apparent from these barriers, the entropy of activation for enantiomerization of *N*-Boc-2-lithiopyrrolidine (Figure 7.2a) is positive, which is contrary to most entropies for activation (which tend to be close to zero or slightly negative). This was explained by a requirement for the bulky *N*-Boc group to rotate during the enantiomerization, thereby displacing nearby solvent.

For efficient dynamic resolution, inversion of the organolithium is required in the presence of the chiral ligand and it would therefore be preferable to determine the kinetics for inversion in the presence of the ligand. The influence of the ligand on the rate of enantiomerization is important, but little study in this area has been done. Recently, the barrier to inversion for *N*-Boc-2-lithiopyrrolidine in the presence of the ligands TMEDA, (–)-sparteine **2** and *N,N′*-diisopropylbispidine was determined.[41] For the ligands TMEDA and (–)-sparteine (for which there is no resolution, so the equilibrium constant K=1), the barrier was reduced slightly (to 19 kcal/mol, Figure 7.2d–e) in comparison with no ligand ($\Delta G^{\ddagger}$ = 21 kcal/mol for this organolithium in Et_2O at –78 °C = 195 K). In contrast, the higher barrier to inversion of the organolithium in the presence of the bulky ligand *N,N′*-diisopropylbispidine ($\Delta G^{\ddagger}$ = 21 kcal/mol, Figure 7.2f) suggests that this ligand does not influence the rate significantly and therefore may not be as tightly bound to the organolithium. The barrier for inversion of the corresponding *N*-Boc-2-lithiopiperidine is lower than that of the pyrrolidine (compare Figure 7.2d and g; at 195 K, the piperidine has a barrier of approximately 17.7 kcal/mol).[42] The rate seems to be sensitive to the presence of TMEDA and this is particularly the case for dynamic resolution. With ligand **1** there is a thermodynamic preference for the (*S*)-enantiomer of *N*-Boc-2-lithiopiperidine (K=3.3) and the barrier to resolution using ligand **1** was found to be much higher in the absence of TMEDA (Figure 7.2h) than in its presence (Figure 7.2i, the value of 17.6 kcal/mol is, unusually, made up of a small enthalpy and a large negative entropy). Indeed, the resolution was found to be first order in TMEDA. There must, therefore, be slow interconversion of the organolithium·chiral ligand complexes in the absence of TMEDA, but coordination of TMEDA enhances the rate of this process. It is not known how general this phenomenon is for

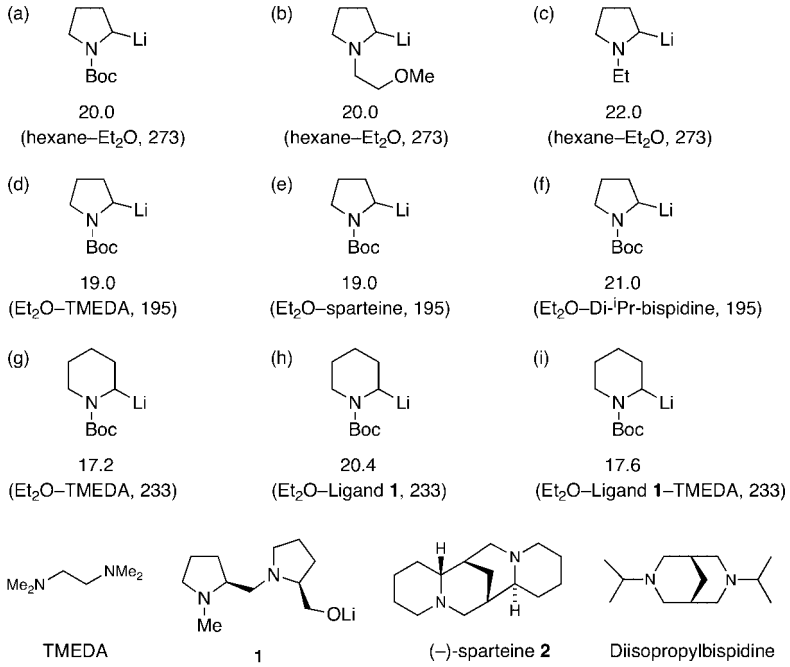


Figure 7.2. Inversion barriers of cyclic chiral organolithiums, $\Delta G^{\ddagger}$ in kcal/mol (solvent, temperature in K).

other chiral organolithiums, although a similar situation has recently been found with *N*-2,3,3-trimethylallyl-2-lithiopyrrolidine.[43]

The barriers to inversion of the organolithiums given above (Figures 7.1 and 7.2) are in the range 8–22 kcal/mol. To gain a feel for how fast the organolithium is interconverting, Figure 7.3 shows how the barrier $\Delta G^{\ddagger}$ is related to the half-life for racemization at four different temperatures (assuming a first order process). Hence, barriers of less than 10 kcal/mol equate to rapid racemization at –78 °C (195 K, $t_{1/2} < 0.1$ sec) and this may well be faster than the rate of reaction with the electrophile. Therefore such organolithiums could undergo dynamic resolution under kinetic control, but lower temperatures or electrophiles that react very rapidly would be required for resolution under thermodynamic control. In comparison, organolithiums with higher barriers to inversion clearly require higher temperatures to promote rapid racemization. For example, a barrier of 17 kcal/mol at 233 K (–40 °C) equates to a half-life, $t_{1/2} \approx 23$ min. Ideally, the barrier will not be too extreme to allow a study of both the kinetic and thermodynamic selectivity. For example, taking the organolithium to a temperature at which the half-life is a few minutes (or less) can be followed by slow addition of the electrophile to determine any kinetic selectivity. In a separate experiment, cooling the organolithium

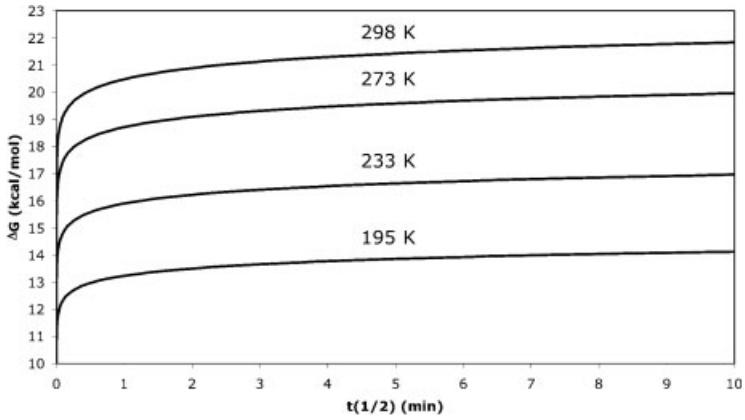


Figure 7.3. Relationship between $\Delta G^{\ddagger}$ and half-life of racemization.

by more than 40 K should freeze the enantiomerization and prevent further interconversion. On exhaustive electrophilic quench the enantiomer ratio of the product would then reflect the thermodynamic ratio of the organolithium complexes.

III. THEORY OF DYNAMIC RESOLUTIONS

Resolution of a chiral compound that is stereolabile (*i.e.* which can interconvert between its enantiomers) can be achieved in the presence of a chiral ligand. Three main types of resolution have been described: dynamic thermodynamic resolution (DTR), dynamic kinetic resolution (DKR) and crystallization-induced dynamic resolution (CIDR).[44] These processes will be discussed in relation to chiral organolithium species.

A. Dynamic Thermodynamic Resolution

Dynamic thermodynamic resolution is the term often used to describe dynamic resolution under thermodynamic control. In this scenario, interconversion of the stereoisomeric organolithium·chiral ligand complexes is slow relative to the rate of substitution ($k_{3\text{–}6}>k_{1\text{–}2}$) (Scheme 7.3).[16] Therefore, at complete conversion, the ratio of the organolithium stereoisomers determines the ratio of isomers of the product. For this assumption, the electrophilic quench must be stereospecific (complete retention or inversion of configuration at the carbanion centre). These reactions are typically best conducted by allowing equilibration of the stereoisomers and then cooling prior to electrophilic quench, such that the rate of interconversion is then

relatively slow (Figure 7.4). In this case, ΔG° determines the ratio of the two stereoisomeric organolithiums and hence the ratio of the two products after electrophilic quench.

For dynamic thermodynamic resolution, there must be interconversion of the enantiomers (or epimers) of the organolithium, and this is generally assumed to occur between the organolithium·chiral ligand complexes [*i.e.* (*R*)-RLi·L* $\rightleftharpoons$ (*S*)-RLi·L*], although it could take place between the uncomplexed organolithiums [*i.e.* (*R*)-RLi $\rightleftharpoons$ (*S*)-RLi] (or a complex with an achiral ligand such as TMEDA or the solvent).

Of course there can be a kinetic component within a dynamic thermodynamic resolution, such that one diastereomeric organolithium·chiral ligand complex may react faster than the other. A difference in the er of the products with changing stoichiometry of the electrophile can provide evidence for dynamic resolution under thermodynamic control (as opposed to under kinetic control, see Section III.B). Therefore, care should be taken to consume all of the organolithium (at a temperature where there is no interconversion relative to the rate of electrophilic quench) for a true resolution under thermodynamic control. Partial electrophilic quench could result in a different er of the product, and this could favour either enantiomer, depending on the relative rates of reaction. If the diastereomeric complex that is thermodynamically more stable (arbitrarily assigned as (*S*)-RLi·L*) reacts faster (Figure 7.4a), then it may be beneficial (in terms of the er of the product) not to run the reaction to full completion, or to carry out further warm–cool protocol(s) part way through addition of the electrophile in order to re-establish the equilibrium in favour of the faster reacting complex (which is being depleted). If the less stable complex reacts faster (Figure 7.4b), then re-equilibration is likely to be detrimental. In this latter case, low conversion leads to products with opposite selectivity.

In either case, for high levels of enantioselectivity, a large energy difference ΔG° is required (ΔG° >1 kcal/mol for a ratio of >9:1 at 233 K). The solvent may influence the ratio of the complexes and their relative rates of reaction with the electrophile, so it is important to screen a selection of solvents.

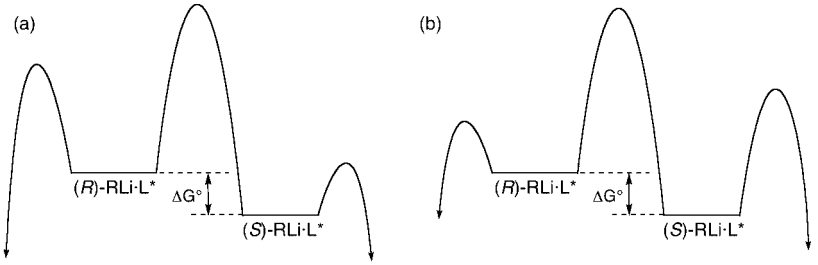


Figure 7.4. Energy diagrams for reactions of diastereomeric organolithiums under dynamic thermodynamic resolution.

B. Dynamic Kinetic Resolution

In contrast to dynamic thermodynamic resolutions, when the rate of interconversion is fast relative to the rate of substitution, then a dynamic kinetic resolution can take place and the product ratio is determined by the difference in the activation energies for the substitution reactions ($\Delta\Delta G^{\ddagger}$) (Figure 7.5).[45] In this case the ratio of the stereoisomeric organolithiums can be inconsequential in relation to the enantiomer ratio of the product, as long as the relative rate of reaction of the stereoisomers is significantly large (Curtin–Hammett kinetics).[46] The diagram shown in Figure 7.5a represents faster reaction of the less stable stereoisomer ($\Delta G_R^{\ddagger} < \Delta G_S^{\ddagger}$), but of course ΔG° could be close to zero or the major stereoisomer could have the lower barrier to reaction (Figure 7.5b). The rates of product formation depend on the terms k_R[(*R*)-RLi·L*] and k_S[(*S*)-RLi·L*]. Thus, for the less stable diastereomeric complex [(*R*)-RLi·L* in this example] to provide the major product, then k_R[(*R*)-RLi·L*] must be greater than k_S[(*S*)-RLi·L*].

In the same way as dynamic resolution under thermodynamic control, the electrophilic quench in a dynamic kinetic resolution must be stereospecific, otherwise mixtures of enantiomers are likely to be obtained. In conventional kinetic resolution (no dynamic equilibration), the maximum yield is 50% for high levels of selectivity. In addition, the selectivity is likely to diminish as the reaction progresses, since there is less of the more reactive stereoisomer. However, dynamic equilibration allows re-establishment of the thermodynamic ratio of the stereoisomers, so dynamic kinetic resolution does not suffer from decay in the enantiomer ratio of the product with increasing conversion. It follows from this that the relative rate of reaction of the stereoisomers does not need to be very large to nevertheless allow a significant enantiomer ratio of the product.

Fortunately, the majority of electrophilic substitutions of chiral organolithiums occur by a polar mechanism and are stereospecific. Reaction with retention or inversion of configuration at the carbanion centre can be evaluated if the configuration of the organolithium is known. There are, however, examples of polar reactions that proceed by a mixture of retention and inversion.[47] If the electrophile removes an electron (single electron transfer, SET) from the organolithium then the subsequent carbon radical reacts stereorandomly. The stereochemistry of electrophilic quench of chiral organolithiums is discussed in a separate Chapter in this Volume.[48] Clearly, when carrying out a dynamic resolution reaction, it is helpful to know whether the organolithium is configurationally stable (and if not, then its rates or at least relative rates of enantiomerization/epimerization and electrophilic substitution) and the steric course of the reaction with the electrophile (retention, inversion, racemization).

Classical kinetic resolution is defined in terms of a resolution as a result of different rates of reaction of the enantiomers with a chiral agent (such as a re-

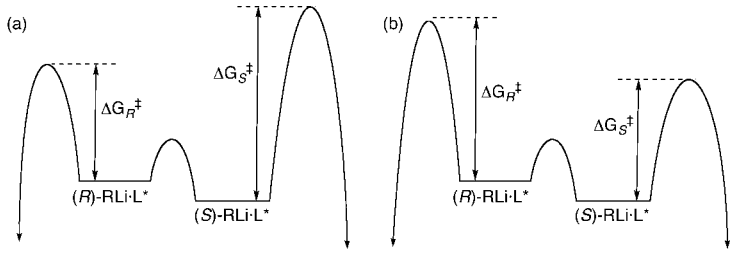


Figure 7.5. Energy diagrams for reactions of diastereomeric organolithiums under dynamic kinetic resolution.

agent, catalyst or solvent). In other words, deracemization occurs in conjunction with an irreversible reaction. This typically results in recovery (in enantioenriched form) of the less reactive starting material. With organolithiums the starting material is not recovered, the organolithiums can interconvert (the dynamic process) and may be resolved by means of the faster reaction of one of the diastereomeric complexes. This is strictly a synthetic reaction and so this process is sometimes referred to as dynamic kinetic asymmetric transformation (DYKAT), rather than as a resolution, particularly when additional stereogenic elements are present in the molecule (see Section IV.E).

C. Crystallization-Induced Dynamic Resolution

A third type of resolution of chiral organolithiums is crystallization-induced dynamic resolution (CIDR), sometimes called asymmetric transformation of the second kind. Enantioenriched crystals can form when interconversion of the diastereomeric organolithiums occurs on the timescale of the crystallization. Of course this requires that the organolithium can crystallize (for example as its complex with a chiral ligand) and that the crystals of one diastereomeric complex are favored. This depends on the relative thermodynamic stability of the crystal lattices of the diastereomers. To achieve effective CIDR it is often necessary to perform a careful study of the concentration, solvent, temperature, and the chiral ligand. With chiral organolithium compounds, addition of a non-polar solvent such as hexane or cyclohexane can sometimes be beneficial to promote crystallization.

As organolithium compounds are typically reactive species, care needs to be taken to ensure the exclusion of moisture and air. The crystals are not commonly isolated but are treated directly with the electrophile. This then minimizes decomposition or interconversion.

In many senses, crystallization-induced dynamic resolution is similar to dynamic resolution under thermodynamic control. Both rely on interconversion of the diastereomeric complexes and the thermodynamic preference for one of these complexes either in the solid or solution phase.

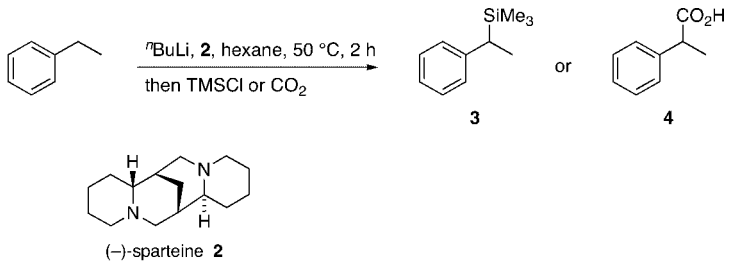
IV. Examples of Dynamic Resolutions

A. Benzylic and Allylic Carbanions

This section describes the formation and reaction of chiral benzyllithium or allyllithium compounds in which no heteroatom is attached to the carbanion carbon. These organolithiums are generally configurationally labile even at low temperature. The earliest and simplest example is the organolithium derived from deprotonation of ethylbenzene, reported by Nozaki and co-workers in 1971.[49] Treatment of ethylbenzene with *n*-BuLi and the chiral ligand (–)-sparteine **2** gave, after electrophilic quench with trimethylsilyl chloride (TMSCl) or CO_2, the products **3** or **4** as a mixture together with products from lithiation of the benzene ring (Scheme 7.4). These showed optical rotation and, by calculating the proportion of the acid **4** (arising from α-lithiation) in the mixture, it was estimated that the optical yield was about 30% (*i.e.* er ~65:35 (*R*):(*S*). The selectivity was suggested to arise from dynamic kinetic resolution, although this has not been confirmed.

A similar organolithium, derived from addition of BuLi to styrene in the presence of (–)-sparteine also gave low enantioselectivity after electrophilic quench with CO_2, probably from the faster reaction of one of the diastereomeric complexes.[50] Some improvement to the er was obtained using 2-methoxystyrene, and this may be a result of improved dynamic resolution or enantioselective addition of BuLi to give an organolithium with enhanced configurational stability.

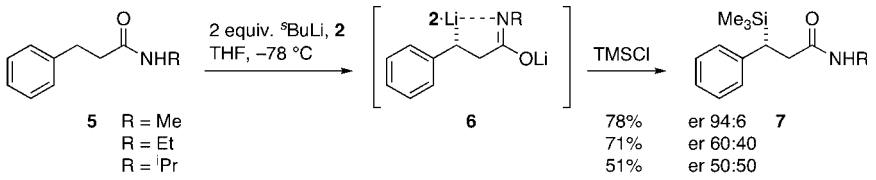
The first examples of high enantioselectivities in the asymmetric substitution of benzylic organolithiums were reported by Beak and co-workers. For example, double proton abstraction of the amide **5** gave the organolithium **6** in the presence of the chiral ligand (–)-sparteine **2** (Scheme 7.5).[51–53] The organolithium **6**, R=Me was quenched with various electrophiles, such as TMSCl, to give the amide **7**, R=Me with high selectivity. However, bulkier R groups (R=Et or ^{i}Pr) resulted in low or no selectivity in the product **7**, and this can be explained by steric interactions of the larger R groups that prevent coordination of (–)-sparteine (**2**) to the intermediate organolithium



Scheme 7.4.

6. Some helpful mechanistic studies were carried out.[52] The yield and enantioselectivity was not altered using the amide **5**, R=Me with one deuterium atom at the benzylic position (racemic). This rules out an asymmetric deprotonation due to the lack of any isotope effect. The presence of coupling between ^{6}Li and ^{15}N in the ^{6}Li NMR spectrum (and in the ^{15}N NMR spectrum) showed that the nitrogen atom of the lithiated amide interacts with the organolithium (as represented by structure **6**, although aggregates are likely present in solution). High levels of enantioselectivity were obtained when the organolithium was generated from the racemic stannane using BuLi·**2**. Therefore the organolithium is configurationally labile at –78 °C. To distinguish between a dynamic resolution under thermodynamic or under kinetic control, the authors investigated the configurational stability on the timescale of the reaction with the electrophile. To do this, they simply used a substoichiometric amount of the electrophile. If a different er of the product is observed in comparison with excess electrophile then this demonstrates that there is configurational stability on the timescale of the electrophilic quench. In a dynamic thermodynamic resolution, one diastereomeric complex may react faster than the other, so the er may be different if the organolithium is quenched only partially. The reverse is not necessarily true: the same er could result from a dynamic kinetic resolution (fast equilibration in comparison to electrophilic trapping) or by a dynamic thermodynamic resolution in which there is no difference in rate of reaction between the diastereomeric complexes. For organolithium **6**, R=Me, it was found that using 0.17 equiv. of TMSCl gave a slightly lower enantioselectivity (product **7**, er 80:20, in comparison with a control experiment that gave er 88:12). This implies that the mechanism follows a dynamic thermodynamic resolution and that the minor diastereomeric complex of **6**·**2** reacts slightly faster than the major complex. By cooling the mixture to –105 °C, addition of 0.17 equiv. TMSCl gave **7**, er 63:37, whereas excess TMSCl gave **7**, er 92:8. This suggests that the organolithium is configurationally stable at –105 °C and that there is (not surprisingly) a slightly larger difference in activation energy for reaction of the diastereomeric complexes at the lower temperature.

The related organolithiums **9** and **11**, derived by double deprotonation of the amides **8**[54] and **10**[55–57] respectively (Figure 7.6), were found to undergo similar asymmetric substitution chemistry with (–)-sparteine (**2**) as the chiral ligand. The benzylic organolithium **9** is configurationally unstable at



Scheme 7.5.

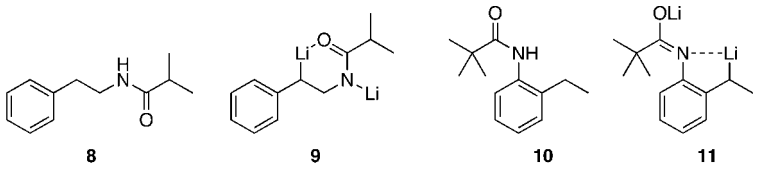
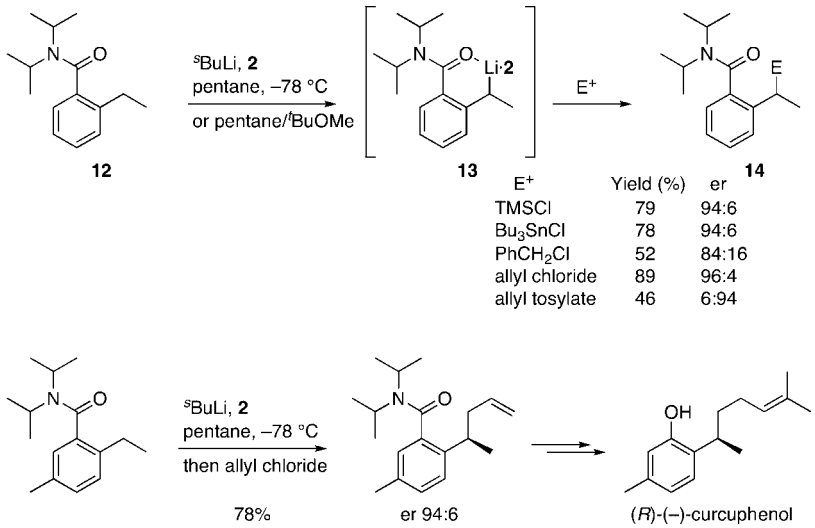


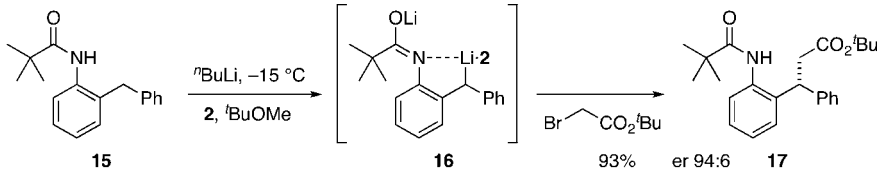
Figure 7.6.

–78 °C, although the organolithium **11** required warming to –25 °C to set up the thermodynamic ratio of the (–)-sparteine complexes. In both these cases, the mechanism follows dynamic resolution under thermodynamic control. It was found that the major diastereomeric (–)-sparteine complex of the organolithium **11** has a lower activation energy on reaction with TMSCl, so it was possible to enhance the er by iterative warm–cool–partial electrophilic quench cycles.[57]

In contrast, the (–)-sparteine complexed organolithium **13**, derived from deprotonation of the amide **12**, reacts with electrophiles by a dynamic resolution under kinetic control.[57] A selection of examples is given in Scheme 7.6.[58–61] Enantiomer ratios were high, particularly using chlorides (rather than other halides) as the electrophile. Remarkably, the opposite major enantiomer was formed using the corresponding alkyl or allyl tosylates. The organolithium **13** is configurationally unstable at –78 °C, as judged by the fact that the same results are obtained if (–)-sparteine is added to the racemic organolithium. Configurational instability of the organolithium was further confirmed by the formation of racemic products when starting with the enantioenriched organostannane and performing tin–lithium exchange [in the absence of (–)-spar-



Scheme 7.6.

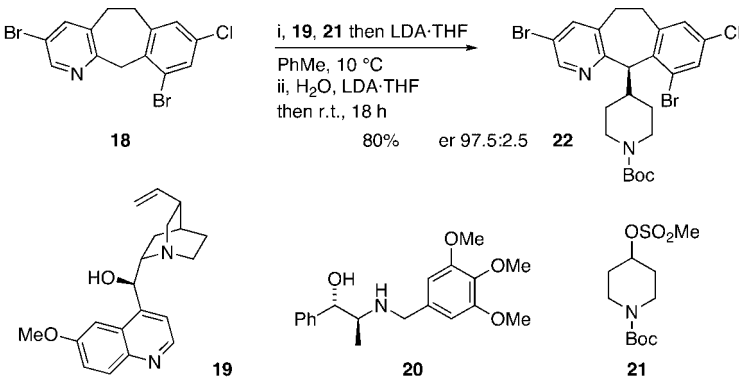


Scheme 7.7.

teine] then electrophilic quench. Interestingly, the initial proton abstraction is enantioselective as determined by using racemic monodeuterated **12**, in which a significant loss of deuterium occurs at the benzylic position despite a large deuterium isotope effect. Therefore, asymmetric deprotonation is followed by racemization of the organolithium **13**. The er of the product (using allyl tosylate or allyl chloride as the electrophile) was independent of the degree of conversion. This result is consistent with a rate of equilibration of the diastereomeric complexes that is faster than electrophilic quench and hence a dynamic kinetic resolution. This chemistry, with the 5-methyl substituted derivative, has been used in a synthesis of (*R*)-curcuphenol (Scheme 7.6), whereas use of a secondary (instead of tertiary) benzamide gave rise to the opposite enantiomer and hence a synthesis of (*S*)-curcuphenol.[62]

Various substituted diarylmethanes have been screened for their asymmetric lithiation–substitution chemistry. A heteroatom in the *ortho* position is desirable, with high selectivities possible using an *ortho*-methoxyethoxy group.[63–65] The example in Scheme 7.7, using 2-benzyl-*N*-pivaloylaniline, is best carried out in the solvent *tert*-butyl methyl ether.[66] Original work in Et_2O gave slightly lower selectivities.[67] Deprotonation of the substrate **15** with *n*-BuLi in *t*-BuOMe can be carried out at various temperatures, although equilibration to the thermodynamic ratio is best achieved at about –15 °C.[68] The mixture can be quenched at this temperature or after cooling. When the concentration was increased from 0.05 M to 0.2 M, the enantioselectivity increased (**17**, yield 85%, er 98:2). A precipitate was observed at the higher concentration and the improved selectivity was ascribed to a crystallization-induced dynamic resolution. The crystallization enhances the inherent thermodynamic preference for one of the diastereomeric organolithium complexes **16**. The product **17** was treated with acid to promote cyclization to the lactam (with loss of the pivaloyl group), which was converted to several tetrahydroquinolines.[68]

Dynamic resolutions of other lithiated diarylmethanes or arylpyridylmethanes using (–)-sparteine are known.[69,70] Variable but sometimes high enantioselectivities have been reported in these reactions and in the related deracemizations of substituted derivatives by protonation of the intermediate organolithium species. In fact, one of the earliest examples of (low) asymmetric induction using a chiral organolithium involved a laterally lithiated pyridine with (–)-sparteine as the chiral ligand.[71] However, (–)-sparte-

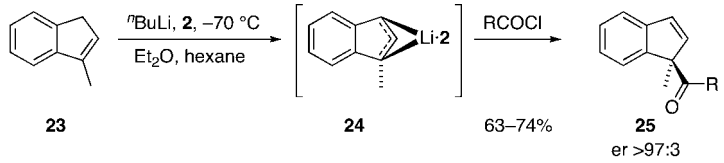


Scheme 7.8.

ine gave no enantioselectivity in the resolution of the organolithium derived from the tricyclic compound **18**, so a range of other ligands was screened (Scheme 7.8).[72] The best results were obtained using quinine (**19**) or the ligand **20** and by addition of one equivalent of water (and an extra equivalent of LDA). The reaction was conducted by adding one equivalent of LDA to the mixture of the substrate **18**, electrophile **21** and ligand **19** (which was deprotonated), followed by addition of water then two equivalents of LDA. The product **22** was isolated with high enantioselectivity (the reaction was scaled up to 33 kg batch size) and was used in the synthesis of a farnesyl protein transferase inhibitor called lonafarnib. The mechanism for the asymmetric induction has not been determined.

Unsymmetrical allyllithium compounds are chiral, with the lithium atom either located at one end or bridging the three-carbon unit.[73] Diastereomeric complexes with chiral ligands could lead to asymmetric substitution. This has been illustrated for the organolithium **24**, formed by treatment of 1-methylindene (**23**) with *n*-BuLi and (–)-sparteine (**2**) in non-polar solvent (Scheme 7.9).[74] On warming, the organolithium crystallizes to essentially a single diastereomeric complex (configuration assigned from the single crystal X-ray analysis of the 1-butylindenyllithium·(–)-sparteine adduct). Reaction with an acid chloride then proceeds with retention of configuration to give the products **25**. An aldehyde can be used as the electrophile after addition of $Ti(O^iPr)_4$, although α-branched aldehydes tended to react at the 3-position for steric reasons. The asymmetric induction arises from a crystallization-induced dynamic resolution, in which there is a preference for the diastereomeric organolithium·(–)-sparteine complex **24**.

Symmetrical allyllithium compounds become chiral when complexed to a chiral ligand. Although the (–)-sparteine complex of lithiated 1,3-diphenylpropene is chiral, its reaction with electrophiles occurred with low levels of enantioselectivity.[75] Very good results, however have been obtained with α-heteroatom substituted allyllithiums, as discussed in the following sections.



Scheme 7.9.

B. Carbanions with an α-Oxygen Atom

Significant advances in the area of chiral organolithium chemistry have been made using α-oxygenated alkyllithium compounds. They can be prepared in high yield by tin–lithium exchange from chiral α-alkoxy-organostannanes. Still and Sreekumar showed that these organolithium compounds (Figure 7.7) are configurationally stable at low temperature and that overall retention of configuration from the stannane to the product is obtained.[76] Although it was not proved, it is likely that the tin–lithium exchange and the subsequent electrophilic quench both occur with retention of configuration. The assumption is a general one and is supported by many observations using organostannanes of known relative or absolute configuration.[77,78]

An important discovery in chiral alkyllithium chemistry was made by Hoppe and co-workers.[79] It was found that treatment of certain *O*-alkyl carbamates with the chiral base *sec*-BuLi·(–)-sparteine allows asymmetric deprotonation α to the oxygen atom with high selectivity (Figure 7.7).[79,80]

Unlike lithiated *O*-alkyl carbamates, Hoppe and co-workers found that diastereomeric organolithium complexes derived from *O*-allyl carbamates such as (*S*)- and (*R*)-**27·2** are configurationally labile and interconvert at –70 °C in pentane solution.[81] Addition of cyclohexane can induce an asymmetric transformation of the second kind by preferential crystallization of one epimer. Treatment of carbamate **26** with *n*-BuLi·**2** in pentane/cyclohexane (7:1.5) at –70 °C leads to crystallization of (*S*)-**27·2**, which on rapid addition of pre-cooled titanium tetraisopropoxide affords enantiomerically enriched titanium compound (*R*)-**28** with stereoinversion (Scheme 7.10).[82,83] The carbamate (*R*)-**28** is configurationally stable below –30 °C and adds to pentanal to give enantiomerically enriched product (*Z*)-*anti*-**29** as a single diastereomer. The methodology was applied successfully to various substituted starting carbamates followed by quenching with a range of electrophiles. The

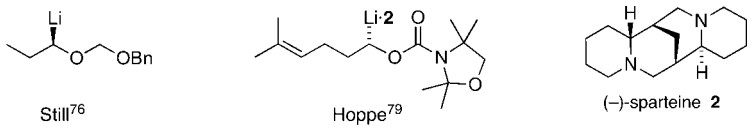
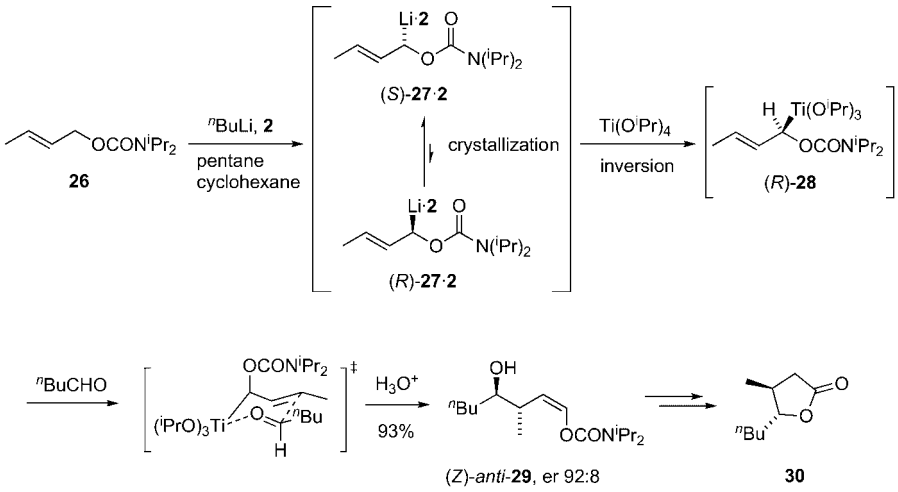


Figure 7.7.



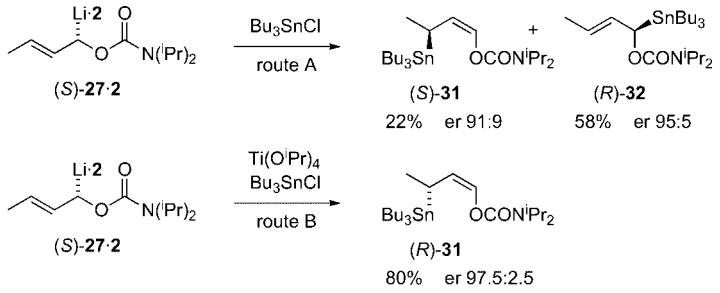
Scheme 7.10.

product (*Z*)-*anti*-**29** was elaborated by conversion to the γ-lactone **30**, also known as (+)-quercus lactone A, found in oak wood.[82]

As an extension to the above protocol, direct stannylation of the lithiated carbamate (*S*)-**27·2** gave a mixture of allylstannane (*S*)-**31** and its isomer (*R*)-**32** (route A, Scheme 7.11), while treatment with titanium isopropoxide (to bring about transmetallation) prior to quenching with tributyltin chloride yielded allylstannane (*R*)-**31** as the sole product (route B, Scheme 7.11).[84] This result suggests that the stannylation reaction follows an *anti*-$S_{E'}$ path with complete 1,3-chirality transfer. The applicability of the methodology was illustrated by treating stannanes (*R*)-**32** and (*R*)-**31** with a range of aldehydes and ketones in the presence of titanium tetrachloride to provide enantioenriched homoaldol products in good yields.

In follow-up papers,[85–87] Hoppe and co-workers explicitly commented about the configurational stability of various lithiated complexes of carbamates. This was elucidated by performing in-situ electrophilic trapping experiments and by exposing to prolonged reaction times. The equilibration of epimeric lithiated *O*-indenyl carbamate·(–)-sparteine complexes was studied by ^{1}H NMR spectroscopy, and by semiempirical quantum-chemical calculations.[86]

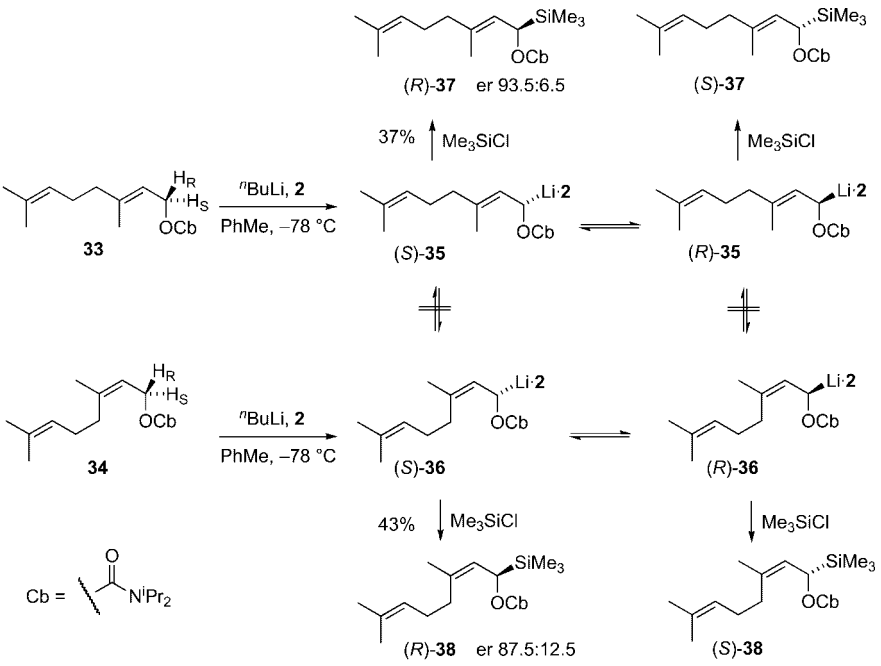
It was found that increased substitution of the allylic carbamates enhances the configurational stability of the chiral organolithium. For example, enantioselective deprotonation of geranyl and neryl carbamates **33** and **34** using *n*-BuLi·(–)-sparteine at –78 °C in toluene in the presence of excess TMSCl gave carbamates **37** ((*R*):(*S*) 93.5:6.5) and **38** ((*R*):(*S*) 87.5:12.5) respectively (Scheme 7.12).[88] The choice of solvent is critical as pentane was found to give lower enantioselectivities. Quenching the lithiated epimeric pairs (*S*)- and



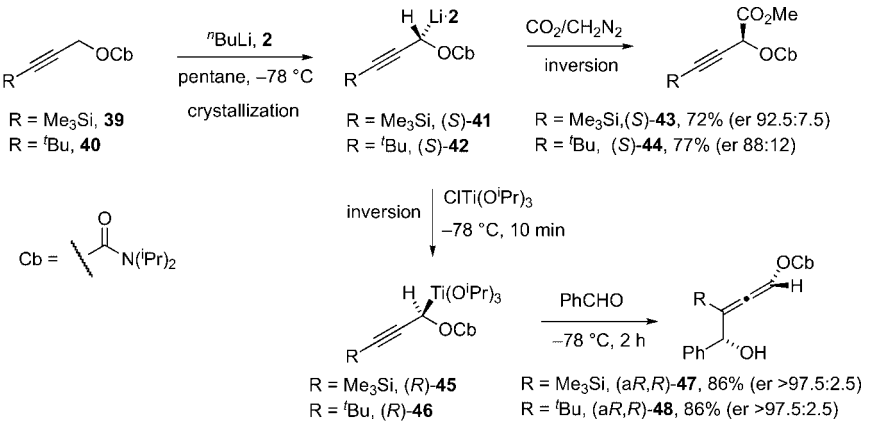
Scheme 7.11.

(*R*)-**35** and (*S*)- and (*R*)-**36** with TMSCl after initial deprotonation resulted in higher yields but lower enantiomeric ratios, suggesting that the organolithiums are configurationally labile in toluene at –78 °C, although inversion is slow ($t_{1/2}$ > 1 h). No isomerisation of the double bond in the lithiated species at –78 °C in toluene, pentane or diethyl ether was observed.

In comparison, lithiated alkynyl carbamates are configurationally unstable at –78 °C in pentane (Scheme 7.13).[89] Treatment of carbamates **39** and **40** with *n*-BuLi·(–)-sparteine generated lithiated carbamates (*S*)-**41** and (*S*)-**42** after selective crystallization-induced dynamic resolution (CIDR). Elec-



Scheme 7.12.



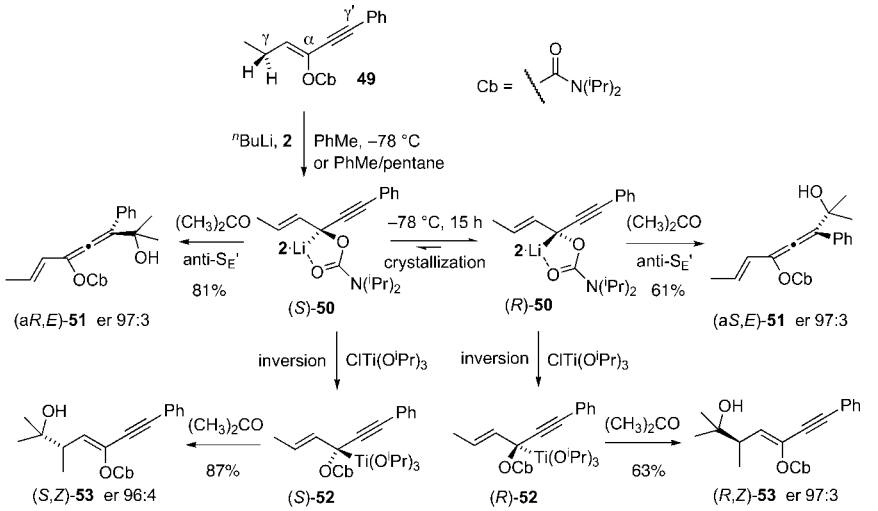
Scheme 7.13.

trophilic quench with dry carbon dioxide/diazomethane gave methyl esters **43** and **44** with inversion. Transmetalation of the organolithiums (*S*)-**41** and (*S*)-**42** using a titanium salt, followed by addition of benzaldehyde led to the highly enantioenriched allenes **47** and **48**.

Highly enantioselective γ-deprotonation of enyne carbamate **49** was achieved using *n*-BuLi·(–)-sparteine in toluene at –78 °C for 30 sec, leading to the kinetically favoured lithiated carbamate (*S*)-**50** (Scheme 7.14).[90] Rapid quenching with acetone occurred at the γ'-position to yield the enantioenriched allene (a*R*,*E*)-**51**. When the reaction was carried out in pentane/toluene at –78 °C for 15 h, it resulted in selective crystallization-induced equilibration to afford the thermodynamically favoured lithiated species (*R*)-**50**. On treatment with acetone the allene (a*S*,*E*)-**51** was obtained in reasonable yield and high enantioselectivity (er 97:3). Lithiated carbamates (*S*)- and (*R*)-**50** underwent transmetallation with $ClTi(O^iPr)_3$ via stereoinversion, followed by acetone quench to give homoaldol products (*S*,*Z*)-**53** and (*R*,*Z*)-**53** respectively with 1,3-chirality transfer.

Nakai and co-workers found that the α-lithiation of methyl benzyl ether (**54**), phthalan (**58**) and isochroman (**59**) using *tert*-BuLi and the chiral ligand **55** in hexane at –78 °C, followed by electrophilic substitution, resulted in moderate to high enantioselectivity (Scheme 7.15).[91–93] Use of diethyl ether or tetrahydrofuran as solvent, *sec*-BuLi as a base and an alkyl halide as electrophile led to a decrease in enantioselectivity as compared to hexane, *tert*-BuLi and carbonyl electrophiles. Chiral bis(oxazoline) ligand **55** proved to be superior to (–)-sparteine for these substrates.

Detailed experimental investigations suggested that the post-lithiation event is the enantio-determining step and lithiated species **56**, **60** and **61** are configurationally labile at –78 °C. High enantioselectivities were proposed to be chiefly due to a dynamic thermodynamic resolution where the rate of

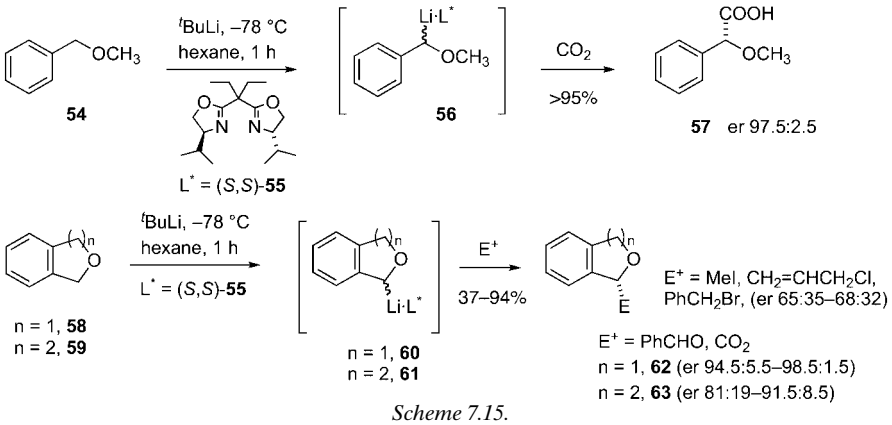


Scheme 7.14.

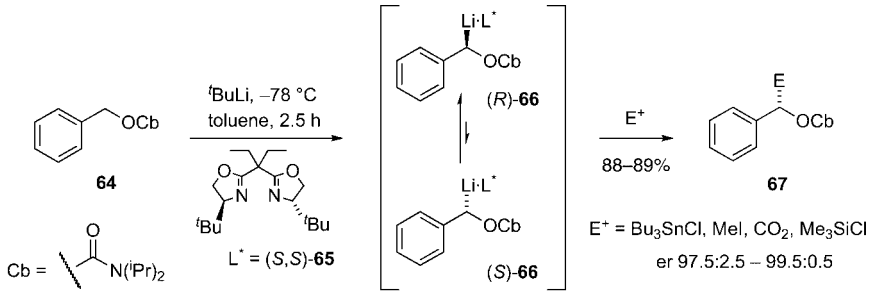
equilibration between the corresponding lithiated diastereomeric complexes is much slower than the rate of electrophilic substitution.

Lete and co-workers described a convenient approach for the synthesis of enantioenriched *syn*-*β*-amino-alcohol derivatives by asymmetric lithiation of an *O*-benzyl carbamate using *sec*-BuLi·(–)-sparteine followed by imine addition in modest to good enantiomeric ratios.[94] The high diastereoselectivity (dr >95:5) was proposed to be due to the stabilization incurred by coordination of lithium to the carbonyl oxygen, while the origin of the enantioselectivity was ascribed to a dynamic thermodynamic resolution.

Hoppe and co-workers reported that lithiated *O*-benzyl carbamates such as (*R*)- and (*S*)-**66** can equilibrate to give preferentially one diastereoiso-



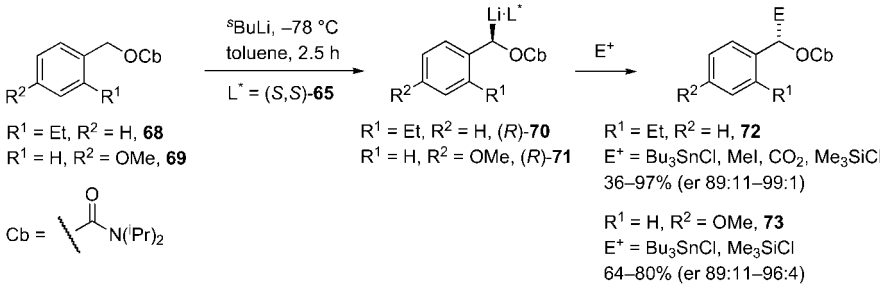
Scheme 7.15.



Scheme 7.16.

mer (Scheme 7.16).[95] Electrophilic quench via inversion affords α-substituted products in good yield with high levels of enantioselectivity. Experimental results reveal that in-situ trapping of organolithiums (*R*)- and (*S*)-**66** with TMSCl afforded the corresponding silane with an er of 54.5:45.5. With prolonged reaction times, enantiomer ratios up to 99.5:0.5 were achieved, which suggests the formation of thermodynamically favoured complex (*R*)-**66** as a result of dynamic thermodynamic resolution. This postulation was supported by quantum chemical calculations. Computational studies indicate that the lithiated complex (*R*)-**66** is more stable than (*S*)-**66** by 1.56 kcal/mol. The methodology was applied to the analogous 1-naphthylmethyl carbamate to afford α-substituted products in excellent yields (91–96%) and enantioselectivities (er up to 99.5:0.5).

The scope of this protocol was extended to the substituted carbamates **68** and **69**. Deprotonation of the carbamates **68** and **69** with *sec*-BuLi·bis(oxazoline) ligand **65** in toluene at –78 °C formed the thermodynamically favoured lithiated carbamates (*R*)-**70** and (*R*)-**71**, which on reaction with different electrophiles gave the products **72** and **73** in moderate to excellent yields with enantiomer ratios up to >99:1 (Scheme 7.17).[96] The energy differences between the diastereomeric lithiated complexes were determined by quantum chemical investigations. These calculations led to the prediction of a thermodynamic preference for the (*R*)-complexes as shown.



Scheme 7.17.

C. Carbanions with an α-Sulfur or Selenium Atom

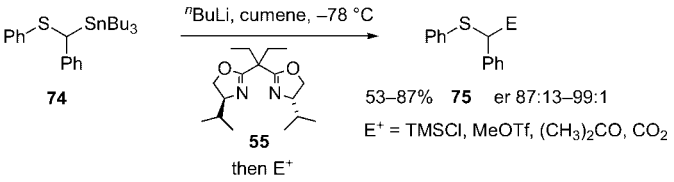
Enantioselective synthesis by chiral α-thio and α-seleno organolithiums is a well-studied, efficient and powerful methodology. α-Sulfenyl carbanions are generally proposed to be more configurationally unstable than α-seleno carbanions and this instability imparts useful properties for asymmetric transformations.

Toru and co-workers investigated the asymmetric substitution of the configurationally labile α-sulfenyl carbanions derived from sulfide **74**. They observed that treatment of the stannane **74** with *n*-BuLi and bis(oxazoline) **55** at –78 °C induced highly stereoselective substitution governed by dynamic kinetic resolution (Scheme 7.18).[97,98] A range of electrophiles was tested and the products **75** were obtained in good to excellent enantioselectivity. Nonpolar solvents such as toluene and cumene were found to enhance the yield and enantioselectivity of the reaction.

By performing a series of experiments (including use of lower temperatures and the Hoffmann test), it was confirmed that high levels of optical purity arose through dynamic kinetic resolution. It was postulated that highly reactive or non lithium coordinating electrophiles proceed with inversion of configuration while less reactive or lithium coordinating electrophiles prefer a pathway involving retention.

The methodology was extended to benzyl 2-pyridyl sulfides and the products were obtained with moderate to high enantioselectivity (er up to 96.5:3.5).[98] Experimental results and a warm–cool procedure confirmed that lithiated diastereomeric complexes interconverted quite slowly below –78 °C and readily at –50 °C. The results illustrated that the reaction followed a dynamic thermodynamic resolution pathway.

Toru and co-workers reported the enantioselective synthesis of chiral sulfides, thiols and diols by the reaction of benzyl sulfides and dithioacetals with *n*-BuLi and an appropriate chiral ligand in cumene solution at –78 °C.[99,100] It was found that lithiated epimeric complexes of benzyl 2-quinolyl sulfide are configurationally stable at –78 °C and the relative energies of the complexes were estimated by applying MO calculations.[99] Quenching the lithiated species with various electrophiles afforded highly enantioenriched α-substituted products in good yields and er up to 97.5:2.5. Reductive cleavage of the quinolyl group from the products using $NaBH_3CN$ in acetic acid gave the cor-

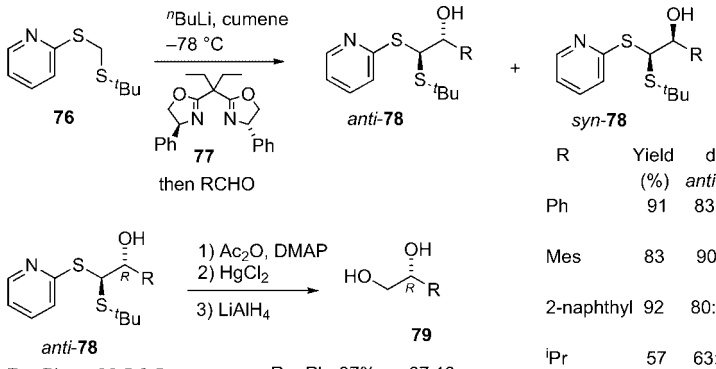


Scheme 7.18.

responding chiral thiols in high yields without any loss of enantiopurity. Low temperature deprotonation experiments confirmed that the reaction pathway proceeded via dynamic resolution under thermodynamic control with inversion of configuration at the carbanion centre.

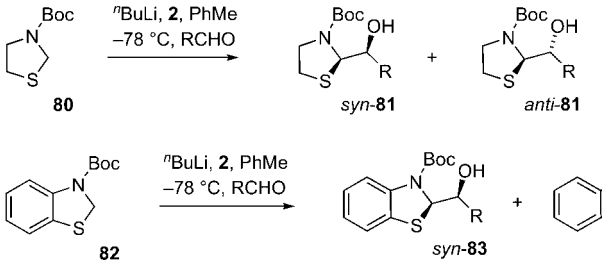
Similarly reaction of α-lithio dithioacetals was found to progress with good enantioselectivity.[100] Treatment of lithiated *tert*-butylthio-(2-pyridylthio)methane (**76**) with aldehydes gave the best combination of enantio- and diastereoselectivity (Scheme 7.19). The major diastereomers of the products **78** were converted to chiral diols **79** using $HgCl_2$ in CH_3CN/H_2O (9:1) without any significant loss of optical purity. To identify the enantiodetermining step during the reaction course, a temperature dependence study was performed. Increasing the temperature to –50 °C and –30 °C slightly lowered the enantioselectivity as compared to that at –78 °C. Similarly lower enantioselectivity was observed when deprotonation was carried out at –95 °C, while deprotonation at –78 °C followed by quenching with benzaldehyde at –95 °C gave almost the same level of enantioselectivity. These results suggested that lithiated epimeric complexes are configurationally stable at temperatures lower than –78 °C and the enantioselectivity was a consequence of dynamic thermodynamic resolution.

Proton abstraction of thiazolidines can provide a chiral acyl anion equivalent. For example *N*-Boc thiazolidine **80** and *N*-Boc benzothiazolidine **82** were investigated for the enantioselective reaction with aliphatic and aromatic aldehydes using *n*-BuLi·(–)-sparteine complex at –78 °C (Scheme 7.20).[101,102] Other diamine ligands did not give comparable selectivities to (–)-sparteine and toluene was found to be the best choice among the solvents used. The reaction proceeded in good to excellent yields with high enantioselectivity for each of the diastereomers formed. Generally the *anti* isomers showed



R	Yield (%)	dr *anti*:*syn*	er *anti* (*syn*)
Ph	91	83:17	92.5:7.5 (88:12)
Mes	83	90:10	92.5:97.5 (84.5:15.5)
2-naphthyl	92	80:20	91.5:8.5 (84.5:15.5)
^{i}Pr	57	63:37	90:10 (82.5:17.5)
^{t}Bu	71	55:45	92:8 (85:15)

Scheme 7.19.



	81			**83**		
R	Yield (%)	dr *syn*:*anti*	er *syn* (*anti*)	Yield (%)	dr *syn*:*anti*	er *syn* (*anti*)
Ph	74	42:58	96.5:3.5 (94:6)	93	60:40	96.5:3.5 (94:6)
p-ClC$_6$H$_4$	65	42:58	80:20 (94:6)	96	51:49	89:11 (94.5:5.5)
2-naphthyl	72	42:58	82.5:17.5 (95:5)	97	nd*	86.5:13.5 (93:7)
^{i}Pr	54	53:47	88.5:11.5 (93.5:6.5)	–	–	–
^{t}Bu	63	51:49	86:14 (93.5:6.5)	–	–	–

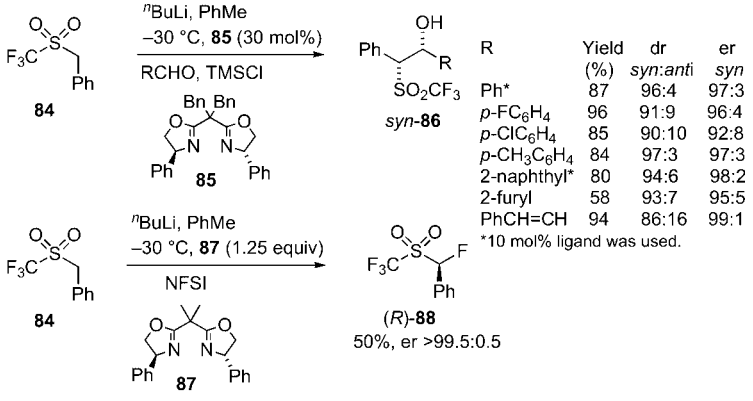
*not determined

Scheme 7.20.

higher enantiopurity than the corresponding *syn* isomers. Both isomers were separated by column chromatography after converting the alcohols to their corresponding acetates.

The configuration of the products was established by conversion to 1,2-diols.[101] The diols were recrystallized from hexane to enhance the enantiomeric purity to 99.5:0.5 and the stereochemical assignment was performed by comparison of the values of specific rotations with those reported. An experimental study using a deficient amount of benzophenone as an electrophile revealed that the reaction followed an asymmetric substitution (rather than asymmetric deprotonation) and was proposed to proceed through a dynamic thermodynamic resolution pathway.

Nakamura and co-workers described the enantioselective reactions of α-sulfonyl carbanions derived from trifluoromethyl sulfones. The methodology was extended to the first substoichiometric enantioselective catalysis of a carbanion α to a heteroatom proceeding through dynamic thermodynamic resolution.[103,104] Reaction of sulfone **84** in the presence of *n*-BuLi and bis(oxazoline) **85** (30 mol%) with aliphatic and aromatic aldehydes resulted in the highly stereoselective synthesis of the alcohols **86** (Scheme 7.21). The electrophile TMSCl was used to suppress the retro-aldol-type reaction by silylation of the formed alkoxide. The reaction gave high yields and selectivities in toluene, whereas a decrease in enantioselectivity was observed when the reactions were carried out in cumene, Et_2O or THF. The use of stoichiometric amount of the ligand gave exclusively the *syn*-isomer. Surprisingly, when 2–10 mol% of the ligand was used, it did not change the enantioselectivity significantly. Enantioselective fluorination of sulfone **84** with *N*-fluoro-



R	Yield (%)	dr *syn*:*anti*	er *syn*
Ph*	87	96:4	97:3
p-FC_6H_4	96	91:9	96:4
p-ClC_6H_4	85	90:10	92:8
p-$CH_3C_6H_4$	84	97:3	97:3
2-naphthyl*	80	94:6	98:2
2-furyl	58	93:7	95:5
PhCH=CH	94	86:16	99:1

*10 mol% ligand was used.

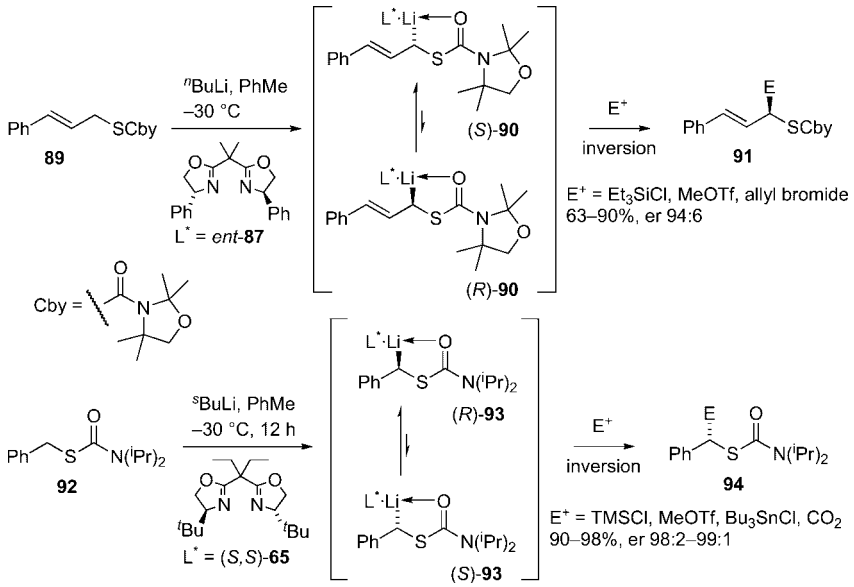
Scheme 7.21.

benzenesulfonimide (NFSI) using ligand **87** gave (*R*)-α-fluorinated sulfone **88** in a moderate yield and very high enantiomeric ratio.

The reaction was proposed to follow a dynamic thermodynamic resolution pathway, which was confirmed by performing experiments at different temperatures and by carrying out a modified Hoffmann test[24] using a deficient amount of electrophile. The catalysis of the dynamic thermodynamic resolution using substoichiometric amounts of chiral ligand was found to be due to the formation of enantioenriched dimers (or oligomers) of the α-lithiated sulfone that precipitated from the mixture of diastereomeric complexes with simultaneous regeneration of the chiral bis(oxazoline) **85**.[104] This, therefore, is an example of CIDR, although as the chiral ligand is not incorporated in the crystals it can be used as a catalyst. The reaction of resultant dimers or oligomers with an aldehyde provided the products with high enantio- and diastereoselectivity. The existence of these dimers was supported by ESIMS and ^{19}F NMR spectroscopy.

In a similar way, α-lithiated allyl aryl sulfides have been investigated for asymmetric substitution. It was found that these substrates reacted with various ketones in the presence of a suitable chiral ligand at –78 °C in hexane to give α-substituted allyl aryl sulfides with high enantiomeric purity (er up to 89:11).[105]

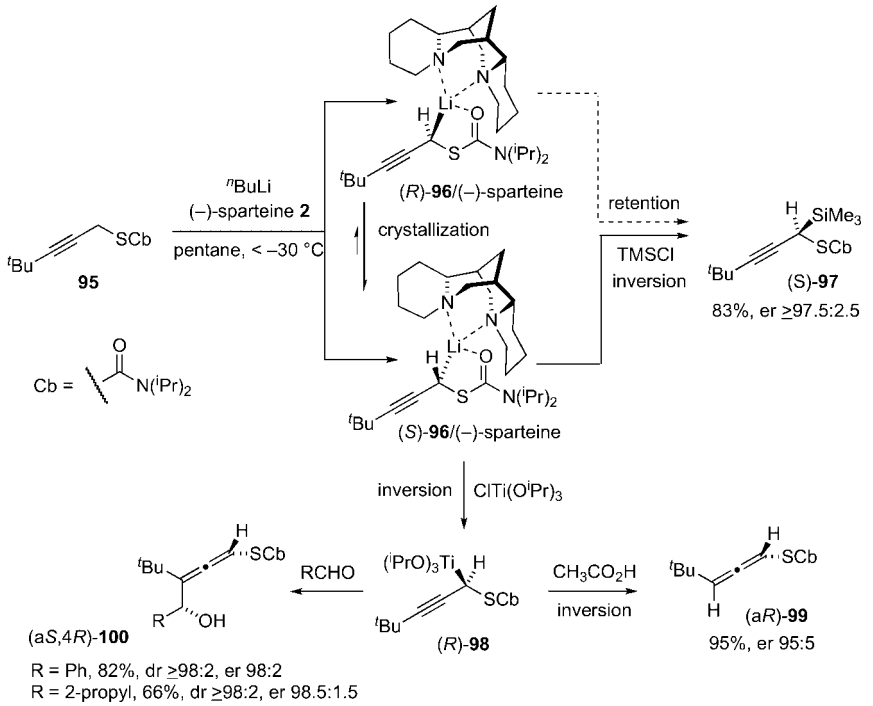
Hoppe and co-workers reported that the organolithium generated as a result of lithiation of *S*-cinnamyl thiocarbamate **89** is configurationally unstable at –30 °C (Scheme 7.22).[106] The use of chiral ligand *ent*-**87** shifted the epimeric equilibrium towards the (*S*)-configured lithiated complex **90** via thermodynamic control. This underwent silylation, alkylation or allylation with inversion of configuration, giving highly enantioenriched products (er up to 94:6). Similarly *S*-benzyl thiocarbamate **92** was found to be configurationally labile at –30 °C and in the presence of bis(oxazoline) **65**, enantiomerically enriched secondary *S*-benzyl thiocarbamates **94** were synthesized (Scheme 7.22).[107]



Scheme 7.22.

The experiments were performed at different temperatures with changes to the deprotonation time and in-situ trapping of the lithiated complexes with TMSCl to confirm that the enantio-determining step was post-lithiation asymmetric substitution through dynamic thermodynamic resolution. The absolute configuration was assigned by single crystal X-ray structure analysis of the methylated and silylated benzyl thiocarbamates.

In the same way, lithiation of the thiocarbamate **95** was investigated. In pentane at temperatures below –30 °C, lithiated diastereomeric complexes (*S*)- and (*R*)-**96/**(–)-sparteine were found to be configurationally labile and precipitated to provide (*S*)-**96/**(–)-sparteine through dynamic thermodynamic resolution by preferential crystallization of the intermediate lithiated complexes (Scheme 7.23).[108] The crystalline structure of the precipitated compound (*S*)-**96/**(–)-sparteine showed a monomeric chelate complex with a four-coordinate lithium cation attached to the carbanion centre, oxo-group and both nitrogen atoms of (–)-sparteine. Electrophilic quench of the precipitate (*S*)-**96/**(–)-sparteine with TMSCl gave the resultant silane (*S*)-**97** in high enantiopurity. Transmetallation of the complex (*S*)-**96/**(–)-sparteine with $ClTi(O^iPr)_3$ occurred via stereoinversion to form intermediate (*R*)-**98** which was quenched with acetic acid to give allene (a*R*)-**99** in excellent yield and selectivity. The titanium intermediate (*R*)-**98** was treated with various aldehydes to provide the corresponding allenes (a*S*,4*R*)-**100** with high selectivities. The methodology was extended to 2-alkynyl aryl sulfides for the synthesis of enantioenriched (er up to 92.5:7.5) and diastereomerically pure

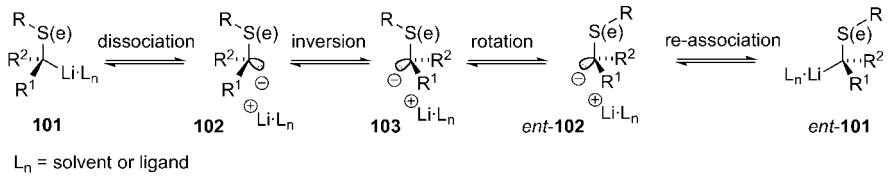


Scheme 7.23.

(dr up to ≥95:5) allenyl 2-pyridinyl sulfides.[109] The products were subjected to highly stereospecific nickel-catalyzed cross-coupling reaction with various aryl zinc reagents to give threefold carbon substituted allenes in a stereoselective manner.

Hoffmann and co-workers investigated the mechanism of the racemization of α-lithiated sulfides or selenides and described that the negative charge in compounds such as **101** is stabilized by n σ* delocalization into the S(e)–R bond, which results in an antiperiplanar arrangement of the S(e)–R and C–Li bonds (Scheme 7.24).[33] They postulated a three-step enantiomerization process for this kind of lithiated substrate. The first step is the dissociation of lithium from the carbon. The second step involves pyramidal inversion of the carbanion, while the third step is the rotation about the carbanion–heteroatom bond. NMR spectroscopic studies and calculations carried out for α-selenoalkyllithium compounds revealed that the rate determining step for racemization is rotation around the carbanion carbon and selenium bond. The same was true for α-thio-substituted carbanions.

It was found that α-phenylseleno alkyllithiums, in the absence of a chiral diamine ligand, racemized at –30 °C, however addition of the ligand changed the rate of racemization and diastereomeric lithiated complexes

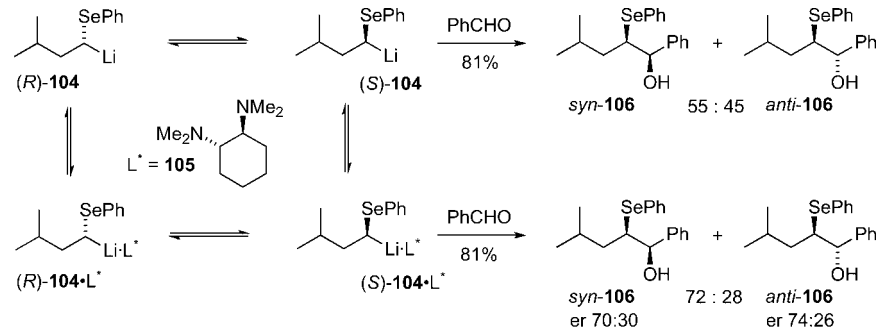


Scheme 7.24.

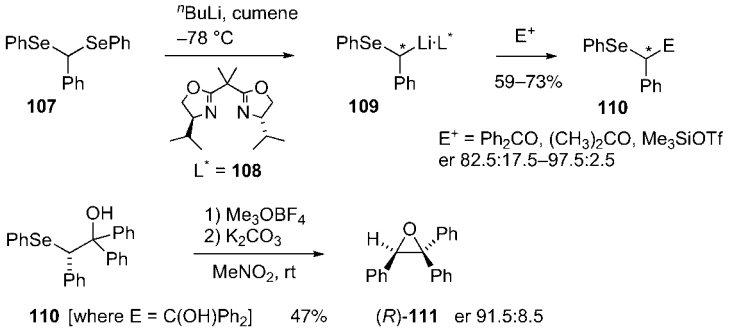
were observed to be configurationally stable at –50 °C.[110] Treatment of the complexed organolithium with benzaldehyde provided the diastereomeric products with an er of 70:30. This reflected the diastereomeric ratio of the lithiated complexes with the chiral diamine ligand. The best er (90:10) was obtained by using tetramethyl(cyclopentane-1,2-diamine) in diethyl ether.[111]

Hoffmann and co-workers further investigated the epimeric complexation of configurationally labile α-phenylselenoalkyllithiums (*R*)- and (*S*)-**104** in diethyl ether (Scheme 7.25).[112] The racemic quench of lithiated species (*R*)- and (*S*)-**104** in the absence of the chiral ligand with benzaldehyde provided the *syn*- and *anti*-**106** adducts in a ratio of 55:45. Chiral diamine **105** gave epimeric species (*R*)- and (*S*)-**104**·L*, which on treatment with benzaldehyde at –60 °C afforded *syn*- and *anti*-**106** products with diastereomeric ratio of 72:28. It was found that complexation of the ligand with lithiated complexes (*R*)- and (*S*)-**104** substantially accelerated the rate of addition to the electrophile. The average enantiomeric enrichment (er 71:29) was found to be close to the diastereomeric equilibrium ratio (70:30) as determined by ^{77}Se NMR spectroscopy.

Nakamura and co-workers reported the enantioselective reaction of diselenoacetals such as **107** in cumene at –78 °C in the presence of *n*-BuLi and a chiral ligand **108** (Scheme 7.26).[113] The resultant lithiated complex **109** was treated with different electrophiles to provide the products with moderate to high enantioselectivities. Use of the ligand (–)-sparteine gave low enantioselectivity in comparison with the bis(oxazoline) **108**. When the reac-



Scheme 7.25.



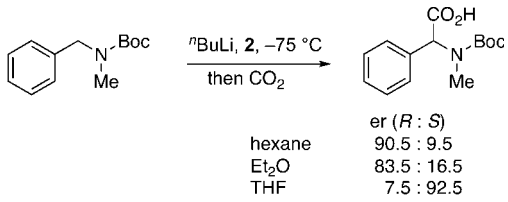
Scheme 7.26.

tion was performed at –50 °C or –90 °C, it resulted in slightly lower enantioselectivities. The absolute configuration of **110** [E = $C(OH)Ph_2$] was found to be (*S*) by converting to the epoxide (*R*)-**111**. It was proposed that the reaction proceeded through dynamic thermodynamic resolution and evidence for this came from using a deficient amount of electrophile, a warm–cool experimental procedure and by analyzing the data obtained from the MO calculations. The protocol was applied to benzyl 2-pyridyl selenide which gave the reverse stereochemical outcome in comparison with the reaction of benzyl phenyl selenide. The methodology was extended to the preparation of axially chiral benzylidenecyclohexanes with high enantioselectivities.[114]

D. Carbanions with an α-Nitrogen Atom

Organolithiums α to nitrogen have most commonly been prepared by proton abstraction (particularly if mesomeric or dipole-stablised) or by tin–lithium exchange.[19] Schlosser and Limat described enantioselective *α*-lithiation of *N*-Boc-*N*-methylbenzylamine using *sec*-BuLi and (–)-sparteine **2** (Scheme 7.27).[115] By using deuterium labelling, the initial enantioenriched chiral (dipole-stabilised) organolithium was found to undergo rapid racemization, but after a while the original selectivity was regained. Experimental results revealed a solvent effect on the resultant stereochemistry of the electrophilic substitution, with THF giving the opposite major enantiomer in comparison with the non-polar solvent hexane. This solvent effect was found consistent for other electrophiles including carbon disulfide, methyl iodide, dimethyl sulfate or ω-deuteriophenylacetylene. It was proposed that the influence of the solvent was due to the coordination of a solvent molecule with the lithiated species.

Beak and co-workers found an enantioselective way to synthesise *N*-Boc-2-substituted pyrrolidines and piperidines by treatment of the carbamates **112** and **113** with *n*-BuLi·(–)-sparteine at –78 °C, followed by warming to

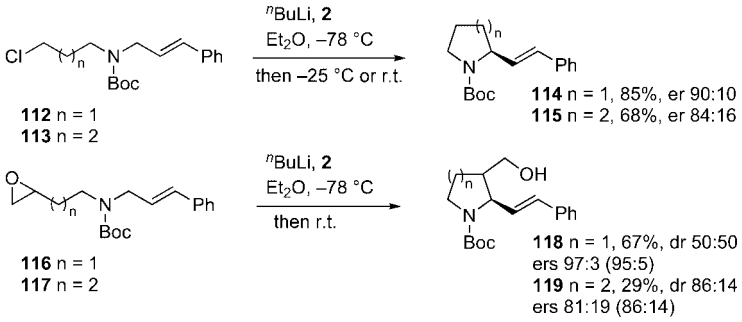


Scheme 7.27.

–25 °C or room temperature (Scheme 7.28).[116] This gave pyrrolidine **114** and piperidine **115** with good enantioselectivity. The methodology was applied to various substituted allyl groups and, as an alternative to the chloride, epoxides such as **116** and **117** could act as the intramolecular electrophile. Using deuterium labelling or tin–lithium exchange on the racemic stannane, it was found that selective deprotonation occurred initially but the organolithium was able to interconvert and the final enantioselectivity arises from an asymmetric substitution.

As an extension to this research, *N*-Boc-*N*-(*p*-methoxyphenyl)cinnamylamine was investigated to determine the reaction pathway for lithiation–substitution reactions with *n*-BuLi·(–)-sparteine.[117] The lithiated complexes were subjected to ^{6}Li and ^{13}C NMR spectroscopic studies and the solution structure of the major allyllithium intermediate was determined to be a monomeric η^3 species (*syn-anti* configuration). For lithiation–silylation or lithiation–alkylation, the asymmetric reaction pathway is complex. At –78 °C, asymmetric deprotonation provides mostly the η^3-*syn-anti* organolithium which is configurationally stable, but on warming to –25 °C the asymmetry derives from a dynamic thermodynamic resolution. In contrast, the minor η^3-*syn-syn* organolithium is configurationally labile at low temperature.

Coldham and co-workers investigated the asymmetric substitution of *N*-Boc-pyrrolidine by deprotonation or tin–lithium exchange (Scheme 7.29).[118] Under conditions for dynamic thermodynamic resolution (equilibration at

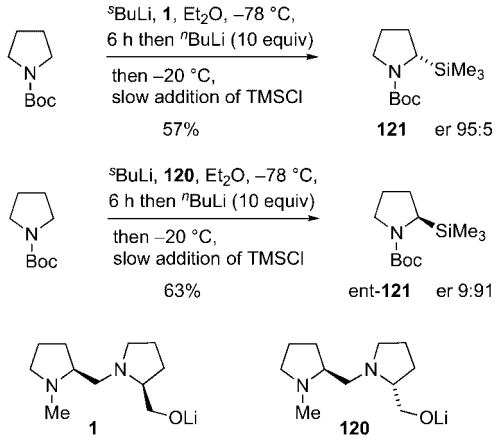


Scheme 7.28.

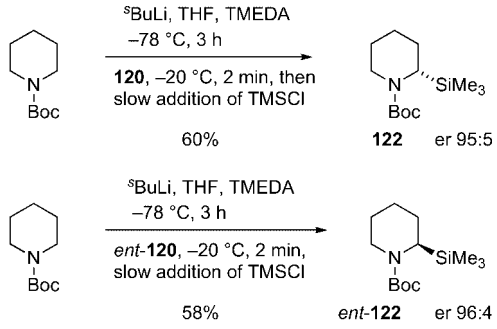
–20 °C then cooling to –78 °C), *N*-Boc-2-lithiopyrrolidine with the chiral ligand **1** gave, after electrophilic quench with TMSCl, the silane **121**, er 42:58 (*S*):(*R*). However it was found that this reaction had a kinetic preference and one diastereomeric species reacted faster than the other. After considerable experimentation, the ligand **1** and excess of BuLi, followed by slow addition of TMSCl at –20 °C was found to give the pyrrolidine **121** with er 95:5 by dynamic kinetic resolution. The use of diastereomeric ligand **120** gave the product with opposite configuration. The reaction is thought to proceed with retention of configuration, so the (*S*)-organolithium·**1** complex is implicated as the more reactive. Unfortunately the reaction was unsuccessful with other electrophiles.

Coldham and co-workers have since investigated the scope of dynamic resolution for *N*-Boc-2-lithiopiperidine. With the chiral ligands **120** and *ent*-**120**, after asymmetric electrophilic substitution using TMSCl as an electrophile, the desired products **122** and *ent*-**122** were obtained with high enantioselectivity via dynamic resolution under kinetic control (Scheme 7.30).[119] An optimization study revealed that the solvent THF gave slightly improved results as compared to Et_2O. The asymmetric induction was found to be dependent on the electrophile, as quenching with Bu_3SnCl, allyl bromide, DMF or Me_2SO_4 resulted in products with little or no enantioselectivity. The use of TMSCl as sacrificial electrophile prior to the addition of different electrophiles gave the desired products with er up to 99:1, albeit with low yield.

As a result of this difficulty in promoting resolution of *N*-Boc-2-lithiopiperidine under kinetic control with a variety of electrophiles, a selection of chiral ligands was tested to promote high er through dynamic thermodynamic resolution. The best results were obtained using diamino-alkoxide ligands and this approach was tolerable to a selection of electrophiles (Scheme



Scheme 7.29.

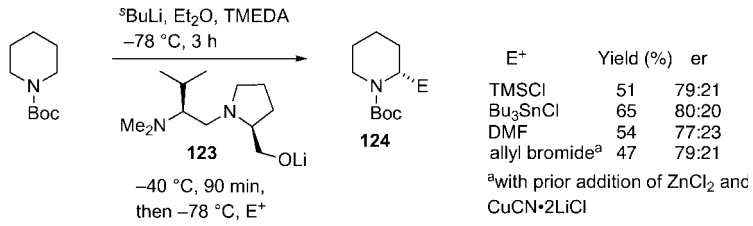


Scheme 7.30.

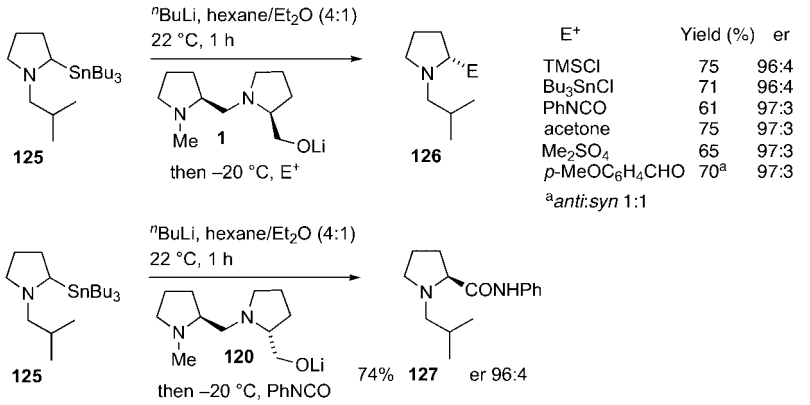
7.31).[120] Several chiral ligands were screened, with enantioselective induction of up to 85:15. For example, the ligand **123** resulted in the products **124** with er of approximately 80:20. The yield was optimum either by using aged *sec*-BuLi or freshly acquired *sec*-BuLi in the presence of ^{i}PrOLi (5 mol%). This chemistry was applied to the formal synthesis of the alkaloid coniine using allyl bromide as an electrophile (after transmetallation to the zinc–cuprate species).

The *N*-Boc group directs proton abstraction α to the nitrogen atom to give a dipole-stabilized organolithium. For amines (rather than amides), the corresponding α-amino-organolithiums can be formed by tin–lithium exchange. Coldham and co-workers reported the first highly enantioselective substitution of such organolithium species by dynamic resolution at ambient temperature.[121]

Transmetallation of racemic organostannanes such as **125** with *n*-BuLi and allowing the equilibration in the presence of the deprotonated ligand **1**, followed by quenching with a selection of electrophiles gave 2-substituted pyrrolidines **126** with high enantioselectivities (Scheme 7.32).[122] By using the diastereomeric ligand **120**, the opposite major enantiomer of the 2-substituted pyrrolidine (**127**) was obtained. Various *N*-substituted pyrrolidines were investigated and it was found that steric bulk of the *N*-substituent enhanced the enantioselectivity, however the rate of transmetallation was reduced



Scheme 7.31.

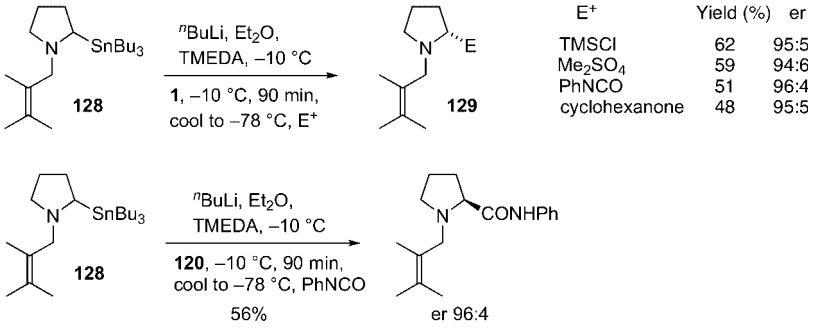


Scheme 7.32.

with larger substituents. The origin of selectivity was proposed to be due to dynamic thermodynamic resolution, in which the rate of reaction with the electrophile was comparatively faster than interconversion of the epimeric lithiated complexes. By using sub-stoichiometric amount of the electrophile, it was confirmed that the minor (rather than the major) diastereomeric complex reacted faster.

This dynamic thermodynamic resolution chemistry was extended to *N*-alkyl-2-lithiopyrrolidines in the presence of chiral ligand, (–)-sparteine **2**.[123] The 2-substituted pyrrolidines were obtained in good yields and with er up to 85:15. It was observed that the major product had opposite configuration compared to that obtained by the asymmetric deprotonation of *N*-Boc-pyrrolidine with (–)-sparteine **2**.

The methodology was later applied to *N*-trimethylallyl-2-lithiopyrrolidine and other *N*-allyl-2-lithiopyrrolidines.[122] Treatment of the stannane **128** with *n*-BuLi generated the organolithium, to which was added the deprotonated ligand **1** or **120** and the resultant diastereomeric lithiated species were allowed to equilibrate at –10 °C for 90 min to set the thermodynamic ratio (Scheme



Scheme 7.33.

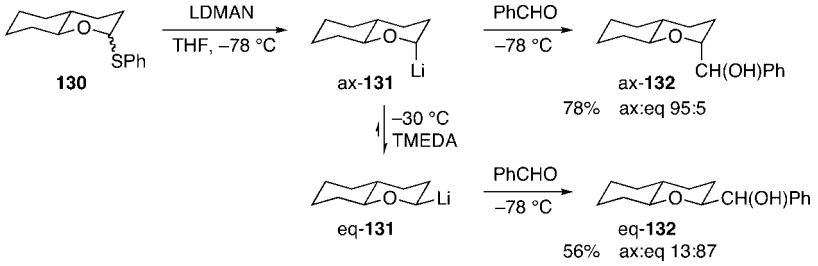
7.33). The reaction mixture was cooled to –78 °C prior to the addition of the electrophile and the products were obtained with er up to 96:4. Deallylation of the products afforded the *N*-unsubstituted pyrrolidines without any loss of enantiopurity. The high selectivity occurred as a result of a thermodynamic preference for one of the diastereomeric complexes. Transmetallation was found to be slow in the absence of TMEDA. Based on recent work, TMEDA was shown to lower the barrier to dynamic resolution.[43] In addition, by using *N*,*N*′-diisopropylbispidine as the achiral ligand, high enantiomer ratios could be achieved using only 15 mol% of the chiral ligand, although the mechanism for catalysis has not been determined.[43]

E. Carbanions with Additional Stereogenic Elements

Dynamic resolution of chiral organolithiums can be induced using external chiral ligands such as (–)-sparteine, other diamines or bisoxazolines as described in the preceding sections. In this final section examples are given in which there is another stereocentre in the molecule. In these cases, the epimeric organolithiums are diastereomeric by virtue of the additional stereocentre in the molecule. Equilibration (by inversion of the organolithium) therefore sets up the thermodynamic ratio of the diastereomers. Electrophilic quench then leads to stereoselective substitution. Hence this chemistry can be considered analogous to the examples in the previous sections that involve dynamic resolution under thermodynamic control. If, however, one diastereomeric organolithium reacts faster than the other, then the asymmetric induction can be considered as a dynamic kinetic resolution or (as there is epimerization not racemization) a dynamic kinetic asymmetric transformation (DYKAT).

One of the earliest examples of this type of resolution was reported by Cohen and Lin (Scheme 7.34).[124] Reductive lithiation of the sulfide **130** (ax:eq 3.4:1) with LDMAN [lithium 1-(dimethylamino)naphthalenide] at low temperature followed by electrophilic quench with benzaldehyde gave the product ax-**132** almost exclusively. This was ascribed to the preferential formation of the axial organolithium ax-**131**. However, on warming to –30 °C, epimerization takes place to give predominantly the equatorial organolithium eq-**131**, and hence on electrophilic quench, the stereoisomer eq-**132** as the major product. Treatment of the sulfide **130** with LDMAN gives an intermediate radical that accepts an electron to give the axial organolithium that is configurationally stable (on the timescale of the reaction) at –78 °C. The equatorial organolithium is thermodynamically more favoured and can be formed at elevated temperatures. Related lithiated cyclohexanes and cyclic acetals display similar properties.[125–127]

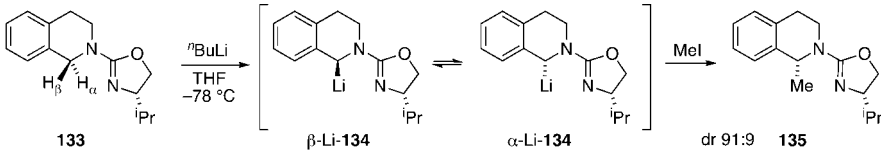
Several research groups have investigated the chemistry of the organo-



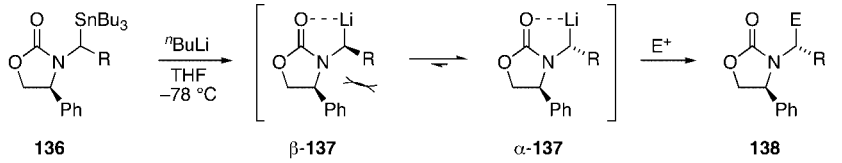
Scheme 7.34.

lithiums formed by deprotonation of various N-substituted tetrahydroisoquinolines (or the related β-carbolines).[128–131] With the oxazoline **133**,[132,133] deprotonation at the benzylic position gives the organolithium **134** and electrophilic quench provides products such as **135** (Scheme 7.35). By using deuterium labelled compounds, the initial deprotonation was found to be stereoselective (removal of H_β:H_α 5.8:1) and rate-determining, but the diastereomer ratio (dr) of the product was independent of any labelling, indicating that there was equilibration of the diastereomeric organolithiums to their thermodynamic ratio. The dr of the product could then be a reflection of this thermodynamic ratio or be a due to the faster reaction of one of the diastereomeric organolithiums. As the selectivity is dependent on the nature of the electrophile, this points to Curtin–Hammett kinetics.[133]

A good example of a dynamic equilibration of diastereomeric acyclic organolithiums uses *N*-lithioalkyl-oxazolidinones (or imidazolidinones).[134–136] The organolithiums **137** can be prepared by tin–lithium exchange from the stannanes **136** (or by proton abstraction when the R group is anion-stabilising such as phenyl) (Scheme 7.36). Either stereoisomer or a mixture of the stereoisomeric stannanes **136** can be used, as the intermediate organolithiums **137** equilibrate rapidly at –78 °C to favour the isomer (α-**137**) with lower steric interactions. The lithium atom coordinates to the carbonyl oxygen atom, so the organolithium β-**137**, in which the R group clashes with the phenyl group, isomerises to α-**137**. Electrophilic quench occurs with retention of configuration to give **138**. Using carbon dioxide as the electrophile this chemistry has been used in a synthesis of L-methionine (after conversion of the oxazolidinone to the amine by Birch reduction with Li/NH_3).[137] Sev-



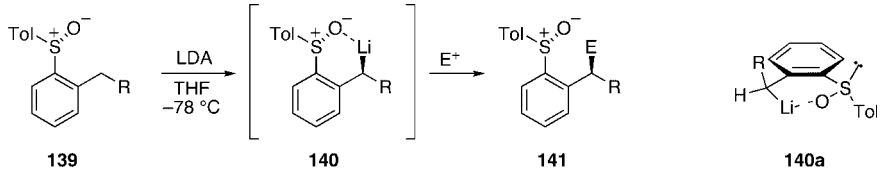
Scheme 7.35.



Scheme 7.36.

eral variations on this idea have been reported.[138–142] The chemistry has been used as an effective chiral formyl anion equivalent using related oxazolidinones and R=SMe or SPh (with later hydrolysis to the formyl group).[31,143,144] A number of other diastereomeric α-heteroatom-substituted organolithiums (in which there is a nearby stereocentre) have been studied.[145–154]

Finally, there are examples of chiral acyclic benzylic organolithiums that can equilibrate and react to give preferentially one diastereomeric product.[155–158] For example, deprotonation has been used to provide a range of substituted 2-*p*-tolylsulfinyl benzyllithiums **140** that can be trapped with different electrophiles (Scheme 7.37).[159–165] The organolithium **140** is thought to prefer one diastereomer in which the tolyl and R groups are located anti to each other (**140a**). After electrophilic quench, the sulfinyl group can be removed to give chiral products with a phenyl group attached to the stereocentre.



Scheme 7.37.

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