Stereochemical Aspects of Organolithium Compounds

Robert E. Gawley (Ed.)

Volume 26 in Topics in Stereochemistry

Jay S. Siegel (Ser. Ed.)

Verlag Helvetica Chimica Acta · Zürich

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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

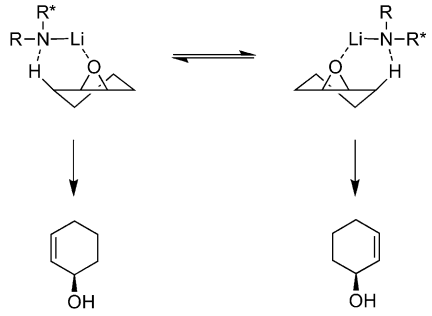
Chiral lithium amide bases have been of significant interest over the past 20 years or so, in reactions that can be broadly described as enantioselective deprotonations. Developments in the methodology, including design and exploration of novel bases, moves towards catalysis, and applications to new 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.

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.

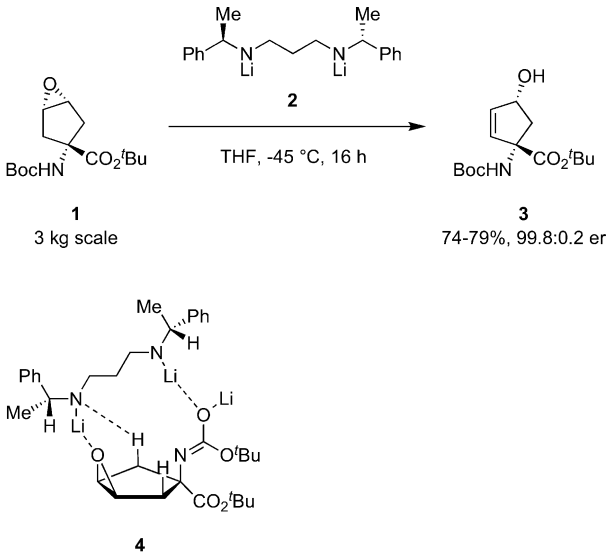
II. ENANTIOSELECTIVE CONVERSION OF EPOXIDES INTO ALLYLIC ALCOHOLS

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.

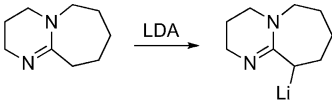


Scheme 1.2.

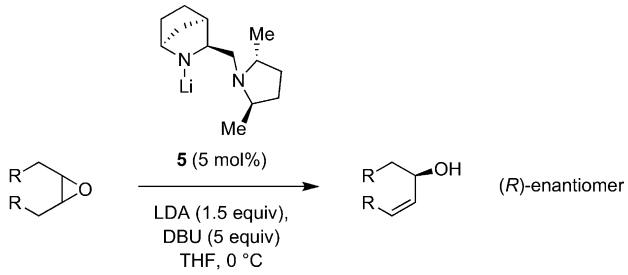
4 was proposed for this efficient asymmetric process, which involved deprotonation of the carbamate NH and chelation of the chiral base to both the lithiated carbamate and the epoxide. This example neatly illustrates the applicability of chiral lithium amides in industrial synthesis.

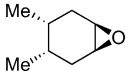
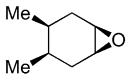
Epoxides have proved to be the best performing substrates in asymmetric deprotonations using sub-stoichiometric quantities of chiral lithium amide. Pioneering studies in this area were provided by the groups of Asami[10,11] and Alexakis.[12] These early examples of the catalytic enantioselective rearrangement 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]



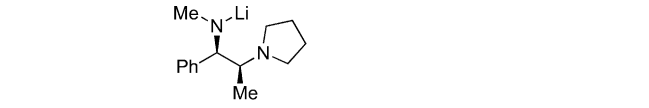
The lithiated DBU forms heterodimers with chiral lithium amides and these might function as the active species for enantioselective deprotonation. Lithiated DBU might otherwise function as a bulk base, or DBU itself could be a solvating ligand. It is worth noting that in Asami's most successful catalytic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

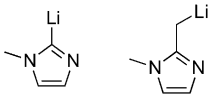


	yield %	er		yield %	er
	81	98:2[a]		94	99:1
	95	>99:1		85	>99:1
	93	>99:1		80	95:5

a) Run at rt.

Scheme 1.3.





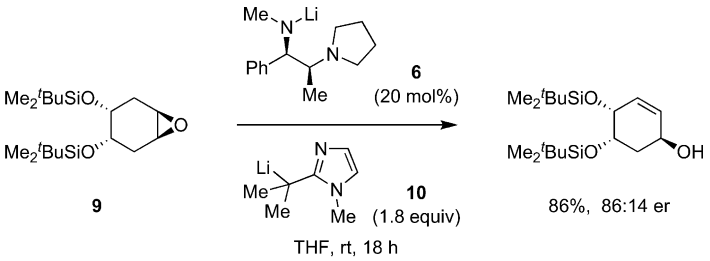
7 **8**

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**



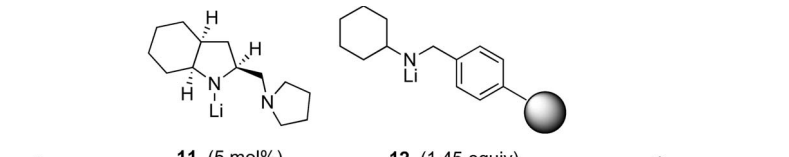
Scheme 1.5.

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.



	yield %	er		yield %	er
	48	84:16[a]		54	97:3
	91	96:4[b]		93	97:3

a) Run at rt, then 55 °C.
b) When LDA (1.95 equiv) was used as the bulk base, the product was obtained in 93% yield and 92:8 er.

Scheme 1.6.

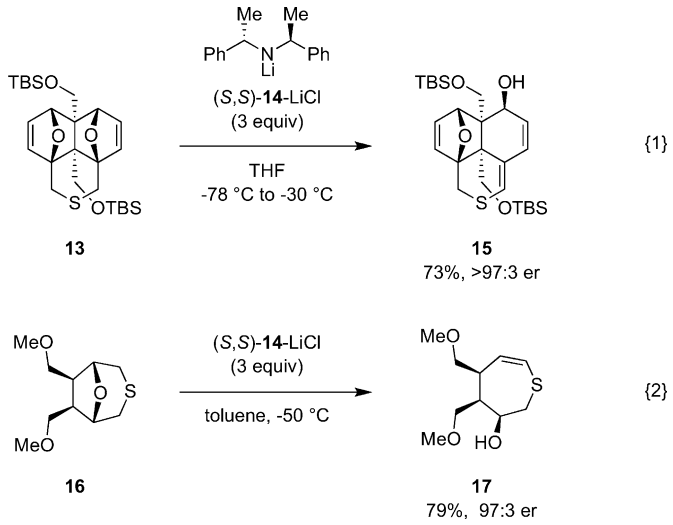
III. ENANTIOSELECTIVE DEPROTONATIONS ADJACENT TO SULFUR

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

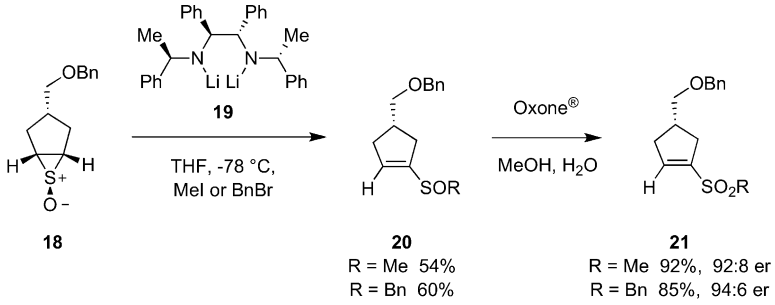


Scheme 1.7.

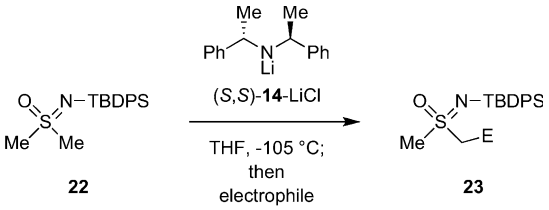
Lautens group.[22] For example, substrate **16** was ring-opened using chiral base (*S*,*S*)-**14**-LiCl to provide alcohol **17** (Scheme 1.7 eq 2).

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.

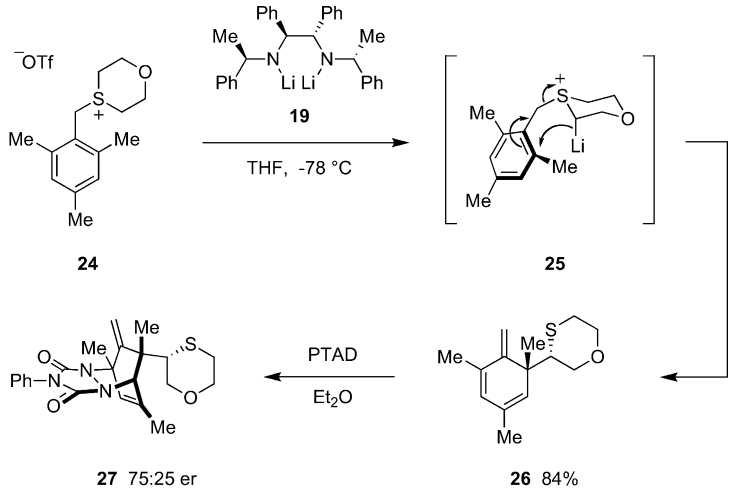


electrophile	yield **23** %	er of **23**
Me_3SiCl	58	80:20
$Ph_2C{=}O$	86	85:15
$Ph_2C{=}NTs$	30	64:36
$2\text{-}BrC_6H_4CH_2Br$	70	78:22

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-

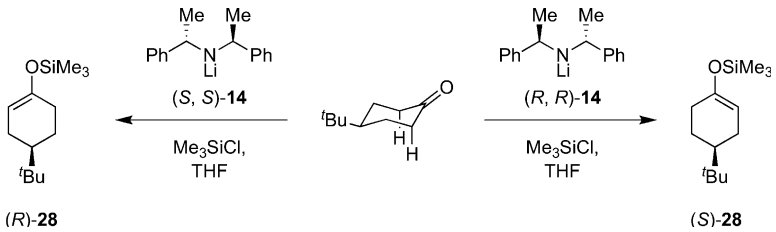


Scheme 1.10.

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

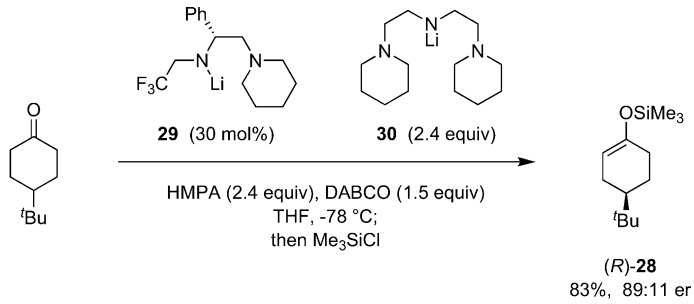
Probably the most important category of chiral-base mediated processes is the symmetry-breaking enolisation reaction, involving cyclic prochiral ketones. In conformationally locked cyclohexanones, such as 4-*tert*-butylcyclohexanone, there is a stereoelectronic preference for removal of the axial protons, 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

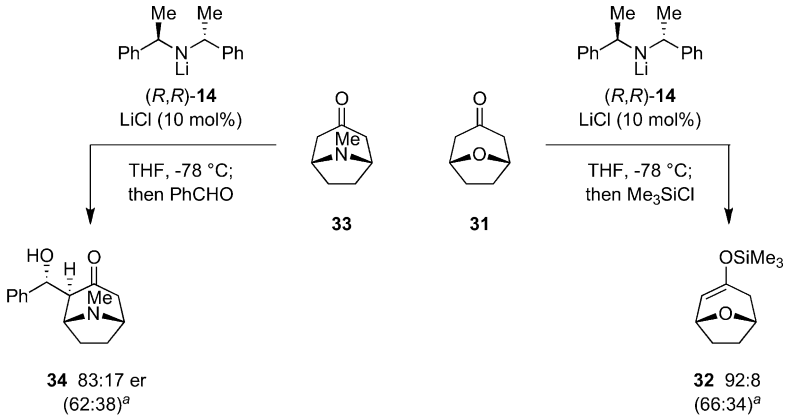
There has been continued interest in the discovery of new chiral lithium amide bases, including polymeric types, and bis-lithium amides. It is also worth reiterating the important discovery of Koga and co-workers, who showed that the enantioselective deprotonation of 4-substituted cyclohexanones can 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.

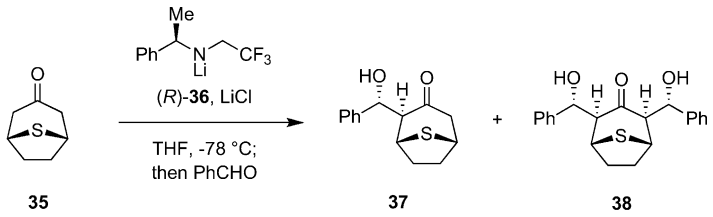
asymmetric deprotonation of cyclic ketones using chiral base methodology. In light of the advances made in the catalytic asymmetric deprotonation of *meso*-epoxides (see Section II), this is somewhat surprising. Perhaps this is because the relative rate of the background deprotonation by the bulk base 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.



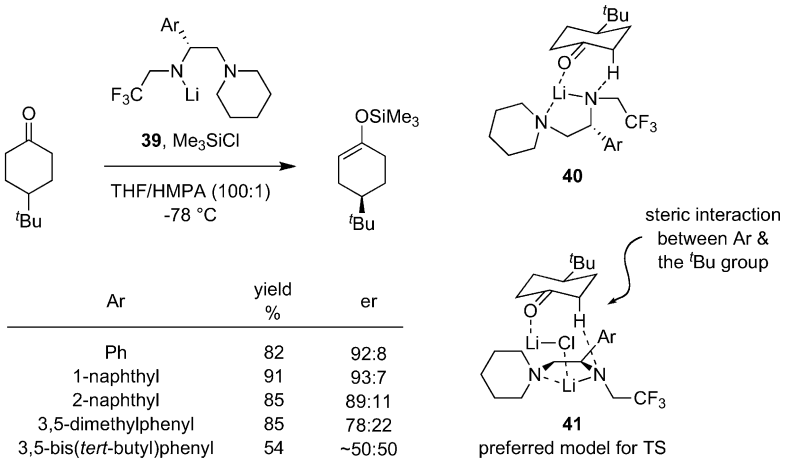
35 37 38

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.

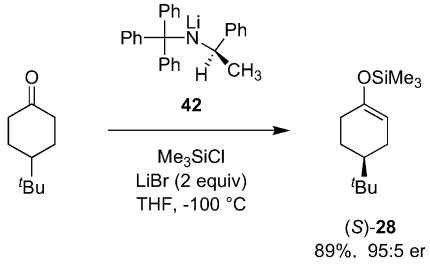
Majewski and co-workers have examined the behaviour of the thiabicyclo[3.2.1]octan-3-one framework upon asymmetric deprotonation because of concerns about reproducibility when using this substrate class.[35] They found that treatment of **35** with chiral lithium amide (*R*)-**36** followed by addition 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.



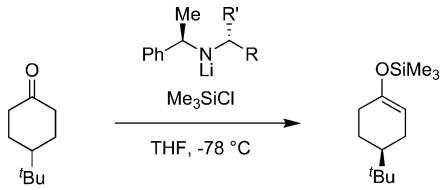
Ar	yield %	er
Ph	82	92:8
1-naphthyl	91	93:7
2-naphthyl	85	89:11
3,5-dimethylphenyl	85	78:22
3,5-bis(*tert*-butyl)phenyl	54	~50:50

Scheme 1.15.

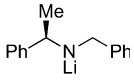
Koga *et al.* have studied bidentate chiral lithium amides **39** having a bulky group other than phenyl on the stereogenic carbon.[38] These bases were assessed for their performance in deprotonation reactions of 4-substituted cyclohexanones. It was found that changing the phenyl group to a more bulky 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**

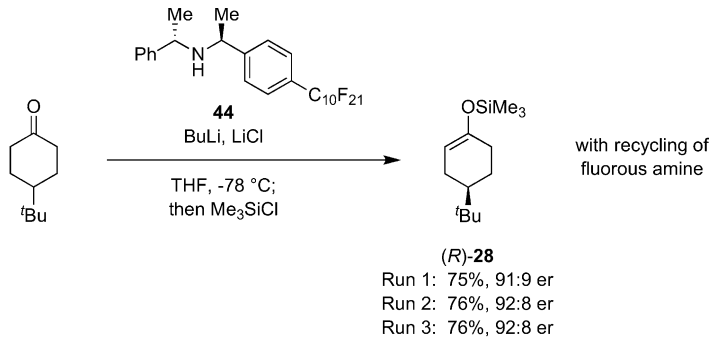
Scheme 1.17.

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.

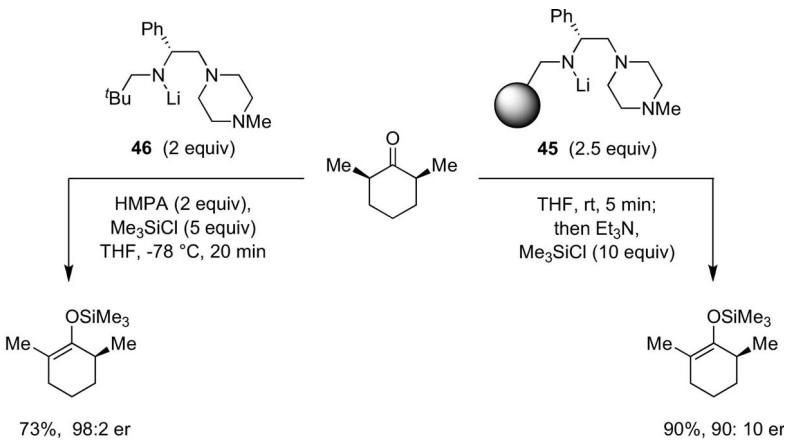
Polymer-supported chiral amines have also been shown to undergo recycling and re-use without loss of reactivity or selectivity.[45] Williard has de-



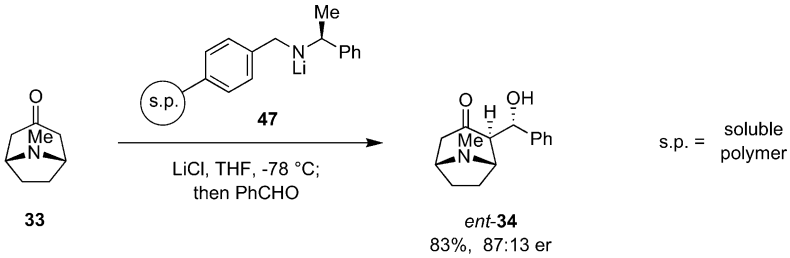
Scheme 1.18.

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.



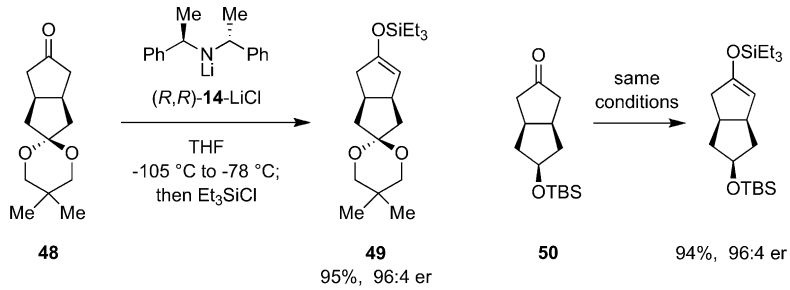
Scheme 1.20.

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*-

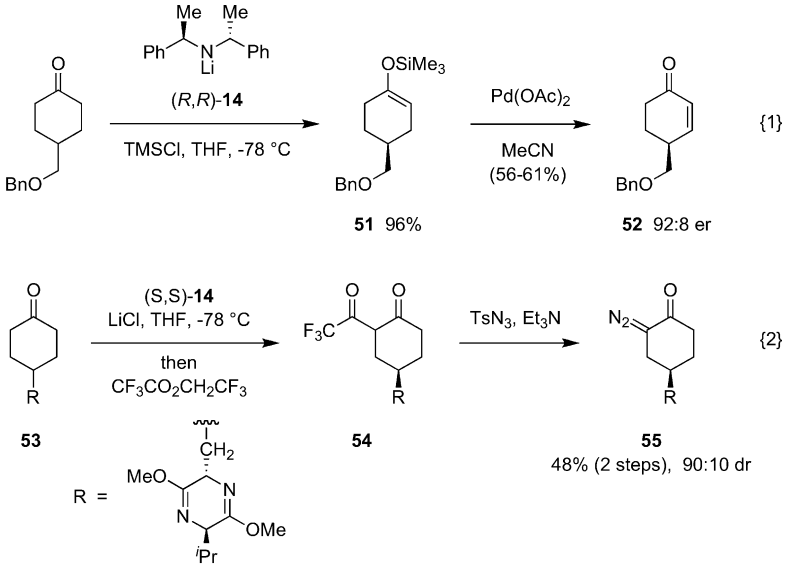


Scheme 1.21.

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.