Recent advances in asymmetric synthesis using chiral lithium amide bases

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REVIEW PERKIN 1

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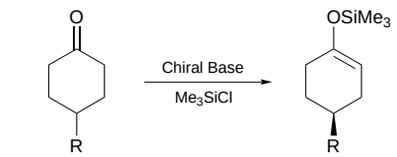
1 Introduction

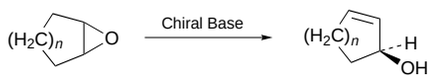
The aim of this review is to bring the reader up to date with the recent and numerous developments in the use of chiral lithium amide bases in asymmetric synthesis. The period up to and including 1990 has previously been reviewed by Simpkins[1] and others[2–4] and will not be covered in detail in this review. In addition, this review only covers the use of lithium amide bases; methods involving the use of an alkyllithium in tandem with a chiral ligand [most successfully, the alkaloid (−)-sparteine] are excluded.[5,6]

Over the last few years there has been a steady increase in the number of research groups exploiting the use of chiral bases. The research efforts have focused on elucidating the structures of the chiral lithium amide bases (both in the solid state and in solution), understanding the role of additives (particularly lithium halides), investigating the effect of chiral base structure on enantioselectivity, discovering new types of asymmetric reactions mediated by chiral bases and using chiral base reactions as key steps in total syntheses.

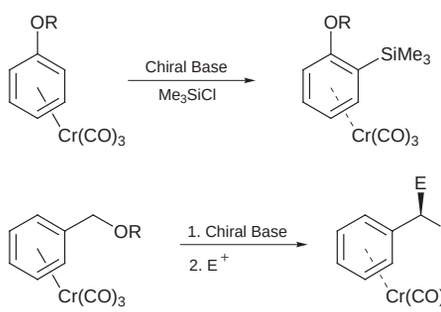
Chiral lithum amide bases have been used successfully in three main types of asymmetric reactions (Sections 2, 3 and 4 of this review): (i) deprotonation of conformationally locked prochiral cyclic ketones (**Scheme 1**); (ii) rearrangement of epoxides to allylic alcohols (**Scheme 2**) and (iii) aromatic and benzylic functionalisation of tricarbonyl (η^6-arene)chromium complexes (**Scheme 3**). All three are examples of asymmetric desymmetrisation: the chiral base discriminates between a pair of protons in a substrate possessing a plane of symmetry to produce an enantiomerically enriched chiral product. Also included in this review are a number of unusual, less well developed applications of chiral bases (Section 5). Finally, the potential of carrying out catalytic asymmetric synthesis with chiral bases has recently been realised; Section 6 summarises the preliminary results.



Scheme 1



Scheme 2



Scheme 3

All of the asymmetric transformations mediated by chiral lithium amide bases that are collected together in this review have been carried out using just 19 different chiral bases. The structures of these commonly used chiral bases are depicted in **Fig. 1**. Although there is a wide variety of chiral base structures, a few trends emerge and the chiral bases fall into four distinct groups. Group A contains chiral bases derived from α-methylbenzylamine [except for (*R*,*R*)-**4** of which chiral bases (*R*,*R*)- or (*S*,*S*)-**1**, originally introduced by Whitesell[7,8] but made popular by Simpkins,[9] are the most important. Chiral bases such as (*R*)-**7**, prepared from phenylglycine,[10] were developed by Koga and the most commonly employed Koga bases are depicted in group B. All of the chiral bases shown in groups A and B (Fig. 1) are available in both enantiomeric forms, are relatively easy to prepare and have been used with much success in enantioselective ketone deprotonations (Section 2). In addition, Simpkins and others have shown that chiral bases (*R*,*R*)- or (*S*,*S*)-**1** are the best ones for aromatic functionalisation of tricarbonyl (η^6-arene)chromium complexes whilst Gibson has recently demonstrated that chiral base **6**, originally introduced by Simpkins,[11] gives the highest levels of asymmetric induction in benzylic functionalisation of tricarbonyl (η^6-arene)chromium complexes (Section 4). However, chiral bases such as those depicted in groups A and B do not generate highly enantiomerically enriched allylic alcohols *via* chiral base-mediated epoxide rearrangement. Instead, for highly enantioselective rearrangement of epoxides to allylic alcohols, chiral bases from group C are used (Section 3). Of these, chiral bases (*R*)-**14** and (*R*)-**15** are similar in structure to Koga's chiral bases (group B) and can easily be prepared in both enantiomeric forms.[9,12–14] Group D contains two chiral bases which have been successfully used in enantioselective aldol reactions (Section 5).

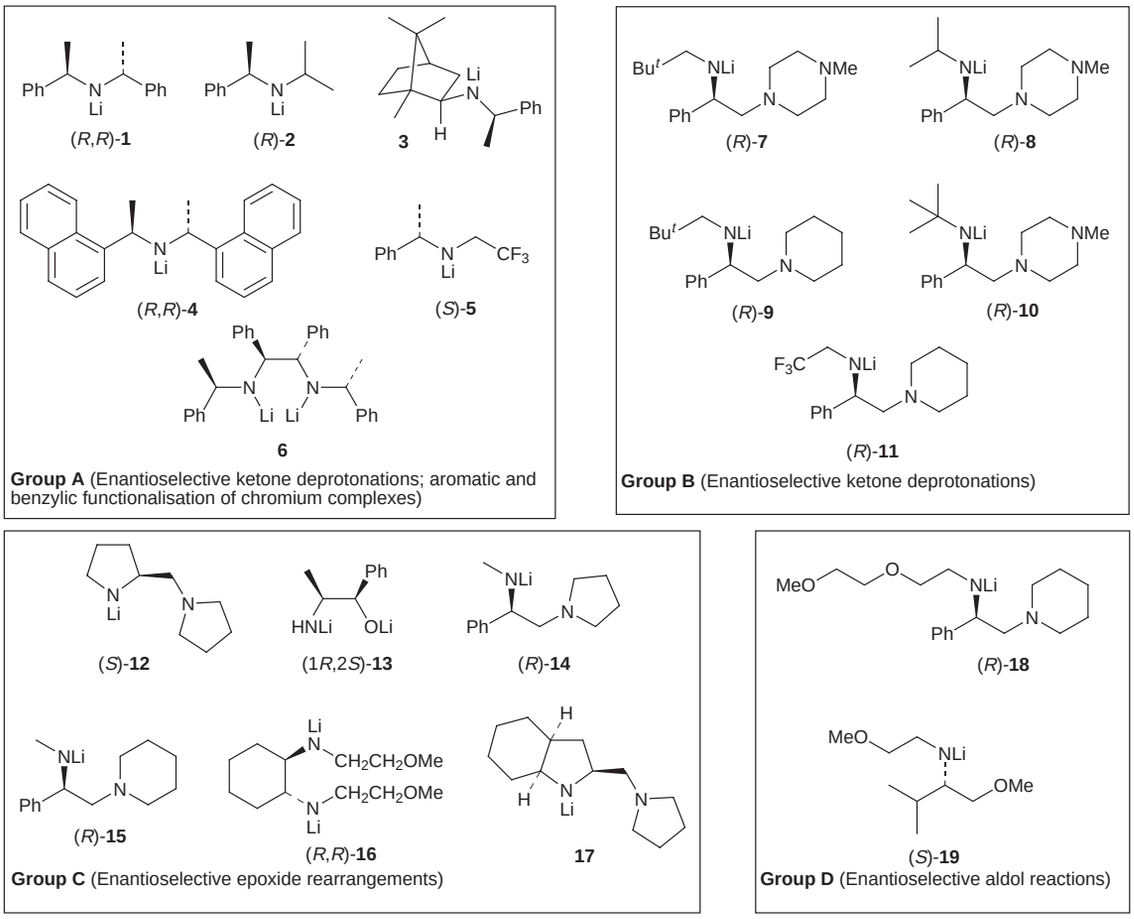
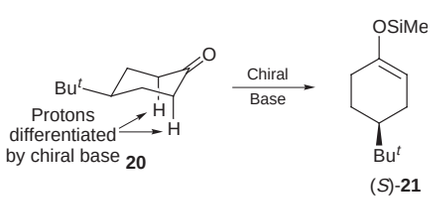


Fig. 1

2 Enantioselective deprotonation of ketones

2.1 Background

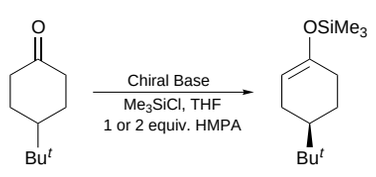
In pioneering work, the research groups of Simpkins[9] and Koga[15] independently recognised that it should be possible to use chiral lithium amide bases to desymmetrise conformationally locked cyclohexanones (*e.g.* **20**). In such systems, there is a stereoelectronic preference for removal of the axial protons and a suitably chosen chiral base should be able to discriminate between the two protons to generate preferentially one enantiomer of silyl enol ether **21** (**Scheme 4**).



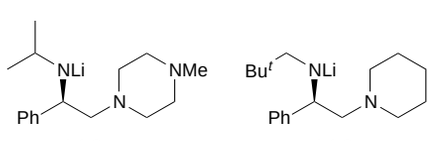
Scheme 4

Koga has recently[16] reported the full details of his study on the 4-substituted cyclohexanone **20** and a selection of the results are summarised in **Scheme 5**. Using Corey's[17] internal quench method with Me_3SiCl (in the presence of HMPA) and chiral bases (*R*)-**8** and (*R*)-**9**, silyl enol ether (*R*)-**21** was generated in good to excellent enantiomeric excess. The results obtained by Simpkins[9] for the same substrate (also under internal quench conditions) using chiral base (*R*,*R*)-**1** are included in **Scheme 6** for comparison.

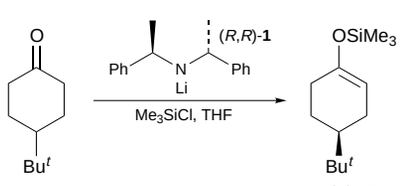
From the results presented in Scheme 5 and Scheme 6, it is useful to draw some important generalisations about enantioselective deprotonation of prochiral cyclic ketones: (i) internal quench conditions are necessary for the best levels of enantioselectivity; (ii) optimal enantioselectivity with Koga's bases (*R*)-**8** and (*R*)-**9** is obtained in the presence of HMPA; (iii) the lower the temperature, the higher the enantioselectivity; (iv)



Chiral Base	Temp/°C	Yield (%)	ee (%)
(*R*)-**8**	–78	87	77
(*R*)-**9**	–78	82	82
(*R*)-**8**	–105	52	89



Scheme 5



Temp/°C	Yield (%)	ee (%)
–78	73	69
–90	66	88

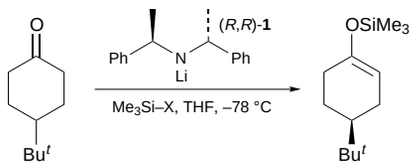
Scheme 6

comparable levels of asymmetric induction can be obtained using chiral bases derived from amines and from diamines.

2.2 Internal *versus* external quench conditions—effect of additives

Both Simpkins and Koga have shown that in order to obtain high levels of enantioselectivity in chiral base-mediated ketone deprotonations, it is necessary to trap the lithium enolates as silyl enol ethers using the Corey internal quench protocol. In order to rationalise why the internal quench conditions worked so much better, attention was focused on the role of lithium chloride which could be generated either by reaction between the chiral base and Me_3SiCl directly[18] or by silylation of the lithium enolate during the course of the reaction. As we shall see, much more information is available on the role of lithium chloride in Simpkins-like asymmetric deprotonations than in deprotonations using Koga's bases.

The first detailed investigation was carried out by Simpkins for the conversion of 4-substituted cyclohexanone **20** into silyl enol ether (*S*)-**21** using chiral base (*R*,*R*)-**1** (**Scheme 7**).[19] There was a significant difference between the enantiomeric excess of silyl enol ether (*S*)-**21** obtained under internal and external quench conditions. More interesting, however, was the observation that an even higher enantioselectivity (83% ee) could be obtained if the externally quenched reaction was carried out in the presence of 0.5 equivalents of lithium chloride (with respect to the chiral base). As part of this study, it was also demonstrated that a much lower enantioselectivity was obtained using Me_3SiBr under internal quench conditions.



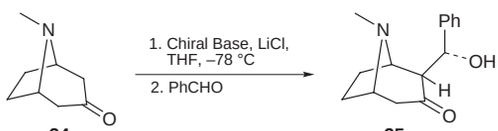
20 (*S*)-**21**

X	Quench	LiCl (equiv.)	ee (%)
Cl	Internal	–	69
Cl	External	–	23
Cl	External	0.5	83
Br	Internal	–	20

Scheme 7

Exactly the same effect was observed by Simpkins with other chiral bases and different substrates. For example, chiral base (*R*,*R*)-**1** was used to convert bicyclic ketone **22** into silyl enol ether **23** of 82–84% ee using either internal quench conditions or external quench conditions with added lithium chloride. With no lithium chloride present in the external quench, silyl enol ether **23** of only 33% ee was obtained. However, only 0.1 equivalents of lithium chloride was needed for the enantioselectivity to reach its maximum; adding more lithium chloride did not appear to make any difference (**Scheme 8**).[20]

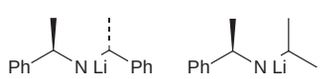
With the knowledge that essentially the same levels of enantioselectivity could be obtained using external quench conditions with added lithium chloride and internal quench conditions, reactions with electrophiles other than Me_3SiCl could now be attempted. Both Simpkins[19,20] and Majewski[21,22] have independently studied the effect of lithium chloride on the enantioselective deprotonation of tropinone **24** followed by trapping with benzaldehyde; their results are summarised and compared in **Scheme 9**. Although there are some small discrepancies in the absolute values of the enantiomeric excesses obtained, the trends in the two sets of results are the same. In the absence of lithium chloride, aldol **25** (as a single *exo*, *anti* diastereoisomer[23]) was obtained in low enantiomeric excess (22–35% ee) with each of the chiral bases (*R*,*R*)-**1** and (*R*)-**2** but, as expected, much better levels of enantioselectivity were observed when lithium chloride was present. For the aldol reactions of tropinone **24**, the best results were obtained when 1 equivalent of lithium chloride was added.



24 **25**

Chiral Base	Simpkins[19,20]		Majewski[21,22]	
	LiCl (equiv.)	ee (%)	LiCl (equiv.)	ee (%)
(*R*,*R*)-**1**	–	24	–	35
	–	–	0.25	78
	0.5	78	0.5	85
			1.0	88
			1.0*	95*
(*R*)-**2**	–	24	–	22
	–	–	0.25	65
	0.5	66	0.5	71
			1.0	68

* Lithium chloride generated by premixing *n*-butyllithium and the hydrochloride salt of the amine precursor to chiral base (*R*,*R*)-**1**

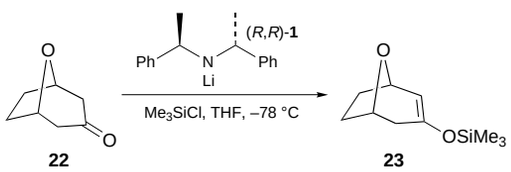


(*R*,*R*)-**1** (*R*)-**2**

Scheme 9

Additionally, Majewski demonstrated that aldol **25** of even higher enantiomeric excess (95% ee) could be generated if an alternative method of introducing the lithium chloride was used. Instead of adding the lithium chloride as a solid, 2 equivalents of *n*-butyllithium were used to deprotonate the hydrochloride salt of the amine thus producing a THF solution of chiral base (*R*,*R*)-**1** and lithium chloride. As well as improving the selectivity of the subsequent enantioselective deprotonation of tropinone **24**, the procedure based on the amine hydrochloride salt has a number of practical advantages. For example, unlike their hydrochloride salts, most chiral amines are difficult to purify and manipulate, are hygroscopic and readily absorb carbon dioxide from the atmosphere; lithium chloride is also difficult to dry and readily absorbs moisture from the air. Use of the hydrochloride salt procedure alleviates these problems.

The effect of other inorganic salts on the aldol reaction of tropinone **24** has also been investigated. When Simpkins carried out the reaction of tropinone **24** with chiral base (*R*,*R*)-**1** followed by reaction with benzaldehyde in the presence of lithium bromide, lithium fluoride, potassium chloride, sodium chloride, sodium bromide or magnesium bromide, aldol **25** was obtained with essentially the same enantiomeric excess as that obtained in the absence of any salts.[19] Similar results were obtained by Majewski using chiral base (*R*)-**2** in the presence of lithium perchlorate and lithium iodide. However, in contrast to the

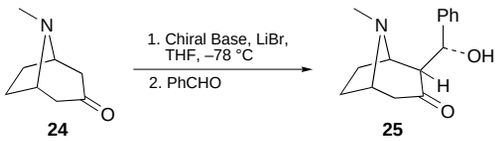


22 **23**

Quench	LiCl (equiv.)	ee (%)
Internal	–	82
External	–	33
External	0.1	84
External	0.7	83
External	1.5	84

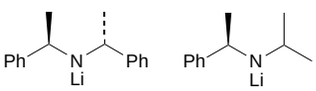
Scheme 8

results presented by Simpkins with chiral base (*R*,*R*)-**1**, lithium bromide was seen to behave in a similar fashion to lithium chloride: aldol **25** of 69% ee was obtained using chiral base (*R*)-**2** and 1 equivalent of lithium bromide for the deprotonation of tropinone **24** (**Scheme 10**).[21]



24 **25**

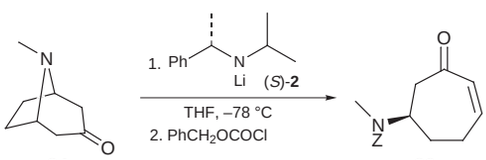
Chiral Base	LiBr (equiv.)	ee (%)
(*R*,*R*)-**1**	0	24
(*R*,*R*)-**1**	0.5	~24
(*R*)-**2**	0	24
(*R*)-**2**	1.0	69



(*R*,*R*)-**1** (*R*)-**2**

Scheme 10

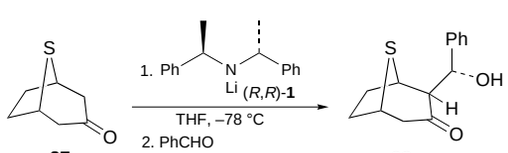
The effect of adding different amounts of lithium chloride on the enantioselectivity of deprotonation of other cyclic ketones and subsequent reaction with different electrophiles has also been explored. The results are summarised in **Scheme 11**,[23,24] **Scheme 12**[25] and **Scheme 13**[21,22] and the trends observed are exactly consistent with those already described. The transformation depicted in Scheme 11 is of particular note as it is a novel chiral base-mediated reaction:[23] treatment of the enantiomerically enriched lithium enolate generated from tropinone **24** with benzyl chloroformate generated enone **26**. The reaction presumably proceeds *via N*-acylation followed by elimination (with concomitant ring opening).



24 **26**

LiCl (equiv.)	ee (%)
–	45
0.1	50
0.5	62

Scheme 11

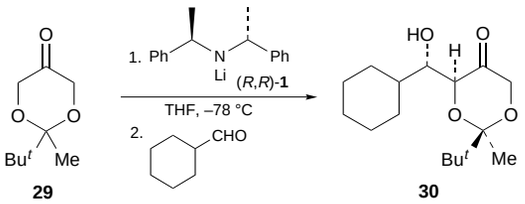


27 **28**

LiCl (equiv.)	ee (%)
–	16
0.1	73
0.6	86
1.0	76

Scheme 12

The only other inorganic salt additive that has been observed to have a significant effect on the enantioselectivity of ketone deprotonations is zinc chloride. Simpkins studied the aldol reactions of bicyclic ketones **22**, **24** and **27** using chiral base

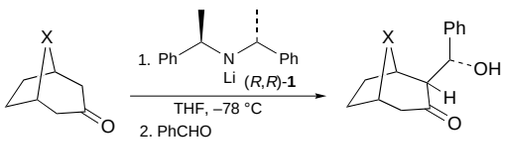


29 **30**

LiCl (equiv.)	ee (%)
–	18
0.25	38
0.5	60
1.0	59

Scheme 13

(*R*,*R*)-**1** in the presence of zinc chloride (**Scheme 14**).[19,25] In a similar fashion to lithium chloride, the enantiomeric excessses of the aldol products improved as the amount of zinc chloride was increased. However, it is interesting to note that in contrast to the lithium chloride effect described above, the enantioselectivities of the aldol reactions tailed off dramatically as the amount of zinc chloride added reached 1 equivalent (*cf.* Scheme 9 and Scheme 13 with Scheme 14).



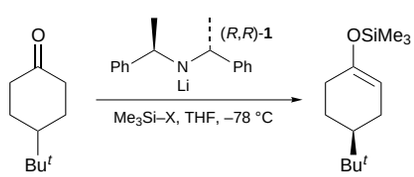
24; X = NMe
22; X = O
27; X = S

25; X = NMe
31; X = O
28; X = S

X = NMe		X = O		X = S	
$ZnCl_2$ (equiv.)	ee (%)	$ZnCl_2$ (equiv.)	ee (%)	$ZnCl_2$ (equiv.)	ee (%)
–	24	–	34	–	15
0.5	85	0.1	74	0.1	76
		0.4	70	0.4	86
		0.6	68	0.6	74
		1.0	47	1.0	21

Scheme 14

Recently, Koga[26] has reinvestigated the enantioselective deprotonation of 4-substituted cyclohexanone **20** using chiral base (*R*,*R*)-**1** under internal and external quench conditions. In particular, he focused on the role of lithium chloride, lithium bromide and lithium iodide in these reactions and has been able to draw some important mechanistic conclusions. The full results are presented in **Scheme 15** (*cf.* the results obtained by Simpkins in Scheme 7).



20 (*S*)-**21**

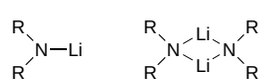
X	Quench	Additive (equiv.)	ee (%)
Cl	Internal	–	90
Br	Internal	–	65
I	Internal	–	31
Cl	External	–	44
Cl	External	LiCl (0.5)	87
Cl	External	LiCl (1.0)	88
Cl	External	LiCl (3.0)	88

Scheme 15

Using internal quench conditions with Me_3SiCl, Me_3SiBr and Me_3SiI, silyl enol ether (*S*)-**21** of considerably higher enantiomeric excess was obtained with Me_3SiCl. These results are consistent with those of Simpkins although the enantiomeric excesses measured by Koga were slightly higher for the same transformation. Lower enantioselectivity (44% ee) was observed when the reaction was carried out with (*R*,*R*)-**1** under external quench conditions with no additives. However, in the presence of 0.5 equivalents of lithium chloride (with respect to the chiral base), the enantioselectivity improved dramatically (to 87% ee) and did not change even when 3.0 equivalents of lithium chloride were used (Scheme 15). In contrast, in order to see the same sort of improvement with lithium bromide under external quench conditions, it was necessary to add 3.0 equivalents of the inorganic salt. This result is consistent with the results reported by Simpkins and Majewski in Scheme 10. Finally, however much lithium iodide was added, there was no improvement in the enantioselectivity over the standard external quench conditions with no additives.

In an attempt to rationalise why enantioselectivities are higher when deprotonations are carried out in the presence of lithium chloride, researchers in this field have turned their attention to the likely solution structures of the lithium amide bases. It is clear that lithium chloride can affect the aggregation state of the lithium amide bases in solution and the formation of a new mixed dimer could account for the different enantioselectivities.

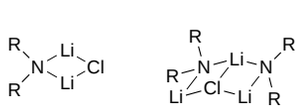
Koga has provided an elegant rationalisation of the results that he obtained for the deprotonation of 4-substituted cyclohexanone **20** using chiral base (*R*,*R*)-**1** (Scheme 15).[26] In the absence of any lithium chloride (external quench conditions), the lithium amide base will probably exist as either the monomer **32** or the homo dimer **33** (**Fig. 2**). ^{6}Li and ^{15}N NMR spectroscopic studies revealed that the homo dimer **33** was by far the major structural component in a THF solution of chiral base (*S*,*S*)-**1**. Indeed, X-ray crystallographic analysis by Simpkins and Mair on crystals of chiral base (*R*,*R*)-**1** obtained from hexane–THF indicated the favourable formation of homo dimer **33**.[27] Koga concluded that homo dimer **33** is the species responsible for the generally poor enantioselectivities observed for deprotonation of ketones under external quench conditions with no added lithium chloride.



32 **33**

Fig. 2

When Koga carried out ^{6}Li and ^{15}N NMR spectroscopic studies on THF solutions of chiral base (*S*,*S*)-**1** in the presence of lithium chloride, two new species were identified. They were shown to be mixed dimer **34** and mixed trimer **35** (**Fig. 3**) in which lithium chloride was incorporated in the solution structures. Mixed trimer **35** has been observed in the solid state: X-ray crystallographic analysis on crystals obtained from a mixture of LDA and lithium chloride indicated a mixed trimer structure **35**.[28] The major component of a THF solution of chiral base (*S*,*S*)-**1** in the presence of more than 0.5 equivalents of lithium chloride is mixed dimer **34** and Koga has suggested that it is this species that is responsible for the highly enantioselective deprotonations of ketones.

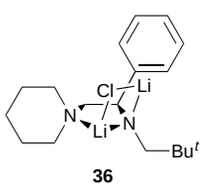


34 **35**

Fig. 3

To summarise, under external quench conditions, poor enantioselectivities are observed for ketone deprotonations using chiral bases such as (*R*,*R*)-**1** and homo dimer **33** (Fig. 2) is believed to be responsible. In contrast, much better levels of enantioselectivity are observed under internal quench conditions (lithium chloride generated by pre-mixing[18] the chiral base and Me_3SiCl or by silylation of the lithium enolate) or under external quench conditions with added lithium chloride. Mixed dimer **34** (Fig. 3) is implicated in these highly enantioselective processes.

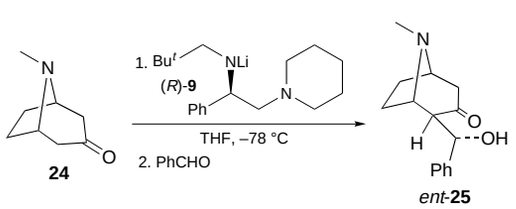
From the results presented so far in this section, it is clear that lithium and zinc chloride have a dramatic influence on the enantioselectivity observed in asymmetric deprotonations of cyclic ketones using chiral bases such as (*R*,*R*)-**1** and (*R*)-**2** which contain only one nitrogen atom. In contrast, the effect of inorganic salts such as lithium chloride on enantioselective ketone deprotonations mediated by chiral bases such as (*R*)-**7**, (*R*)-**8** and (*R*)-**9** (derived from diamines) has not been studied in much detail at all. This is particularly surprising since better enantioselectivities are also observed using these chiral bases under internal quench conditions with Me_3SiCl and presumably lithium chloride also plays an important role in these deprotonations. Indeed, Koga[29] has obtained ^{6}Li and ^{15}N NMR spectroscopic evidence to suggest that the species responsible for highly enantioselective ketone deprotonations under internal quench conditions with Me_3SiCl is mixed dimer **36** (**Fig. 4**) (*cf.* mixed dimer **34** in Fig. 3) and not a homo dimer.[30]



36

Fig. 4

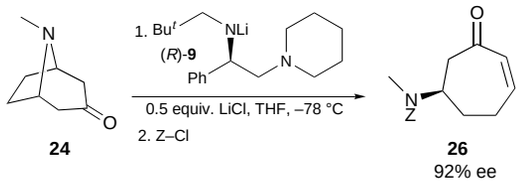
Majewski has used chiral base (*R*)-**9** to carry out ketone deprotonations in the presence of lithium chloride under external quench conditions. For example, and perhaps surprisingly, he found that the enantioselectivity of deprotonation of tropinone **24** using chiral base (*R*)-**9** followed by reaction with benzaldehyde was insensitive to the presence of lithium chloride. With or without lithium chloride added, the enantiomeric excess of the obtained aldol product *ent*-**25** was always 90% (**Scheme 16**).[21] The rearrangement of tropinone **24** into enone **26** using chiral base (*R*)-**9** in the presence of 0.5 equivalents of lithium chloride proceeded with high enantioselectivity (92% ee) (**Scheme 17**).[24] It would be interesting to see whether the same level of enantioselectivity was obtained if the lithium chloride was excluded since Majewski's results suggest that lithium chloride is not a prerequisite for high enantioselectivity in ketone deprotonations with chiral bases such as (*R*)-**9** which are generated from diamines.



24 *ent*-**25**

LiCl (equiv.)	ee (%)
–	90
0.5	90
1.0	90

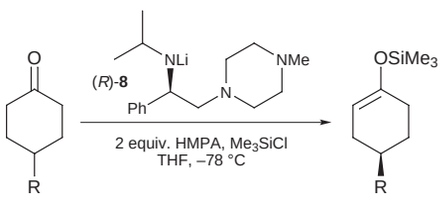
Scheme 16



Scheme 17

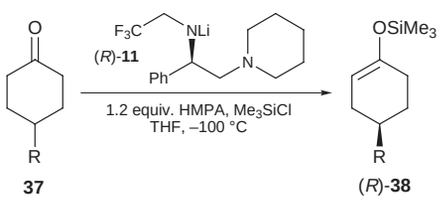
2.3 Scope and use in synthesis

Enantioselective deprotonation of 4-substituted cyclohexanones **37** under internal quench conditions with Me_3SiCl is probably the most well studied chiral base-mediated transformation. In an attempt to understand this process more fully, Koga has meticulously examined the effect of different chiral bases on the enantioselectivity of deprotonation of cyclohexanones **37**. The results are summarised in **Scheme 18** and **Scheme 19** and should be compared with the results obtained by Simpkins (Scheme 6).



R	Yield (%)	ee (%)
Bu^t	87	77
Ph	93	75
Pr^i	85	78
Me	68	46

Scheme 18

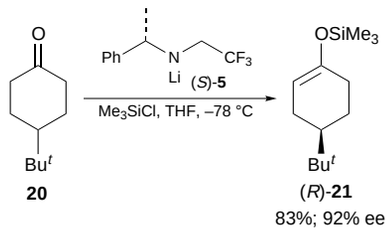


R	Yield (%)	ee (%)
Bu^t	88	93
Ph	95	93
Pr^i	92	95
Me	76	94

Scheme 19

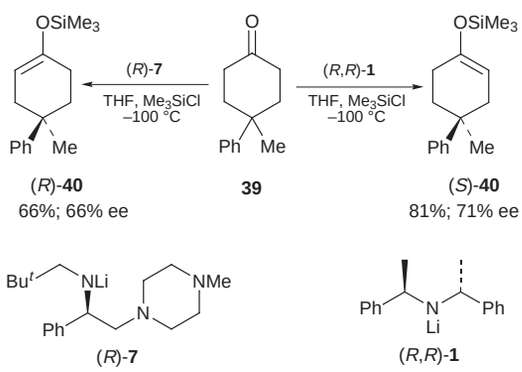
Koga found that with chiral base (*R*)-**8**, silyl enol ether (*R*)-**38** of 75–78% ee was generated when the 4-substitutent was sterically demanding but, with a small substituent (R = Me), the enantioselectivity dropped to a low 46% ee (Scheme 18).[16] In contrast to these results, much higher enantioselectivities across *all* of the four different 4-substituted cyclohexanones could be obtained if chiral base (*R*)-**11** (containing a trifluoromethyl substituent on one of the nitrogen atoms) was used (Scheme 19).[31,32] Koga has also varied the aromatic substituent in chiral bases such as (*R*)-**8** but this resulted in little improvement in enantioselectivity.[29] Very recently, Knochel used a novel C_2 symmetric chiral base containing a ferrocenyl group to generate silyl enol ether **21** with up to 67% ee.[33]

Although the results presented in Scheme 19 are impressive, there are some drawbacks: HMPA is required for optimum enantioselectivity and chiral base (*R*)-**11** is generated from a diamine which has a somewhat lengthy preparation.[10] Presumably with these drawbacks in mind, Koga has recently reported a highly enantioselective deprotonation of cyclohexanone **20** using a structurally simpler chiral base (*S*)-**5** (also containing a trifluoromethyl group). This reaction generated silyl enol ether (*R*)-**21** of 92% ee *in the absence of* HMPA (**Scheme 20**).[34]



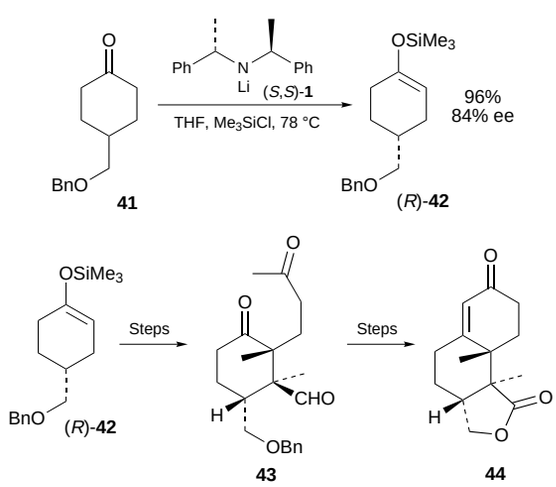
Scheme 20

There has only been one report of the use of chiral bases to enantioselectively deprotonate a 4,4-disubstituted cyclohexanone. Honda used a selection of the chiral bases developed by Simpkins and Koga to deprotonate cyclohexanone **39** under internal quench conditions (**Scheme 21**).[35] The best results were obtained with chiral bases (*R*)-**7** and (*R*,*R*)-**1** and it is interesting to notice that the enantioselectivities were lower than the corresponding reactions with 4-substituted cyclohexanones (*cf.* Scheme 6, Scheme 18, Scheme 19 and Scheme 20).

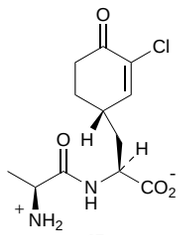


Scheme 21

The high enantioselectivities obtained for the deprotonation of simple 4-substituted cyclohexanones using chiral bases has prompted other research groups to use the methods for total synthesis. For example, A. B. Smith used chiral base (*S*,*S*)-**1** in tandem with Me_3SiCl (internal quench conditions) to generate a high yield of the functionalised silyl enol ether (*R*)-**42** of 84% ee. This compound was then further elaborated into cyclohexanone **43** and thence into tricyclic enone **44**, an advanced intermediate for the synthesis of the tremorgenic indole alkaloid penitrem D (**Scheme 22**).[36] A similar strategy was used by Wild to complete an asymmetric synthesis of the antimycotically active natural product chlorotetaine **45** (**Fig. 5**).[37,38]



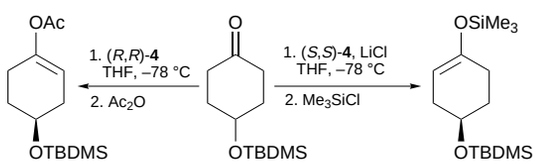
Scheme 22



45

Fig. 5

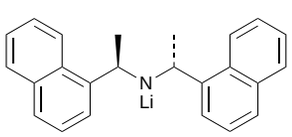
Majewski has studied in detail the enantioselective deprotonation of protected 4-hydroxycyclohexanones such as **46**. For example, deprotonation using chiral base (*R*,*R*)-**4** and trapping with acetic anhydride under external quench conditions generated enol acetate (*S*)-**47** of 74% ee.[39] However, when the same deprotonation reaction was carried out using chiral base (*S*,*S*)-**4** in the presence of lithium chloride followed by external quench with Me_3SiCl, silyl enol ether (*R*)-**48** of 90% ee was generated in 90% yield (**Scheme 23**).† Majewski demonstrated the usefulness of such an asymmetric process by converting silyl enol ether (*R*)-**48** into dihydroaquilegiolide **49** (**Fig. 6**), a naturally occurring butenolide isolated from the rhizome and caulis of *Sinomenium acutum*.[40] Recently, Parker has used virtually the same desymmetrisation approach to complete an asymmetric synthesis of the enyne A-ring synthon of the 1α-hydroxy vitamin D.[41]



(*S*)-**47**
65%; 74% ee

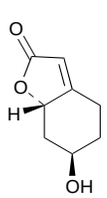
46

(*R*)-**48**
90%; 90% ee



(*R*,*R*)-**4**

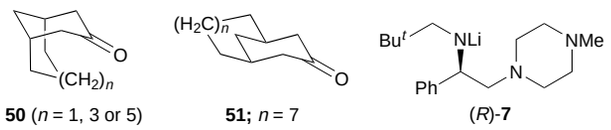
Scheme 23



49

Fig. 6

Enantioselective deprotonation of bicyclic ketones has also been studied. For example, Paquette used Koga's chiral base (*R*)-**7** to convert a range of bicyclic ketones (**50** and **51**) (**Fig. 7**) into enantiomerically enriched silyl enol ethers. The reactions were carried out in the presence of HMPA under external quench conditions: from ketones **50**, silyl enol ethers of 36% ee ($n = 1$), 100% ee ($n = 3$) and 95% ee ($n = 5$) were obtained whilst ketone **51** was converted into the corresponding silyl enol ether of 47% ee.[42] The simpler *cis*-3,5-dimethylcyclohexanone has previously been converted into the silyl enol ether by Koga[43] and, more recently, by Majewski[44] with similar levels of asymmetric induction. During research directed towards an asymmetric synthesis of reiswigin A, MaGee studied the enantioselective deprotonation of bicyclic ketone **52**. The highest level of enantioselectivity was obtained using Koga's chiral base (*R*)-**7** in combination with Me_3SiCl but without added HMPA (**Scheme 24**).[45]

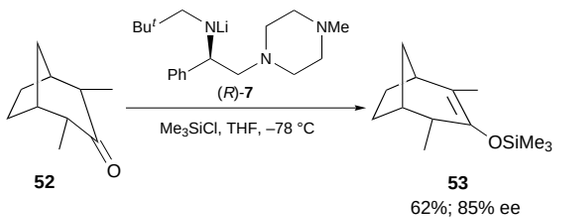


50 (n = 1, 3 or 5)

51; n = 7

(*R*)-**7**

Fig. 7

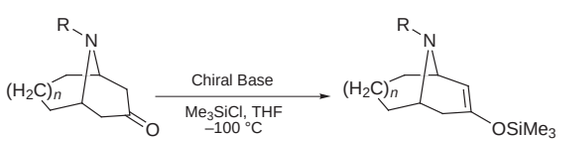


52

53
62%; 85% ee

Scheme 24

In order to prepare enantiomerically enriched building blocks for alkaloid synthesis, Momose has extensively studied the enantioselective deprotonation of a range of carbamate-protected azabicyclic ketones **54** using Koga's chiral base (*R*)-**10**. Irrespective of the ring size, silyl enol ethers of ⩾90% ee were obtained under internal quench conditions (**Scheme 25**).[46,47] These silyl enol ethers were then used as key intermediates in the synthesis of a number of naturally occurring alkaloids such as (+)-pinidine hydrochloride, (+)-monomorine I and (−)-indolizidine 223AB (**Fig. 8**).[48,49]

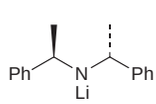


54

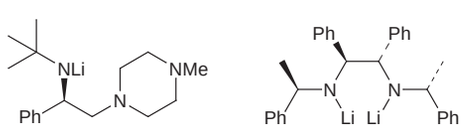
55

Chiral Base	R	n	Yield (%)	ee (%)
(*R*)-**10**	CO_2Bn	0	89	90*
(*R*)-**10**	CO_2Me	1	94	93*
(*R*)-**10**	CO_2Bn	2	75	90*
(*R*,*R*)-**1**	CO_2Me	0	–	15–20
6	CO_2Me	0	84	78

* Product is *ent*-**55**



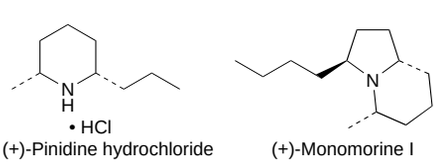
(*R*,*R*)-**1**

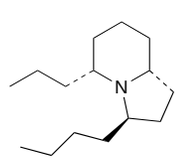


(*R*)-**10**

6

Scheme 25





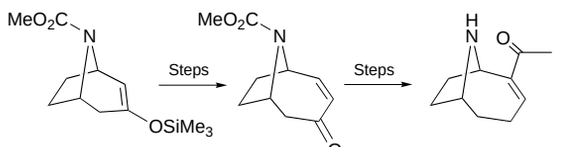
(–)-Indolizidine 223AB

Fig. 8

In contrast to Momose's results, when Simpkins used chiral base (*R*,*R*)-**1** to deprotonate the carbamate-protected tropinone

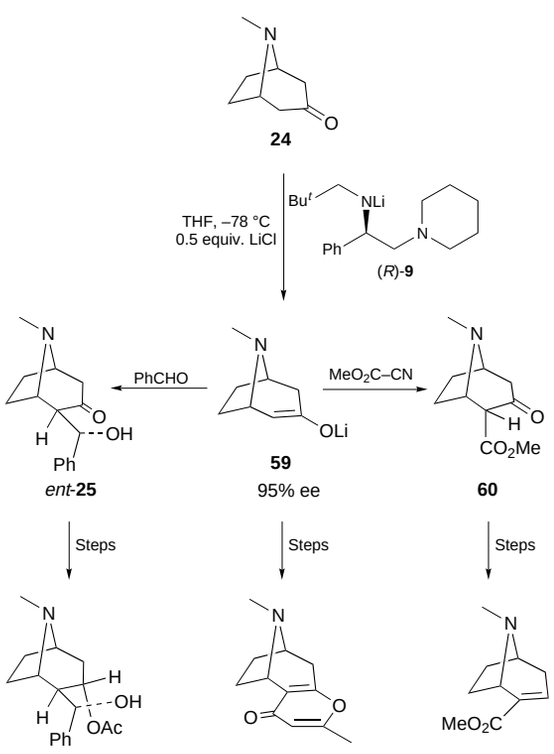
† The absolute stereochemistry of silyl enol ether **48** in the original paper (see ref. 40) was reported incorrectly.

54 ($n = 0$; R = CO_2Me), silyl enol ether **55** ($n = 0$; R = CO_2Me) of low enantiomeric excess was produced (Scheme 25). This is particularly surprising as the corresponding deprotonation of tropinone **24** using the same chiral base proceeeds with much higher enantioselectivity provided lithium chloride is present (Scheme 9). However, by employing dilithiated chiral base **6**, Simpkins was able to synthesise silyl enol ether **55** ($n = 0$; R = CO_2Me) of 78% ee which was then used in the total synthesis of (−)-anatoxin a **58**, an agonist of the acetylcholine receptor (**Scheme 26**).[50]



Scheme 26

Enantioselective deprotonation of tropinone **24** using chiral bases is a particularly well studied transformation[19–24] and Majewski has used such a desymmetrisation process as the starting point in the synthesis of a number of alkaloids. The chiral bases developed by Simpkins and Koga work just as well as each other in the asymmetric deprotonation of tropinone **24**. As an example, treatment of tropinone **24** with Koga's chiral base (*R*)-**9** in the presence of 0.5 equivalents of lithium chloride generated lithium enolate **59** of 95% ee as shown after trapping with electrophiles. In this way, Majewski was able to prepare a wide range of alkaloids such as *ent*-knightinol **61**, *ent*-isobellendine **62** and *ent*-anhydroecgonine **63** as shown in **Scheme 27**.[51,52]



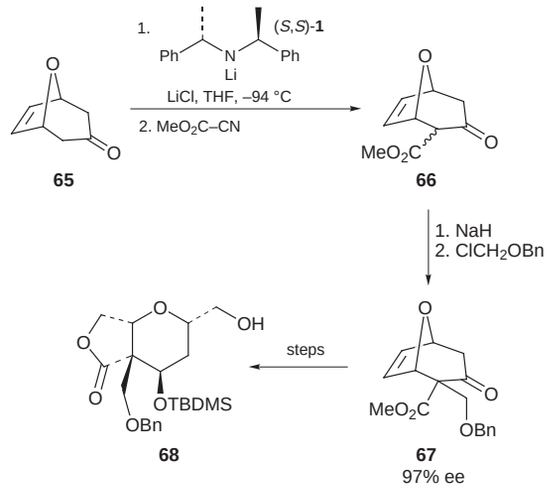
Scheme 27

Other bicyclic ketones, structurally related to tropinone **24,** have also been deprotonated using chiral bases. Simpkins has been particularly active in this area studying the enantioselective deprotonation of ketones **22** and **64** (**Fig. 9**) and then using the silyl enol ether products in *C*-nucleoside synthesis.[53,54]

In related work, Hoffmann deprotonated bicyclic ketone **65**

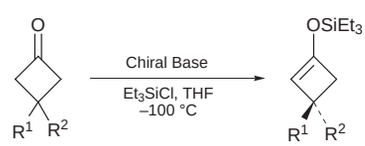
Fig. 9

using chiral base (*S*,*S*)-**1** in the presence of lithium chloride under external quench conditions and trapped the resulting enolate with Mander's reagent to produce a diastereomeric mixture of adducts **66**. Subsequent enolisation of **66** using sodium hydride and stereoselective alkylation with benzyloxymethyl chloride afforded ketone **67** of 97% ee which was elaborated to **68**, an intermediate in the synthesis of the marine natural product lasonolide A (**Scheme 28**).[55]



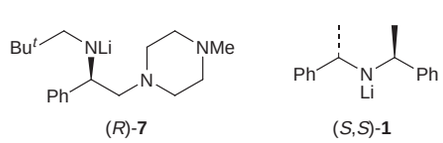
Scheme 28

Interestingly, there have been no reports on the use of chiral bases in the enantioselective deprotonation of cyclopentanones. Honda, however, has used chiral bases to deprotonate 3-substituted cyclobutanones **69** (**Scheme 29**).[56]



Chiral Base	Additive (equiv.)	R^1	R^2	Yield (%)	ee (%)
(*R*)-**7**	HMPA (1.0)	Ph	H	68	47
(*R*)-**7**	HMPA (1.0)	Ph	Me	68	78
(*S*,*S*)-**1**	–	Ph	H	67	92
(*S*,*S*)-**1**	–	Ph	Me	85	12*

* Reaction carried out at –78 °C



Scheme 29

With a monosubstituted cyclobutanone, highest enantioselectivity (92% ee) was observed when chiral base (*S*,*S*)-**1** was used under internal quench conditions (with triethylsilyl chloride). In contrast, for a 3,3-disubstituted cyclobutanone, the use of chiral base (*R*)-**7** in the presence of HMPA gave optimum enantioselectivity. Oxidative cleavage of the silyl enol ethers produced from deprotonating both the mono- and di-substituted cyclobutanones generated a range of interesting lactones and acids (**Fig. 10**). Honda's synthetic work included

the preparation of lactone **74**, a compound which has previously been converted into the antitumour antibiotic (−)-methylenolactocin.[57] In addition, by applying the asymmetric desymmetrisation strategy to more functionalised cyclobutanones, Honda was able to prepare the naturally occurring (−)-savinin[58] and the phosphodiesterase inhibitor (−)-rolipram[59] (**Scheme 30**).

In principle, it should be possible to use a chiral base to effect a kinetic resolution of a chiral ketone *via* enantioselective deprotonation. However, this approach has so far not met with much success and only a handful of examples have been reported.[60–62] Most recently, Simpkins has used chiral bases to kinetically resolve chiral imidazolinones[63] and β-lactams[64] and he has also reported a regiodivergent resolution mediated by a chiral base.[65]

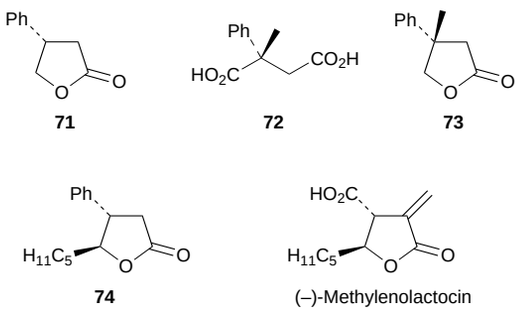
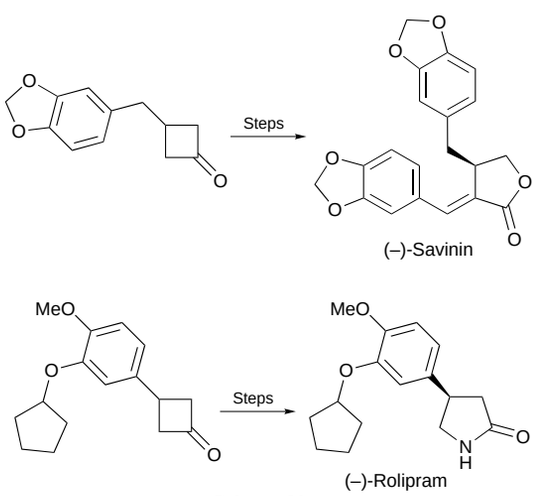


Fig. 10



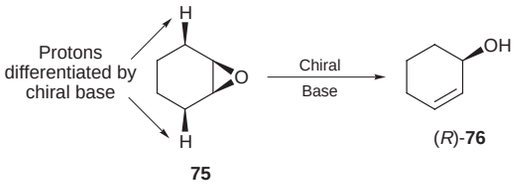
Scheme 30

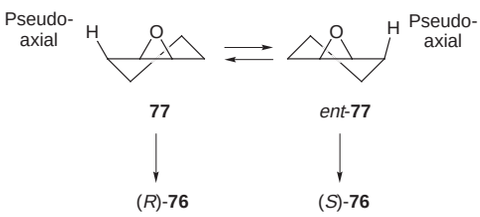
3 Enantioselective rearrangement of epoxides to allylic alcohols

3.1 Background

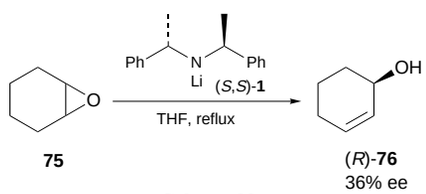
The rearrangement of epoxides to allylic alcohols using non-chiral lithium amides (*e.g.* lithium diethylamide) is a well-known synthetic transformation which has previously been reviewed.[66] The preferred mechanism for the rearrangement process with cyclohexene oxides involves *syn* β-elimination of a pseudo-axial proton[67] although with cyclopentene oxides, an α-lithiation mechanism cannot be ruled out.[68] It was Whitesell who first realised that it should be possible to use a chiral lithium amide base to differentiate between the two *syn* β-protons in cyclohexene oxide **75** and hence produce enantiomerically enriched allylic alcohol **76** (**Scheme 31**). In fact, because of the preferred *syn* β-elimination of a pseudo-axial proton, the chiral base actually distinguishes between enantiotopic conformations **77** and *ent*-**77**.

In 1980, Whitesell treated cyclohexene oxide **75** with chiral base (*S*,*S*)-**1** (containing about 20% of the *meso* isomer) in refluxing THF and obtained optically active allylic alcohol (*R*)-**76** (**Scheme 32**) in moderate enantiomeric excess (*ca.* 36% based





Scheme 31

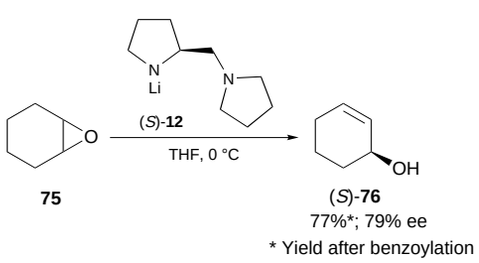


Scheme 32

on optical rotation).[7] Although the enantiomeric excess of allylic alcohol **76** generated in this way was not spectacularly high, the results demonstrated the principle of using a chiral base to discriminate between a pair of enantiotopic protons in a symmetrical epoxide. Perhaps most importantly of all, however, Whitesell's work was the first ever example of enantioselective deprotonation using a chiral lithium amide base.

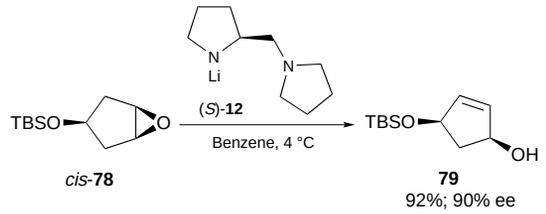
Since 1980, a number of research groups have developed the reaction further and have improved on Whitesell's seminal contribution. These developments (up to September 1996) have been documented by Simpkins,[1] Asami[69] and Hodgson[70] in comprehensive reviews. For this reason, only a selection of the key results will be summarised in this section so as to set the scene for the most recent developments in the epoxide rearrangement reaction.

Chiral lithium amide bases incorporating either a second nitrogen atom or a lithium alkoxide (Group C; Fig. 1) have proved to be the most successful types of chiral bases in epoxide rearrangement reactions. For example, when Asami repeated Whitesell's reaction with cyclohexene oxide **75** using the proline-derived chiral base (*S*)-**12**, allylic alcohol (*S*)-**76** was produced with a much improved 79% ee‡ (**Scheme 33**).[71,72] Subsequently, chiral base (*S*)-**12** was used by Asami to rearrange a variety of other cyclic and acyclic epoxides with reasonable levels of enantioselectivity.[71–73] Of particular note, rearrangement of *meso* cyclopentene oxide *cis*-**78** afforded allylic alcohol **79** of 90% ee (**Scheme 34**).[74–76]



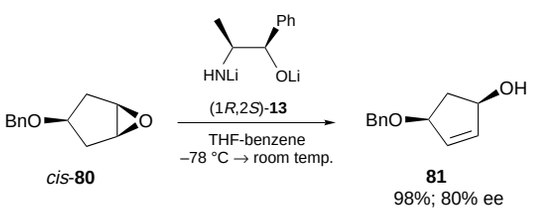
Scheme 33

‡ The originally reported enantioselectivity for this transformation was 92% (see refs. 71 and 72) but this was based on an incorrectly reported maximum optical rotation for allylic alcohol **76**.



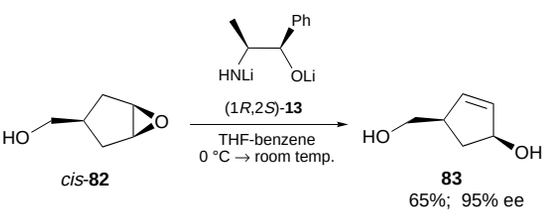
Scheme 34

Murphy has described the use of a different type of chiral base for effecting enantioselective rearrangement. Schlosser had found that a mixed base system composed of a lithium amide and an alkoxide was particularly efficacious in epoxide rearrangement reactions.[77] Based on Schlosser's results, Murphy rearranged epoxide *cis*-**80** using the dilithiated chiral base (1*R*,2*S*)-**13** (derived from norephedrine) and produced allylic alcohol **81** of 80% ee (**Scheme 35**).[78] The significance of this result is that both enantiomers of chiral base **13** are readily available thus allowing access to both enantiomeric series of allylic alcohols.



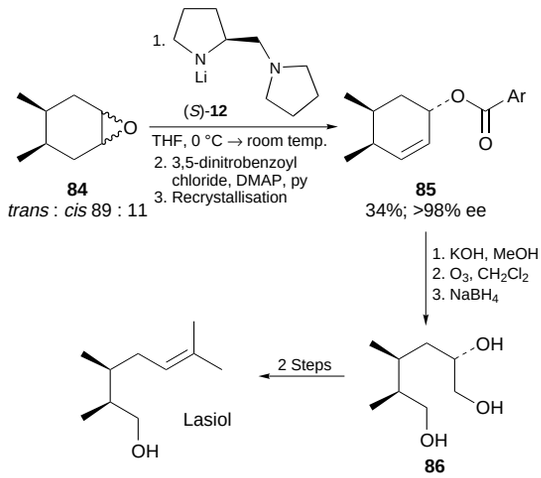
Scheme 35

Hodgson has also used the dilithiated chiral base (1*R*,2*S*)-**13** to convert the *unprotected* epoxide *cis*-**82** into allylic alcohol **83** of ⩾95% ee (**Scheme 36**).[79,80] This reaction is of particular interest since no allylic alcohol product was produced if the hydroxy group in *cis*-**82** was protected. Furthermore, the sense of asymmetric induction in the conversion of epoxide *cis*-**82** into allylic alcohol **83** was opposite to that reported by Murphy for the rearrangement of epoxide *cis*-**80** to allylic alcohol **81** (*cf.* Scheme 35 and Scheme 36) even though the same enantiomer of chiral base was used in each case. The simplicity of this chemistry is demonstrated by the fact that both (+)-**83** and (−)-**83** are now commercially available.[81]



Scheme 36

The high enantioselectivities obtained for the chiral base-mediated rearrangement of epoxides to allylic alcohols has prompted many research groups to use the methods as a key step in a number of synthetic endeavours. These include the total synthesis of carbovir,[80,82] lasiol,[83] faranal,[84] untenone A,[85] iridomyrmecin,[81] norleukotriene D_4 analogues[86] and intermediates for prostaglandin[74–76] and leukotriene synthesis.[87] As a representative example, Mori's synthesis of lasiol is summarised in **Scheme 37**.[83] An 89:11 mixture of epoxides *trans*- and *cis*-**84** was rearranged using Asami's chiral base (*S*)-**12** to produce a crude product which was benzoylated and recrystallised to give a 34% yield of enantiomerically pure **85**. Subsequent methanolysis and ozonolysis with reductive work-up afforded triol **86** which was converted into the insect pheromone lasiol.

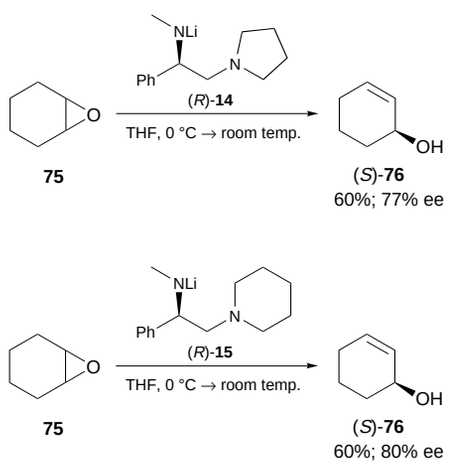


Scheme 37

3.2 Recent developments

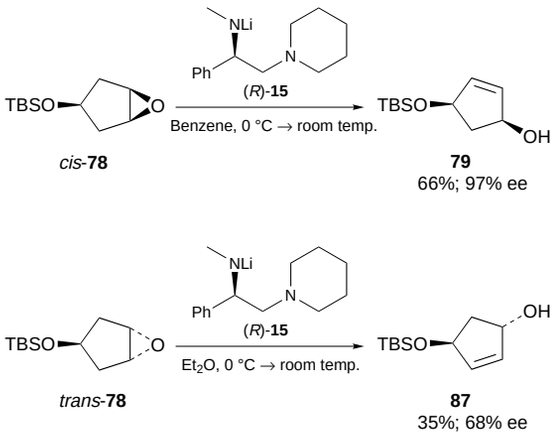
A large amount of research effort has been invested on the enantioselective epoxide rearrangement reaction. However, up until very recently, there were three serious limitations associated with the methodology that had been developed: (i) Asami's proline-derived chiral base (*S*)-**12** had wide applicability but allowed access to *only one* enantiomeric series of allylic alcohol products; (ii) dilithiated chiral base **13** (derived from norephedrine) was readily available in both enantiomeric forms but this chiral base had very limited substrate scope and (iii) except for the norephedrine-derived chiral bases, the enantioselectivity of epoxide rearrangement was invariably no better than 80%.

In order to address these limitations, Singh has recently described a significant advance in the enantioselective rearrangement of epoxides to allylic alcohols.[88–91] Singh decided to carry out rearrangement reactions using chiral bases similar in structure to those developed by Koga for ketone deprotonations (Section 2) and the initial results were very encouraging. For example, rearrangement of cyclohexene oxide **75** using either chiral base (*R*)-**14** or (*R*)-**15** generated allylic alcohol (*S*)-**76** with up to 80% ee (**Scheme 38**).[91] Since it is equally easy to prepare either enantiomer of chiral bases **14** and **15**, this methodology enables either enantiomer of allylic alcohols such as **76** to be prepared. Chiral bases such as (*R*)-**15** also have wider scope: Singh used chiral base (*R*)-**15** to rearrange *meso*-cyclopentene oxides *cis*- and *trans*-**78** (**Scheme 39**).[90,91] With epoxide *cis*-**78**, allylic alcohol **79** of 97% ee was produced and this is the highest level of enantioselectivity known for an epoxide rearrangement reaction.



Scheme 38

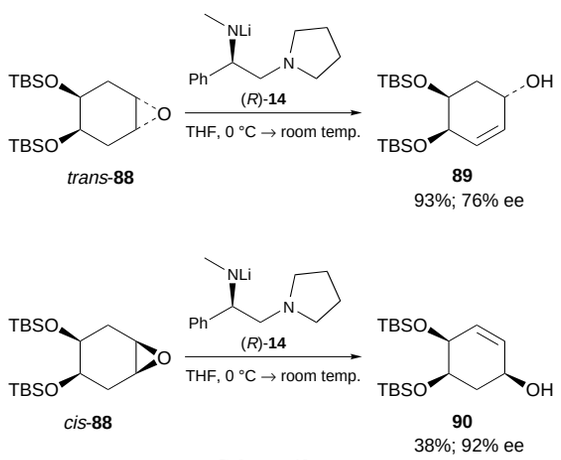
The effect of additives on the asymmetric deprotonations of ketones was discussed at length in Section 2.2. In contrast,



Scheme 39

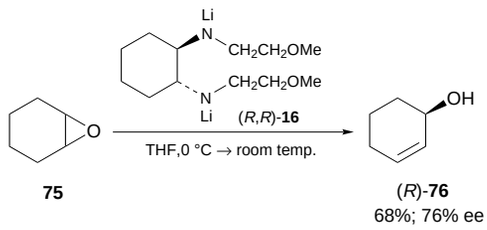
the effect of additives such as lithium halides on the enantioselectivity of epoxide rearrangements has not been investigated in any detail. Singh has demonstrated that rearrangement of cyclohexene oxide **75** using chiral base (*R*)-**14** proceeded with lower levels of enantioselectivity in the presence of lithium chloride or lithium *tert*-butoxide than when the additives were omitted.[91] Although a number of epoxide rearrangement reactions using lithium amide bases and additives such as lithium or potassium *tert*-butoxide have been reported, there has been no discussion of the effect of these additives on asymmetric induction.[77,92,93]

O'Brien has extended the use of the methodology developed by Singh. Thus, chiral base (*R*)-**14** was used to convert the *meso*-cyclohexene oxide *trans*-**88** into allylic alcohol **89** of 76% ee. Interestingly, the diastereomeric epoxide *cis*-**88** rearranged to allylic alcohol **90** of higher enantiomeric excess (92% ee) *via* a more sluggish reaction using the same chiral base (*R*)-**14** (**Scheme 40**).[94] During work on the total synthesis of lasiol (Scheme 37),[83] Mori also noticed that epoxide *cis*-**84** rearranged with higher enantioselectivity than the corresponding *trans*-epoxide.

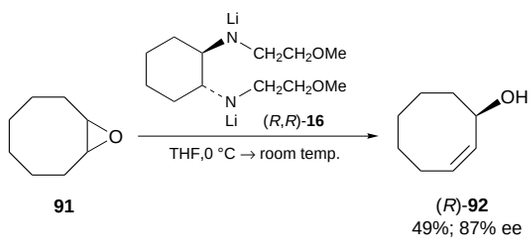


Scheme 40

Presumably guided by Murphy and Hodgson's successful use of dilithiated norephedrine as a chiral base for epoxide rearrangement reactions, Alexakis has recently reported the conversion of epoxides to allylic alcohols using dilithiated chiral bases such as (*R*,*R*)-**16** derived from C_2 symmetric diamines.[95] Treatment of cyclohexene oxide **75** with chiral base (*R*,*R*)-**16** produced allylic alcohol (*R*)-**76** of 76% ee (**Scheme 41**) which is comparable to the enantioselectivity observed by Asami[72] and Singh[91] using chiral bases (*S*)-**12** and (*R*)-**15** respectively. More interestingly, when Alexakis used chiral base (*R*,*R*)-**16** to rearrange cyclooctene oxide **91**, allylic alcohol (*R*)-**92** of 87% ee was obtained (**Scheme 42**) which is the highest reported level of enantioselectivity for this particular reaction.

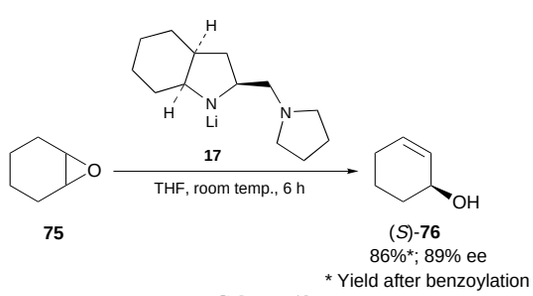


Scheme 41



Scheme 42

The most recent development in the epoxide rearrangement reaction has been described by Asami. In a search for even higher levels of enantioselectivity in the rearrangement of cyclohexene oxide **75**, Asami designed chiral base **17** which is clearly a modified version of his proline-derived chiral base (*S*)-**12** (**Scheme 43**). When this new chiral base was employed in the rearrangement reaction, allylic alcohol (*S*)-**76** of 89% ee was generated in 86% yield (Scheme 43).[96] Although chiral base **17** is only readily available in one enantiomeric form, Asami's result represents a significant improvement on previous enantioselectivities for this transformation (*cf.* Scheme 43 with Scheme 32, Scheme 33, Scheme 38 and Scheme 41). Furthermore, sub-stoichiometric amounts of chiral base **17** (0.2 equivalents) can be used in conjunction with LDA to generate allylic alcohol (*S*)-**76** with essentially the same enantiomeric excess (Section 6.1).



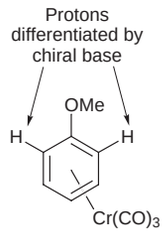
Scheme 43

4 Enantioselective reactions of tricarbonyl (η^6-arene)chromium complexes

4.1 Aromatic functionalisation

Tricarbonyl (η^6-arene)chromium complexes are useful intermediates in organic synthesis.[97] In principle, it should be possible to generate chiral non-racemic chromium complexes using chiral bases to distinguish between the two *ortho* protons in prochiral chromium complexes such as **93** (**Fig. 11**). In complex **93**, the *ortho* protons are activated to metallation by the *ortho*-directing methoxy substituent and the process would proceed *via* direct asymmetric metallation of the aromatic ring.

Traditionally, the preparation of enantiomerically enriched tricarbonyl (η^6-arene)chromium complexes has involved either classical resolution or the use of a chiral auxiliary.[98] More recently, other asymmetric methods[99] have emerged for the aromatic functionalisation of prochiral chromium complexes

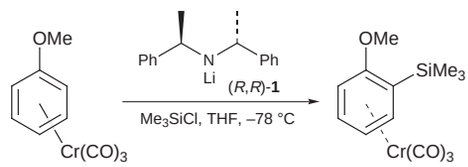


93

Fig. 11

including the use of chiral bases described by the research groups of Simpkins, Kündig and Schmalz. Uemura[100] has also described a similar approach using *n*-butyllithium in the presence of chiral diamines [*e.g.* (−)-sparteine] but as this does not involve the use of a chiral lithium amide base, it will not be discussed further here.

The synthesis of an enantiomerically enriched chromium complex *via* asymmetric metallation of a prochiral tricarbonyl (η^6-arene)chromium complex using a chiral lithium amide base was first demonstrated in 1994 by Simpkins. Thus, treatment of chromium complex **93** with chiral base (*R*,*R*)-**1** and Me_3SiCl under internal quench conditions afforded silylated complex **94** of 84% ee (**Scheme 44**).[101,102] Recrystallisation gave a 50% yield of enantiomerically pure (>97% ee) silylated chromium complex **94**.

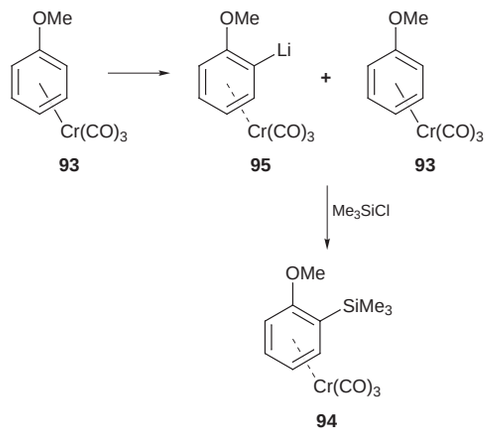


93 **94**
83%; 84% ee

Scheme 44

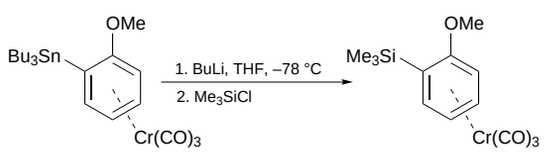
Before discussing the scope of asymmetric aromatic functionalisation of tricarbonyl (η^6-arene)chromium complexes, it is useful to summarise some of the mechanistic details of the reaction of complex **93** with chiral bases.[103] Firstly, Simpkins noticed that metallation of chromium complex **93** was complete after 5 minutes at −78 °C under internal quench conditions with Me_3SiCl or under external quench conditions if lithium chloride (0.5 equivalents) was added. In contrast, if there was no lithium chloride present, complete metallation of **93** required 3 hours at −78 °C. Clearly, lithium chloride affects the *rate* of metallation of complex **93** and Simpkins has postulated that a mixed aggregate of the chiral base with lithium chloride is responsible for the increase in rate of metallation. This is in contrast to the deprotonation of ketones (Section 2) where lithium chloride affects the enantioselectivity rather than the rate.

Simpkins also noticed that the enantiomeric excess of silylated complex **94** generated under external quench conditions with Me_3SiCl was dependent on the metallation time. In fact, the longer the metallation is left before trapping with Me_3SiCl, the lower the enantiomeric excess of silylated complex **94**. Since it is known that complete metallation in the absence of lithium chloride requires 3 hours, any quenching before the 3 hours is up involves trapping of any lithiated complex **95** and metallation and trapping of non-metallated complex **93** which will be rapid (and presumably highly enantioselective) because lithium chloride will be generated *in situ* (**Scheme 45**). Thus, there must be a process occurring during the slow metallation which leads to racemisation of the initially generated metallated complex **95** otherwise the enantiomeric excess of silylated complex **94** would be high irrespective of the metallation time. Simpkins was able to show that metallated complex **95** was configurationally stable at −78 °C since stannane **96** of 84% ee was converted stereospecifically into silylated complex *ent*-**94** (**Scheme 46**). Finally, since metallation of stannane **96** followed by treatment with chromium complex **93** generated *racemic* silylated complex **94**, he concluded that racemisation of metallated complex **95** occurs *via* non-stereoselective proton transfer between **95** and non-metallated **93** (Scheme 45).



93 **95** **93** **94**

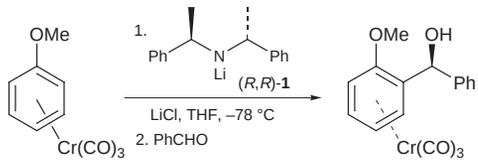
Scheme 45



96 (84% ee) *ent*-**94** (84% ee)

Scheme 46

The mechanistic results described above have also allowed Simpkins to develop suitable reaction conditions for the enantioselective metallation of chromium complex **93** and subsequent reaction with other electrophiles. Thus, metallation of complex **93** using chiral base (*R*,*R*)-**1** in the presence of lithium chloride followed by addition of benzaldehyde generated complex **97** of 65% ee (**Scheme 47**).[102,103]



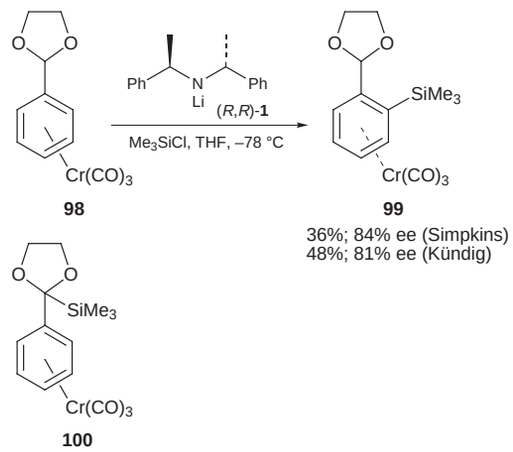
93 **97**
67%; 65% ee

Scheme 47

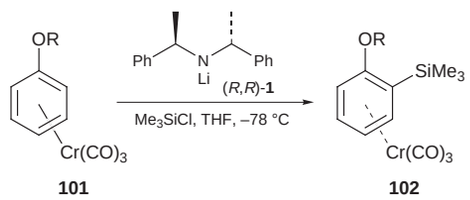
Independently of the initial results reported by Simpkins, Kündig has investigated the enantioselective metallation of prochiral tricarbonyl (η^6-arene)chromium complexes using chiral lithium amide bases.[104] In fact, both groups have reported the asymmetric synthesis of the silylated chromium complex **99** *via* metallation of acetal complex **98** using chiral base (*R*,*R*)-**1** under internal quench conditions (**Scheme 48**).[101,102,104] With complex **98**, the yield of silylated complex **99** was not particularly high since benzylic metallation and subsequent silylation (to give **100**) was a significant alternative reaction pathway.

Since the highest enantioselectivities for metallation of prochiral chromium complexes using chiral bases were initially obtained under internal quench conditions with Me_3SiCl, these conditions have been employed by Simpkins and Kündig on a variety of substrates. With alkoxy-substituted chromium complexes **101**, Simpkins found that increasing the size of the alkyl group increased the enantioselectivity (*e.g.* with R = Pr^i, **102** of 90% ee was produced) but there was no metallation of the sterically hindered complex **102** with R = Bu′ (**Scheme**

49).[101,102] In order to achieve high yields and good levels of enantioselectivity in the asymmetric metallation of carbamate-substituted chromium complex **103**, Kündig used chiral base **3** and trapped the resulting lithium derivative with a range of electrophiles (**Scheme 50**).[104]

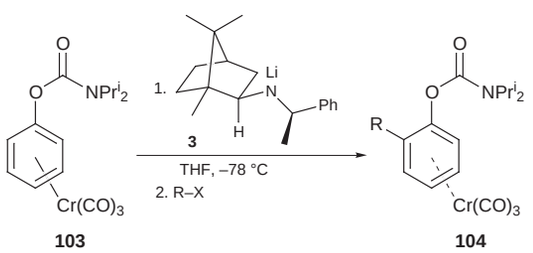


Scheme 48



R	Yield (%)	ee (%)
Me	83	84
Et	82	81
Pr^i	65	90
Bu^t	0	–
CH_2OMe	76	80

Scheme 49



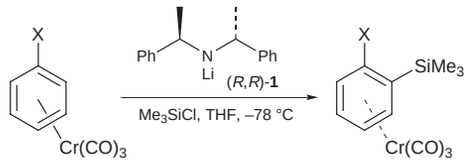
R-X	Yield (%)	ee (%)
Me_3Si-Cl	86	67
MeO_2C-Cl	71	73
Me_2NCO-Cl	85	68
Me-I	93	64
OHC-NMe_2	93	69

Scheme 50

When *ortho*-directing substitutents other than alkoxy or carbamate groups were employed in the asymmetric metallation process, the results were not as impressive. For example, Simpkins demonstrated that halogen-substituted complexes gave silylated products with either poor enantioselectivities or low yields (**Scheme 51**). Similarly, with amide substituents, enantioselectivities of no greater than 50% were observed (Scheme 51).

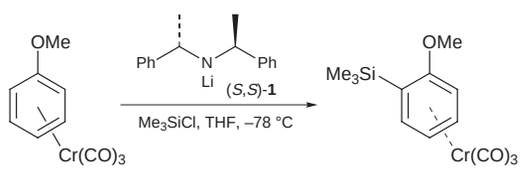
Schmalz has described the most recent contribution to the area of enantioselective metallation–silylation of prochiral chromium complexes.[105] Initially, he repeated the conversion of chromium complex **93** into **94** originally reported by Simpkins. When Schmalz used chiral base (*S*,*S*)-**1** under slightly different conditions to those described by Simpkins (Scheme 44), a 95% yield of silylated complex *ent*-**94** of 88% ee was obtained (**Scheme 52**).

Kündig then applied his optimised conditions of metallation–silylation to a range of prochiral 1,2-disubstituted tricarbonyl (η^6-arene)chromium complexes. The results are summarised in **Scheme 53**. In all cases where a 1,2-dimethoxy substituent was present good levels of enantioselectivity were

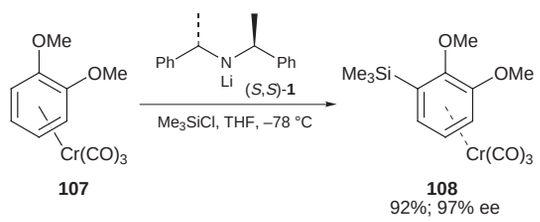


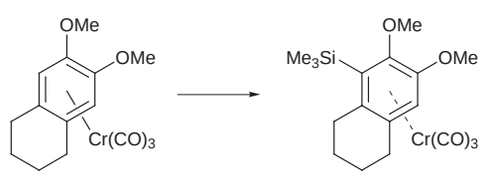
R	Yield (%)	ee (%)
Cl	27	51
F	57	16
$CONPr^i_2$	87	48
$N(Me)COBu^t$	65	44

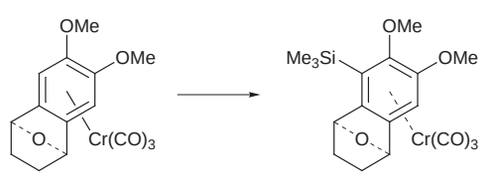
Scheme 51

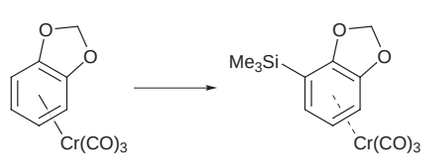


Scheme 52







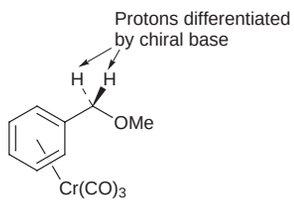


Scheme 53

observed. Of particular note was the generation of chromium complex **108** of 97% ee in 92% yield. However, when the corresponding cyclic acetal **113** was used, the enantioselectivity of the process dropped to less than 10%.[105]

4.2 Benzylic functionalisation

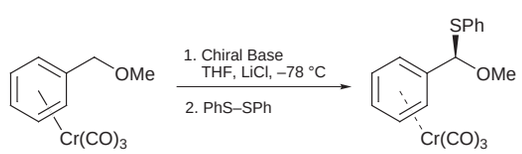
The previous section was concerned with aromatic metallation of tricarbonyl (η^6-arene)chromium complexes and, when Simpkins and Kündig studied the reaction of the acetal chromium complex **98** (Scheme 48), they both observed that benzylic substitution (to give achiral **100**) occurred. However, Simpkins and Gibson independently recognised that by suitable choice of benzylic tricarbonyl (η^6-arene)chromium complexes, enantioselective deprotonation using chiral bases would be a viable route into enantiomerically enriched chromium complexes. For example, a chiral base could be used to differentiate between the benzylic protons in a chromium complex such as **115** (**Fig. 12**).



115

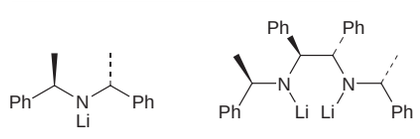
Fig. 12

Gibson has studied the enantioselective benzylic lithiation and substitution of chromium complex **115**. Initially, chiral base (*R*,*R*)-**1** was used in combination with lithium chloride for the deprotonation, and reaction with diphenyl disulfide furnished complex **116** of low enantiomeric excess (22% ee). However, a spectacular improvement in enantioselectivity was observed when dilithiated chiral base **6** was employed under exactly the same conditions: chromium complex **116** of 97% ee was generated in 86% yield (**Scheme 54**).[106] A similar improvement in enantioselectivity was also observed by Simpkins for the asymmetric benzylic functionalisation of the chromium complex **117** when he changed from chiral base (*R*,*R*)-**1** to chiral base **6** (**Scheme 55**).[102,107] Notice that there is an inherent diastereoselectivity in this reaction with metallation occurring preferentially *trans* to the sterically demanding chromium tricarbonyl group. Clearly, for benzylic lithiation of chromium complexes, it appears that chiral base **6** is the base of choice for optimal enantioselectivity. By making use of the configurational stability[108] conferred upon benzylic organolithiums of chromium complexes, Gibson has also described the conversion of the enantiomerically enriched chromium complexes into tertiary benzyl ether complexes.[109]



115 **116**

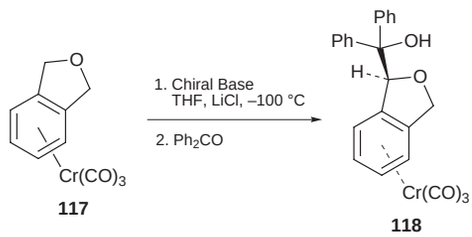
Chiral Base	Yield (%)	ee (%)
(*R*,*R*)-**1**	52	22
6	86	97



(*R*,*R*)-**1** **6**

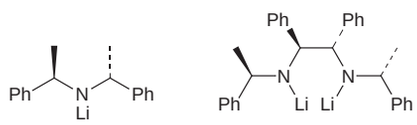
Scheme 54

Gibson has provided the most detailed investigation of enantioselective benzylic functionalisation of tricarbonyl (η^6-arene)-chromium complexes. As can be seen from the results presented in **Scheme 56**, changing the alkoxy group or the electrophile made no difference to the levels of asymmetric induction.[106] In all cases, substituted chromium complexes **120** of very high enantiomeric excess were obtained.



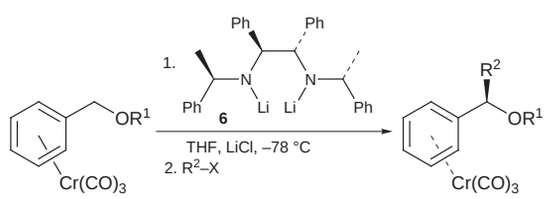
117 **118**

Chiral Base	Yield (%)	ee (%)
(*R*,*R*)-**1**	72	75
6	70	99



(*R*,*R*)-**1** **6**

Scheme 55

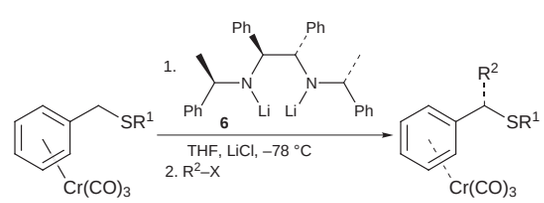


119 **120**

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

Scheme 56

Similarly, when Gibson attempted enantioselective lithiation of the corresponding benzyl sulfide complexes **121**, high enantioselectivities were observed and a selection of the results are shown in **Scheme 57**.[110] On close inspection of these recent results, it can be seen that the sense of asymmetric induction with the benzyl sulfides (Scheme 57) is *opposite* to that obtained with the corresponding benzyl ethers (Scheme 56) even though the same enantiomer of chiral base **6** was used in each case.

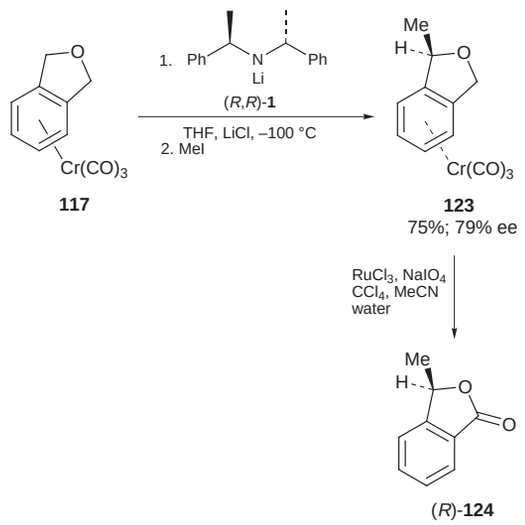


121 **122**

R^1	R^2	Yield (%)	ee (%)
Me	Bn	91	88
Me	$C_{11}H_9$	93	88
Me	Me_3Si	62	89
Bn	Me	84	91
Bn	$C_{11}H_9$	83	91

Scheme 57

Although the methodology is still in the process of being developed, Simpkins has already demonstrated that the enantiomerically enriched chromium complexes prepared *via* benzylic lithiation can be used as intermediates in synthesis. For example, he prepared lactone (*R*)-**124** of 79% ee by oxidatively decomplexing the chromium from complex **123** (**Scheme 58**).[102,107]



Scheme 58

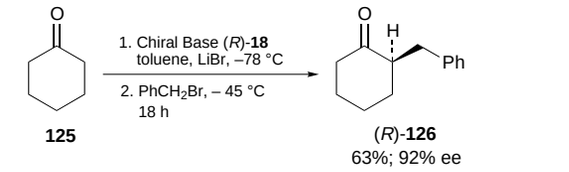
5 Miscellaneous uses of chiral bases

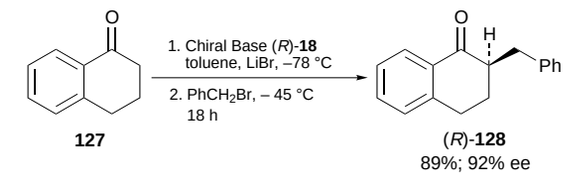
In contrast to the examples described in Section 2 where chiral bases were used to prepare *chiral* silyl enol ethers, the generation of a prochiral enolate *via* deprotonation using a chiral base followed by subsequent reaction with an electrophile can also produce enantiomerically enriched products. The enantioselectivity arises because the resulting chiral amine is complexed to the lithium enolate (presumably as an aggregate) and can thus direct the electrophile preferentially to one of the two enantiotopic faces of the enolate. In this type of process, the chiral base acts as a non-covalently bound chiral auxiliary and the many examples reported up to 1991 have already been reviewed by Simpkins.[1] Since then, there have been a few developments and, in selected cases very high enantioselectivities have been described.

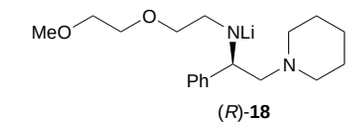
Koga has investigated the alkylation of lithium enolates generated from cyclohexanone **125** and 1-tetralone **127** using chiral base (*R*)-**18**. Provided the initial deprotonation and reaction with benzyl bromide were carried out in toluene with added lithium bromide, alkylated products **126** and **128** were generated in high enantiomeric excess (92% ee) (**Scheme 59**).[111] Chiral base (*R*)-**18** with two extra chelating alkoxy groups and the presence of lithium bromide were crucial for the success of these reactions. In addition, Koga has also successfully used chiral base (*R*)-**18** in diastereoselective alkylations of chiral lithium enolates.[112]

Chiral bases have also been used in aldol reactions.[113–115] For example, Landais used chiral base (*S*)-**19** in combination with a number of additives for the aldol reaction between ketone **129** and benzaldehyde. Aldol (2*S*,3*S*)-**130** of 78% ee was generated as a single *syn* diastereomer in reasonable yield (**Scheme 60**).[116] Using a similar mixture of additives and reagents, ester **131** was converted into *anti*-aldol (2*R*,3*R*)-**132** of 60% ee (Scheme 60). As with Koga's results, Landais observed the highest levels of enantioselectivity when the chiral base had extra chelating alkoxy groups.

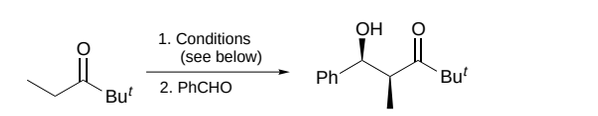
Koga has also studied the aldol reaction of ester **133** using chiral base (*R*)-**18**. Thus, deprotonation of ester **133** with LDA and chiral base (*R*)-**18** followed by reaction with benzaldehyde and acetylation generated predominantly *anti*-aldol (2*S*,3*R*)-

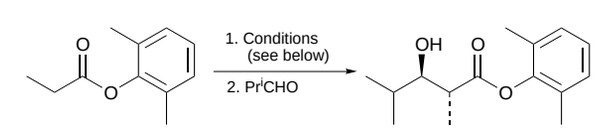




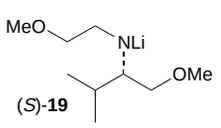


Scheme 59



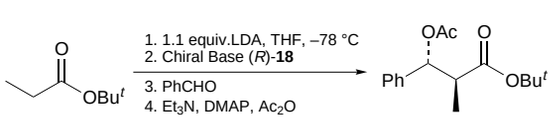


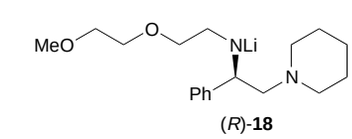
Conditions:1.2 equiv. Chiral Base (*S*)-**19**, 1.2 equiv. LDA, 1.2 equiv. BuLi 2.4 equiv. TMEDA, THF, –100 °C



Scheme 60

134 of 94% ee (**Scheme 61**).[117] It is interesting to note that the sense of asymmetric induction using chiral base (*R*)-**18** was opposite to that observed by Landais when he used chiral base (*S*)-**19** with ester **131** (*cf*. Scheme 60 and Scheme 61).

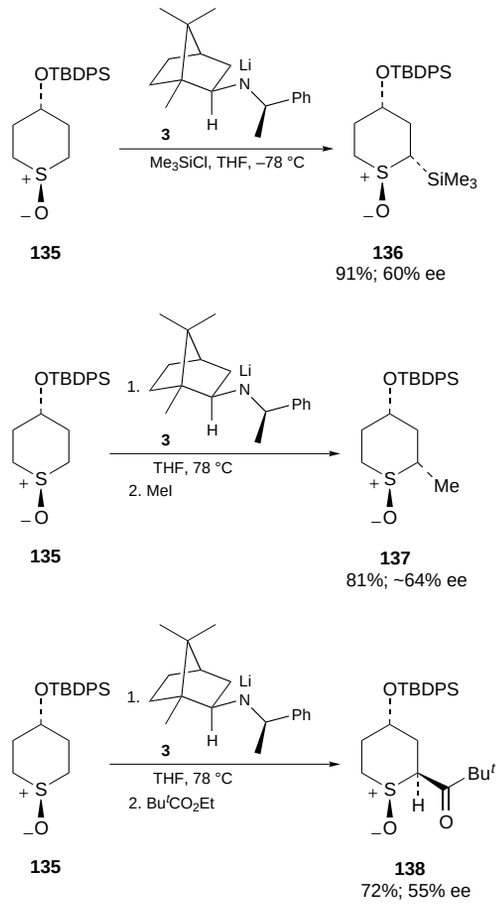




Scheme 61

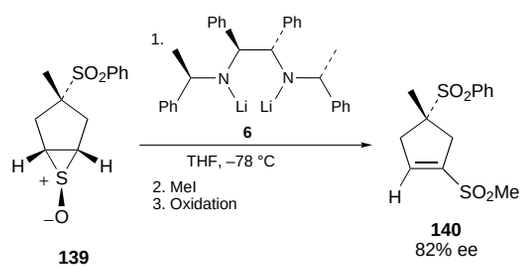
As can be seen from the results obtained by Koga and Landais (Scheme 59, Scheme 60 and Scheme 61), it is possible to carry out highly enantioselective alkylations and aldol reactions with prochiral lithium enolates using chiral lithium amide bases. However, only a few highly enantioselective reactions have been documented to date and the methodology is not as well developed as the areas that have formed major sections of this review.

The enantioselective generation and functionalisation of heteroatom stabilised carbanions using chiral bases is an area that has not received much attention. However, Simpkins has studied the asymmetric functionalisation of thiane oxide **135**. Enantioselective deprotonation of thiane oxide **135** using chiral base **3** followed by reaction with a range of electrophiles furnished adducts **136**, **137** and **138** of about 60% ee (**Scheme 62**).[118,119] These products were then further elaborated[120–122] to produce, after desulfurisation, useful chiral building blocks.



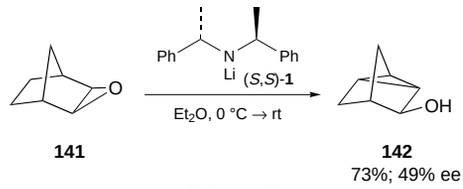
Scheme 62

More recently, Simpkins has used chiral bases to rearrange episulfoxides to alkenyl sulfoxides. Thus, treatment of a single diastereomer of episulfoxide **139** with dilithiated chiral base **6** followed by trapping with methyl iodide and oxidation afforded alkenyl sulfone **140** of 82% ee (**Scheme 63**).[123] This is the first example of such an enantioselective rearrangement.



Scheme 63

Hodgson has also been searching for new reactions in which to apply chiral lithium amide bases. For example, he found that *exo*-norbornene oxide **141** rearranged to enantiomerically enriched nortricyclanol **142** (49% ee) if chiral base (*S*,*S*)-**1** was used in place of LDA (**Scheme 64**).[124,125] In this case, the reaction proceeds *via* α-lithiation of epoxide **141**, followed by carbene formation and C–H insertion.



Scheme 64

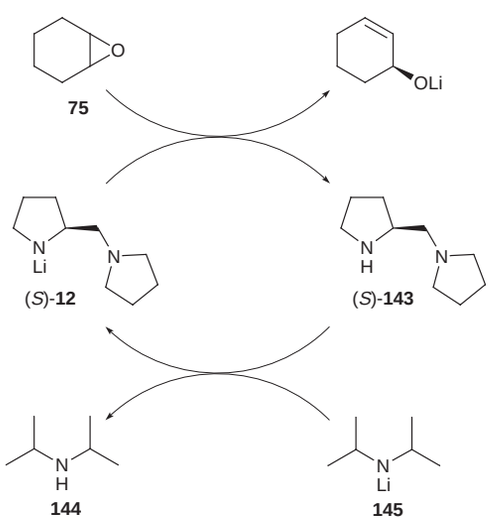
Other applications of chiral bases have been reported. Simpkins has recently used chiral base (*R*,*R*)-**1** to kinetically resolve a mixture of atropisomeric amides[126] and the same researcher has also described the use of chiral base (*R*,*R*)-**1** in the asymmetric metallation of ferrocene.[127]

6 Outlook—catalytic asymmetric uses of chiral bases

Current research into the use of chiral lithium amide bases in synthesis has reached the point where it is now possible to carry out a range of chiral base-mediated asymmetric transformations with high enantioselectivity. A very desirable situation would be if these transformations could be carried out using a sub-stoichiometric amount of the chiral base. For this approach to be successful, a way of regenerating the chiral lithium amide base from the amine (its protonated form) is required.

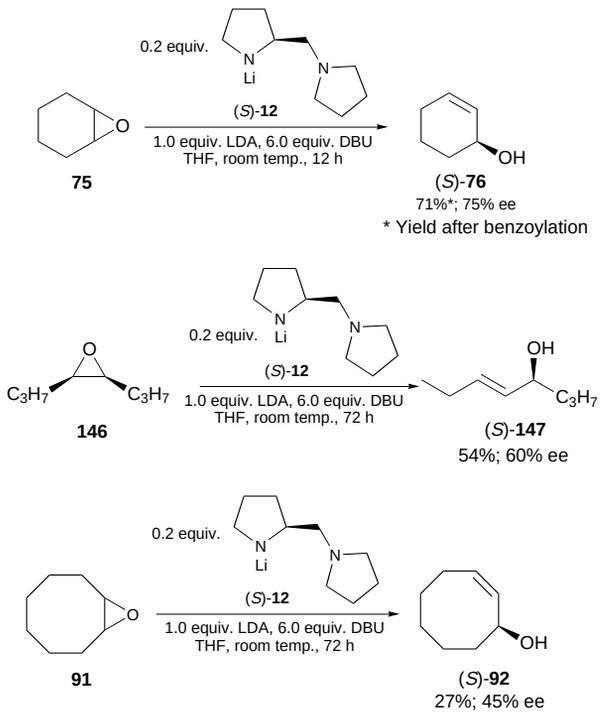
6.1 Rearrangement of epoxides to allylic alcohols

The first example of the use of chiral lithium amide bases in catalytic enantioselective deprotonation was reported for the epoxide rearrangement reaction by Asami in 1994.[128] Asami had noticed that chiral base (*S*)-**12** rearranged cyclohexene oxide **75** more readily than did LDA and from this observation, he concluded that it ought to be possible to develop a catalytic enantioselective process based on the catalytic cycle depicted in **Scheme 65**. Asami reasoned that LDA **145** could be used to regenerate the chiral lithium amide base from its protonated form (*S*)-**143**. The success of this approach would rely on the fact that cyclohexene oxide would not be rearranged at an appreciable rate by achiral LDA **145**.



Scheme 65

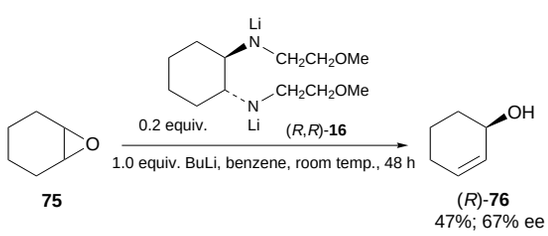
Based on this reasoning, Asami attempted the rearrangement of cyclohexene oxide **75** using 0.2 equivalents of chiral base (*S*)-**12** in the presence of 1 equivalent of LDA. Provided the reaction was carried out in the presence of excess DBU, a good yield of allylic alcohol (*S*)-**76** of 75% ee was obtained (**Scheme 66**).[128] The level of enantioselectivity with cyclohexene oxide **75** under these catalytic conditions is essentially the same as that obtained with a stoichiometric quantity of chiral base (*S*)-**12**



Scheme 66

(Scheme 33). In addition, other epoxides can be converted into enantiomerically enriched allylic alcohols using the catalytic process (Scheme 66).

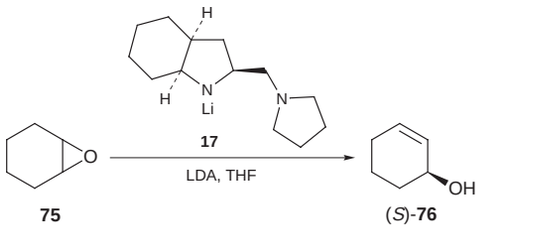
Alexakis has also reported the catalytic enantioselective rearrangement of cyclohexene oxide **75** to allylic alcohol (*R*)-**76** of 67% ee using the dilithiated chiral base (*R*,*R*)-**16** (**Scheme 67**).[95] In this case, *n*-butyllithium is used to regenerate the chiral base and it is perhaps a little surprising to discover that *n*-butyllithium and cyclohexene oxide **75** are compatible with each other at room temperature.



Scheme 67

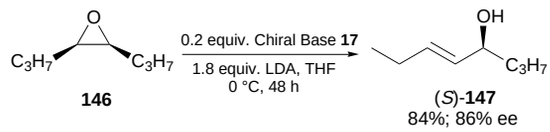
When Asami attempted the catalytic rearrangement of cyclohexene oxide **75** using chiral base **17**, he found that it was no longer necessary to employ excess DBU to get a successful catalytic process. Instead, treatment of cyclohexene oxide **75** with 0.2 equivalents of chiral base **17** and 1.8 equivalents of LDA produced a very high yield of allylic alcohol (*S*)-**76** of 88% ee after just 6 hours at room temperature (**Scheme 68**).[96] Reducing the amount of chiral base **17** to only 0.05 equivalents did not significantly reduce the enantioselectivity of the process and optimum enantioselectivity (94%) was obtained using 0.2 equivalents of chiral base **17** and 1.8 equivalents of LDA at 0 °C for 20 hours (Scheme 68).

The new catalytic conditions using chiral base **17** represent a significant advance in chiral base chemistry. Asami was also able to show that acyclic epoxides, notoriously poor substrates for the asymmetric rearrangement reaction, can be converted into allylic alcohols with high levels of enantioselectivity. For example, using a catalytic amount of chiral base **17**, epoxide **146** was transformed into allylic alcohol (*S*)-**147** of 86% ee (**Scheme 69**).



Equiv. **17**	Equiv. LDA	Temp (°C)	Time (h)	Yield (%)	ee (%)
0.2	1.8	rt	6	95	88
0.05	1.95	rt	12	93	85
0.2	1.8	0	20	89	94

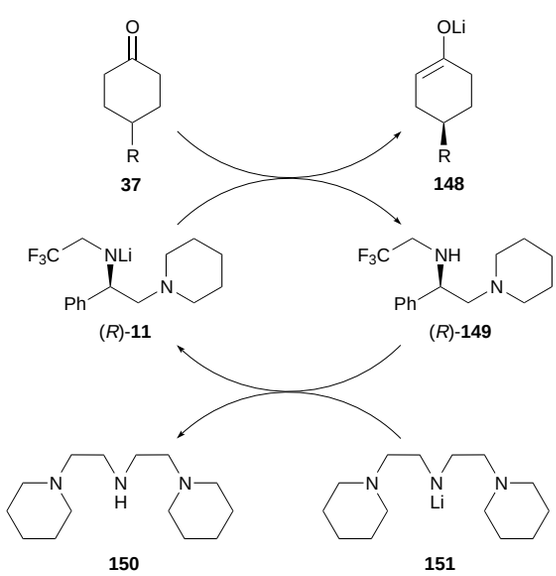
Scheme 68



Scheme 69

6.2 Ketone deprotonation and enolate alkylation

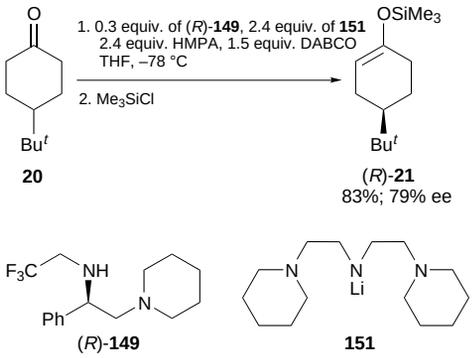
Koga has reported an approach to the catalytic asymmetric deprotonation of 4-substituted cyclohexanones which has a similar basis to that described by Asami for the catalytic asymmetric epoxide rearrangement. The catalytic cycle that Koga proposed to set up is shown in **Scheme 70**. In this case, the chiral base would be regenerated by using a stoichiometric amount of achiral lithium amide **151**. It was suggested that catalysis would be possible since lithium amides with two coordinating nitrogen groups (as in **151**) are less reactive in ketone deprotonations than those such as (*R*)-**11** derived from diamines.



Scheme 70

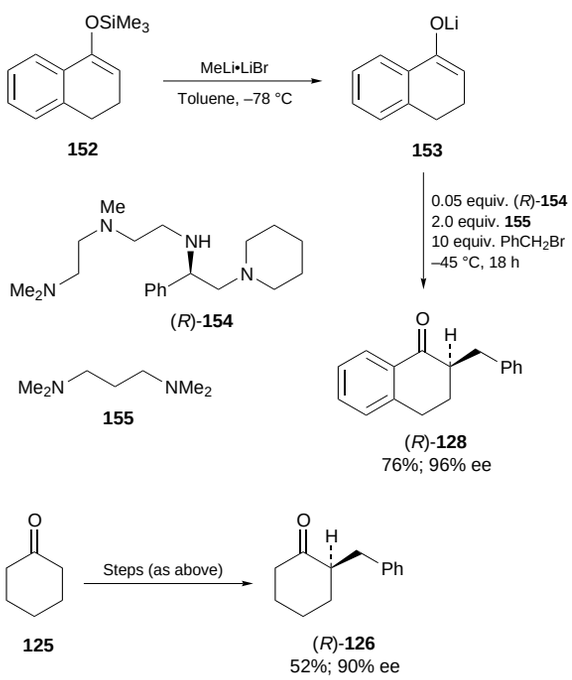
The optimum conditions required the use of excess DABCO and HMPA as additives and the enolate was trapped with Me_3SiCl under external quench conditions since *N*-silylation of (*R*)-**149** occurred with an internal quench. Using these procedures with cyclohexanone **20**, 0.3 equivalents of (*R*)-**149** and 2.4 equivalents of **151** generated silyl enol ether (*R*)-**21** of 79% ee (**Scheme 71**).[129] Although the enantioselectivity is slightly lower than that obtained using a stoichiometric amount of chiral base (*R*)-**11** (Scheme 19), this result clearly demonstrates the success of the catalytic cycle.

Koga has also reported a catalytic version of the stoichiometric enolate alkylation reaction described in Scheme 59. Generation of lithium enolate **153** in the presence of lithium



Scheme 71

bromide followed by reaction with benzyl bromide using 0.05 equivalents of tetraamine (*R*)-**154** and 2.0 equivalents of diamine **155** gave alkylated product (*R*)-**128** of 96% ee (**Scheme 72**).[130] The catalytic reaction was successful because the lithium enolate **153** is activated to alkylation by complexation of diamine (*R*)-**154**. In the absence of diamine (*R*)-**154**, less than 1% of alkylation product was obtained. Cyclohexanone **125** was also successfully alkylated under catalytic conditions (Scheme 72).



Scheme 72

7 Conclusion

The developments in chiral base chemistry over the last seven years are numerous. Currently, it is possible to carry out a range of asymmetric transformations with >90% enantioselectivity using chiral bases. Furthermore, as chiral base methodology has developed, total syntheses incorporating chiral base-mediated asymmetric desymmetrisation steps have become more prevalent. The most exciting recent development is the catalytic use of chiral bases and this is likely to pave the way for the next generation of research into the use of chiral lithium amide bases in synthesis.

From the information collected together in this review, it is possible to identify the four most important and most useful chiral bases, namely (*R*,*R*)-**1**, **6**, (*R*)-**7** and **17** (and their enantiomers). It is reasonable to suggest that, with these four chiral bases at our disposal, it should be possible to carry out any new lithium amide-mediated asymmetric transformation with a good level of enantioselectivity.

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