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ASYMMETRIC SYNTHESIS USING HOMOCHIRAL LITHIUM AMIDE BASES

PAUL J. COX and NIGEL S. SIMPKINS *

Department of Chemistry, University of Nottingham

University Park, Nottingham, NG7 2RD

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1. INTRODUCTION

The last decade or so has seen great advances in the area of asymmetric synthesis.[1] Insight gained into the steric and electronic factors controlling such processes has enabled the rational design and use of chiral auxiliaries in a plethora of diastereoselective transformations. Reactions which involve the intermolecular transfer of asymmetry (absolute asymmetric induction) are, however, less common. The development of such methods, particularly those involving catalytic reagents, remains a challenging problem.

The aim of this review is to illustrate the potential of optically active lithium amides in asymmetric synthesis and, in particular, intermolecular chirality transfer. In this regard two fundamentally distinct processes can be distinguished:-

(a) One in which the optically active lithium amide selects between enantiotopic protons in kinetically controlled deprotonations of achiral or prochiral substrates.

(b) One in which the optically active lithium amide base acts initially simply as a strong base, deprotonating a substrate to give a prochiral carbanion, e.g. an enolate. The stereochemical outcome of subsequent reactions of the anion can then be influenced due to the complexed chiral secondary amine, or extra lithium amide acting as a non-covalently bound chiral auxiliary.

As will be described below other applications of these bases exist, such as unusual regiocontrol in enolisation of homochiral ketones, which fall into neither category.

Because of the common misinterpretation of the term chiral, and the awkwardness and ambiguity of 'optically active', we shall adopt the term homochiral lithium amide (or HCLA) to describe the optically active lithium amides employed in this chemistry - despite the fact that in some cases the optical purity of the bases used has been somewhat doubtful (see for example references 5(b) and 28).

The ubiquitous use of lithium amides in organic synthesis suggests a multitude of potential applications for their homochiral counterparts. The attraction of the reactions described in (a) and (b) above lies in the possibility of conducting direct and efficient asymmetric induction, with easy preparation and recovery of the 'reagent'. HCLA base chemistry also offers some unique entries to optically active materials which are highly complementary to better-established methods. The reactions described herein surely represent merely the first fraction of the potential applications of HCLA base chemistry in organic synthesis.

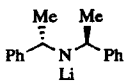
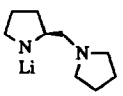
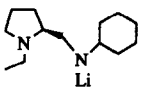
2. ASYMMETRIC DEPROTONATIONS

2.1 Enantioselective Rearrangement of Epoxides to Allylic Alcohols

The rearrangement of an epoxide to an allylic alcohol with a lithium amide is known to involve removal of a proton *syn* to the epoxide oxygen[2] and is though to proceed via a cyclic six-membered transition state, Scheme 1. When the epoxide is prochiral then the use of a chiral lithium amide results in enantioselective rearrangement, to give optically active products.

Scheme 1

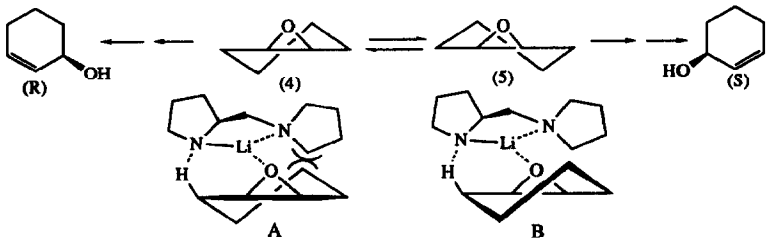
Such a process was first realised by Whitesell and Felman who studied the effect of a number of mono- and dialkyl chiral lithium amides, including (**1**), on the epoxide ring-opening of cyclohexene oxide,[3] Scheme 2, entry 1. Although the optical purities observed were modest this seminal contribution paved the way for subsequent investigations. Later work by Asami, employing lithium amides readily available from (*S*)-proline, e.g. (**2**) and (**3**), which contain an internal chelation site, has resulted in major improvements to the levels of asymmetric induction reported by Whitesell, Scheme 2, entry 2.[4a-c]

Entry	Base	Solvent	Reaction Temp	Additive	Chemical Yield (%)	ee (%)	Ref.
1	 (1)	THF	Reflux	-	65	31 (*R*)	3
2	 (2)	THF	0°C	-	77	92 (*S*)	4a
3	 (3)	THF	0°C	HMPA (1.65eq.)	80	78 (*R*)	4b

Scheme 2

The rearrangements carried out by Whitesell and Felman were conducted at reflux in THF. In the first report by Asami, reactions carried out at 0°C, and at -78°C, followed by warming to room temperature, gave comparable results.[4a] Most later work has been carried out at or near 0°C, and it appears that at much lower temperatures these reactions are very slow indeed.

Asami explained the enantioselectivity observed with HCLA (**2**) by proposing that the base distinguishes between the two conformations (**4**) and (**5**), Scheme 3.

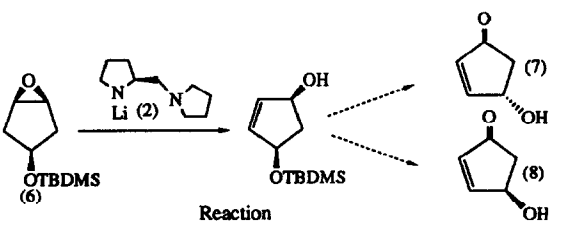


Scheme 3

Two transition states A and B can be visualised for the process, each involving removal of a proton in a pseudoaxial orientation. The product with (*S*)-configuration predominates because of the unfavourable interaction expected in transition state A.

Amides derived from (*S*)-proline also provide access to the (*R*)-antipode of cyclohexenol when the lithium amide grouping is situated on the proline side chain, e.g. Scheme 2, entry 3.[4b] These bases give optimum levels of asymmetric induction when used in conjunction with additives which can coordinate lithium, i.e. HMPA. Remarkably a reversal in the absolute stereochemistry of the product obtained from the reaction was observed on increasing the bulk of the ring *N*-alkyl group in (**3**) from ethyl to *tert*-amyl.

The use of (*S*)-proline derived amides in conjunction with additives such as HMPA or DBU is the most efficient way of effecting the rearrangement of a number of cyclic (cyclopentene and cyclooctene oxides, 15-50% ee) and acyclic ((*Z*)-2-butene and (*Z*)-4-octene oxides 59-72% ee) epoxides.[4b,c] The role of the additive in these reactions is still unclear. At first sight the addition of a powerful donor solvent, which might interfere with the chelation between base and substrate, indicated in the transition states shown above, might be expected to be detrimental to the reaction. However, clearly this is not the case, and it is possible that the presence of additives results in deaggregation of associated lithium amide in solution, thereby resulting in a more effective reagent.



Entry	Solvent	Reaction Temp	Yield	ee	Ref.
1	THF	4°C	76%	66%(*S*)	5a
2	Benzene	4°C	92%	90%(*S*)	5a
3	THF	0°C	65%	50%(*S*)	5b
4	Benzene	0°C	73%	76%(*S*)	5b

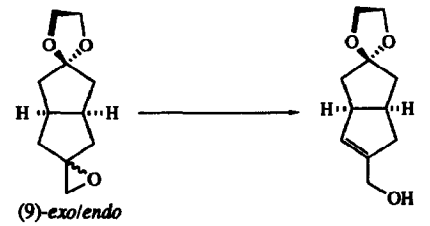
Scheme 4

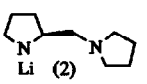
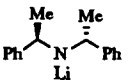
One of the more synthetically useful substrates studied is the protected *cis*-hydroxy epoxide (**6**) which can be readily manipulated into the (*S*)- or (*R*)-4-hydroxy-2-cyclopentenones, (**7**) and (**8**), following initial enantioselective epoxide opening.[5] These compounds are useful precursors to prostanoids and other cyclopentanoid natural products.

The rearrangement of cyclopentene oxide (**6**) has been investigated by two groups working independently. However, there is some discrepancy in the levels of optical purity attained by each group in comparable experiments, Scheme 4, c.f. entries 1 vs 3 and 2 vs 4. Leonard has attributed these differences to the methods employed for measuring the level of induction.[5b] In general there seems to be some confusion in comparison of optical purities, obtained by comparison of optical rotation data, and enantiomeric excesses (ee), obtained by direct analysis of the ratio of enantiomers in the mixture (or diastereomeric derivatives thereof), which are not necessarily equivalent. Leonard also expressed some concern about the optical purity of proline-derived secondary amines prepared by some literature procedures.

From the results obtained so far using simple epoxides it appears that cyclic substrates give the best results, and that both chelating substituents in the substrate and solvent effects can have a dramatic influence on the level of enantioselectivity obtained.

Very recently the application of this methodology to the rearrangement of the spiro epoxide (**9**) was described by Leonard, Scheme 5.[6]



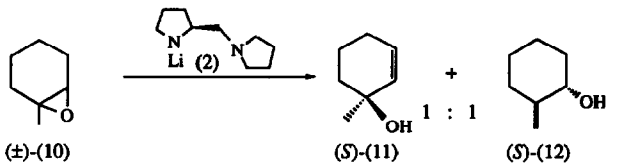
Base	Solvent	Yield	ee	(±)
 Li (2)	THF	58%	21%	(+)
	Benzene	35%	45%	(-)
	THF	50%	76%	(+)

Scheme 5

It is interesting to note that in the above discussion the proline-derived bases are superior to the α-methyl benzylamine derived base, c.f. entrys 1 vs 2, Scheme 2. In the case of the spiro epoxide (**9**), however, the converse is true, i.e. the benzylamine-derived base gives superior enantioselectivity. It would also appear that the choice of solvent is critical to this reaction to the extent that the enantioselectivity of the proline base is reversed on changing from THF to benzene. The low chemical yields with this particular substrate appear to be due to the non-reactivity of the *endo* isomer present in the *exo*/*endo* epoxide mixture.

In order to synthesise the (*S*)-enantiomer of 1-methyl-2-cyclohexen-1-ol (**11**) an aggregation

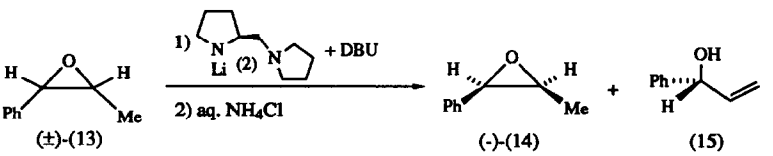
pheromone of the female Douglas fir beetle, Mori reacted (±)-methylcyclohexene oxide (**10**) with lithium amide (**2**).[7] The resulting rearrangement reaction gave a 52% yield of a 1:1 mixture of the desired product (**11**) and the exocyclic alkene (**12**). From its specific rotation (**11**) was estimated to have an ee of about 80%, and although (**12**) was optically active its ee was not determined.



(±)-(10) (*S*)-(11) (*S*)-(12)

Scheme 6

In addition to providing optically active products from prochiral epoxides, HCLA bases have been used to generate optically active materials from racemic epoxides such as (**13**) via a kinetic resolution process.[8] In these reactions a deficiency of base (**2**) (used together with DBU) is employed to convert the faster reacting enantiomer present in the mixture to the allylic alcohol (**15**) whilst the slow reacting enantiomer is recovered as unreacted epoxide (**14**), Scheme 7. It was shown that high enantiomer discrimination was possible for *cis*-disubstituted epoxides, while only moderate selectivity was observed for *trans*-disubstituted and terminal epoxides.



(±)-(13) (-)-(14) (15)

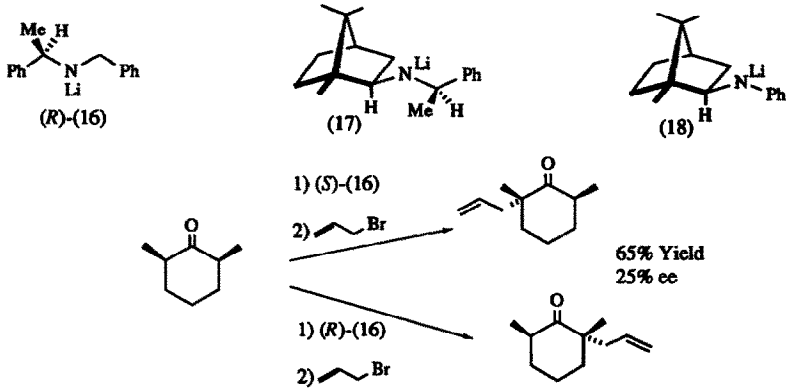
(2)	:	(±)-(13)	Yield	ee%	Yield	ee%
3	:	4	31%	>95	60%	33
1	:	3	67%	30	21%	72

Scheme 7

2.2 Prochiral Ketones

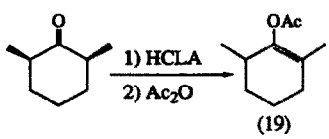
A major area of application of HCLA base chemistry has been reactions in which a symmetrically substituted, cyclic, prochiral ketone is converted directly into optically active products via selective removal of one of a pair of enantiotopic protons. We will term this process asymmetric deprotonation for convenience. Most of the chemistry carried out so far involves the use of substituted cyclohexanones, in which conformational anchoring of the system should result in the base selecting between two axially orientated protons, for stereoelectronic reasons.

Our initial experiments in this area involved asymmetric deprotonation of *cis*-2,6-dimethylcyclohexanone with lithium amide (**16**), followed by direct alkylation with allyl bromide, Scheme 8.[9,10]



Scheme 8

Although in these early experiments the ee of the derived products was low, the principle of discriminating between two enantiotopic hydrogens by the use of an optically active lithium amide base had been established. Subsequent experiments resulted in some improvement in the ee of products available from the reaction, and other electrophilic quenches of the intermediate enolates were carried out, for example with acetic anhydride to give chiral enol acetate (**19**), Scheme 9.

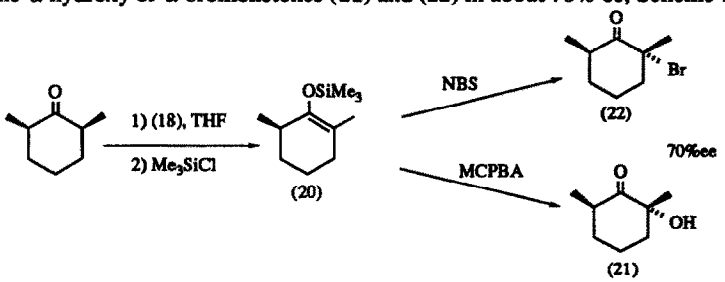


HCLA	ee
(*R*)-(16)	29% (*R*)
(17)	65% (*S*)
(18)	74% (*R*)

Scheme 9

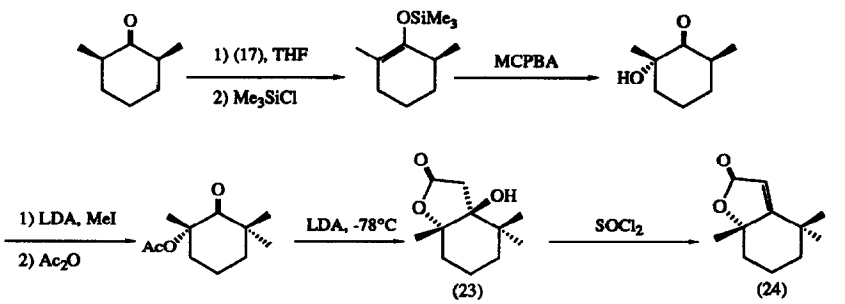
The formation of such chiral enol derivatives reinforced our assertion that the reaction proceeds by kinetically controlled enantioselective deprotonation, i.e. that the asymmetry is produced in the deprotonation step, and that other possibilities involving enamines or enolate-amine complexes could be ruled out. The *O*-acylation to give optically active enol acetate (**19**) was used as a standard reaction to compare the efficiency of amide bases, and it was found that the camphor derived base (**18**) gave the highest ee.

The synthetic potential of silyl enol ether (**20**), formed in the same way, is illustrated in its conversion to the α-hydroxy or α-bromoketones (**21**) and (**22**) in about 70% ee, Scheme 10.



Scheme 10

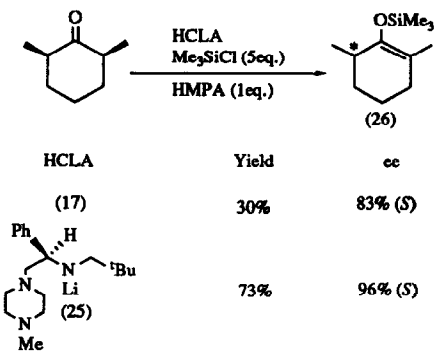
We have used the antipode of hydroxyketone (**21**), formed in 66% ee, in a very short asymmetric synthesis of the lactones (5*S*, 6*S*)-aeginetolide (**23**) and (5*S*)-dihydroactinidiolide (**24**), Scheme 11.[11] Enantiomeric enrichment of the final product was possible by recrystallisation to give optically pure dihydroactinidiolide.



Scheme 11

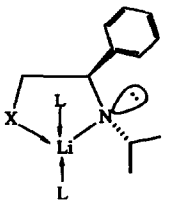
Subsequent studies, using Corey's *in situ* TMSCl quench technique, with base (**17**) gave the enol silane with the improved ee of 83% (c.f. 70% for 'external' quench), although in a diminished chemical yield of 30%.[10]

The superiority of this *in situ* technique has been further demonstrated by Koga, who, using HCLA (**25**), has prepared the enol silane (**26**) with (*S*) configuration in 73% yield and 96% ee.[12]



Scheme 12

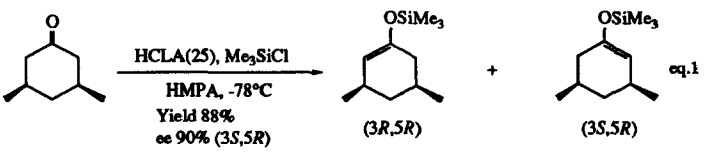
In this work optimal results were obtained with lithium amides containing internal ligation sites such as the nitrogen atoms of the piperazine ring in base (**25**). Common to all these amides is the ability to exist in a five-membered chelate structure such as (**27**) where the lone pair to be used in deprotonation has a fixed orientation relative to the sterically bulky groups present. The generally high levels of asymmetric induction achieved with such bases might be attributed to this more organised conformationally restrained structure, and possibly less base aggregation.

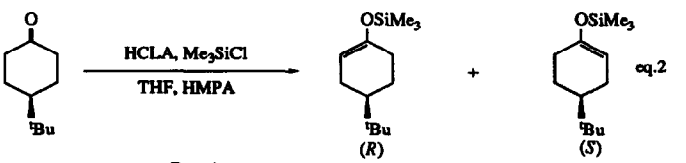


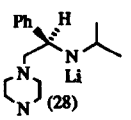
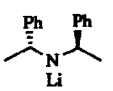
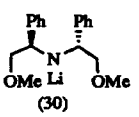
(27)

Optimum enantioselectivities are usually observed when bases having internal ligation sites are employed in conjunction with one equivalent of HMPA per vacant coordination site on the tetravalent lithium cation of the amide base, i.e. 1 equivalent for base (**25**) and two for (**27**). This rule of thumb does not, however, apply to systems which do not contain internal ligation sites, in which case the best results are obtained without HMPA.

The *in situ* TMSCl quench technique has been applied to the enantioselective deprotonation of other symmetrically substituted cyclohexanones including 3,5-dimethylcyclohexanone (eq. 1),[12] and 4-*tert*-butylcyclohexanone (eq. 2),[10,13] Scheme 13.





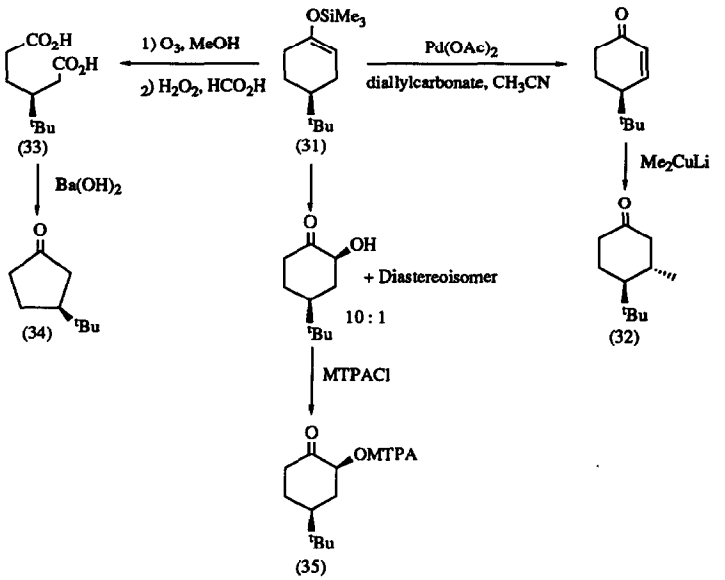
HCLA	Reaction Temp	HMPA (eq.)	Yield (%)	ee (%)	Ref.
 (28)	-78°C	1	87	84 (*R*)	13a
	-105°C	1	51	97 (*R*)	13a
 (29)	-78°C	0	73	69 (*S*)	13b
	-90°C	0	66	88 (*S*)	13b
 (30)	Reaction conducted in toluene/HMPA No other data provided			84 (*R*)	14

Scheme 13

These studies indicate that lower reaction temperatures, i.e. even lower than -78°C, result in higher enantioselectivities, although perhaps at the cost of chemical yield. It is also interesting to note

that the additional ligation sites present in base (**30**) did not result in any enhancement of ee when compared with base (**29**), although the reaction conditions used are not strictly comparable.[14]

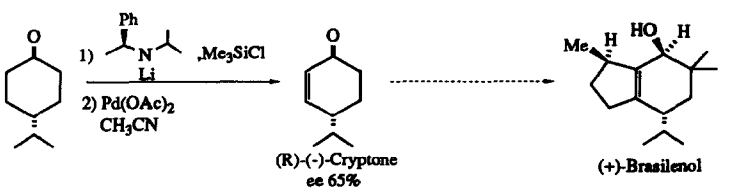
The figure of 97% ee quoted in Scheme 13 has been contradicted by some of our own results in which we obtained the same enol silane with a consistantly higher optical rotation, but a lower ee (88%) as estimated by carrying out the conversions shown in Scheme 14.[10,13b]



Scheme 14

The versatility of the silyl enol ether moiety is once again demonstrated by the conversion of the starting enol silane (**31**) into a number of interesting optically active derivatives. Optical rotations of the previously known compounds (**32**), (**33**) and (**34**), as well as NMR studies on the MTPA derivative (**35**) all give consistent estimates of the ee of the enol silane (**31**). Since in previous studies the enol silanes appeared to give derived products without observable racemisation, we believe the discrepancy between our results and those of Koga could be due to an inaccuracy in his extrapolation to calculate the maximum rotation for (**31**).

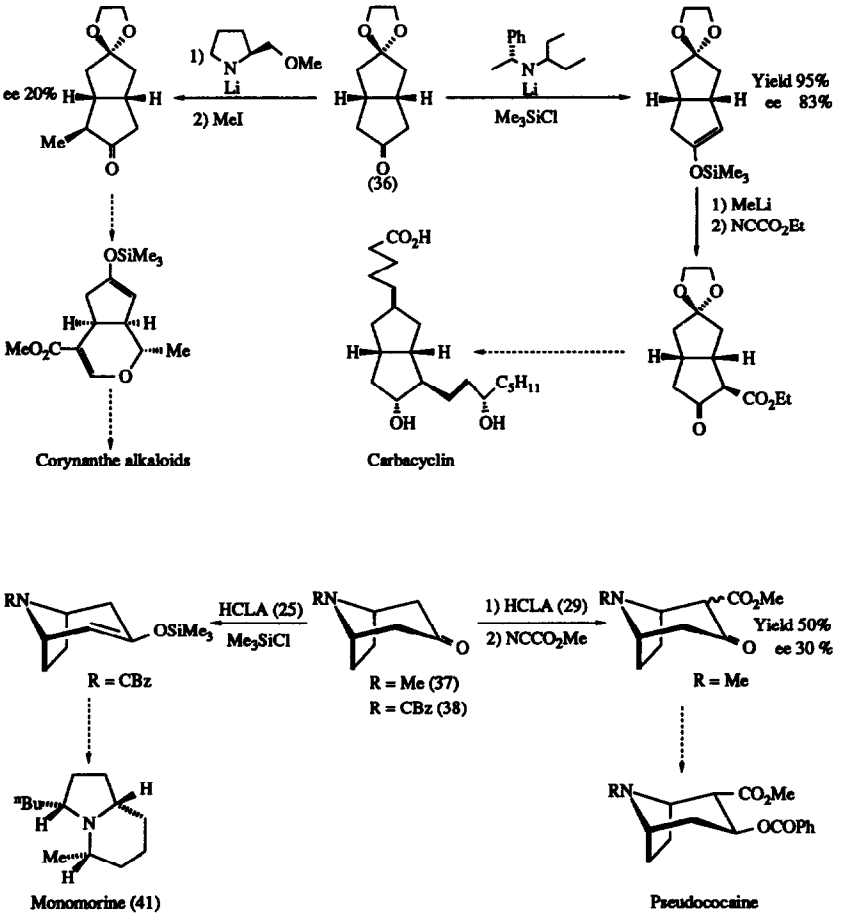
The *in situ* TMSCl quench methodology has found application in the total synthesis of the marine metabolite (+)-brasilenol reported by Greene, Scheme 15. As in our synthesis of dihydroactinidiolide recrystallisation allowed preparation of the optically pure final product.[15]

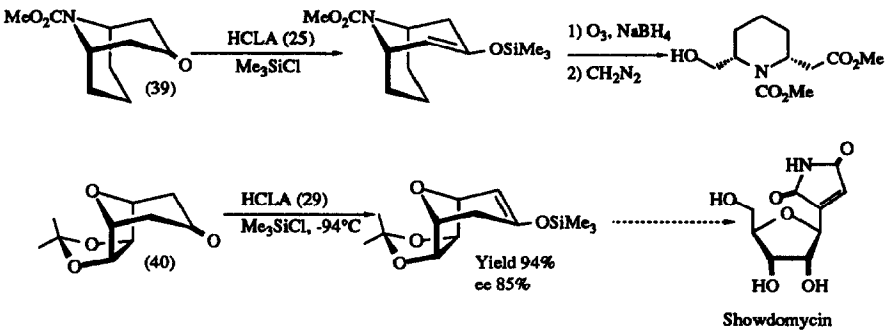


Scheme 15

Enantioselective desymmetrisation has not been restricted to prochiral cyclohexanones. Recent studies have employed *cis*-bicyclo[3.3.0]octan-3,7-dione acetal (**36**),[16] 8-azabicyclo[3.2.1]octan-3-ones (**37**)[17] and (**38**),[18] 9-azabicyclo[3.3.1]nonan-3-one (**39**)[19] and 8-oxabicyclo[3.2.1]octan-3-one (**40**)[20] as substrates for HCLA reactions. All have obvious synthetic value. Thus (**36**) has been used to make key precursors to carbacyclin[16a] and corynanthe[16b] alkaloids, and tropanone (**37**) has been transformed into cocaine analogues.[17] Whilst azabicyclic ketone (**38**) has been manipulated into (+)-monomorine (**41**),[18] a trail pheromone of the pharaoh ant, the larger ring homologue (**39**) provides access to *cis*-2,6-disubstituted piperidines.[19]

We have carried out similar chemistry using oxabicycle (**40**), which is a proven intermediate for the synthesis of a wide range of *C*-nucleosides, e.g. showdomycin, Scheme 16.



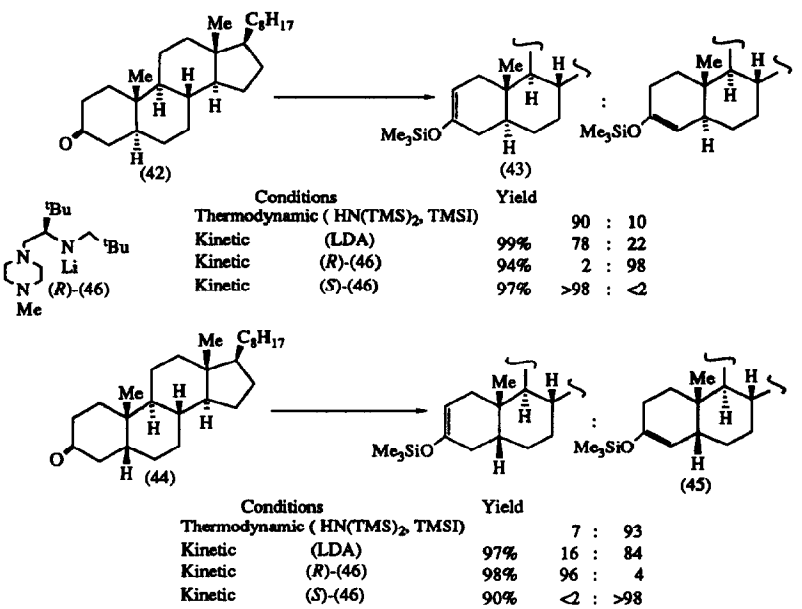


Scheme 16

It is apparent that in many cases the asymmetric deprotonation approach may enable by far the most rapid entry to chiral compounds derived from such cyclic systems, often in very good ee. A major problem with this chemistry is our poor understanding of the reaction, and the consequent empirical choice of HCLA, and tuning of reaction conditions required for each substrate. If these hurdles can be overcome then this type of reaction should become widely accepted as a route to optically active synthetic intermediates.

2.3 Unsymmetrical Ketones

Via a process akin to the enantioselective deprotonations discussed above, chiral lithium amides have been used in the regioselective enolisation of optically active 3-keto steroids, Scheme 17.[21]



Scheme 17

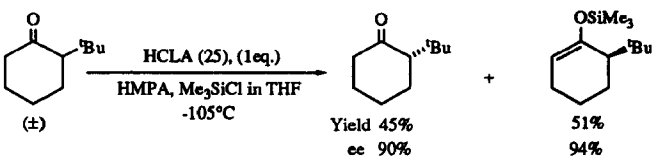
Under conditions of kinetic or thermodynamic control 3-cholestanone (**42**) provides the Δ^2-enol silane (**43**) as the major product of deprotonation while 3-coprostanone (**44**) provides the Δ^3-enol silane (**45**) predominantly.

However, if chiral lithium amides are employed under kinetic control the regioselectivity can be increased or reversed.

In these reactions toluene was used in place of the more usual solvent THF. Clearly the tendency of the HCLA to abstract a hydrogen preferentially from one of the two α-sites can override the usual regioselectivity of enolisation inherent in the steroidal ketones. Unfortunately the sense of regioselectivity observed in three of the four systems examined was not easily explained by analogy with earlier deprotonations, thought to occur via axial hydrogen abstraction from a conformationally locked chair conformation. Koga suggested the possibility of deprotonation via a skew boat conformation to explain these anomalies.

2.4 Kinetic Resolution of Racemic Ketones

In addition to providing optically active products from prochiral ketones, HCLA bases have been used to generate optically active materials from racemic ketones via a kinetic resolution process. In these reactions a deficiency of base is employed in order to convert the fast reacting enantiomer present in the mixture into its derived enol silane, whilst the slow reacting enantiomer is recovered as unreacted ketone.[22]

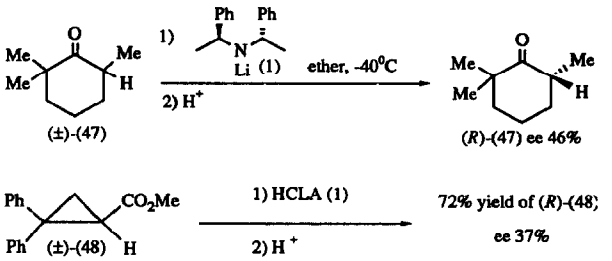


Scheme 18

As with the work described above studies have centred on the use of cyclohexanone derivatives. The enantiomers of racemic 2-substituted cyclohexanones (i.e. 2 substituent = Me, ^{i}Pr, Ph and ^{t}Bu), have been separated in this way, e.g. 2-*tert*-butylcyclohexanone, Scheme 18.

Unusually, both the recovered ketone and the silyl enol ether product could be obtained in high optical purity from reactions which had been allowed to proceed about 50% to completion, attesting to the quite substantial relative rates attainable in such reactions, i.e. up to $k_{rel} = 44$.

This chemistry has some precedent in an earlier report by Eleveld and Hogeveen.[23] They described some interesting HCLA base chemistry conducted using racemic 2,2,6-trimethylcyclohexanone (**47**) and base (**1**) Scheme 19.



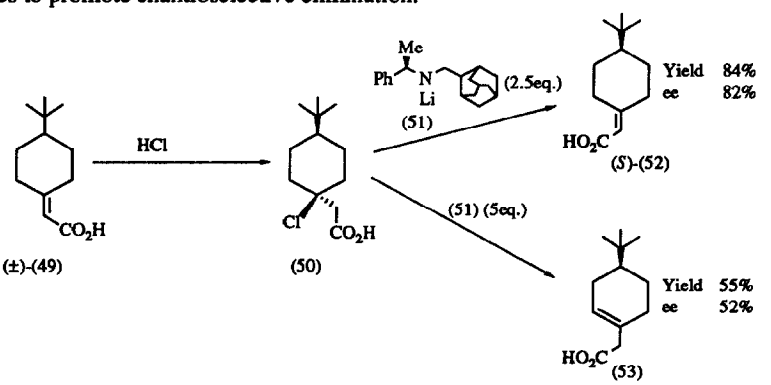
Scheme 19

Treatment of the starting ketone with this base at -40°C followed by quenching with aqueous HCl gave optically active ketone in 63% yield and 46% ee. This result was shown to be due to a kinetic resolution process which relies on partial deprotonation of the starting ketone (no induction was obtained at either -80°C or at 0°C). Since the intermediate enolate is not removed as a derivative but is simply reprotonated the maximum ee which could be expected from the reaction was 50%.

Ester (**48**) underwent a parallel deprotonation/protonation sequence to give optically enriched material which would again appear to arise from kinetic resolution.

2.5 Enantioselective Dehydrohalogenation

A report from Duhamel and coworkers describes an enantioselective dehydrohalogenation reaction leading to axially dissymmetric compounds.[24] Thus deracemisation of 4-*tert*-butyl-cyclohexylidene acetic acid (**49**) was achieved via the hydrochlorinated intermediate (**50**) using chiral lithium amides to promote enantioselective elimination.

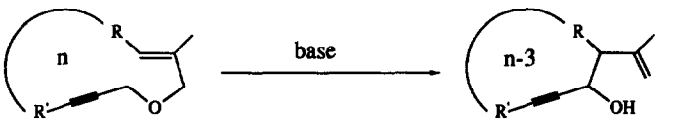


Scheme 20

These reactions are conducted by treatment of the β-halogenated acid with more than two equivalents of lithium amide, and so the dehydrohalogenation presumably occurs on the carboxylate salt coordinated to free secondary amine and/or additional lithium amide. It was found that the use of adamantyl base (**51**) combined with the use of the chloride (**50**), rather than the corresponding

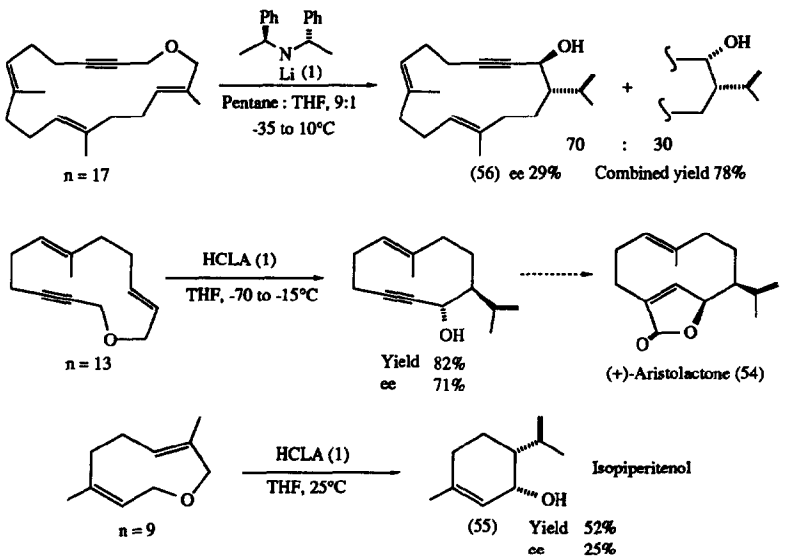
bromide, gave the maximum asymmetric induction (82% ee). Further studies have provided insight into the factors affecting the enantioselectivity and enabled an extension of the chemistry to provide the deconjugated acid (**53**), also in optically active form.[25]

2.6 [2,3]-Wittig Rearrangement



Scheme 21

Over the past few years Marshall has examined the [2,3]-sigmatropic rearrangement of macrocyclic allylic propargylic ethers to give ring contracted carbocycles via the Wittig rearrangement, Scheme 21. A natural extension of the work involved experimentation with the use of HCLA bases to effect the transformation with concommitant induction of absolute asymmetry.[26-28]



Scheme 22

Optimum enantioselectivities varied depending on the ether ring size, with the 13-membered propargylic ether providing the highest ee values of the systems studied to date. Acyclic systems did not give optically active products.[28] The results are difficult to rationalise, but certain effects appear to be ruled out. For example, if the induction were due to the formation of an optically active, configurationally stable carbanion, or anion-secondary amine pair, then the induction might be expected to be as high in the case of a 17-membered ring as for the 13-membered ring. The rearrangement to form a six-membered ring is very reluctant to proceed, even at higher temperatures than normally used. It appears that the 13-membered ring possesses the best balance of flexibility,

which allows the reacting centres to come into close proximity (smooth reaction at low temperature), whilst also having some rigidity which constrains the *re/si* orientation of the carbanion with the allylic ether double bond.

As indicated in Scheme 22, Marshall and Lebreton have utilised this methodology to synthesise and prove the absolute configuration of (+)-aristolactone (**54**),[26] to synthesise *p*-menthane derivatives (**55**)[27] and to prepare cembranoid precursors (**56**).[28]

3. NON-COVALENTLY BOUND CHIRAL AUXILIARIES

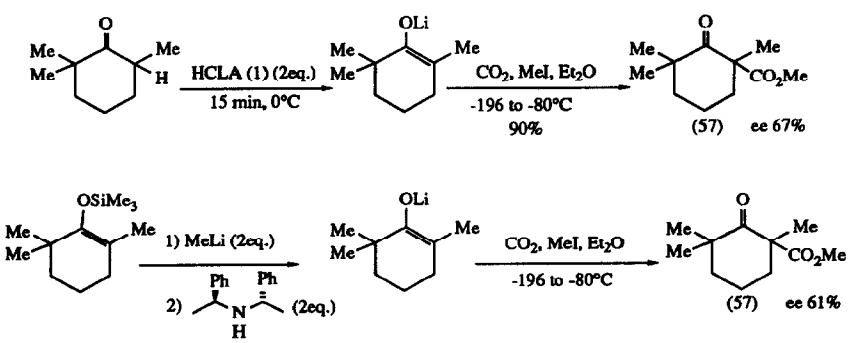
3.1 Reactions of Enolates

The stereochemical course of the reaction of an achiral or prochiral enolate, generated with a HCLA base, and an electrophile, e.g. an aldehyde, can be influenced by complexation of the lithium enolate and the liberated secondary amine, to provide enantiomerically enriched products. We have chosen to describe this type of process as one in which the optically active secondary amine acts as a non-covalently bound chiral auxiliary.

The reactions of a variety of achiral enolates have been reported and are listed below according to the nature of the enolate precursor.

3.1.1 Cyclic Ketones

In Section 2.4 it was described how 2,2,6-trimethylcyclohexanone underwent a kinetic resolution when it was partially deprotonated at -40°C using a HCLA base.[23] If, however, the enolisation is performed at 0°C, then complete deprotonation occurs to give a prochiral enolate, which has been shown to undergo an enantioselective carboxylation on treatment with CO_2 followed by MeI, Scheme 23.[29]



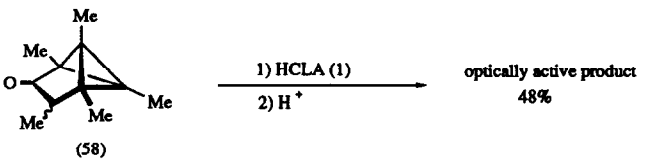
Scheme 23

The reaction is remarkable in that it must be carried out by condensing CO_2 onto the frozen enolate solution at -196°C, followed by warming to -80°C. It is also important to have an additional equivalent

of the lithium amide present in the mixture. Under these conditions the ketoester (57) was obtained in up to 67% ee. Similar enantioselectivity is observed when the enolate is generated from the corresponding enol silane and then reacted in the same way. The mechanism of the reaction is somewhat obscure, but could involve the chelation of CO_2 to some complex between the prochiral enolate and the optically active lithium amide prior to face-selective carboxylation. It should be noted that there is strong evidence for such association beween enolates and secondary amines. Seebach has recently described the structure and reactivity of lithium enolates in a superb review article, which includes X-ray structures of lithium enolates coordinated with amines, ethers and even LDA.[30]

Seebach has also described a remarkable phenomenon which can occur when enolates generated using lithium amides are reacted with electrophiles, and which he has called the secondary amine effect. Thus in the attempted deuteration of certain enolates, formed using lithium amides, little or no deuterium could be incorporated, even by adding a large excess of perdeuteroacetic acid. Somehow it is the hydrogen that was originally removed from the substrate that is returned on quenching! Starting with a deuterated ketone the same effect is seen on trying to quench with a proton source. This fascinating effect clearly has implications for absolute stereocontrol if the lithium amide used in the deprotonation is optically active.

Another report from Hogeveen's laboratory describes a reaction in which ketone (58) was treated with a large excess of HCLA (1) and simply quenched with water to give optically active (58), Scheme 24.

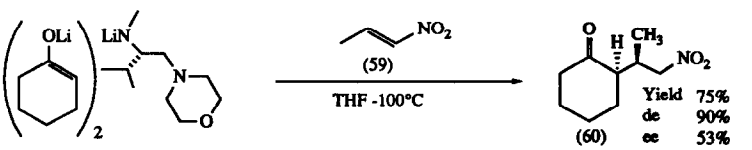


Scheme 24

This phenomenon is clearly a result of the secondary amine effect noted above, and indeed Hogeveen also noted exactly the same effects in his kinetic resolution studies described in Section 2.4.

The aldol reactions of cyclopentanone and cyclohexanone with benzaldehyde in the presence of chiral additives including chiral lithium amides have been studied by Seebach, and the results are summarised in his recent review.[30] Unfortunately the enantioselectivities reported to date have been disappointing (ca. 25% maximum).

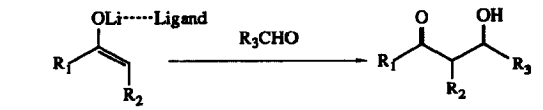
More effective is the reaction of the enolate generated from cyclohexanone with nitroolefin (59) providing the conjugate addition product (60) in 53% ee, Scheme 25.

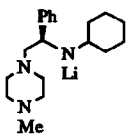
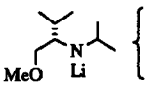


Scheme 25

3.1.2 Acyclic Ketones

The aldol reaction of methyl[32] and ethyl[33] ketones with aldehydes in the presence of chiral lithium amides provide products with good enantiomeric excess, Scheme 26.



Ligand	R_1	R_2	R_3	Yield (%)	ee (%)	Ref.
	Ph	H	1-Naph	88	86	32
 (61)	^{t}Bu	Me	Ph	93	68 (*S, S*)	33a
	^{t}Bu	Me	1-Naph	85	77 (*S, S*)*	33b

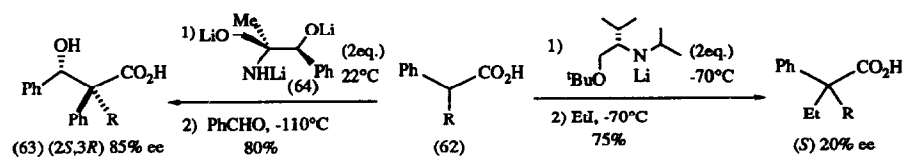
*ee of *erythro* diastereomer; *erythro* : *threo*, 97:3.

Scheme 26

The process is most efficient when both the ketone and aldehyde contain bulky substituents. It was found that good levels of enantioselection are possible only when the aldol reaction is conducted in the presence of excess chiral lithium amide. Reactions using only one equivalent of lithium amide gave only low levels of induction, leading the authors to propose that the lithium amide is more strongly coordinated to the lithium enolate than the corresponding secondary amine. Presumably the reaction could therefore be achieved by using two equivalents of HCLA base. However Shioiri and coworkers adopted the interesting alternative of employing a 1:1 mixture of HCLA and LDA in the initial enolisation.[33] Presumably the pKa values of the two amines involved are such that the LDA acts as base in the initial deprotonation and subsequent proton exchange between the remaining HCLA and the thus-formed diisopropylamine does not occur.

3.1.3 Carboxylic Acids

Shioiri and coworkers have also described the alkylation of dianions derived from carboxylic acid (**62**) (R = H, Me) using HCLA bases, to give products in optically active form.[34] This report is not straightforward to analyse, since in many cases both the chemical and optical yields are rather poor (ee 2-24%), and also one of the starting acids is achiral, whilst the other, being racemic, might also be subject to kinetic resolution, Scheme 27.

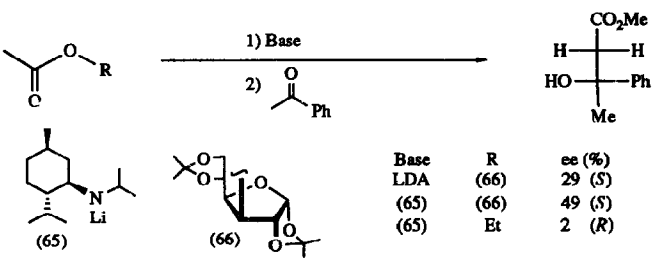


Scheme 27

The same acid undergoes aldol-type reactions with benzaldehyde to give products such as (**63**) in up to 85% ee when base (**64**) is used to generate the dianion.[35] Interestingly, in this study the presence of at least one anionic site, in addition to the NLi group required for the deprotonation, was found to be necessary for good levels of asymmetric induction. Thus, as in the Shioiri work described in Section 3.1.3 an anion appears to associate more effectively with the intermediate enolate than a neutral species such as a secondary amine.

3.1.4 Esters

The use of HCLA base (**65**) in the reaction of esters also containing a diacetone glucose chiral auxiliary (**66**), with methyl phenyl ketone, results in improved asymmetric induction, compared to reactions using the auxiliary alone, e.g. Scheme 28.[36]



Base	R	ee (%)
LDA	(66)	29 (*S*)
(65)	(66)	49 (*S*)
(65)	Et	2 (*R*)

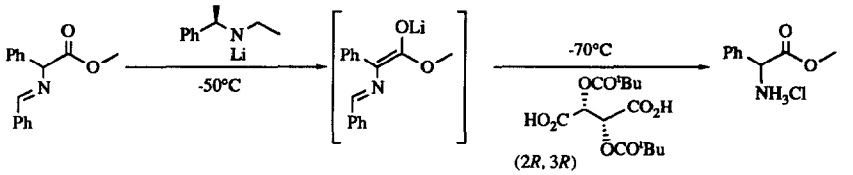
Scheme 28

Very low levels of induction were obtained when comparable reactions were run using the HCLA base with a simple ethyl ester.

3.1.5 α-Aminoester Derivatives

The synthesis of natural and unnatural amino-acids, in optically active form, is an area in which there is currently intense activity.[37] It is therefore not surprising that HCLA bases have found application in this field.

Studies from the laboratories of Duhamel have centred on the deprotonation of Schiff bases of racemic α-aminoesters with lithium amides, followed by enantioselective reprotonation of the intermediate prochiral enolate to give optically active products.[38] The reactions can be carried out using simple achiral lithium amide bases, followed by addition of a homochiral proton source, for example a tartrate derivative. However, better results could be obtained by using a combination of HCLA base for the deprotonation and an optically active acid for the reprotonation.[39] The overall process amounts to a deracemisation, Scheme 29.

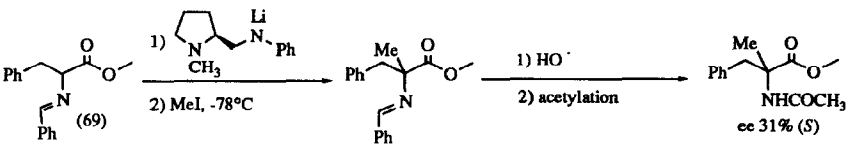


Schiff base	Acid	ee (%)	Yield (%)
Racemic	(2*R*, 3*R*)	70 (*S*)	85
Racemic	(2*S*, 3*S*)	6 (*R*)	75
Racemic	(2*R*, 3*R*)	69 (*S*)	80

Scheme 29

Overall inversion of configuration can also be achieved when the starting α-aminoester is optically active.

Interestingly it was found that the use of a HCLA base for deprotonation could be bypassed by substituting LHMDS, and then simply adding the more basic chiral secondary amine to the so-formed enolate prior to reprotonation.[40]

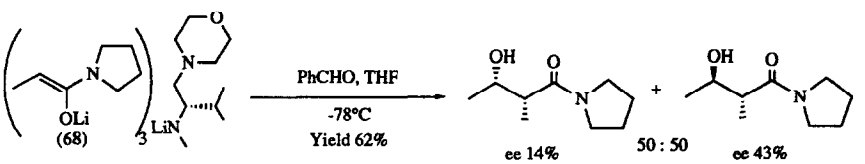


Scheme 30

An independent study by Yamashita has described an analogous study to effect the methylation of α-aminoester derivative (**67**), Scheme 30, to give optically active products, although in substantially lower ee than that available in the protonation reactions mentioned previously.[41]

3.1.6 Amides

Seebach and collaborators have effected the condensation of the amide enolate (**68**) with benzaldehyde, in the presence of a chelating HCLA, to give optically active aldol products, Scheme 31.

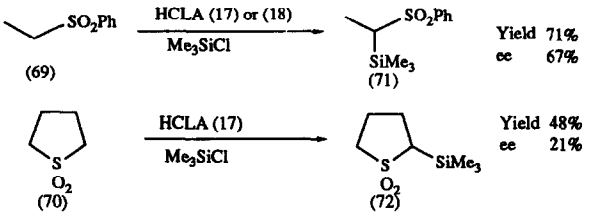


Scheme 31

One of the two diastereomeric products formed could be obtained in up to 43% ee depending on the precise reaction conditions.

3.2 Sulphones

Treatment of the sulphones (**69**)[42] or (**70**)[43] with camphor-derived HCLA bases (**17**) and (**18**) and TMSCl under Corey's internal quench conditions gave the corresponding silylated sulphones (**71**) and (**72**) in up to 67% ee and 21% ee respectively, Scheme 32.



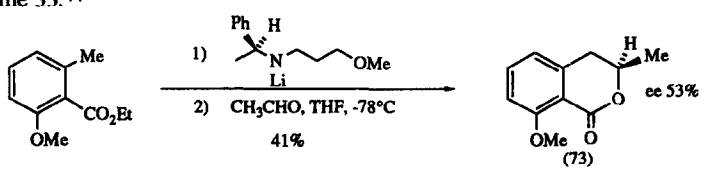
Scheme 32

As in some of the work already described there is some ambiguity in the interpretation of these results which could arise either from an initial selection between enantiotopic hydrogens, or via a non-covalent auxiliary effect. Either way the induced asymmetry at the sulphone α-carbon atom is transient, since external electrophilic quenches give the racemic product. The absolute configurations of the silyl sulphone products have not been determined.

Unexpectedly, bases (**17**) and (**18**) both gave (-)-(**71**), when previously in ketone desymmetrisation reactions they had provided enantiocomplementary results. This may indicate that a different mechanism is operating in this process, presumably involving a transient carbanion-chiral amine association.

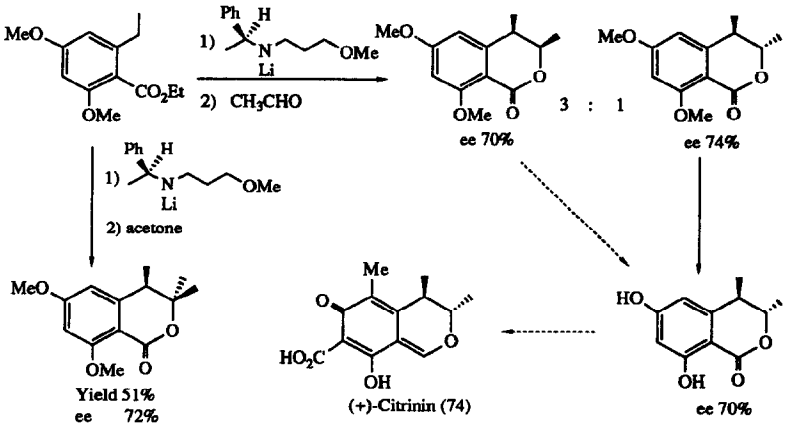
3.3 *ortho*-Toluate Carbanions

Work by Regan and Staunton has shown that the use of an associated chiral amine to induce asymmetry is possible in the aldol-type reactions of *ortho*-toluate carbanions, to give optically active products, Scheme 33.[44]



Scheme 33

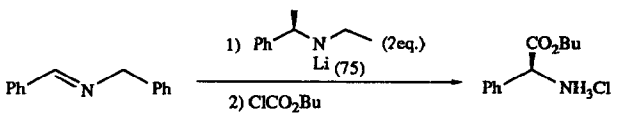
This methodology has been applied to the synthesis of Mellein methyl ether (**73**)[44] and (+)-citrinin (**74**),[45] the latter being obtained optically pure after recrystallisation, Scheme 34.



Scheme 34

3.4 *N*-Benzylidene Benzylamine

The complex produced by deprotonation of *N*-benzylidene benzylamine with chiral base (**75**) reacts with carboxylating agents to give alkylphenylglycinates with up to 40% ee, Scheme 35.[46]



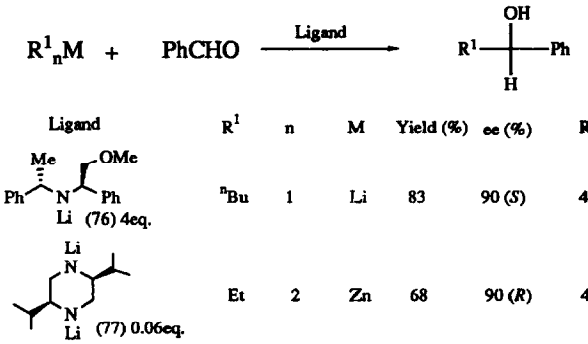
Scheme 35

This represents an alternative approach to the preparation of optically active α-amino acids by enantioselective protonation or alkylation described in Section 3.1.5, and is related to the enantioselective carboxylation reaction by Hogeveen using CO_2.

3.5 Addition of Organometallics to Aldehydes

The addition of n-butyllithium to benzaldehyde can be achieved in up to 90% ee if the reaction is performed in the presence of a HCLA base.[47] It should be noted that for these reactions bases with internal ligation sites provide superior levels of enantioselectivity.

Alternatively, secondary alcohols are available with up to 90% ee via the reaction of a dialkylzinc reagent and an aldehyde in the presence of catalytic amounts of chiral dilithium piperazine (**77**), Scheme 36.[48]

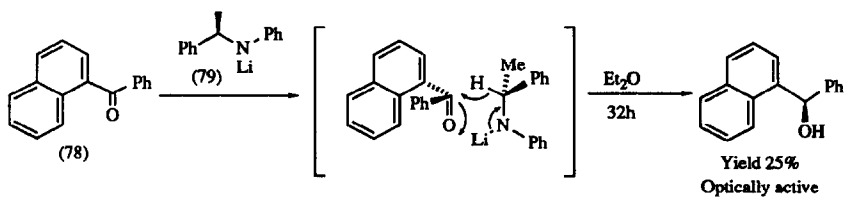


Scheme 36

4. OTHER APPLICATIONS OF HCLA BASES

4.1 Reduction of a Ketone

The first application of chiral lithium amides was reported in 1969 by Wittig who described the reduction of phenyl-α-naphthylketone (**78**) with chiral base (**79**).[49] Unlike the other processes discussed so far the amide is consumed during the reaction, Scheme 37.

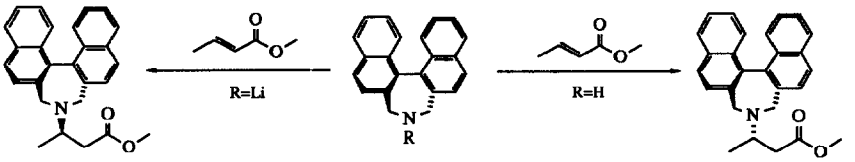


Scheme 37

With the current surge of interest in the use of HCLA bases this reaction perhaps deserves further examination, although it will almost certainly be limited in scope to non-enolisable substrates.

4.2 Michael Addition of Lithium Amide to Acrylates

The 1,1'-binaphthyl-derived lithium amide (**80**) undergoes Michael addition to methyl crotonate to give the product (**81**) in up to 98% de.[50] The corresponding amine, however, provides the opposite diastereomer with 61% de, Scheme 38.



Scheme 38

Force-field modelling has been used to explain this phenomena.[51]

Provided that the benzylic carbon-nitrogen bonds in such products can be cleaved then the transformation in Scheme 38 represents the enantioselective addition of an ammonia synthon, and a potentially useful entry into β-aminoesters.

5. CONCLUSION

Chiral lithium amides have been shown to undergo intermolecular chirality transfer in a wide variety of applications. Work in this area, however, is still in its infancy and further studies are required to optimise these reactions and gain higher levels of asymmetric induction on a wider variety of substrates.

A major obstacle in development of this chemistry is our poor understanding of the transition states involved in these stereoselective proton transfer reactions. Further detailed study of the reagents and reaction conditions used, as well as intermediates in some cases, will hopefully advance this area of chemistry from its present, rather empirical, stage of development into a powerful, predictively useful, and broadly applicable branch of asymmetric synthesis.

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