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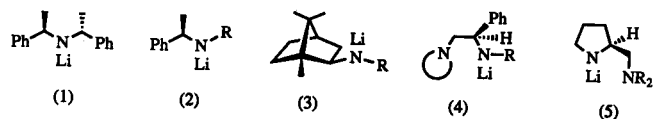
Over the past few years we have been involved in the development of chiral lithium amide bases as reagents for asymmetric synthesis. These reagents allow a new and novel approach to non-racemic target molecules involving enantiomer recognition and enantiotopic group differentiation. Examples include the conversion of a prochiral ketone into a non-racemic enol silane by use of chiral lithium amide and the asymmetric synthesis of chromium complexes using the same base. Important aspects of these reactions will be discussed, including application of the asymmetric enolisation approach to the synthesis of anatoxin-a and extension of the use of chiral bases in organometallic synthesis to ferrocenes.

Keywords: asymmetric synthesis; chiral lithium amide bases.

CHIRAL LITHIUM AMIDE BASES

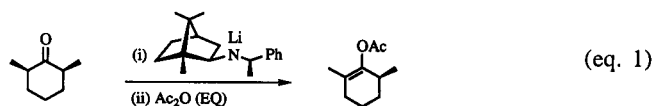
One of the most commonly employed reactions in organic synthesis involves the formation of a reactive carbon nucleophile by a metallation process. Despite the fundamental nature of this important reaction, which is applicable to a vast range of organic compounds, asymmetric variants of the deprotonation reaction, using chiral bases, have not been extensively explored. We have been examining "asymmetric deprotonation" chemistry using chiral lithium amides, which are essentially chiral variants of the commonly used lithium amide base LDA, and describe herein some of our recent findings¹.

Typical bases employed in asymmetric deprotonation chemistry are exemplified by chiral lithium amides 1-5. We have mainly used the *bis*-phenylethylamide 1 which offers the advantages of C₂-symmetry, resulting in very good levels of asymmetric induction in many cases, and is very easily prepared in either enantiomeric form. Even simpler phenylethylamine derived bases, of general structure 2 (e.g. R = ⁱPr, cyclohexyl), are also effective in some instances, but do not usually give such good levels of asymmetric induction as base 1. Other examples include the sterically hindered base 3, available via reductive amination of camphor, and lithium amides 4 and 5, derived from phenyl glycine and proline respectively. The latter types have largely been utilised by other groups working in this area, and are not dealt with further in this review.

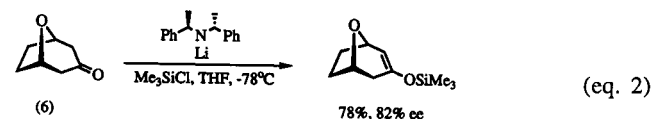


ASYMMETRIC DEPROTONATION OF CYCLIC KETONES

The first type of chiral base-mediated process which we have examined involves the breaking of a symmetric plane in a cyclic prochiral ketone, as exemplified by our very first effort using *cis*-2,6-dimethylcyclohexanone, eq.1².



The symmetrical ketone is converted into a chiral, non-racemic product by a process which involves kinetically-controlled discrimination between two enantiotopic α -hydrogens. We subsequently extended this principle to a range of other ketones, for example the oxabicyclic [3.2.1] ketone 6, finding that the base 1 gives good levels of enantiomeric excess using the Me₃SiCl *in situ* quench (ISQ) protocol, eq.2³.



We subsequently questioned the need for an *in situ* quench (the ISQ protocol involves premixing of the chiral base with Me₃SiCl *prior* to addition of the ketone substrate), and found that much lower levels of asymmetric induction were available by using the more traditional method of enolisation *followed* by electrophilic quench (termed external quench - EQ).

We decided that, since enolate equilibration should not be a factor in such low temperature reactions, the different results must be due to the different composition of the reaction mixture under the two sets of reaction conditions. Under EQ conditions the enolisation is allowed to proceed to completion before the addition of Me₃SiCl, thus allowing the lithium enolate to accumulate as the reaction progresses. In the ISQ reactions the enolate is presumably quenched immediately so that enolate does not accumulate, *but LiCl is liberated as the enolisation proceeds*. Since both lithium enolates and lithium halides are known to form mixed aggregates with lithium amides, we realised that the formation of such species in the enolisation mixture could lead to modified enantioselectivity.

SALT EFFECTS IN ASYMMETRIC ENOLISATIONS

We chose to focus on the effect of LiCl on the enantioselectivity of a range of ketone enolisations and found a dramatic improvement in the ee of products obtained from EQ reactions

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if LiCl (about 0.1 equiv.) was added⁴. Values of enantiomeric excess for a number of ketone/base combinations under EQ, ISQ and the new "plus salt" conditions (termed EQ+LiCl) were shown to follow the same trend (Fig.1), the addition of salt substantially improving the normal EQ result - often to a level comparable with the ISQ results.

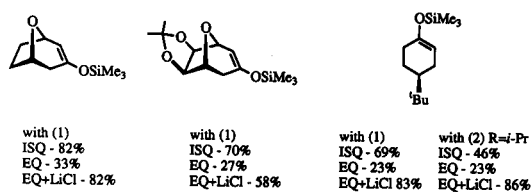
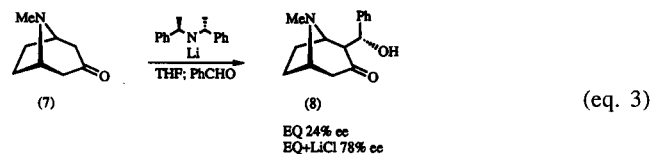


Figure 1. Values of ee for enol silanes formed, under ISQ, EQ or EQ+LiCl conditions, from the corresponding ketones.

One significant consequence of this finding is that high levels of asymmetric induction, previously limited to the Me₃SiCl-ISQ protocol, can be achieved with a range of other electrophiles. This is illustrated by the conversion of tropinone **7** into the benzaldehyde aldol **8** in better enantiomeric excess than had been previously possible, eq. 3⁵.



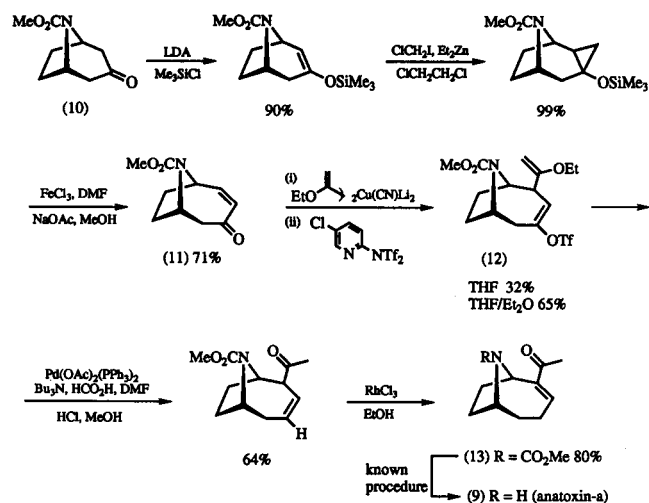
A NEW SYNTHESIS OF ANATOXIN-A

The realisation that the tropinone skeleton could be modified to allow the synthesis of several types of alkaloid natural product prompted us to devise an asymmetric synthesis of anatoxin-a **9**, based on the type of enolisation shown in eq. 3⁶. To date, we have completed a racemic synthesis of this alkaloid, as shown in Scheme 1, which utilises a ring expansion of a silyloxycyclopropane as the key step. Thus, enol silane formation from tropinone derivative **10** was followed by cyclopropanation and ring expansion by treatment with FeCl₃ in DMF to give the key homotropane enone **11**. Completion of the synthesis then required introduction of a suitable side chain unit, followed by functional group manipulation. This was achieved by reaction of **11** with a higher order cyanocuprate, generated using lithiated ethyl vinyl ether, and quenching of the intermediate regioselective enolate with Comin's triflate reagent to give **12**. Hydrogenolysis of the enol triflate was followed by hydrolysis of the vinyl ether side chain, subsequent RhCl₃-mediated isomerisation of the carbon-carbon double bond into conjugation with the carbonyl function then furnishing protected anatoxin derivative **13**. This compound had been prepared in previous synthesis of anatoxin and therefore completed a formal synthesis of the alkaloid.

Work is now underway to repeat this synthetic sequence with non-racemic material originating from a chiral lithium amide base reaction. Either enantiomer of anatoxin should be available by this route and it is hoped that material of 80-90% ee, expected from the chiral base reaction, should allow preparation of enantiomerically pure materials following enantiomeric enrichment.

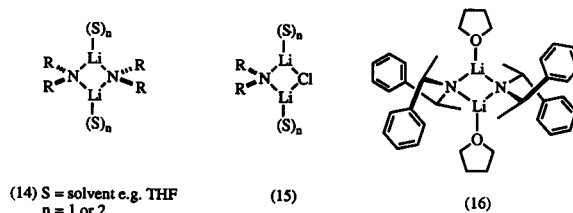
TOWARDS UNDERSTANDING CHIRAL LITHIUM AMIDE BASE REACTIONS

Having described the basic elements of the chiral base chemistry, and one synthetic application involving the alkaloid



Scheme 1. A new synthesis of Anatoxin-a.

anatoxin-a, we return to the question of the origins of the enantioselectivity in the asymmetric enolisations and possible explanations for the dramatic salt effects on the levels of induction. A major problem in rationalising the chiral base reactions is the complex behaviour of lithium amide bases in solution. Simple lithium amide bases, such as LDA, have been demonstrated to be aggregated, both in the solid state and in solution. In THF the important species is often a bridged dimer such as **14**, and intriguingly such dimers have been shown to be subject to modification to mixed aggregates **15** by the addition of lithium salts - especially LiCl⁷. We have recently determined the dimeric structure if chiral lithium amide **1** by X-ray crystallography and shown that it has the expected bridging Li-N-Li-N core structure shown in **16**⁸.



At present it seems that dimers such as **16** could well be the reactive species in chiral base reactions in the absence of salt. It is therefore tempting to ascribe the improved enantioselectivities of the chiral base reactions in the presence of LiCl to the conversion of dimeric base **16** into a more stereoselective mixed aggregate related to **15**. The relatively high levels of induction seen under the Me₃SiCl-ISQ conditions could also be due to mixed aggregate formation, the necessary LiCl being generated as the enolate quench proceeds.

The development of a transition state model which explains the sense of the enantioselective deprotonations is therefore complicated by the possible intervention of a range of complex aggregated species. We are currently considering transition state models of the deprotonation involving aggregates as the reactive species, based on the proposals of Seebach⁹, and Williard¹⁰, as well as the more conventional Ireland-type models which invoke monomeric lithium amide. Whatever the origins of the enantioselectivity it is clear that a range of ketones examined so far (by our own group and several others) can be transformed into non-racemic products by lithium amide **1** with predictable absolute stereochemical outcome (Fig. 2). In each case the hydrogen highlighted is that removed preferentially, the outcome being represented in general form by **17**.

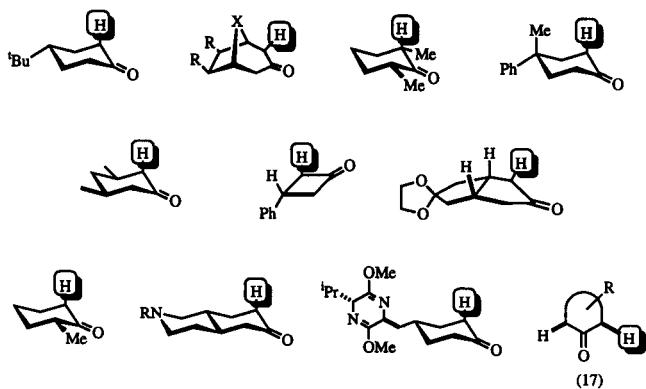
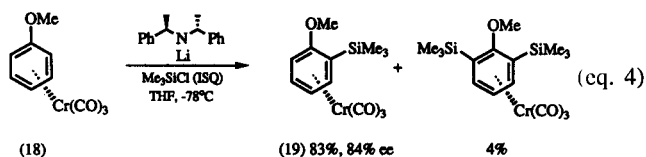


Figure 2. Pattern of asymmetric deprotonations using HCLA base (1).

SYNTHESIS OF CHIRAL TRICARBONYL(η^6 -ARENE) CHROMIUM COMPLEXES

Subsequent to our initial chiral base reactions involving the symmetry-breaking operation of cyclic ketones, we have demonstrated a range of other applications of chiral lithium amide bases including kinetic resolution of ketones and lactams¹¹. We also extended the scope of the chemistry beyond reactions of carbonyl compounds by demonstrating asymmetric deprotonations of cyclic sulphoxides¹². Most recently, we have achieved a new and very direct synthesis of chiral tricarbonyl(η^6 -arene) chromium complexes, for example transformation of anisole complex **18** into the chiral product **19**, eq. 4¹³.



The *ortho*-silylated complex **19**, initially formed in 84% ee, is easily enantiomerically enriched by recrystallisation to give material of >97% ee. Other examples of complexes prepared by this new and direct approach are shown in Fig. 3. From the limited data available, it appears that prochiral complexes having oxygen-containing substituents give the best results. In the case of complex **18** we found that the use of an Me₃SiCl-ISQ was important, since in the absence of an electrophilic quench the metallated complex undergoes rapid equilibration¹⁴. This effect was traced to an intermolecular proton transfer involving **18** and lithio-**18**, but was found not to interfere in

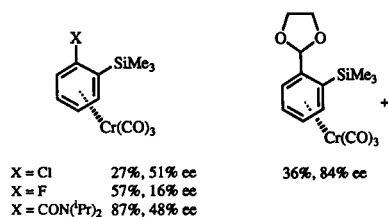
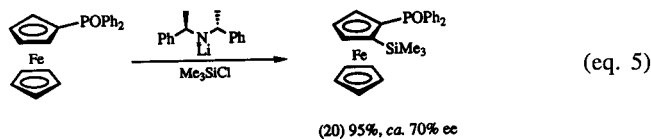


Figure 3

asymmetric metallations of most other complexes.

Finally, we have an indication of a further extension of this method to the synthesis of chiral ferrocenes such as **20**, eq. 5¹⁵.



Such chiral complexes have value as catalysts in a range of asymmetric transformations, such as asymmetric hydrogenation.

CONCLUSION

The above examples give some idea as to the present scope of chiral lithium amide chemistry. We are continuing our efforts in developing this chemistry in terms of new chiral base-mediated transformations, synthetic applications and chiral base design.

ACKNOWLEDGEMENTS

I am very grateful to the dedicated and talented postgraduate and postdoctoral coworkers who have made this work possible. Their names, and those of our sponsors and collaborators, can be found in the articles cited above.

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