Pure & Appl. Chem., Vol. 68, No. 3, pp. 691–694, 1996.
Printed in Great Britain.

Recent advances in asymmetric synthesis using chiral lithium amide bases

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Abstract: The use of chiral lithium amide bases for the asymmetric transformation of ketones and certain organometallics is described, including the effect of added salts on the enantiomeric excess achieved and an application involving the total synthesis of the alkaloid anatoxin-a.

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. 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 findings.[1]

Typical bases employed in asymmetric deprotonation chemistry are exemplified by chiral lithium amides **1–5**. We have mainly used the the *bis*-phenylethylamide **1** which offers the advantages of C_2-symmetry, resulting in very good levels of asymmetric induction in many cases, and is very easily prepared in either enantiomeric form.

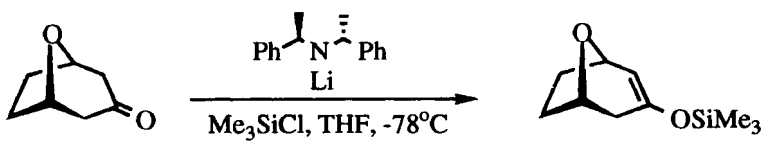
(1) (2) (3) (4) (5)

Simpler phenylethylamine derived bases, of structure **2** (e.g. R = ^{i}Pr, cyclohexyl), are also effective in some instances; other examples include the hindered base **3**, available by reductive amination of camphor, and amino-acid derived lithium amides **4** and **5**.

Asymmetric Deprotonation of Cyclic Ketones

The first type of chiral base-mediated process which we have examined involves the breaking of a symmetry plane in a cyclic prochiral ketone, for example the oxabicyclic [3.2.1] ketone **6**, which gives good levels of enantiomeric excess using the Me_3SiCl *in situ* quench (ISQ) protocol, Scheme 1.[2]

Scheme 1



(6) (7) 78%, 82% ee

We subsequently questioned the need for an *in situ* quench (the ISQ protocol involves premixing of the chiral base with Me_3SiCl *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

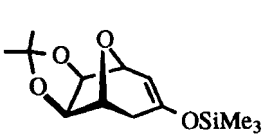
reaction conditions. Under EQ conditions the enolisation is allowed to proceed to completion before the addition of Me_3SiCl, thus allowing the lithium enolate to accumulate as the reaction progresses. In the ISQ reactions the enolate is presumably quenched immediately so that enolate does not accumulate, *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 if LiCl (about 0.1 equiv.) was added.[3] 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, e.g. **7–9**, the addition of salt substantially improving the normal EQ result - often to a level comparable with the ISQ results.

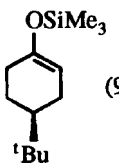
(7)

with (1)
ISQ - 82%
EQ - 33%
EQ+LiCl - 82%



(8)

with (1)
ISQ - 70%
EQ - 27%
EQ+LiCl - 58%



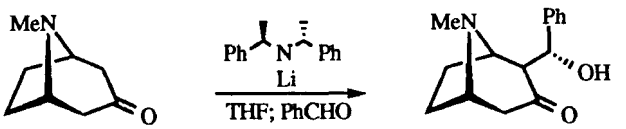
(9)

with (1)
ISQ - 69%
EQ - 23%
EQ+LiCl 83%

with (2) R=*i*-Pr
ISQ - 46%
EQ - 23%
EQ+LiCl - 86%

One significant consequence of this finding is that high levels of asymmetric induction, previously limited to the Me_3SiCl-ISQ protocol, can be achieved with a range of other electrophiles. This is illustrated by the conversion of tropinone **10** into the benzaldehyde aldol **11** in better enantiomeric excess than had been previously possible, Scheme 2.[4]

Scheme 2



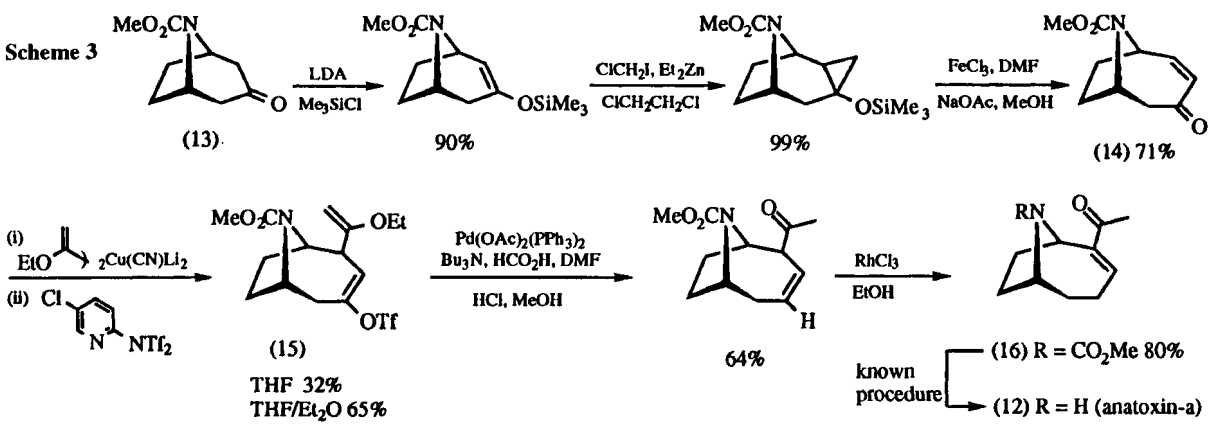
(10)

(11) EQ 24% ee
EQ+LiCl 78% ee

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 **12**, based on the type of enolisation shown in Scheme 2. To date, we have completed a racemic synthesis of this alkaloid, as shown in Scheme 3, which utilises a ring expansion of a silyloxycyclopropane as the key step.[5]

Scheme 3



(13)

90%

99%

(14) 71%

(15)

THF 32%
THF/Et_2O 65%

64%

(16) R = CO_2Me 80%

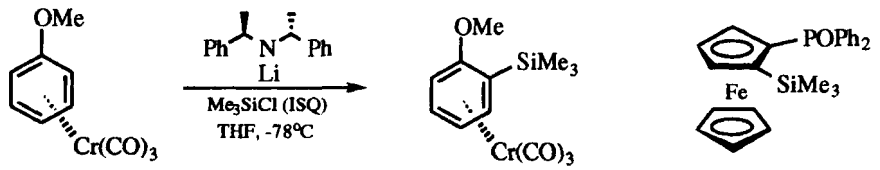
(12) R = H (anatoxin-a)

Thus, enol silane formation from tropinone derivative **13** was followed by cyclopropanation and ring expansion by treatment with $FeCl_3$ in DMF to give the key homotropane enone **14**. Completion of the synthesis then required introduction of a suitable side chain unit, followed by functional group manipulation. This was achieved by reaction of **14** with a higher order cyanocuprate, generated using lithiated ethyl vinyl ether, and quenching of the intermediate regiospecific enolate with Comin's triflate reagent to give **15**. Hydrogenolysis of the enol triflate was followed by hydrolysis of the vinyl ether side chain, subsequent $RhCl_3$-mediated isomerisation of the carbon–carbon double bond into conjugation with the carbonyl function then furnishing protected anatoxin derivative **16**. This compound had been prepared in previous syntheses 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.

Synthesis of Chiral Organometallics

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 lactams.[6] We also extended the scope of the chemistry beyond reactions of carbonyl compounds by demonstrating asymmetric deprotonations of cyclic sulphoxides.[7] 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 **17** into the chiral product **18**, Scheme 4.[8]

Scheme 4



(17) (18) 83%, 84% ee (19) 95%, *ca.* 70% ee

The *ortho*-silylated complex **18**, initially formed in 84% ee, is easily enantiomerically enriched by recrystallisation to give material of >97% ee. Other complexes have also been prepared by this new and direct approach, from the limited data available it appears that prochiral complexes having oxygen-containing substituents give the best results.
In the case of complex **17** we found that the use of an Me_3SiCl-ISQ was important, since in the absence of an electrophilic quench the metallated complex undergoes rapid equilibration.[9] This effect was traced to an intermolecular proton transfer involving **18** and lithio-**18**, but was found not to interfere in 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 **19**.[10]

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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