Chem. Soc. Rev., 1990, **19**, 335–354

MELDOLA LECTURE*

New Stereoselective Reactions in Organic Synthesis

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1 Introduction

Our studies in organic chemistry have been concerned with the development of new methods for organic synthesis, especially stereoselective synthesis, and the application of such methods to synthetic problems, *i.e.* target synthesis. Two areas of interest are described in this article, the first involving a new approach to the synthesis of optically active compounds, and the second a new preparation of vinyl sulphones which are important intermediates in the synthesis of alkenes.

2 Asymmetric Synthesis Using Chiral Lithium Amide Bases

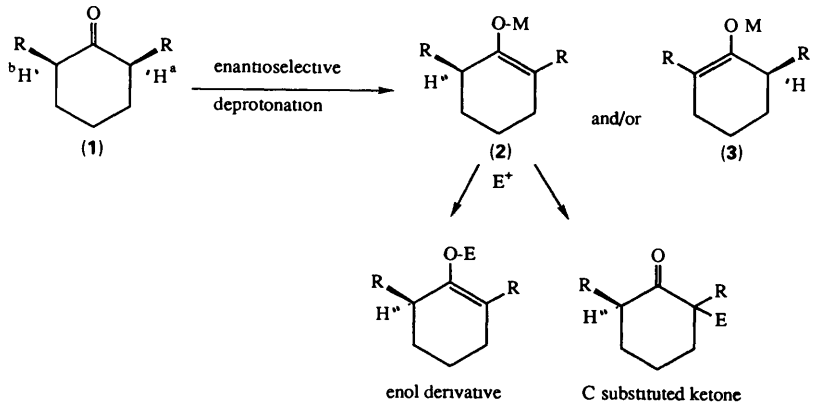
There is a continuing need for new direct methods for the synthesis of optically active compounds. Although great advances have been made in this area there are still very few asymmetric methods which are general, direct, and efficient in terms of yield and enantiomeric excess (ee).[1] Optically active carbonyl compounds represent an important group of intermediates for chiral synthesis and yet their preparation is only possible (in general) using indirect methods. The present state-of-the-art technology for the preparation of such compounds usually involves the use of chiral auxiliaries, which despite providing elegant solutions to this synthetic problem, nevertheless present significant drawbacks in terms of requiring multi-step reaction sequences and auxiliary recovery/recycling *etc.* Ultimately of course it would be highly desirable to replace such methods with direct processes using only catalytic quantities of non-covalently bound chiral inducers, *i.e.* asymmetric catalysis. As a first step in the direction of using non-covalently bound reagents for the asymmetric synthesis of optically active carbonyl compounds we have investigated a new process involving removal by a chiral base of one of the enantiotopic protons α to the carbonyl group of prochiral or meso ketones. This leads to a chiral enolate that can be alkylated to yield an optically active, chiral product.[2]

This type of process is illustrated in Scheme 1 for the reaction of a *cis*-2,6-disubstituted cyclohexanone starting material (1). Ketone (1) has two enantiotopic hydrogens ^{a}H and ^{b}H which could be removed by a base to give enolates (2) or (3), respectively, where M represents a metal (usually lithium).

* Delivered at a Perkin Division Symposium on General and Synthetic Methods at the Scientific Societies' Lecture Theatre, London W1, on 25 January 1990.

[1] Asymmetric Synthesis Volumes 1 – 5, ed. J. D. Morrison, Academic Press, 1983 1985, London.

[2] N. S. Simpkins, *Chem. Ind.*, 1988, 387.



Need chiral equivalent of LDA for kinetically controlled asymmetric deprotonation

$$R_2NH \xrightarrow{BuLi} R_2NLi$$

R = readily available chiral group

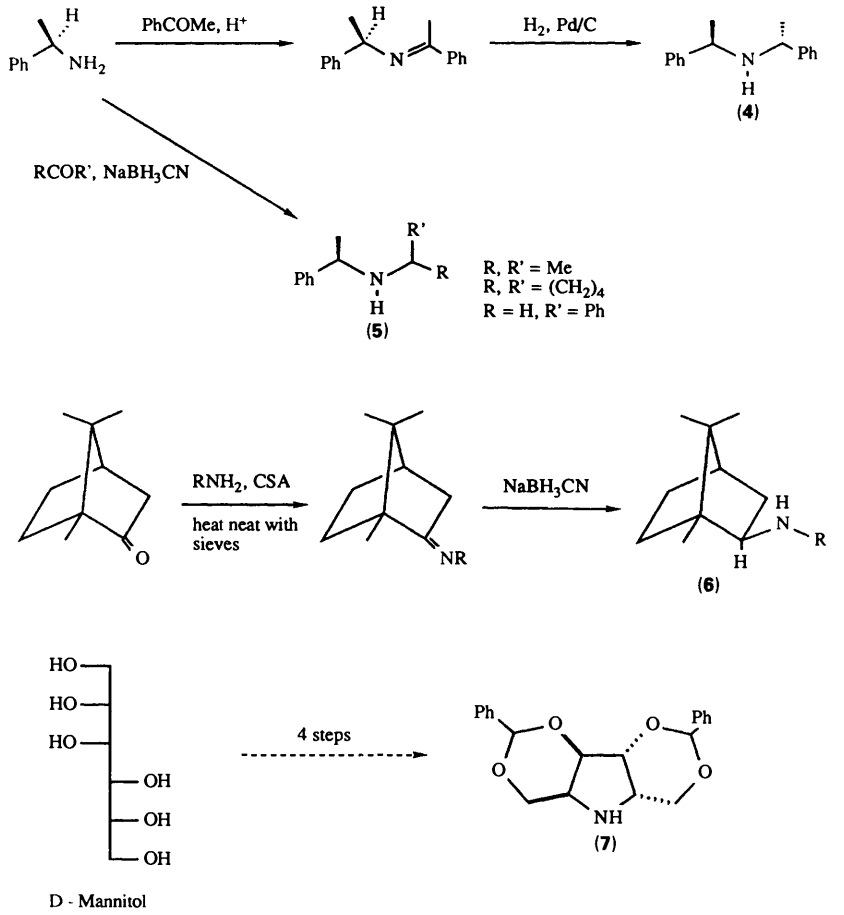
Scheme 1

Clearly in this process the prochiral starting material is converted into one or other of two chiral enolates, and the opportunity for asymmetric synthesis lies in preferentially forming one enolate rather than the other If this were possible the chiral enolate, *e g* (2), could be further transformed in the usual way, by electrophilic trapping on carbon or on oxygen, to give useful chiral products The key point to realise is that the step in which the chirality is first generated is the deprotonation step which must therefore require an optically active base We anticipated that this chemistry would be best carried out using strong bases under kinetically controlled conditions (especially to avoid enolate equilibration) and so chiral lithium dialkylamides presented themselves as likely candidates for this type of reaction Although such bases had been used previously in a few examples of asymmetric processes there were no reports at this time of their use in the type of process outlined in Scheme 1

We therefore required a number of suitable optically active (pure) secondary amines which, as the corresponding dialkylamides, would act as chiral equivalents of LDA A number of these have been prepared as illustrated in Scheme 2

Amine (4) was prepared according to the original procedure,[3] although it should be noted that there is an error in the optical rotation and the assignment of absolute configuration of the base quoted in that report A variety of amines of general structure (5) were also prepared using a convenient one-pot procedure

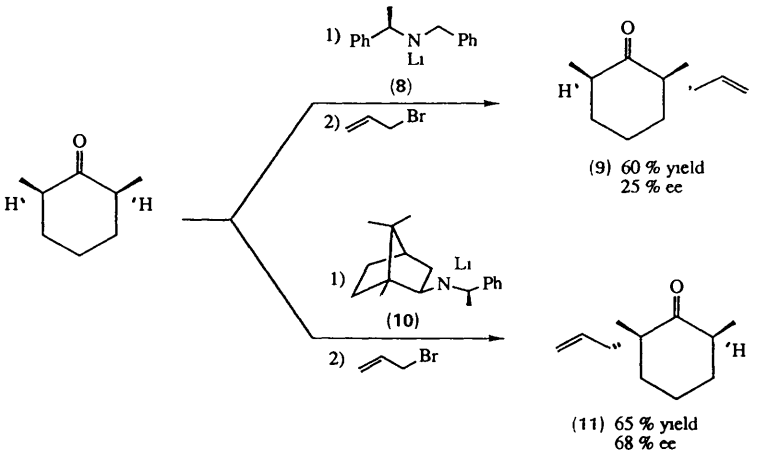
[3] C G Overburger N P Marullo and R G Hiskey *J Am Chem Soc* 1961 **83** 1374



Scheme 2

which involves reaction of (*R*)-α-methylbenzylamine with a carbonyl compound in the presence of $NaBH_3CN$. Some rather more bulky bases were also prepared by a two-step reductive amination procedure starting with (+)-camphor. In these cases forcing conditions were required to effect the initial condensation of camphor with primary amines, the intermediate imine being isolated before reduction to give secondary amines of formula (6). We were also interested in preparing C_2 symmetric bases having a pyrrolidine skeleton, since these compounds have proved very effective in asymmetric synthesis.[4] We were successful in preparing amine (7) by the route reported by Shing's group;[5]

[4] J. K. Whitesell, *Chem. Rev.*, 1989, **89**, 1581.
[5] T. K. M. Shing, *Tetrahedron*, 1988, **44**, 7261.



Scheme 3

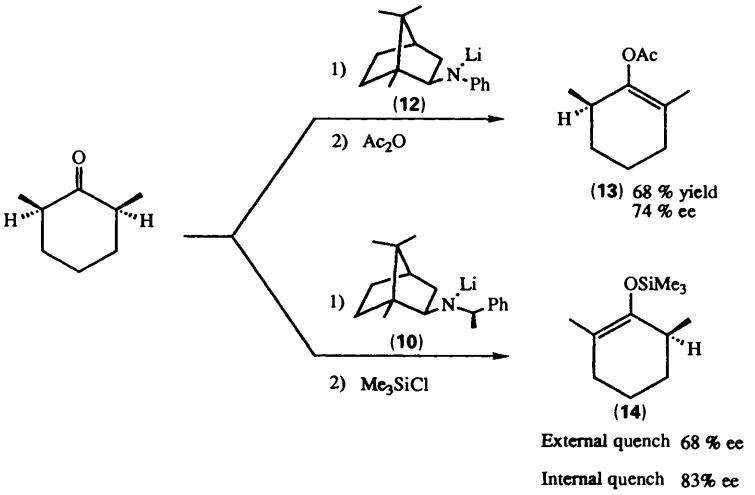
however this base has largely proved unsuitable for the purpose of generating the corresponding lithium amide

In our very earliest experiments we chose *cis*-2,6-dimethylcyclohexanone as the prochiral starting material and used lithium amide (8), Scheme 3 In these reactions the lithium amide is generated by addition of BuLi to a solution of secondary amine in THF, and then the mixture is cooled (usually to -78 °C) before addition of the starting ketone [6] The addition of allyl bromide to the reaction carried out using (8) then gave the optically active alkylated ketone (9) in about 60% yield Examination of the ^{1}H NMR spectrum of this product (in comparison with the corresponding racemic compound) in the presence of optically active lanthanide shift reagents indicated an ee of 25% The absolute stereochemistry of the product was at this point inferred from it's CD spectrum (using the ketone octant rule) The use of the enantiomer of base (8) under identical conditions yielded the enantiomeric product in similar yield and ee

At this point we briefly investigated the effect of other solvents on the reaction and found diethyl ether and dimethoxyethane to be less satisfactory than THF The addition of HMPA (*ca* 10% v/v) to the chiral base prior to addition of the ketone was also detrimental to the results, although HMPA could be added when deprotonation was complete in order to speed up the final alkylation step

The use of the more bulky lithium amide (10) proved more effective in these reactions, giving the alkylated ketone (11) in 68% ee The first deprotonations using (10) proved problematic with products arising from attack of BuLi on the starting ketone This problem was solved by generating the lithium amide at room temperature Clearly the bulky nature of this secondary amine makes

[6] C M Cain R P C Cousins G Coumbandes and N S Simpkins *Tetrahedron* 1990 **46** 523



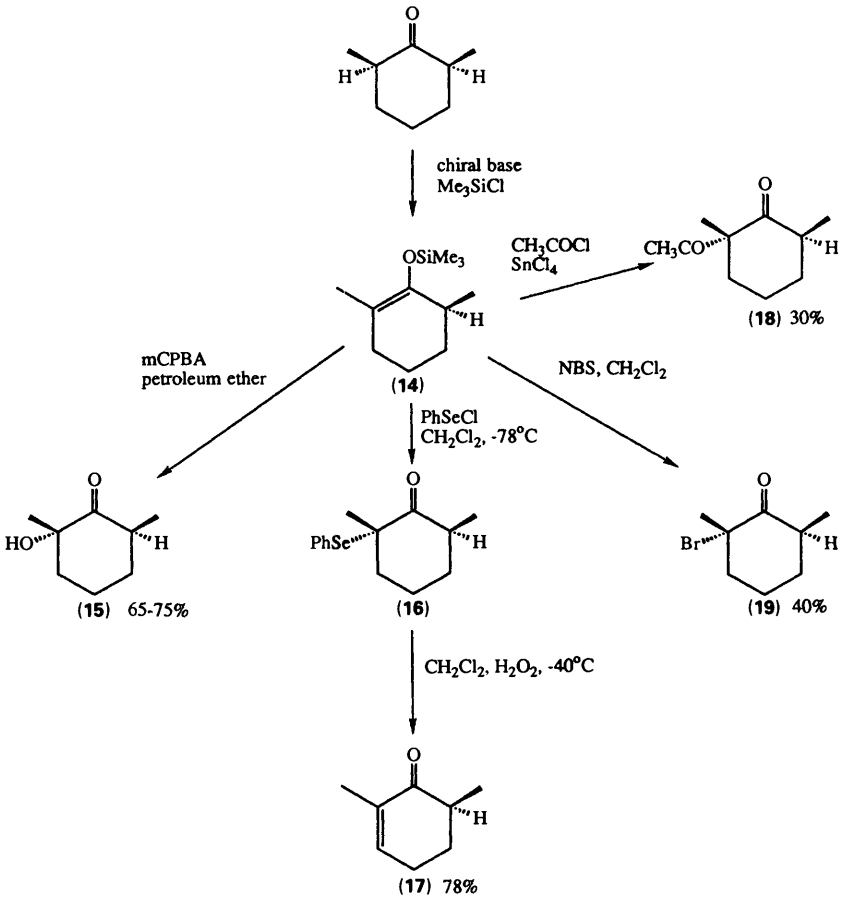
Scheme 4

proton removal by BuLi rather slow compared to, say diisopropylamine.

The alkylated derivatives (9) and (11) proved less than ideal for estimating the ee of reactions using new bases. Firstly, minor amounts of the other diastereomeric product were also produced, and secondly the products were rather volatile. We therefore investigated the preparation of alternative enol derivatives including enol acetates and silyl enol ethers, Scheme 4.

Thus addition of acetic anhydride to the enolate generated using the camphor-derived base (12) gave the enol acetate (13) in 68% yield. This sample proved to have an ee of 74%, this estimation being simplified by clear splitting of the OCO*Me* signal of the enol acetate function in chiral shift ^{1}H NMR experiments. The formation of enol acetate (13) (or enantiomer) proved to be the best method for directly estimating the efficiency of chiral bases in these reactions, the products being stable, and not so volatile as (9) and (11).

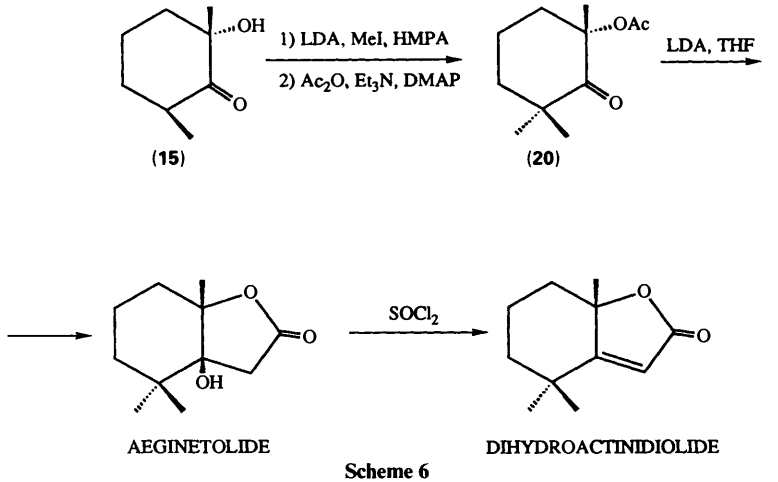
The more synthetically versatile silyl enol ether (14) could also be prepared, for example using base (10), by electrophilic quenching with excess Me_3SiCl (note the enantiocomplementary result to that using base (12)). Here two distinct protocols were followed. The first involved deprotonation of the ketone as usual, followed by the addition of Me_3SiCl (external quench). This gave silyl enol ether of similar optical purity to the enol acetate formed using the same base (the silyl enol ethers were not amenable to direct ee measurement; the ee indicated is that of derived products, *vide infra*). The second procedure involved premixing the Me_3SiCl with the chiral lithium amide prior to addition of the starting ketone (internal quench). This method gave improved ee (83%) although the chemical yield in this case was rather low, 30—35%. The internal quench procedure proved more effective on other ketone substrates, *vide infra*.



Scheme 5

The optically active silyl enol ether (14) formed in this way was converted into a number of products as indicated in Scheme 5. This chemistry followed established procedures, allowing the synthesis of products (15)—(19) in optically active form, in each case the ee being estimated using chiral shift reagents. In addition we checked the ee of (15) by forming diastereoisomeric Mosher esters; the results matched with those obtained using shift reagents. Since the ee estimates of these products were close to the ee of the enol acetate formed using the same chiral base, the silyl enol ether (14) appears to react without diminution of ee. The formation of the known enone (17) also allowed further confirmation of our assignment of absolute configuration.

To demonstrate the potential of this new method for the preparation of



Scheme 6

optically active, chiral starting materials for asymmetric synthesis we undertook a brief synthesis of the naturally occurring lactones (5*S*)-aeginetolide and (5*S*,6*S*)dihydroactinidiolide (we actually prepared the antipodes of the naturally occurring compounds), Scheme 6.[7]

Thus methylation of the dianion of (15) (66% ee), followed by acylation gave acetate (20) which was further transformed to the targets following literature procedures. The synthesis further strengthened our assignment of absolute stereochemistry, and after optical enrichment by recrystallization allowed us to prepare optically pure dihydroactinidiolide.

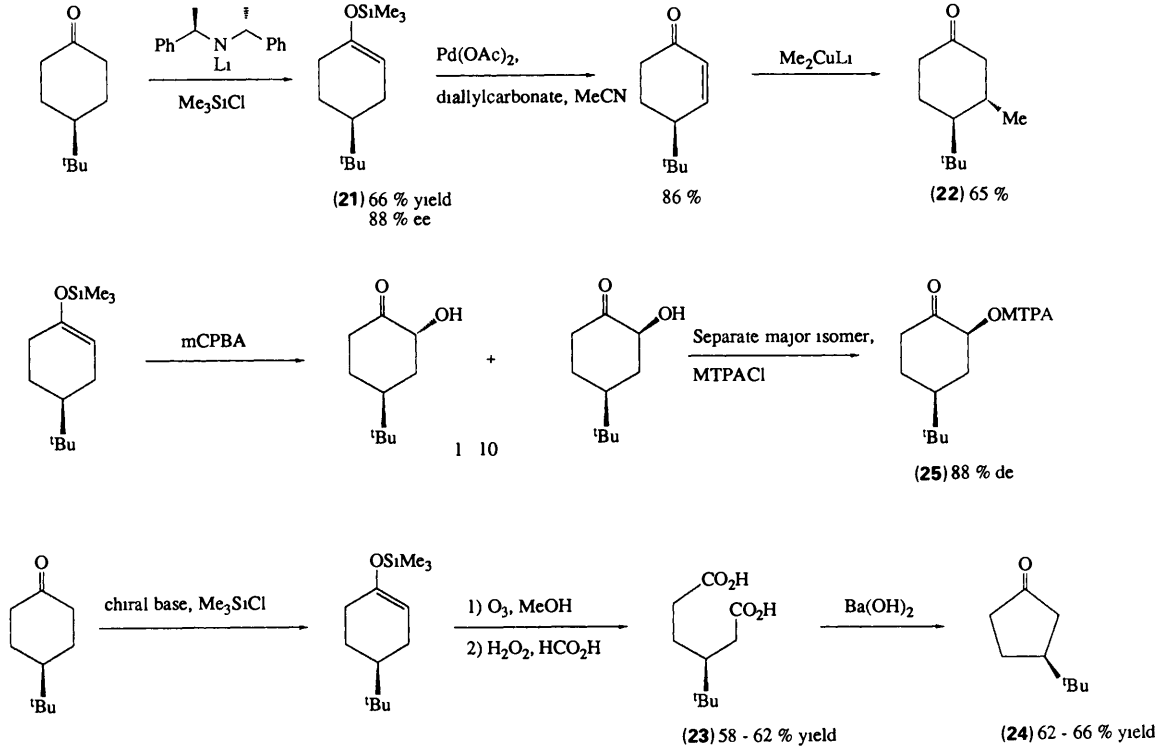
In later experiments using 4-t-butylcyclohexanone as starting material we were able to prepare the silyl enol ether (21) in up to 88% ee, Scheme 7.[8] Here we estimated the ee of (21) by conversion into the known compounds (22), (23), and (24) (at several ee levels) as well as making Mosher derivatives of α-hydroxy ketone products *i.e.* (25).

These sequences serve to illustrate that the asymmetric deprotonation method can be used to produce not only varied cyclic products but also acyclic compounds such as diacid (23).

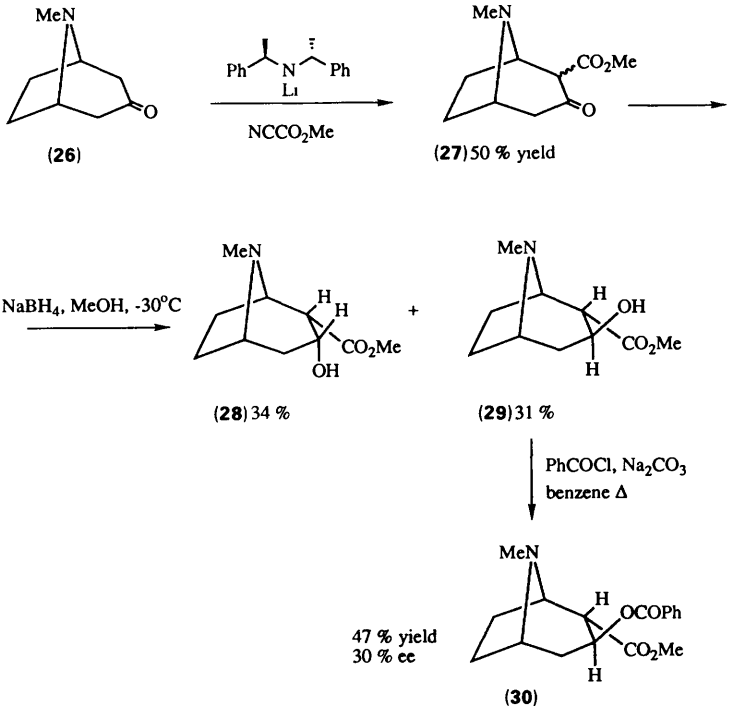
Presently we are examining the reactions of bridged heterocyclic ketones, such as tropinone (26), with chiral bases, since the optically active products from such reactions appear to have potential in the synthesis of alkaloids such as cocaine and anatoxin.

Using the chiral base derived from amine (4), and quenching with $NCCO_2Me$ (Mander's reagent) we have converted tropinone to the optically active β-ketoester (27), Scheme 8. Subsequent reductions using $NaBH_4$ in methanol gave

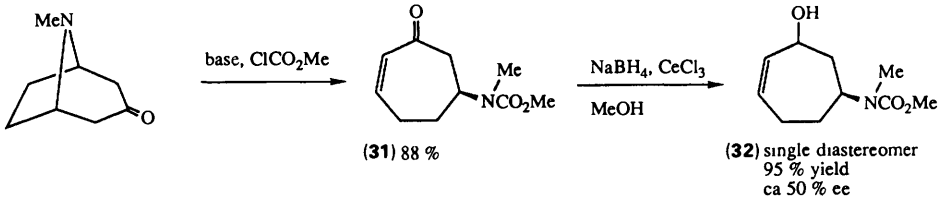
[7] C. M. Cain and N. S. Simpkins, *Tetrahedron Lett.*, 1987, **28**, 3723.
[8] R. P. C. Cousins and N. S. Simpkins, *Tetrahedron Lett.*, 1989, **30**, 7241. See also reference 6.


Ph N Ph
Li
Me3SiCl
OSiMe3
tBu
Pd(OAc)2,
diallylcarbonate, MeCN
Me2CuLi
Me
(21) 66 % yield
88 % ee
86 %
(22) 65 %
mCPBA
OH
1 10
Separate major isomer,
MTPACl
OMTPA
(25) 88 % de
chiral base, Me3SiCl
1) O3, MeOH
2) H2O2, HCO2H
CO2H
Ba(OH)2
(23) 58 - 62 % yield
(24) 62 - 66 % yield

Scheme 7



Scheme 8



Scheme 9

mixtures of the epimeric alcohols (28) and (29). Benzoylation of (29) gave (30) a known epimer (at C-2) of natural cocaine. Judging from the optical rotation of this material and from Mosher ester results using alcohol (29) the intial asymmetric deprotonation process proceeds in a disappointing 30% ee. Efforts to improve this result are continuing.

Whilst we were carrying out this investigation we observed that treatment of tropinone with LDA, followed by addition of $ClCO_2Me$, resulted in the clean formation of ring-opened product (31), Scheme 9. This product was formed even more efficiently using the chiral base derived from (4), and in this case was also

optically active. An estimate of the ee of this material was obtained by reduction to allylic alcohol (32) (relative stereochemistry unknown) and then making Mosher and camphanic ester derivatives. The ee of this material (*ca.* 50%) appears to be rather better than that obtained for (30) which is an encouraging indication that the ee of (30) available by this route can be improved.

Finally, we have initiated some studies using chiral lithium amides as reagents for kinetic resolution. Scheme 10 shows some of our rather modest early results using racemic 2-methyl- and 3-methylcyclohexanone.[9] In both cases treatment of the starting ketone with a deficiency of chiral base results in the preferential deprotonation of one enantiomer, thus giving optically active silyl enol ether product, *e.g.* (33), and optically active recovered starting material (both rather volatile). Other workers in this area have recently confirmed the usefulness of this approach,[10] and have achieved very high levels of enantioselection in kinetic resolutions of a variety of substituted cyclohexanones. Rather than duplicate work in this area we are now investigating such reactions using non-cycloalkanone substrates such as sulphones and sulphoxides, but these studies are not yet well developed.

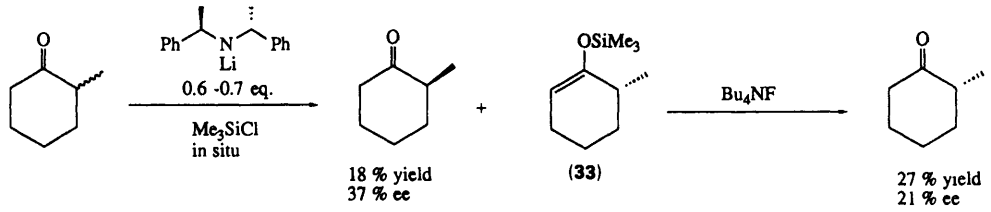
Clearly one of the major problems with the asymmetric deprotonation method at this early stage is the difficulty in predicting the best base to achieve optimal results in any particular case. Similarly for the method to be useful we should be able to predict which enantiomeric product will result from a particular deprotonation experiment. As more reactions are tried some patterns of deprotonation are appearing. For example, using the base derived from (4) the stereochemical pattern shown in Scheme 11 is observed. We look forward to a time when the method can be applied predictively to a wide variety of substrates with confidence in both the stereochemical outcome and ee.

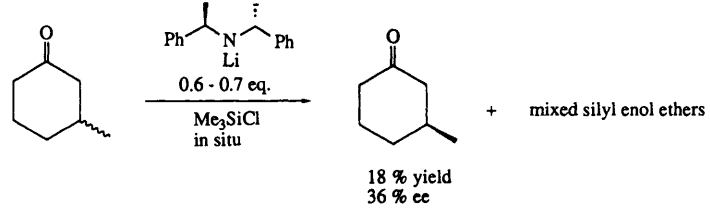
3 A New Stereoselective Synthesis of Vinyl Sulphones

Another area of organic chemistry which has been of interest to us is the use of sulphones in synthesis. Pioneers in this area such as Marc Julia (the Centenary lecturer on this occasion) have particularly influenced our activities in this area, which recently resulted in a new synthesis of vinyl sulphones starting with esters.[11]

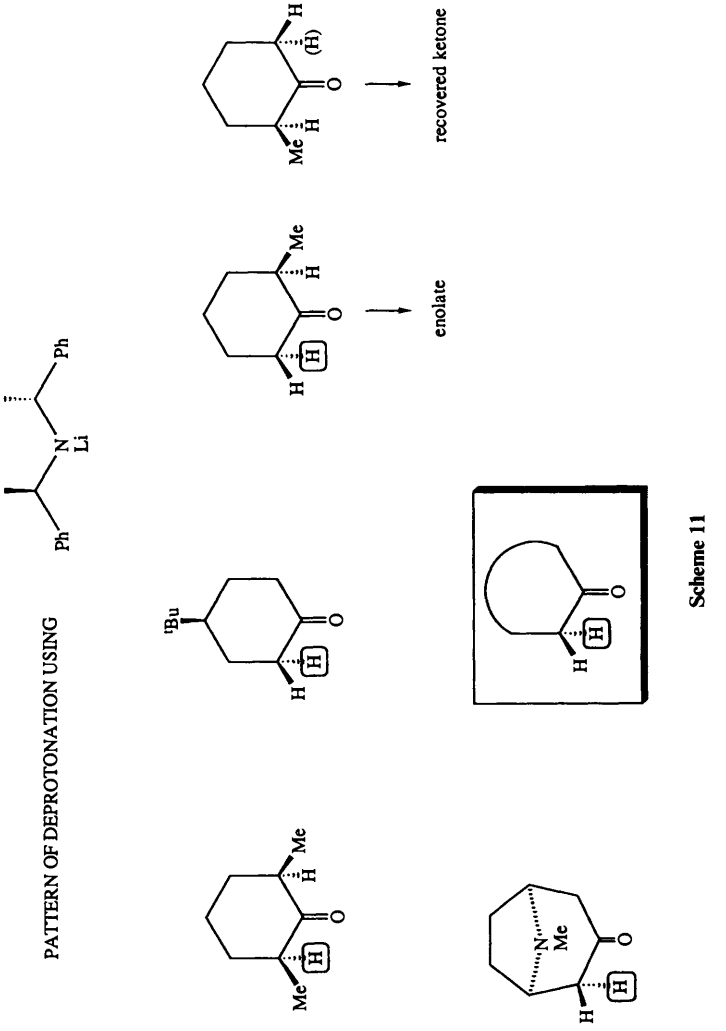
Our efforts in this area commenced with the finding that enolization of certain β-ketosulphones, *e.g.* (34) followed by quenching on oxygen with reactive electrophiles, especially acid chlorides, gave enol derivatives in stereoselective fashion, *e.g.* (35), Scheme 12. The pivalate derivatives shown proved most stable, the (*Z*)-isomer being available pure on a large scale by recrystallization or chromatography. We anticipated that these compounds could serve as oxygenated vinyl sulphones and should undergo addition–elimination reactions with suitable nucleophiles, particularly organometallics. A key question was whether an overall substitution of the carboxylate group for a carbon group (R) could be effected with control of stereochemistry, Scheme 12.

[9] R. P. C. Cousins and N. S. Simpkins, unpublished results.
[10] H. Kim, H. Kawasaki, M. Nakajima, and K. Koga, *Tetrahedron Lett.*, 1989, **30**, 6537.
[11] G. M. P. Giblin and N. S. Simpkins, *J. Chem. Soc., Chem. Commun.*, 1987, 207.


Ph
N
Ph
Li
0.6 -0.7 eq.
Me3SiCl
in situ
18 % yield
37 % ee
OSiMe3
(33)
Bu4NF
27 % yield
21 % ee

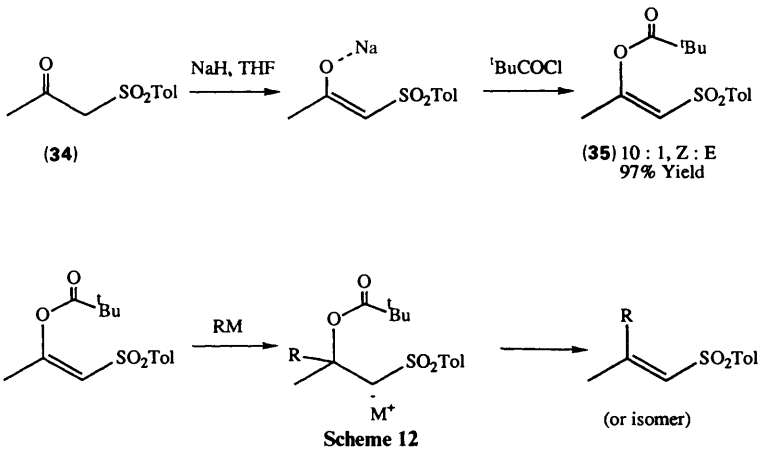

Ph
N
Ph
Li
0.6 - 0.7 eq.
Me3SiCl
in situ
18 % yield
36 % ee
mixed silyl enol ethers

Scheme 10



Scheme 11

Scheme 11



Scheme 12

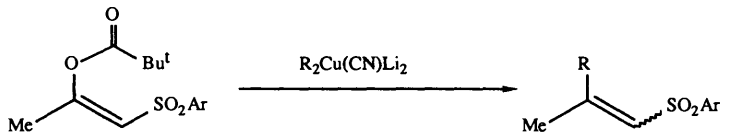
After many disappointing results with Grignard reagents and various organocuprate recipes we found that our enol pivalate derivatives reacted extremely well with Lipshutz[12] higher order cuprates, *i.e.* $R_2Cu(CN)Li_2$, Table 1. Good to excellent yields of substituted products were obtained, with one stereoisomer predominating in each case. We rationalized the results in terms of a stereoelectronically controlled addition–elimination mechanism as indicated in Scheme 13.

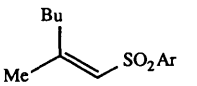
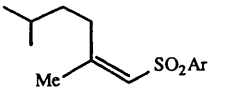
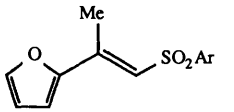
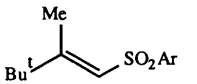
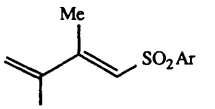
Thus initial *syn* carbometallation (well precedented for reactions of cuprates with other unsaturated compounds such as acetylenes) would initially give an α-sulphonyl carbanion intermediate (36) which could then rapidly undergo *anti*-elimination to give product (37), having the new group *cis* to the sulphone (overall retention) providing the interaction arrowed is not too great. This is the result observed with small, *i.e.* straight chain and α-unbranched cuprates. With more sterically demanding groups we believe that elimination to give (37) is retarded (arrowed interaction now larger) allowing anion (36) to epimerize to (38) which can then undergo easier *anti*-elimination to give the (*E*)-product (39). This model has served to predict the outcome of other reactions tried with different sulphone substrates, *e.g.* as in Table 2. The results of reactions using $Bu_2Cu(CN)Li_2$ at different temperatures also seem to fit this picture, with reactions at higher temperatures giving progressively more of the (*E*)-product [by more facile anion epimerization (36) $\rightleftharpoons$ (38), Table 3].

We have also reacted the prenylated derivatives (40) with $Me_2Cu(CN)Li_2$ to give vinyl sulphone (41), Scheme 14. This sequence illustrates how the enol pivalates originate from the corresponding esters, by means of homologation using dilithiated methylphenylsulphone. We hoped that compound (41) would

[12] B. H. Lipshutz, R. S. Wilhelm, and J. A. Kozlowski, *Tetrahedron*, 1984, **40**, 5005; B. H. Lipshutz, *Synthesis*, 1987, 325.

Table 1

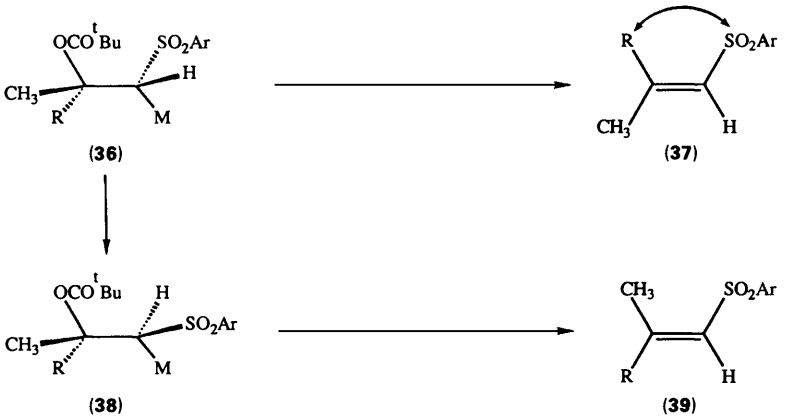


R	%	Z:E	Major Isomer
Me	82	–	
Bu	100	58:1	
^{i}Pent	85	30:1	
2-Furyl	62	1:40	
Bu^t	81	1:20	
Isopropenyl	84	1:40	

find use in terpene synthesis, however this would require stereoselective elaboration, either by substitution of the sulphone group (*i.e.* alkylative desulphonylation) or by substitution of H[1], followed by reductive or alkylative desulphonylation.

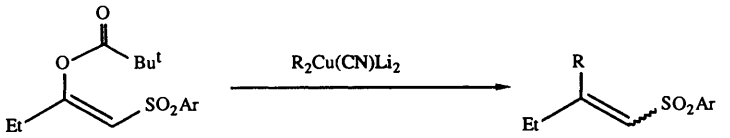
The possibilities for further stereoselective transformation of these vinyl sulphones have been briefly investigated. We hoped to access tri- and tetra-substituted alkenes by the strategies outlined in Scheme 15, and illustrated using vinyl sulphone (42). Thus alkylation of (42) *via* a derived vinylic anion should be possible using the method of Eisch, to give (43).[13] Either (42) or (43) might be

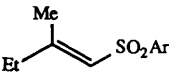
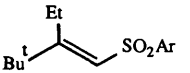
[13] J. J. Eisch and J. E. Galle, *J. Org. Chem.*, 1979, **44**, 3279.



Scheme 13

Table 2



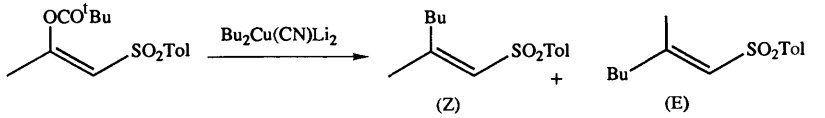
R	%	Z:E	Major Isomer
Me	83	1:50	
Bu t	94	No (Z) Detected	

further substituted using Julia's method involving reaction with Grignard reagents under transition metal catalysis, to give (44) or (45) respectively.[14] Alternatively non-alkylative desulphonylation of (43) would give (46).[15]

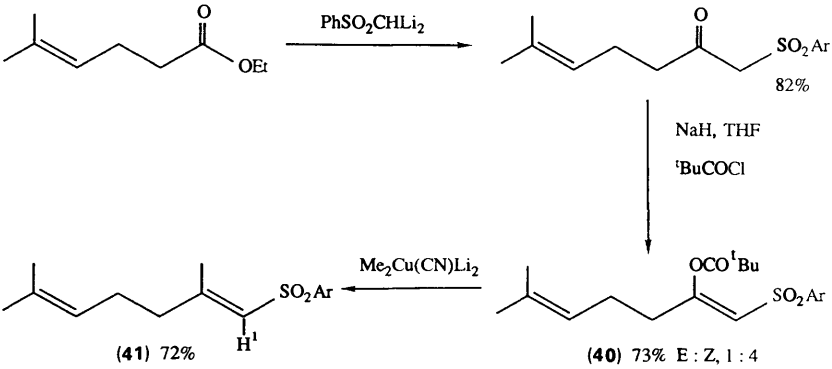
Our initial results in this area have been rather disappointing. Whereas the literature procedures for stereoselective desulphonylation work well for α,β-disubstituted vinyl sulphones, with β,β-disubstituted compounds the reactions are generally very poor. Scheme 16 illustrates a few of these results. The initial

[14] J.-L. Fabre, M. Julia, and J.-N. Verpeaux, *Bull. Soc. Chim. Fr.*, 1985, 174.
[15] J. Bremner, M. Julia, M. Lannay, and J.-P. Stacino, *Tetrahedron Lett.*, 1982, **23**, 3265.

Table 3



Temp' °C	Ratio	
-78	58	1
-30	2.7	1
0	1	2.5
25	1	2.5



Scheme 14

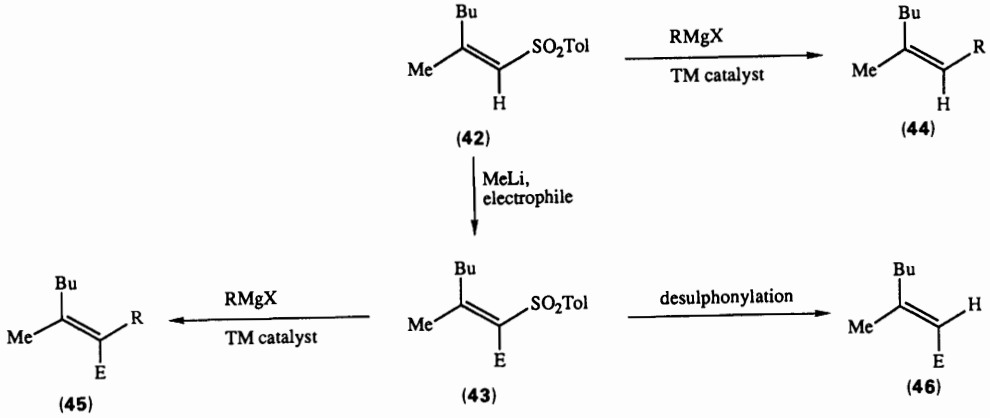
substitution of vinylic hydrogen to give products such as (47) and (48) is reasonably effective, but subsequent desulphonylation using Ra–Ni, Na/Hg, or $Na_2S_2O_4$ is not successful. Alternative direct alkylative desulphonylation of (42) appears a little more promising, with (49) being obtained as a major product using vinylmagnesium bromide with $Ni(acac)_2$ catalysis.

Despite the problems encountered in usefully transforming the vinyl sulphones into other products we were interested in the possibility of using this chemistry to homologate amino acids. One example of this work is shown in Scheme 17 in which L-proline is converted stereoselectively into the optically active vinyl sulphone (50). We have yet rigorously to eliminate the possibility of partial racemization in this process, although this appears unlikely from evidence gathered so far.[16]

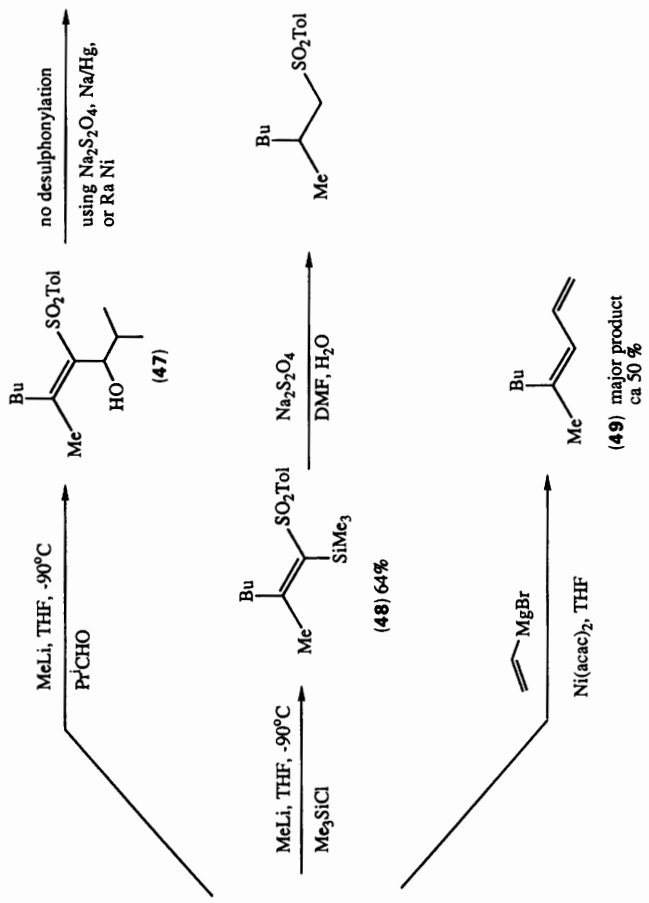
Finally, we have found an alternative use for the enol pivalate derivatives derived from proline. This involves the use of these compounds as substrates for intramolecular radical cyclization as outlined in Scheme 18.

Thus, analogous chemistry to that described above is conducted on a proline

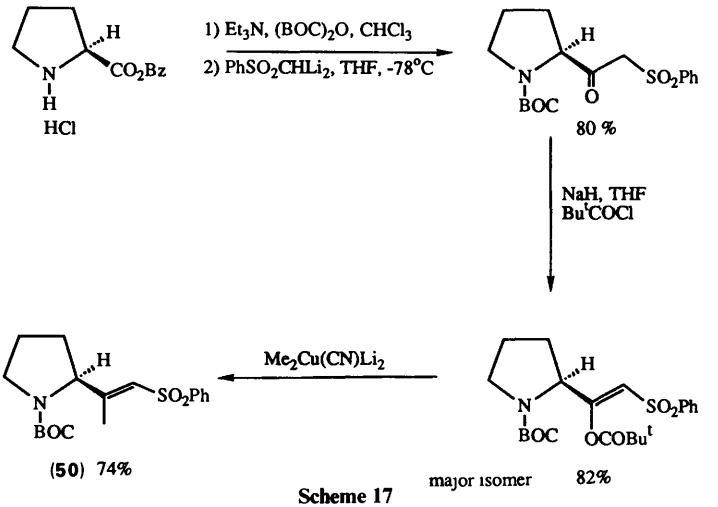
[16] S. Connolly and N. S. Simpkins, unpublished results.



Scheme 15 *A strategy for synthesis of tri- and tetra-substituted alkenes?*


MeLi, THF, -90°C
PrⁱCHO
Bu
SO2Tol
Me
HO
(47)
no desulphonylation
using Na2S2O4, Na/Hg, or Ra Ni
MeLi, THF, -90°C
Me3SiCl
Bu
SO2Tol
Me
SiMe3
(48) 64%
Na2S2O4
DMF, H2O
Bu
SO2Tol
Me
(42)
MgBr
Ni(acac)2, THF
Bu
Me
(49) major product ca 50 %

Scheme 16

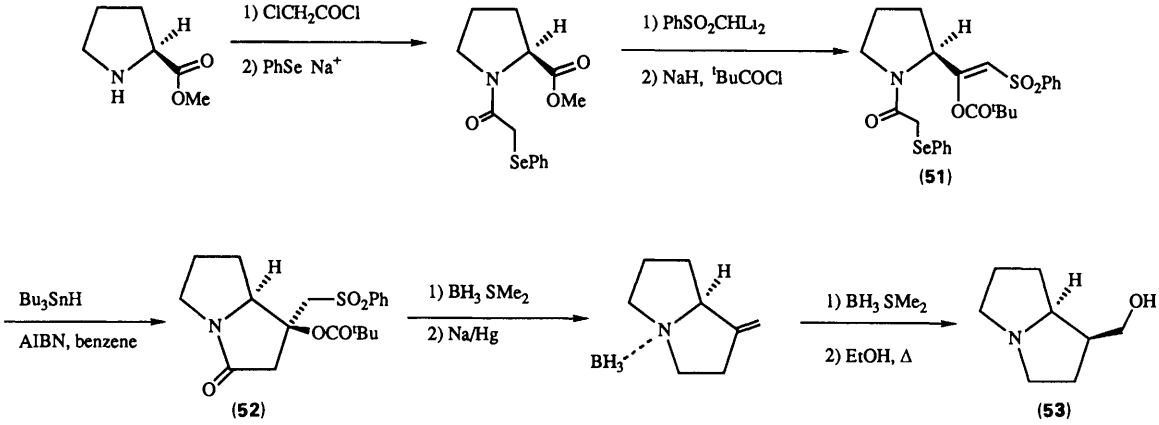


Scheme 17

ester having an α-phenylselenoacetyl group on the ring nitrogen. Cyclization of the key intermediate (51) occurs on treatment with Bu_3SnH/AIBN in refluxing benzene to give compound (52) having the essential pyrrolizidine alkaloid skeleton. We have very recently carried out preliminary studies aimed at converting (52) into naturally occurring pyrrolizidines, and have succeeded in synthesizing isoretronecanol (53). We are presently in the process of optimising this chemistry and most importantly confirming the stereochemical integrity of the final product.[16]

Thus it appears that enol pivalate derivatives derived from esters *via* β-keto sulphones may provide useful avenues to a variety of products using organometallic or radical chemistry.

Acknowledgements. I should like to thank all of my co-workers and collaborators who have contributed to our research programme. The names of those involved in the chemistry described in this article appear in the references to our work.



Scheme 18 *Synthesis of the pyrrolizidine alkaloid isoretronecanol*