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Stereocontrol in organic synthesis using silicon compounds

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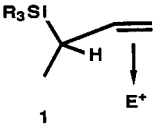
Abstract—The high level of stereocontrol already found for electrophilic attack on a double bond adjacent to a chiral centre carrying a silyl group has been extended to hydroboration reactions, a Diels-Alder reaction, and to the vinylogous version, the S_E2'' reaction. A new method for converting the phenyldimethylsilyl group into a hydroxyl is also reported.

INTRODUCTION

We have recently been studying the stereochemistry of electrophilic attack on a double bond adjacent to a chiral centre (1)(refs. 1-5), and have found that a chiral centre carrying a silyl group, a carbon group, and hydrogen usually gives rise to a high level of stereocontrol, presumably because the three groups are well differentiated both electronically and sterically.



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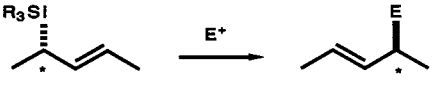
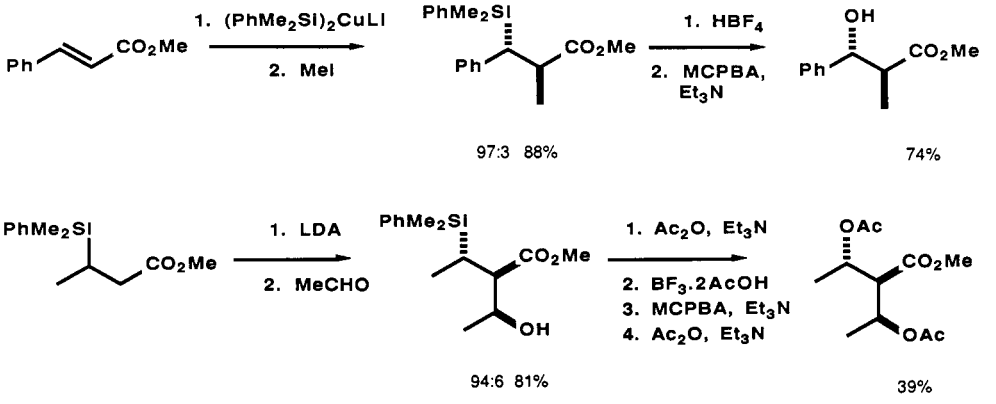
Scheme 1



In one line of work, we (refs. 2 and 3), and others (ref. 6) have established that allylsilanes react with electrophiles with a high level of anti stereospecificity, giving 1,3 transposition of chiral centres (Scheme 1).

In another line of work, we have shown that enolate ions with a β-silyl group give high levels of stereocontrol in alkylation (refs. 3 and 4) and aldol (ref. 5) reactions, setting up 1,2- and 1,2,3-related chiral centres (Scheme 2).

Scheme 2



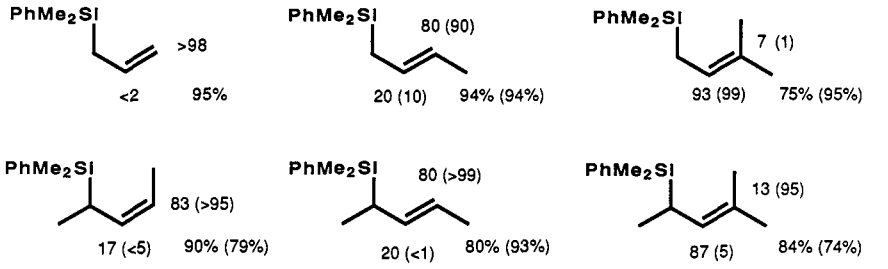
In connection with this work we have also shown that the phenyldimethylsilyl group can be converted into a hydroxyl group in two simple steps with retention of configuration (ref. 7).

In this lecture I want to describe our extension of this work in four directions: (i) a study of the hydroboration of allylsilanes, (ii) the development of an improved method for converting the phenyldimethylsilyl group to a hydroxyl, (iii) a brief study of cycloaddition reactions, and (iv) the beginning of a study of S_E2'' reactions, with a view to probing how much of the stereoselectivity that we observe is electronic in origin.

HYDROBORATION OF ALLYSILANES

The hydroboration of allylsilanes has only been studied with simple allylsilanes, allyldimethyl(phenyl)silane, for example, giving only the γ-silylalcohol with borane-THF (ref. 8). This result already implies that the silyl group has a significant effect on the regiochemistry of hydroboration, since 1-butene gives a detectable amount (7%) of 2-butanol (ref. 9). Since we now have available several versatile syntheses of symmetrical and unsymmetrical allylsilanes (refs. 10 and 11), we decided to look at the regiochemistry of hydroboration, using borane.THF and 9-BBN.

Scheme 3



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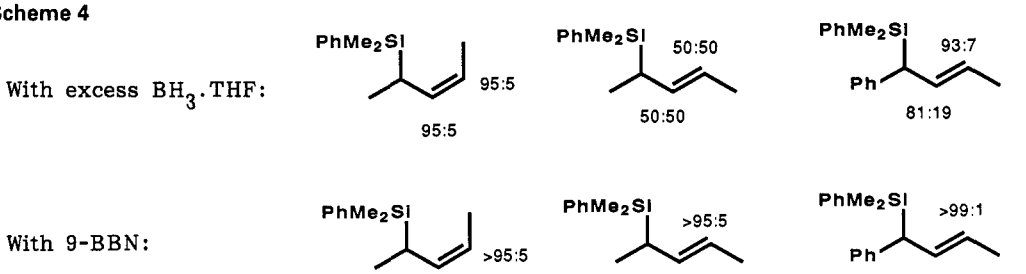
The numbers on the structures in Scheme 3 are the normalised ratios indicating the proportion of alcohols isolated after hydroboration with an excess of borane.THF followed by treatment with alkaline hydrogen peroxide. The numbers in parentheses are the results for 9-BBN, where it is especially evident that the silyl group exerts a substantial directing effect most noticeable in the allylsilane **2**.

Having established that the regiochemistry is well controlled by the presence of the silyl group, we then examined the stereochemistry in those cases where there is any stereochemistry to observe.

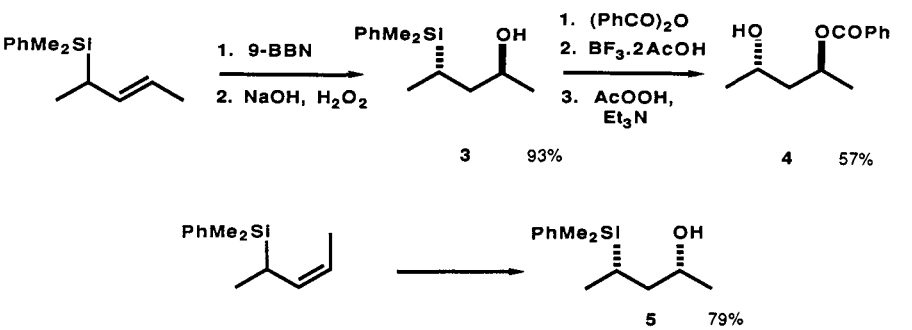
Scheme 4



Scheme 4 shows our results as anti:syn ratios for each regioisomer, where anti and syn are defined as the lower and upper surfaces, respectively, in **1**. Again, 9-BBN gives excellent control, allowing us to prepare the β-silyl alcohols **3** and **5** (Scheme 5) in good overall yield.

In the former case we confirmed that the silyl group could be converted into a hydroxyl **3** → **4** in the usual way. This route is a stereocontrolled 1,3-diol synthesis in which each hydroxyl group is derived from a different metal.

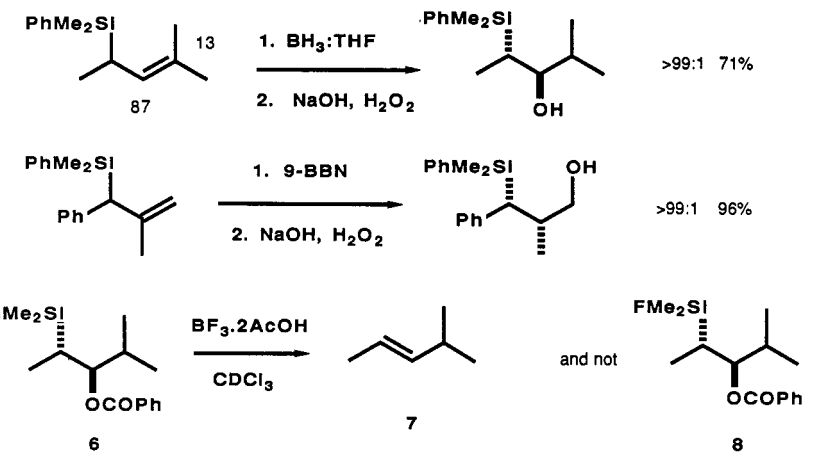
Scheme 5



IMPROVED METHOD FOR CONVERTING THE $PhMe_2Si$ GROUP TO OH

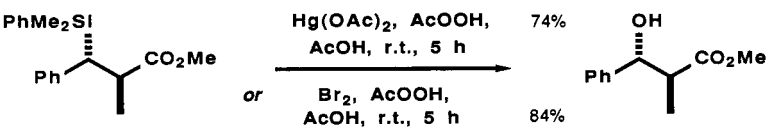
Hydroboration can also be used to create stereocentres with a 1,2 relationship as in the examples in Scheme 6, but in the first of these we meet a new problem: the β-silylalcohol arrangement is incompatible with our method for converting a phenydimethylsilyl group into a hydroxyl, because the acid used to remove the phenyl ring causes β-elimination **6** → **7** rather than protodesilylation **6** → **8**.

Scheme 6



To solve this and other problems we have invented a much improved method for converting the phenyldimethylsilyl group into a hydroxyl. In the new method (Scheme 7) we have

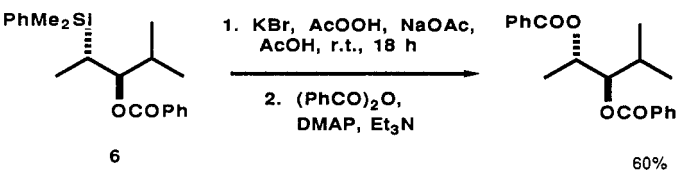
Scheme 7



changed the electrophile for the removal of the phenyl ring, replacing the proton with either of the softer electrophiles bromine or mercuric ion, both of which are compatible with peracid The two-step sequence now takes place in one operation (ref. 12). Bromine is effective even in a buffered solution of peracetic acid in acetic acid, and what is more it can be generated in situ from bromide ion by the peracetic acid.

This simple procedure works for the conversion of β-silylalcohol derivatives such as **6** into diol derivatives (Scheme 8).

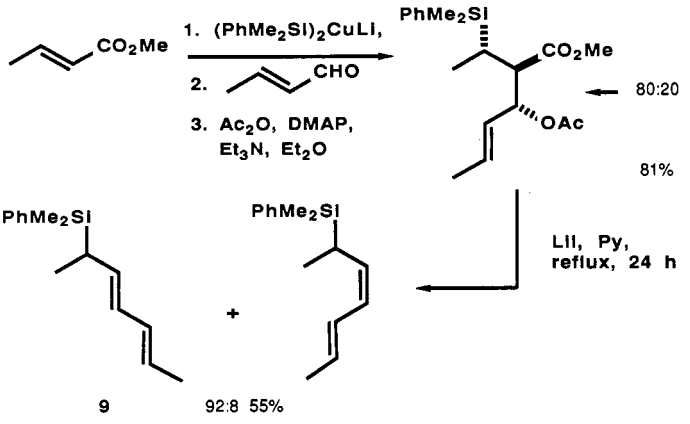
Scheme 8



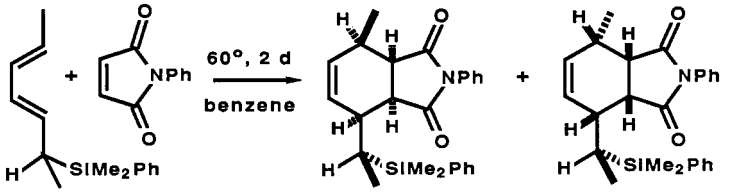
CYCLOADDITION REACTIONS

Following our general plan of finding out how effectively the silicon-bearing chiral centre controls the stereochemistry of reactions at a double bond **1**, we moved from straightforward electrophilic attack through hydroboration to a reaction more obviously identifiable as a cycloaddition reaction. It was already known that a dipolar cycloaddition to an allylsilane takes place predominantly syn to the silyl group (ref. 13). Since this reaction was anomalous, we looked at the corresponding Diels-Alder reaction. First we had to make the diene **9**, which was easy (Scheme 9) using a modification of one of our established methods (ref. 11) for making allylsilanes. The modification is that the methoxycarbonyl and acetate groups can be removed in one operation using lithium iodide. This only works for allylic acetates, and it is stereoselective for the formation of E,E-dienes rather than stereospecific.

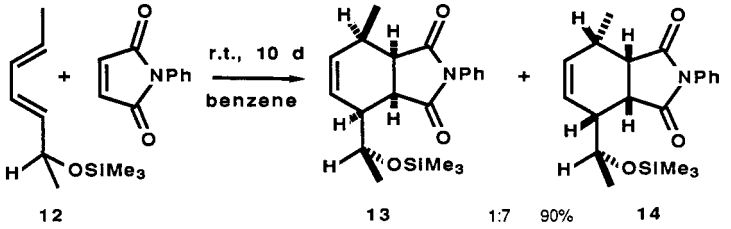
Scheme 9



Scheme 10

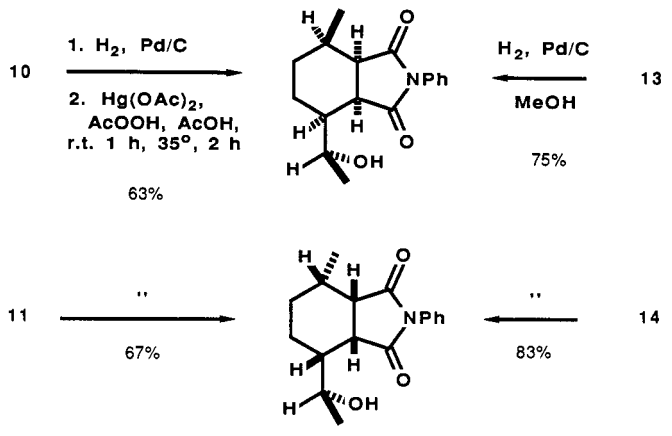


The diene **9** reacted with N-phenylmaleimide to give two adducts **10** and **11** in a ratio of 82:18 (Scheme 10). This contrasts not only with the dipolar cycloaddition but also with the corresponding reaction in which the chiral centre differs only in having an oxygen function in place of the silyl group: the diene **12** was already known to give two adducts **13** and **14** in a ratio of 1:7 (ref. 14).



We easily proved that our adducts, **10** and **11**, had the structures shown by correlating them (Scheme 11) with Franck's adducts, **13** and **14**, using one of our new methods for converting the silyl group into a hydroxyl as described above.

Scheme 11

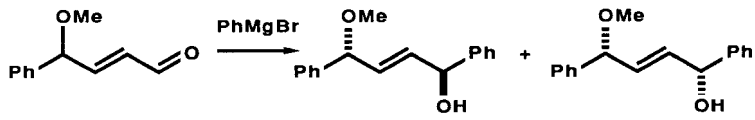


IS THE DIASTEREOSELECTIVITY A STERIC OR ELECTRONIC EFFECT ?

We were not surprised at the opposite sense to the diastereoselectivity in the Diels-Alder reactions of the dienes **9** and **12**: the former has a silyl group, which is a large σ-donating and π-withdrawing group, and the latter has a comparatively unhindered σ-withdrawing and π-donating group. The contrast could hardly be more complete. That the phenyldimethylsilyl group ought to impart significantly different properties upon the molecules it is in compared to the effect of a hydroxyl group has been one of our reasons for developing the idea of using a phenyldimethylsilyl group as a masked hydroxyl, and it is particularly satisfying to see such a clear demonstration of the effect here. What is not clear is the extent to which the effect is electronic or steric in origin. This is a fundamental problem not easily solved. There is evidence that the electronic component is small, since a silyl group and a phenylsulphonyl group have very similar effects on the diastereoselectivity of osmylation and epoxidation (ref. 15), but theoreticians continue to predict electronic effects in the same sense (ref. 16). The same problem comes up in the corresponding nucleophilic attack on a π-bond, where Felkin provided an influential account of the steric origin for Cram's rule (ref. 17) and Anh added an electronic component (ref. 18).

In an attempt to probe this problem, we studied the possibility of finding a vinylogous version of Cram's rule, where the chiral centre would be conjugated to the carbonyl group but not close enough to it to have any steric influence upon the diastereoselectivity of attack upon it. One of our results (Scheme 12)(ref. 19) illutrates how unsuccessful we were in

Scheme 12

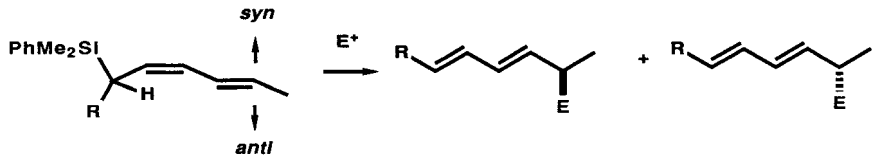


50:50 99%

finding any evidence for an electronic effect, although we were not surprised, given the low selectivity found for other reactions of this type already known (e.g. ref. 20). Nevertheless, we did consider the possibility that the corresponding electrophilic reaction might be a better probe, since we had abundant evidence that the chiral centre with silicon on it was a powerful controlling influence. Furthermore, we now had a diene synthesis that enabled us to embark upon a study of the vinylogous version of any of the reactions described above. We chose the S_E2'' reaction, which is a vinylogous version of the reaction in Scheme 1.

S_E2'' REACTIONS

To tackle this problem was a substantial undertaking: we have several choices to make and we have to carry out a number of chemical reactions to get an answer. In the first place we have to choose an electrophile for the general S_E2'' reaction **15** → **16** + **17**; then we have to



15 **16** *anti* **17** *syn*

choose double bond geometries and the R group for the diene **15**; we have to synthesise the diene we have chosen, and it has to be substantially enriched in one enantiomer (homochiral, optically active) and of known chirality; we have to carry out the reaction; we have to measure the relative amounts of **16** and **17** (the e.e.); and finally we have to prove which of the products is **16** and which **17**. We have done all these things, and yet we are still not able to answer the question, how much of the stereoselectivity is electronic in origin. What we have observed is that the S_E2'' reaction can be highly stereoselective.

Choice of electrophile and diene

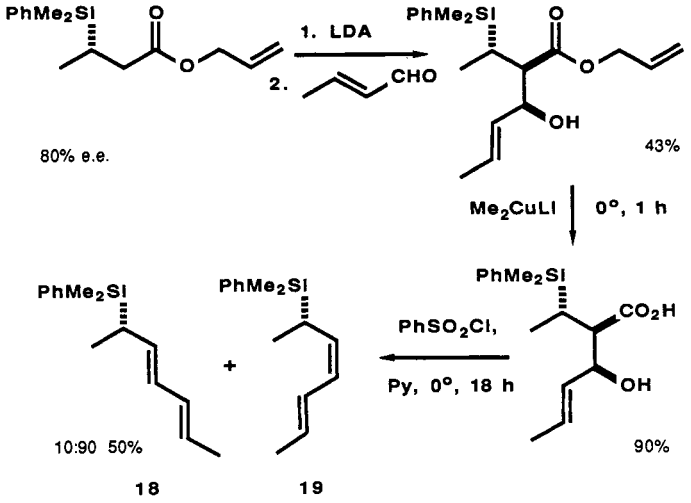
We chose the reaction of isobutyraldehyde with the dienylsilane **19**, because this type of reaction was known to be clean with achiral dienylmethylsilanes (ref. 21). The double bond adjacent to the chiral centre was chosen to be Z. This arrangement is known to increase the stereoselectivity in allylsilane reactions (refs. 15 and 22), because it fixes the geometry

more firmly in that illustrated in **1**, and this should apply equally to the diene system. For the double bond undergoing attack, we chose an E geometry, because in simple allylsilanes this gives better anti to syn ratios (ref. 23), referring now to the diasteroisomeric relationship of the two chiral centres on the zig-zag chain. Finally, the choice of R group as methyl was suggested by the small influence the nature of that group has on diastereoselectivity when the double bond adjacent to it is Z (refs. 15 and 22), and by exploratory work with a phenyl group for R, which was not encouraging from the point of view of getting workable yields of product.

The synthesis of the diene

Since the reaction in Scheme 9 is only stereoselective for the E,E-diene, we needed to return to our original method for a stereospecific synthesis of the Z,E-diene **19**. This worked reasonably well (Scheme 13) but was not quite as stereospecific as it had been when the second double bond was not present (ref. 11), giving some of the E,E-diene **18** along with the diene we wanted, **19**.

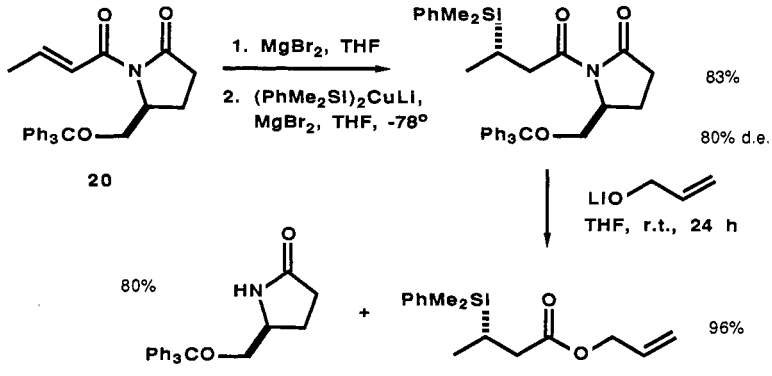
Scheme 13



We, were able to carry out the synthesis with enantiomerically enriched reagents because we had already established that the conjugate addition of our silyl-cuprate reagent to Koga's crotonoyl derivative **20** proceeded with high diastereoisomeric excess in the sense illustrated in Scheme 14, and the chiral auxiliary could be removed (and recovered) by treatment of the product with lithium allyloxide (ref. 24).

The small amount of E,E-diene **18** had to be removed, since a stereoselective reaction from that isomer would probably give the enantiomer of the product from the diene **19**, and would therefore dilute the enantiomeric excess we were looking for. This was easy, using the Diels-Alder reaction described above, in which the Z,E-diene **19** did not participate.

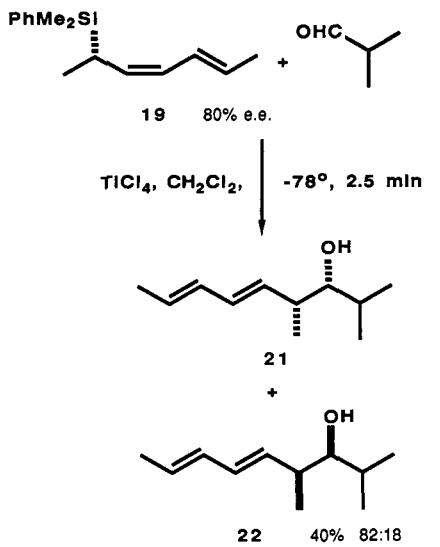
Scheme 14



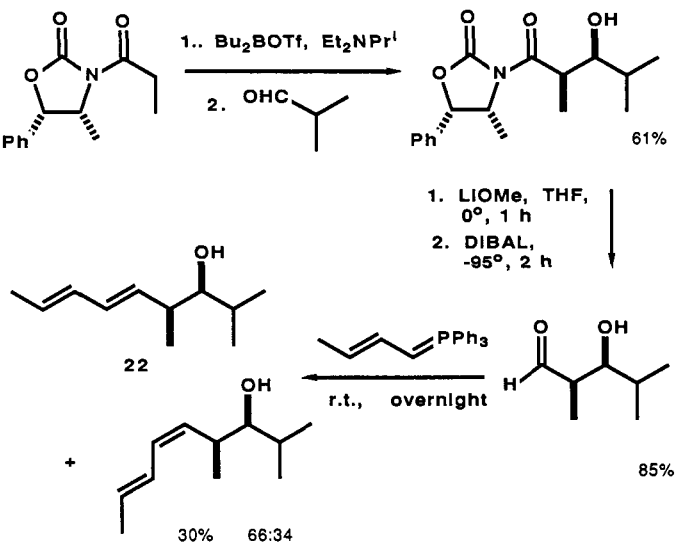
The reaction

The reaction itself proceeded reasonably well (Scheme 15) giving the syn alcohols **21** and **22** as the major isolated products in a ratio of 82:18. We measured the e.e. using their esters with Mosher's acid, and integrating the ^{19}F NMR spectrum of the mixture. To prove the sense of the stereoselectivity, we prepared an authentic sample of the product **22** (Scheme 16) using Evans' method for setting up the chiral centres (ref. 25).

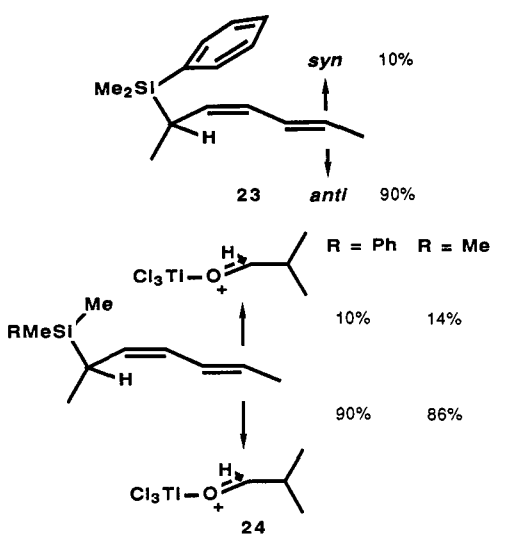
Scheme 15



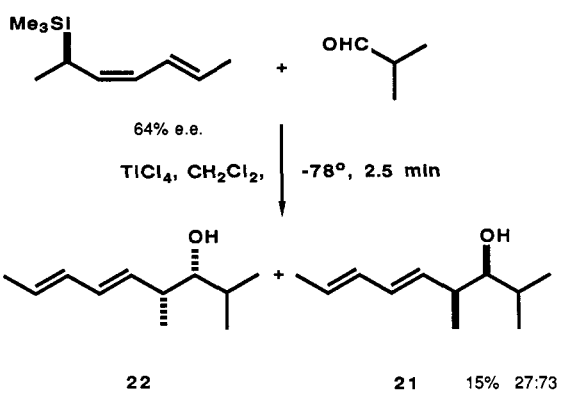
Scheme 16



The starting diene had an e.e. of 80% and the product an e.e of 64%, which means that we can now identify this S_E2'' reaction as having a remarkable 90:10 selectivity in favour of the anti reaction **23**. However, it is not at all unreasonable to ascribe this entirely to steric effects, since the phenyl group can quite easily interfere with syn attack of the electrophile. We are therefore no nearer to a definitive answer to our question.



Scheme 17



The next stage was to repeat the chemistry above, with some small differences, using a trimethylsilyl group in place of the phenyldimethylsilyl group, and, as it happens, in the opposite enantiomeric series. The result was a reaction (Scheme 17) showing overall 86:14 stereoselectivity in favour of the anti process, in other words insignificantly different from the reaction when the phenyldimethylsilyl group was present. Thus the phenyl group is not the cause of steric interference as in **23**.

In spite of the remarkable transmission of chiral information from one chiral centre to another five atoms away, we are still no nearer to a firm conclusion, because the transition state for the particular reaction we have been investigating has an electrophile carrying a large group, the Lewis acid inevitably present, and this could easily reach far enough to feel the steric effect of a trimethylsilyl group, as illustrated crudely in **24**, which also summarises our results so far. The two trigonal carbons will not approach each other precisely at 90°, and it may be that the Lewis acid and the silyl group are not at all near each other; nevertheless, they could be close, and any possibility of steric effects operating destroys the argument that the chiral centre is transmitting an electronic effect to the π-bond undergoing diastereofacial attack. We shall continue this study by looking for smaller electrophiles that react in the general sense of **15** → **16** + **17**.

Acknowledgement

I am happy to be able to thank the four graduate students who contributed in so many ways to the unpublished work described in this lecture: **Nick Lawrence** (Schemes 3, 4, 5, 6, and 8), **Philip Sanderson** (Scheme 7), **Achintya Sarkar** (Schemes 9, 10, 11, 13, and 16), and **Nicholas Kindon** (Schemes 13, 14, 15, and 17).

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