

## Stereocontrol in Organic Synthesis Using Silicon Compounds

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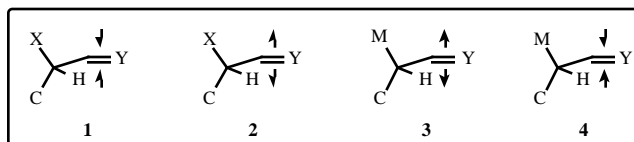
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**Abstract:** Electronic control of diastereoselectivity is discussed; only electrophilic attack adjacent to a stereogenic centre carrying an electropositive element **3** makes a coherent story.

### INTRODUCTION

Substituent effects on *reactivity* are well established, as is the language with which to explain them. An electronegative element X is a  $\pi$ -acceptor and a  $\sigma$ -donor, and the balance between these effects changes from the dominance of the former to the dominance of the latter, as we go from right to left along the periodic table. Carbon substituents have less dramatic and more various effects, ranging from the  $\pi$ -neutral but  $\sigma$ -donor alkyl groups, through the  $\pi$ -donor or acceptor alkenyl and aryl groups, to the  $\pi$ - and  $\sigma$ -withdrawing carbonyl and C-X groups. Electropositive elements M are the opposite of electronegative elements, being  $\sigma$ -donors and  $\pi$ -acceptors, but they are less familiar perhaps when they are not themselves the site of reaction. When they are simply substituents modifying the reactivity, only the least electropositive elements can survive, and foremost among these is silicon. The  $\pi$ -effect of a silyl group, stabilising cations, is a consequence of its  $\sigma$ -donor character, and the ability to stabilise an  $\pi$ -anion is a consequence of its  $\pi$ -acceptor character.

Substituent effects on *stereoselectivity* are much less well established, and there is no consistent language with which to discuss them, except perhaps for straightforward steric effects, where one can often say, in the absence of any electronic effects that a reagent will attack from the less hindered side. But it is precisely the electronic effects that I want to discuss today, hoping, but largely failing as we shall see, to tease out a simple way of understanding their influence. We shall concentrate on the four fundamental cases: nucleophilic attack **1** and **4** and electrophilic attack **2** and **3** on a double bond adjacent to a stereogenic centre carrying either an electronegative atom X or an electropositive atom M.



### DISCUSSION

To understand how an electronic effect might be transmitted into the  $\pi$ -framework in such a way as to make the two sides of the  $\pi$ -bond different, we would like to apply molecular orbital theory. If we look in Fig. (1) at the atomic orbitals that contribute to the C—X bond and the  $\pi$ -bond, we see that none of the  $p_x$ ,  $p_y$  or  $p_z$  orbitals can have any effect

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that would differentiate the top and bottom of the  $\pi$ -bond—the p-orbitals are either orthogonal ( $p_x$  and  $p_y$ ) or equally placed ( $p_z$ ) with respect to the top and bottom surfaces. Only the s-orbital on the carbon atom of the  $\pi$ -bond can have any effect, illustrated in Fig. 1 for a hybrid between the  $\pi$  orbital and the s-orbital on the first carbon atom of the double bond, where the s orbital is arbitrarily given the same sign (shaded) as the s-orbital on the neighbouring carbon and the top surface of the p orbital. In this case the upper lobe is increased in size, and, since this is a filled orbital, we can expect it to encourage electrophilic attack on that surface. The complication is that there is no easy way to choose the sign of the s atomic orbital for each of the molecular orbitals created from these components, let alone in the appropriate frontier orbital, although an attempt has been made [1].

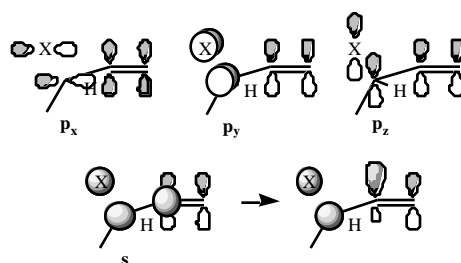
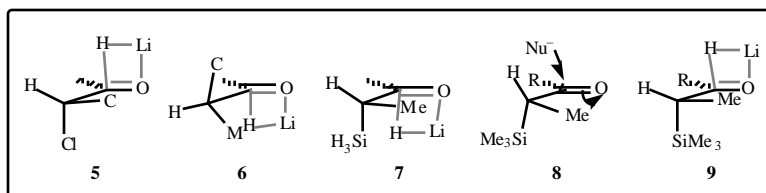


Fig. (1). Only mixing in the s atomic orbital can make the two surfaces of a  $\pi$ -bond differ.

Thus we are unable easily to explain the way electronic effects can be transmitted into a  $\pi$ -bond. Many attempts have been made [2], but none yet commands everyone's allegiance. We turn, therefore, to the experimental observations, to see what coherence there is there.

### NUCLEOPHILIC ATTACK ON A CARBONYL GROUP

The longest known reactions in any of these classes are nucleophilic attack on a carbonyl group **1** ( $Y=O$ ) governed by Cram's rule, and most convincingly explained by Felkin and Anh. The electronic effect, which Anh added to Felkin [3], says that, in the absence of chelation, one counts an electronegative substituent as the large group, whatever its actual size. High level calculations by Frenking [4] agree that the lowest-energy transition structure **5** fits the rule. Furthermore, it is understandable, since both the hydride nucleophile and the electronegative chlorine atom carry an excess of negative charge, and they repel each other.



Strict application of this version of Anh's rule when the polar substituent is an electropositive group M places the incoming nucleophile *anti* to the carbon group **6**, since carbon is now the most electronegative element [5]. In support of this analysis, a calculation by Paddon-Row [6] at the same level as Frenking's gave the lowest-energy transition structure **7**, which also has preferred attack from below (if we keep the order of the three substituents on the stereogenic centre constant, as it is throughout this paper). This is understandable too, because the negatively charged nucleophile will be attracted to the

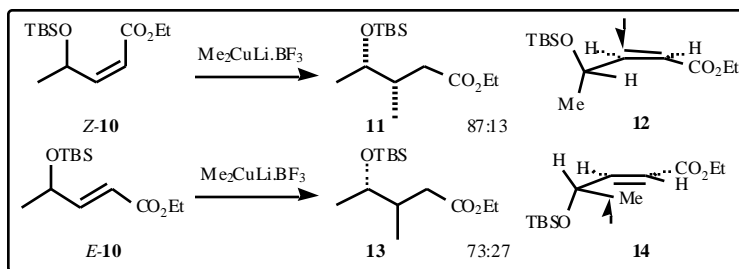
positively charged silicon atom. The only problem with this story is that it is not in agreement with observation—almost all examples of this type of reaction take place from above in the sense **8**. We have recently repeated the Paddon-Row calculation using the trimethylsilyl group in place of the unsubstituted silyl group. The lowest-energy transition structure proved to be **9** [7], in agreement with observation. We conclude that the effect is largely steric, and that the electronic effect detected in Paddon-Row's calculation is overridden—the trimethylsilyl group effectively buries its positively charged core.

### NUCLEOPHILIC AND ELECTROPHILIC ATTACK ON A C=C DOUBLE BOND

When we turn to the more complicated story for attack on a C=C double bond ( $Y=CR_2$ ), we have four situations **1-4** to discuss, and we shall take them in that order.

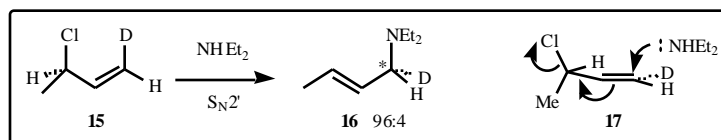
#### Nucleophilic Attack on a C=C Double Bond with a Neighbouring Electronegative Substituent **1** ( $Y=CR_2$ )

At first sight we might expect the rule to be the same as Felkin's and Anh's, and this is what is observed in the representative reaction **Z-10** **11** [8], with attack favoured from above. But the reason is not the same: in the first place the medium-sized group no longer easily fits 'inside', as it is called, more or less eclipsing the C=C double bond in the way that it prefers to eclipse the C=O double bond in all the structures **5-9**, and secondly, attack apparently takes place syn to the electronegative element **12**.



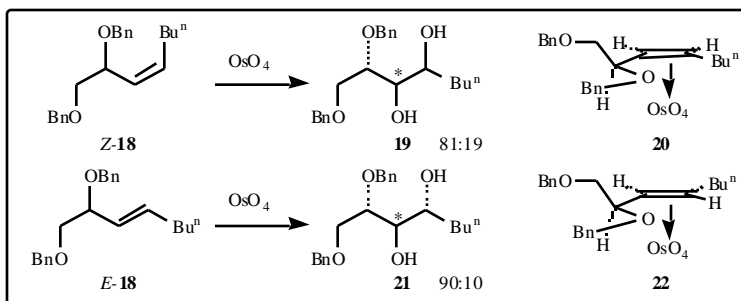
Furthermore, the sense of attack changes from above to below when the double bond geometry is changed, with **E-10** giving largely the diastereoisomer **13**. The attack is still apparently from the side carrying the electronegative substituent **14**, but now the methyl group sits 'inside'. We shall often see this 'inside methyl' effect, which complicates the story most tiresomely by not always showing up.

The pattern of attack syn to the electronegative element is not always observed, but seems to be more common than not. It is certainly not restricted to organocuprate reactions, and it is clearly not what might be expected by comparison with the Anh rule. Suggestions have been made that the nucleophile is delivered intramolecularly following coordination to the electronegative element, but this seems unlikely for the conjugate addition of malonates, for example, or for the  $S_N2'$  reaction **15** **16** [9], which is stereospecifically syn **17**, like most but not all  $S_N2'$  reactions.



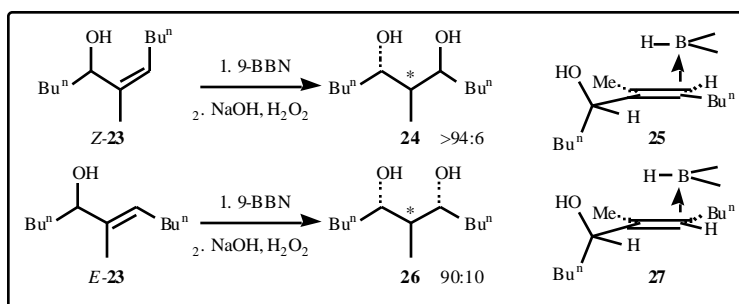
### Electrophilic Attack on a C=C Double Bond with a Neighbouring Electronegative Substituent 2 ( $Y=CR_2$ )

The reaction of osmium tetroxide on an alkene is electrophilic in character, and typically follows the pattern shown in the reactions of the alkenes **Z-18** and **E-18** [10].

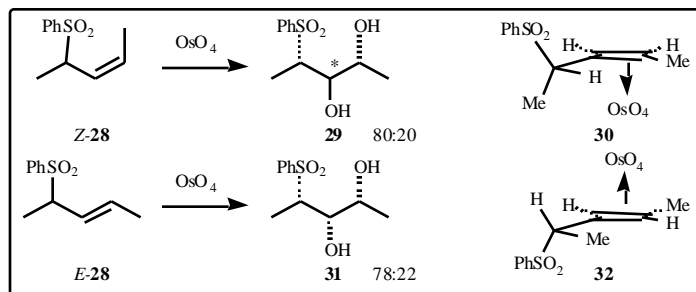


The explanation usually offered (although not in ref. 10) is that the C—O bond, if it were conjugated to the  $\pi$ -bond, would be deactivating. Attack by an electrophile therefore takes place with the C—O bond 'inside' **20** and **22**, out of conjugation, and the stereochemistry is simply attack on the less hindered side.

In contrast, the hydroboration of the alkenes **23** appears to take place with the hydrogen atom inside, and with attack **25** and **27** from the same side as the electronegative atom, which this time is the medium-sized group [11].

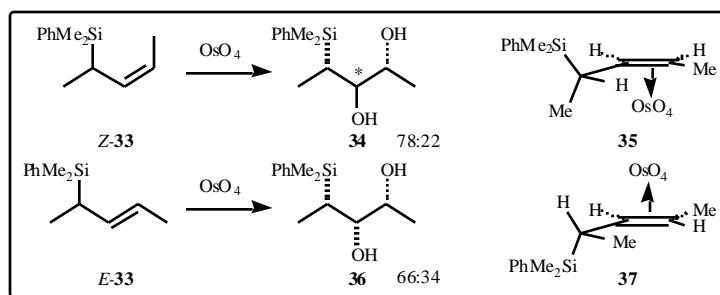


And in another variation, the osmium tetroxide reaction on the sulfones **28** appears to take place with the hydrogen atom inside in the *Z*-alkene and with the methyl group inside with the *E*-alkene, and with attack **30** and **32** from the opposite side from the electronegative atom [12]. In this case, Vedejs suggests that the sulfone is too large to sit inside.

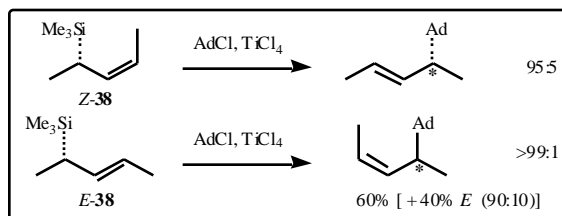


### Electrophilic Attack on a C=C Double Bond with a Neighbouring Electropositive Substituent 3 (Y=CR<sub>2</sub>)

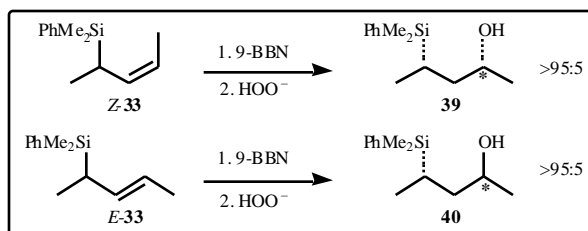
Vedejs also looked at a similar reaction, replacing the allylsulfones **28** with the corresponding allylsilanes **33**, for which he found that the diastereoselectivities, both in sense and in degree, were essentially the same as for the sulfones [12]. He argued that since the sense of attack is the same whether the substituent is an electronegative element or an electropositive element, the diastereoselectivity in both cases is simply controlled by a steric effect, with the methyl group sitting inside in the *E*-alkenes **32** and **37**, when there is only a small energetic penalty, exposing a relatively very unhindered upper surface.



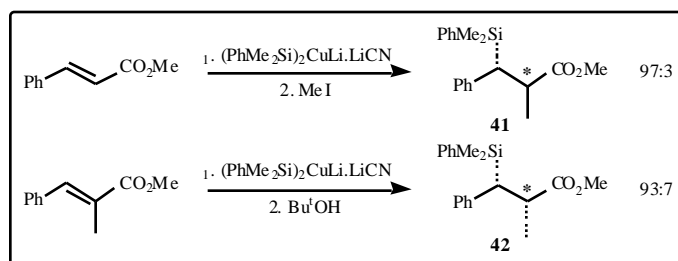
Our own work [13] has shown the same pattern of attack reliably anti to the silyl group in a wide variety of reactions, some showing the 'inside methyl' effect and some not. The best studied of the reactions showing this pattern is the S<sub>E</sub>2' reaction of allylsilanes **38**, in which the stereochemical information is transferred from C-1 to C-3 [14]. The *E*-isomer *E*-**38** reacts a little over half the time (60:40, as revealed by the double bond geometry in the product) in the 'methyl inside' conformation, but all the reactions are stereospecifically highly anti.



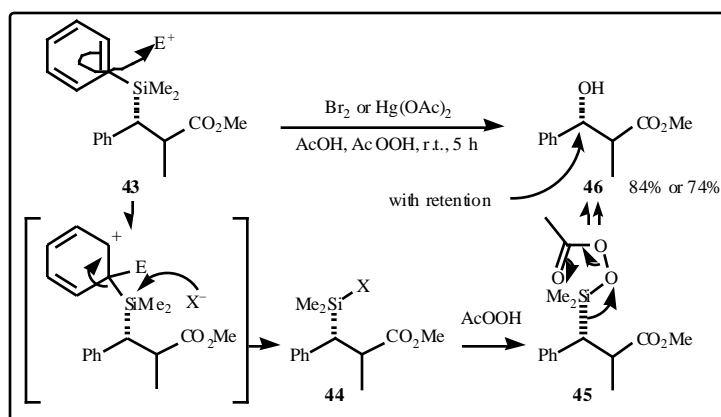
Similarly, hydroboration is highly anti, except that both geometries *Z*-**33** and *E*-**33** react with 9-BBN in the conformation with the hydrogen atom inside [15].



Another reaction with high levels of attack anti to the silyl group is enolate alkylation and protonation, where either diastereoisomer **41** or **42** can be obtained with almost equal ease by exchanging the resident group and the electrophile [16].



In the last two reactions, the silyl group remains in the molecule, and to use the stereochemical information embedded in it a reaction is needed in which the silyl group is converted into something more generally useful in synthesis.

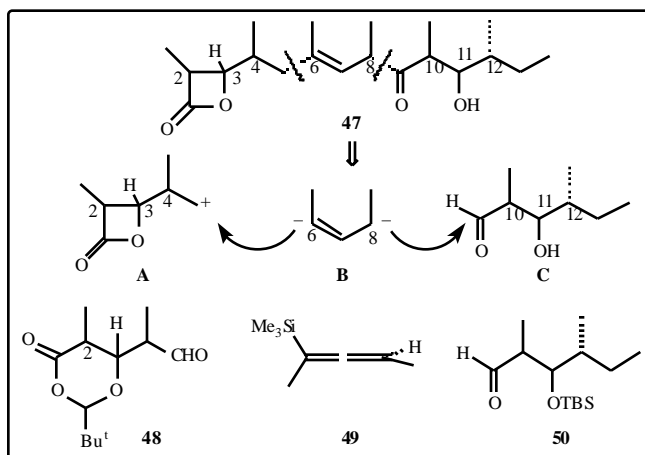


This reaction is the silyl-to-hydroxy conversion **43** **46** [17], which takes place in two stages: the removal of the phenyl group by an ipso electrophilic substitution **43** **44**, using bromine or mercuric ion, and the oxidative rearrangement step, using peracid or a peroxide, in which the carbon groups attached to the silicon atom move to the electrophilic oxygen atom **45** (arrows) with the usual retention of configuration seen in all [1,2]-sigmatropic rearrangements to electrophilic atoms.

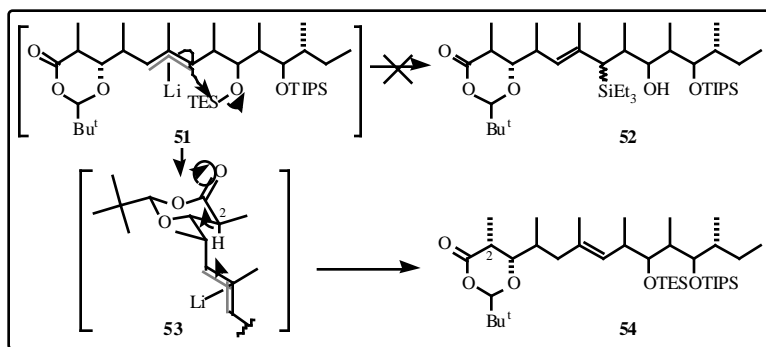
Using one or more of the four kinds of reactions seen immediately above, we synthesised ten natural products having one, two, three or four stereogenic centres [18], and have also been working on the synthesis of ebelactone A **47**, which has seven stereogenic centres and one double bond to be controlled. The plan was to synthesise the three fragments **A**, **B** and **C**, each enantiomerically enriched, and with *all the relative stereochemistry and the double bond geometry controlled by the presence of the silyl group*.

This was a more substantial target, requiring us to invent solutions to some of the problems, but constraining us so severely that we were not able actually to synthesise this molecule. We did control all the relative stereochemistry by making each of the molecules **48**, **49** and **50** as our fragments **A**, **B** and **C**, respectively, and we reported this work in an earlier lecture in this place [19].

Since then, we have joined the pieces together, but an inversion of the stereocentre at C-2 occurred in the step involving the allyllithium intermediate **51**. This compound was designed to abstract the silyl group on the C-9 oxygen atom in a reaction (arrows) with good precedent [20]. Had it done so, the allylsilane **52** would have undergone a clean



regioselective protodesilylation placing the double bond between C-6 and C-7, and with the right geometry.



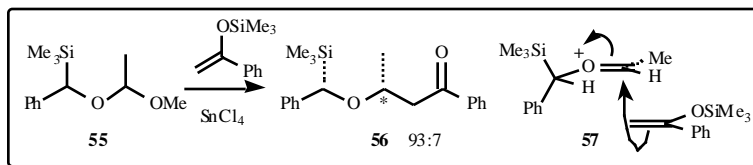
In the event the allyllithium intermediate **51** calamitously took the proton off C-2 **53** (arrows), and the resulting enolate reprotoneated on the less hindered side of the dioxanone ring, inverting the configuration at C-2 in the product **54**. As a result, we made 2-epi-ebelactone A, and even that largely as the 11-benzenesulfonate, because the  $\gamma$ -lactone was so slow to form, being cis disubstituted, that the C-11 hydroxyl was esterified.

In spite of this setback, we had proved yet again that electrophilic attack on a double bond with a neighbouring electropositive element was a reliable strategy for the control of relative stereochemistry in open-chain systems. In all probability, the stereoselectivity is a consequence only of the steric effect of the large silyl group, but it cannot be unhelpful that any electronic effect is probably in the same direction—encouraging attack anti to the silyl group.

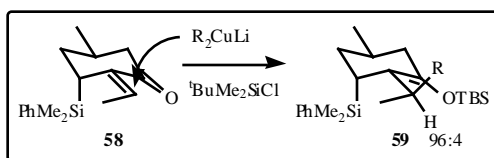
#### Nucleophilic Attack on a C=C Double Bond with a Neighbouring Electropositive Substituent 4 ( $Y=CR_2$ )

Nucleophilic attack on such systems, where the steric and electronic effects might be opposing each other, has hardly been investigated. The nearest known reaction was on an intermediate in the reaction of the acetal **55** with a silyl enol ether, where the

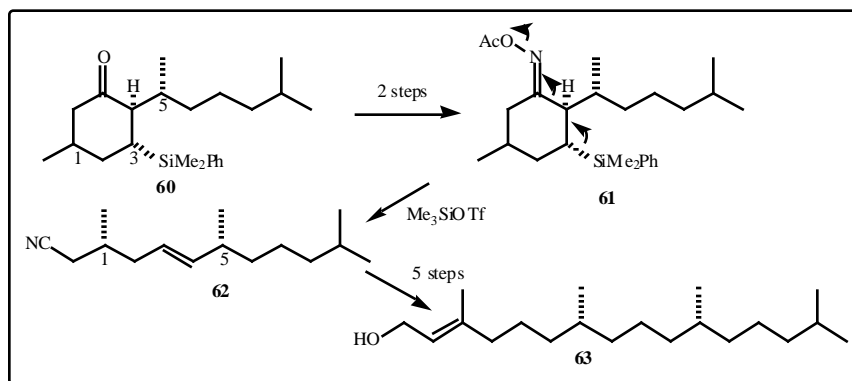
diastereoselectivity followed what might be expected for attack on the less hindered side, anti to the silyl group, in the conformation **57** [21].



In our first work in this area, we investigated the enone **58**, which also underwent nucleophilic attack anti to the silyl group to give the silyl enol ether **59** (R=Et) with a high degree of diastereoselectivity [22]. The conformation **58** was calculated to have the lowest energy, in spite of the large group's being axial, and it is also the conformation adopted in the solid state, as shown by a low-temperature X-ray structure.

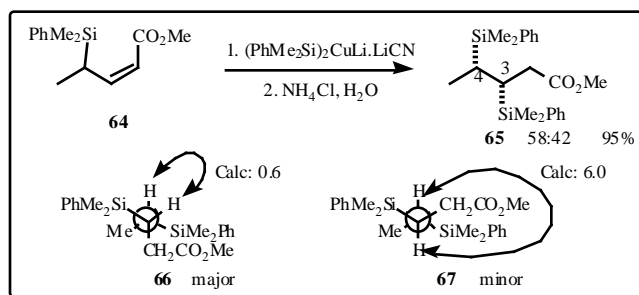


Following this result, we repeated the reaction with the isohexylcuprate to give the silyl enol ether **59** (R=isohexyl), and used this to prepare the ketone **60** in a synthesis of ( $\pm$ )-phytol **63**. The fragmentation **61** **62** revealed the open-chain 1,5-relationship, and the remaining carbons were attached in a prenylation reaction between a silyl dienol ether and the aldehyde derived from the nitrile **62**.

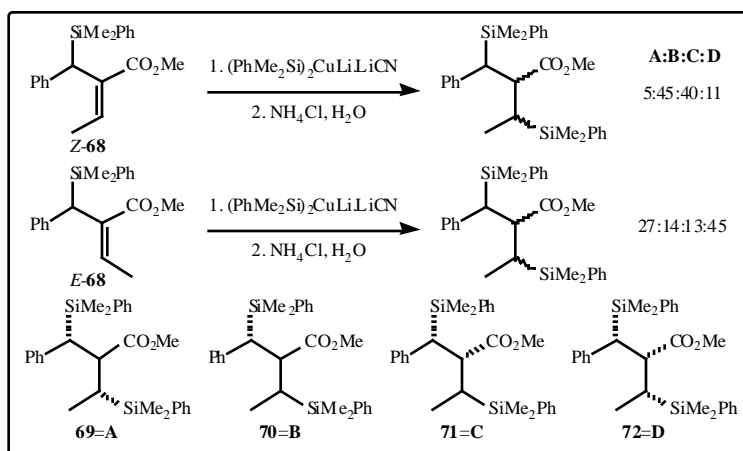


However, these results were in a relatively rigid system **58**, and we wanted to know how well the silyl group controlled the diastereoselectivity directly in an open-chain system. We therefore examined the  $\alpha,\beta$ -unsaturated ester **64**, moderately confident, since we deliberately chose a *Z*-isomer that attack would take place anti to the silyl group in the conformation with the hydrogen atom inside. Our thinking was prejudiced by the accumulated experience with electrophilic attack, coupled with the results immediately above, that steric effects could explain the diastereoselectivity that we and everyone else had seen—there was no evidence for any difference in nucleophilic attack from that seen so regularly in electrophilic attack. In the event, we were surprised to find that there was little diastereoselectivity (58:42). Insofar as there was any diastereoselectivity, the major product, judging by the

coupling constant between the protons on C-3 and C-4 ( $J$  1.1 Hz for the major and 6.7 for the minor), was the isomer **65** we had not expected [23]. A coupling constant argument was fairly reliable in this system, since the values are so different, and they so nearly match those calculated from an assessment of the Boltzmann distribution of the low energy conformations, summarised in the Newman projections **66** and **67**.

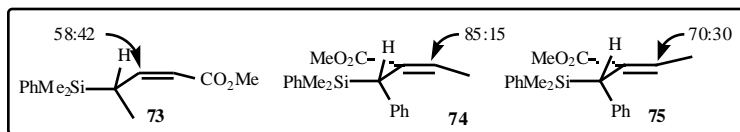


Another  $\alpha,\beta$ -unsaturated ester **68**, available as *E*- and *Z*-isomers, was more complicated, because there were two starting materials, and four products from each, two pairs reflecting the diastereoselectivity we were interested in, and two reflecting the diastereoselectivity in the protonation step, which was unlikely to be predictable. We were able to pick out the four isomers from the  $^1\text{H-NMR}$  signals [23], and labelled them **A**, **B**, **C** and **D**. They were formed in ratios such that **B** and **C** were the major pair from the *Z*-isomer, and **A** and **D** from the *E*-isomer. The isomers **A** and **D** were separable, free of the others, but the isomers **B** and **C** were only obtained as a mixture. To cut a long story short, we were able, by silyl-to-hydroxy conversions, and cyclic acetal syntheses, to identify them as the isomers **69-72**, respectively.



The unexpected outcome again is that the major products are those that appear to follow from attack *syn* to the silyl group. We suggest that there may be an electronic component resembling the 'inside oxygen' effect. Electrophilic attack when there is a neighbouring electronegative group has the O—C bond 'inside', since it would be deactivating if it were conjugated. Nucleophilic attack when there is a neighbouring electropositive group might take place more rapidly when the Si—C bond is more or less orthogonal to the double bond, since it would be deactivating if it were conjugated. To explain our results it would

have to be 'outside', summarised in **73**, **74**, and **75**, which is not unreasonable, since the silyl group is surely too large to sit 'inside'.



## CONCLUSIONS

Of the four systems **1-4**, only the third, electrophilic attack on a double bond with an adjacent stereogenic centre carrying a silyl group, is consistent and satisfyingly well explained. Some of the others are highly effective and reliable in total synthesis, and have all been much used, provided that there is good literature precedent. But they are not well explained, and the precedents must be close. The last system **4**, nucleophilic attack on a double bond with the stereogenic centre carrying a silyl group, has been examined with all too few reactions, and most of those cuprates—it needs more study before generalisations are safe.

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