

Chapter 3

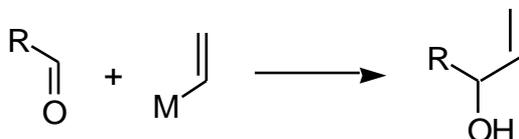
Model Coupling Work

3.1 Model Coupling of Fragment A to Fragment BC

3.1.1 Introduction

Williams' attempt to couple fragment A to fragment BC (the product of coupling fragments B and C) by forming the vinyl lithium species of BC failed (see chapter 2), but this may well have been simply a result of the small scale of the reaction, where the presence of a tiny quantity of water could easily have quenched the vinyl lithium. However, we thought that given the base- and nucleophile-sensitivity of fragment A, and the wide range of vinylmetal species in the literature available for these sorts of coupling, a better choice could probably be made, affording milder conditions.

3.1.2 Vinylmetal-Aldehyde Couplings



Scheme 3.1

Many vinylmetals are known to add efficiently to aldehydes, and below we consider very briefly some of the features of this chemistry for several of the more common

organometallics. Extensive reviews of this area are available, so the following remarks will be restricted to general observations.¹⁹⁸ Organometallics with β -hydrogens are frequently troublesome, because β -elimination (and consequent reduction of the carbonyl compound) often takes place faster than nucleophilic addition. Vinylmetals, however, are not normally subject to β -elimination, as loss of hydrogen from an sp^2 carbon atom is less favourable, and so reduction is not normally a significant competing process (scheme 3.1).

Mg: Vinyl Grignards¹⁹⁹ can be readily prepared from vinyl halides in THF²⁰⁰ (the reaction does not take place in ether), and nucleophilic addition to carbonyl compounds takes place *via* a 6-membered cyclic transition structure (figure 3.1)²⁰¹ to give allylic alcohols.²⁰²

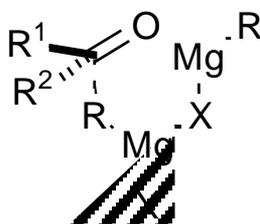


Figure 3.1

Li: Williams used the vinyl lithium approach in her attempted coupling (see chapter 2), and generally results are good.²⁰³ However, organolithiums are quite basic, and this has the potential to cause difficulties with our sensitive fragment A; less basic nucleophiles are available (see below).

Zn/Cd/Hg: Organozincs^{204,205} are less reactive than organolithiums; ketones are generally unreactive, and addition to aldehydes is relatively inefficient. However, addition of Lewis acids greatly improves the reactivity, and allylzincs are highly reactive. Vinylzincs, though more reactive than alkylzincs, are not very reactive.²⁰⁶

Organocadmium reagents^{205,207} do react efficiently with aldehydes, but the higher thermal and photochemical instability makes their preparation more difficult. Organomercury compounds do not add to aldehydes.²⁰⁵

Ti/Zr: Organotitanium and organozirconium reagents²⁰⁸ are highly selective for aldehydes and are generally considerably stable. Vinyltitaniums with aldehydes give allylic alcohols in reasonable yield.²⁰⁹

Cu: Organocuprates²¹⁰ more commonly react 1,4 than 1,2 when given a choice, but will undergo direct addition to aldehydes under favourable conditions. The reaction is often incomplete, and this is especially so with vinylcuprates.²¹¹

Al: Organoaluminiums²¹² have similar behaviour to Grignards, but condensation of enolisable carbonyl compounds is an important feature of organoaluminium chemistry.²¹³

Ce: Organocerium compounds²¹⁴ are often highly nucleophilic and relatively non-basic; however, there is only moderate aldehyde over ketone selectivity.

Cr: Organochromium reagents²¹⁵ are readily formed either from organolithiums/Grignards/-organoaluminiums with chromium(III) halides; e.g.,



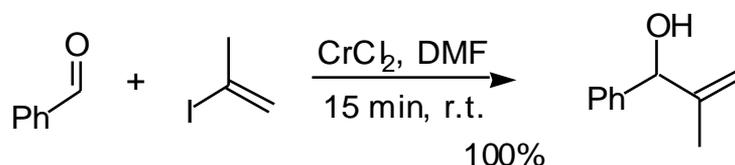
or under Barbier conditions (*in situ*) by reduction of organohalides with chromium(II) chloride. The latter method is possible owing to the fact that chromium(II) is insufficiently reducing to reduce the carbonyl compound starting material. The advantage of proceeding directly from organohalide to organochromium without an organolithium intermediate is that a wider range of functionality can be tolerated in the starting materials than would be possible in the presence of a highly reactive organolithium. The disadvantage is that it requires two

equivalents of expensive and possibly carcinogenic chromium(II) chloride, preventing this from being an industrially viable process.

Organochromiums are generally highly selective for the aldehyde functionality, and are regioselective for 1,2- over 1,4-addition. For these reasons, chromium is our choice of metal, and the Nozaki-Kishi reaction is described below.

3.1.3 The Nozaki-Kishi Reaction

Takai first reported in 1983 that vinylchromium species, formed from vinyl halides with chromium(II) chloride, add to aldehydes in quantitative yield (scheme 3.2).²¹⁶

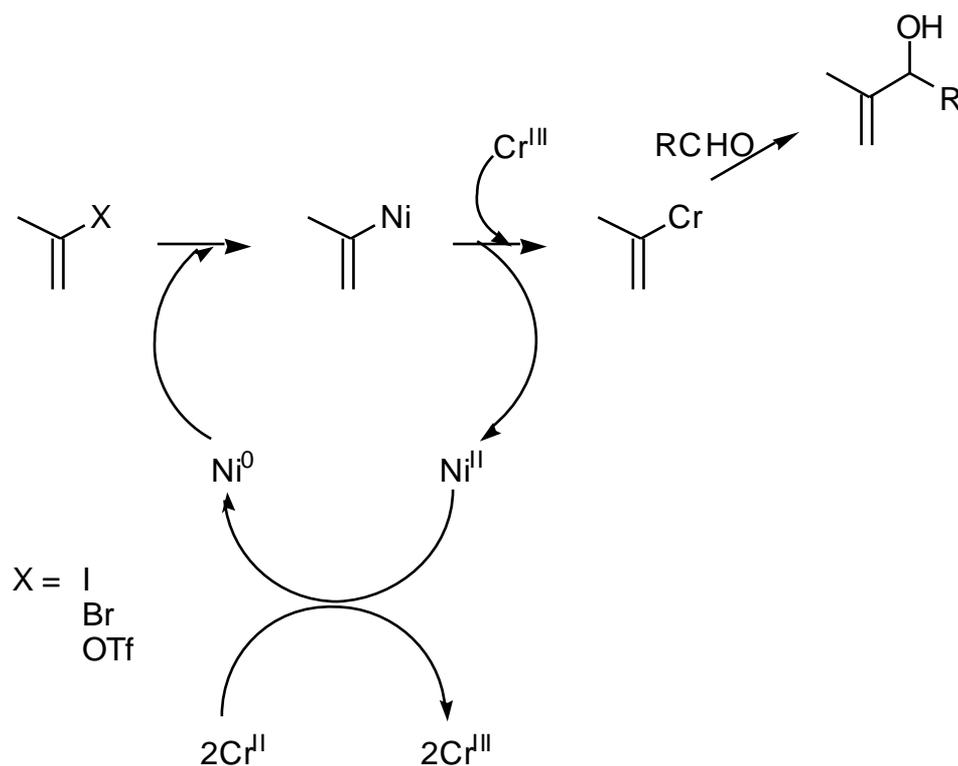


Scheme 3.2

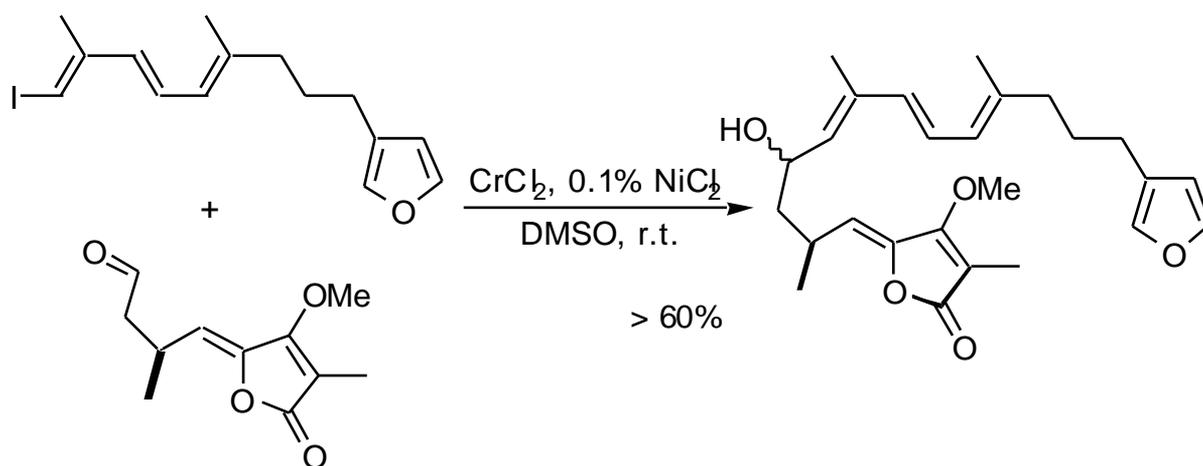
This reaction is highly selective for aldehydes, and operates very cleanly at room temperature, but its success was noticed to depend crucially on the nature of the chromium(II) chloride source. Eventually, Takai²¹⁷ and Kishi²¹⁸ simultaneously and independently found that nickel(II) ions are essential for the reaction to take place; high purity chromium(II) chloride, free from nickel contamination, leads to little reaction—addition of a catalytic amount of nickel(II) chloride led to reproducible results. Nowadays, so-called *Nozaki-Kishi* reactions²¹⁹ are always performed with ~0.1% added nickel(II) chloride. Neither the chromium(II) chloride nor the nickel(II) chloride needs to be especially pure, though both must be completely dry, and oxygen must be rigorously excluded from the reaction. A likely catalytic cycle using the nickel has been proposed (scheme 3.3).²¹⁷ Two equivalents of chromium(II) chloride reduce nickel(II) chloride to nickel(O), and oxidative addition of the vinyl iodide (or bromide/triflate) to the nickel(O) gives the vinylnickel(II) compound.

Transmetalation with some of the chromium(III) salt gives the active vinylchromium species, which then reacts with the aldehyde. The regenerated nickel(II) can then be reduced by more chromium(II) chloride.

The reaction also works in a similar way for vinyl triflates;²¹⁷ in either case, the double bond geometry is extremely well preserved.



Scheme 3.3



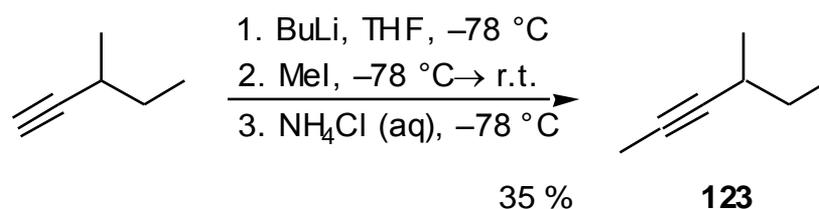
Scheme 3.4

Recently, a catalytic Nozaki-Kishi reaction using quantitative manganese (nontoxic and inexpensive) has been developed, which works equally well with chromium(II) chloride or the much cheaper and non-air-sensitive chromium(III) chloride.²²⁰⁻²²² Several intramolecular Nozaki-Kishi reactions have been achieved,²²³ and Kishi has discovered the beneficial effects of adding 4-*t*-butylpyridine to the reaction.²²⁴

Many recent total syntheses have used the Nozaki-Kishi reaction to join complex multifunctional fragments with excellent yield and selectivity.²²⁵ One example is Uenishi's synthesis of (-)-ircinianin, shown in scheme 3.4.²²⁶

3.1.4 Nozaki-Kishi Model Reactions

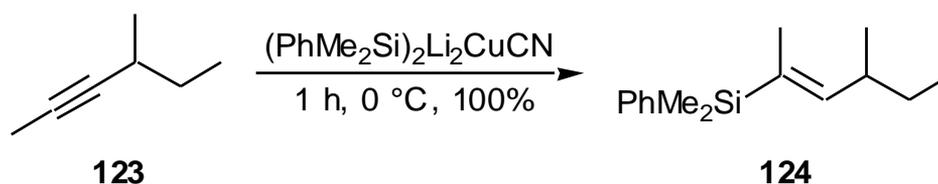
Having chosen the Nozaki-Kishi reaction as the method for joining fragment A to fragment BC, we decided to model the coupling using, initially, isobutyraldehyde for fragment A and a simple vinyl iodide **125** in place of fragment BC. We decided to test the alkyne \emptyset vinylsilane \emptyset vinyl iodide \emptyset coupling sequence (see chapter 2), and so began by making the simple alkyne **123** from commercially available 3-methylpent-1-yne.



Scheme 3.5

Treatment with *n*-butyllithium in THF at -78°C was followed by addition of methyl iodide and warming to room temperature (scheme 3.5).²²⁷⁻²²⁹ The reaction seemed to work well, but separating the relatively volatile product from the THF was problematic. Using ether as solvent made this much easier, but led to appreciable quantities of butyl iodide (presumably formed *via* $\text{BuLi} + \text{MeI} \emptyset \text{BuI} + \text{MeLi}$), which was difficult to remove. Pure material was obtained in low yield from reaction in THF followed by distillation using a Vigreux column,

but decomposition was evident (contents of the distillation flask turning brown) during the course of the distillation.



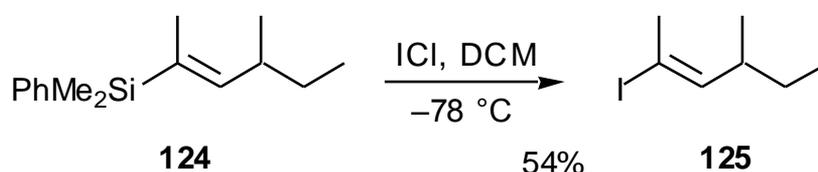
Scheme 3.6

In contrast to these difficulties, silylcupration of the alkyne **123** took place quantitatively when it was added to the silylcuprate reagent formed at 0 °C from dimethyl(phenyl)silyllithium and copper(I) cyanide in THF (scheme 3.6).¹³⁷ The product vinylsilane **124** was stereochemically and regiochemically pure (NMR) and was contaminated only with large quantities of silicon by-products [e.g., tetramethyl(diphenyl)disiloxane], which were easily removed by column chromatography in light petroleum, and dimethyl(phenyl)silane, which was particularly prevalent when older batches of silyllithium were used. This latter material was difficult to remove.

It is generally found in the silylcupration of alkynes that the silyl and copper groups are introduced *syn*.^{190,230} If the reaction is now worked up, the resulting vinylcopper species captures a proton with retention of configuration, thus leading to the *E*-double bond geometry. The steric bulk of the silyl group causes it to prefer the position next to the smaller of the two groups on the ends of the starting alkyne—the methyl group rather than the isobutyl group in this case—and this accounts for the striking regioselectivity of the reaction (opposite to that seen in alkylcupration). This is the first time that silylcupration has been performed on an alkyne in which only steric effects differentiate the two ends.

For ease of work-up in all these silylcupration reactions, it is important that after quenching the reaction with basic saturated ammonium chloride solution the mixture is stirred vigorously in air until the aqueous layer has become a clear blue (showing that all the copper is in the +2 oxidation state).

Having successfully prepared the vinylsilane **124**, we turned our attention to its transformation into the vinyl iodide **125**. Many reagents are available for the iododesilylation of vinylsilanes, including iodine,²³¹ iodine with Lewis acids,²³² iodine monochloride in dichloromethane¹⁹¹ or carbon tetrachloride,²³³ *N,N*-dipyridyliodonium tetrafluoroborate,²³⁴ and *N*-iodosuccinimide in acetonitrile.²³⁵ The stereochemistry of the reaction is dependent in a relatively sophisticated fashion on the iodinating agent and on the substitution pattern of the vinylsilane (see below).^{100,236,237} Archibald investigated a number of different reagents, and found that in her model series the best results were obtained using Miller's procedure;¹⁹¹ i.e., 1.1 equivalents of iodine monochloride in dichloromethane at $-78\text{ }^{\circ}\text{C}$.¹⁵⁷ Consequently this was the method used by Williams in her synthesis of fragment BC, and the obvious method for us to use too.



Scheme 3.7

Hence, we treated vinylsilane **124** with iodine monochloride under Miller's conditions (scheme 3.7). The difficulty associated with this reaction is that, as reported by Miller, the intermediate adduct is "extremely sensitive to both light and heat," so that the reaction has to be performed in the dark. On exposure to light, a pink coloration quickly develops, which is readily removed by washing with sodium thiosulfate solution (hence, presumably it is iodine). (Having iodine present in the product is potentially worrying, as it could in principle scramble the double bond geometry by repeated addition to and elimination from the olefinic products.) The crude product is contaminated with silicon by-products, iodobenzene, iodine and other materials, but chromatography (also in the dark) led to a pure sample of the vinyl iodide in 54% yield.

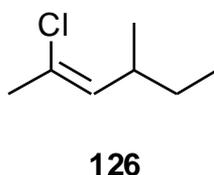
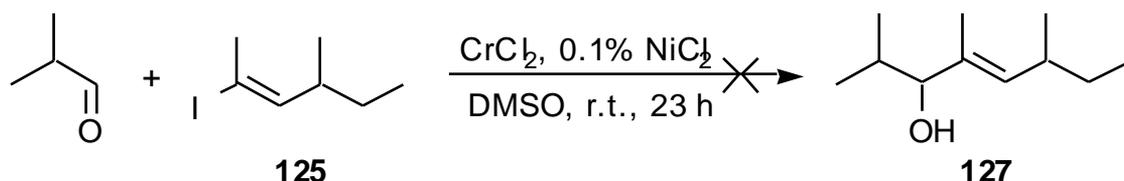


Figure 3.2

We saw no evidence for the formation of the vinyl chloride isomer **126** (figure 3.2), analogous to the one obtained by Williams,¹³⁷ which can be produced in this reaction by chloride ion attack on the cyclic iodonium ion intermediate, followed by elimination of dimethyl(phenyl)silyliodide (see below). It seemed that the reaction had taken place with excellent regio- and stereospecificity, only one isomer, assumed to be vinyl iodide **125**, being seen in the NMR spectrum. (The geometry of the double bond was not verified by means of NOE experiments, because of the instability of the material—performing these after the Nozaki-Kishi coupling will give us the same information and additionally confirm the retention of configuration in that step.)

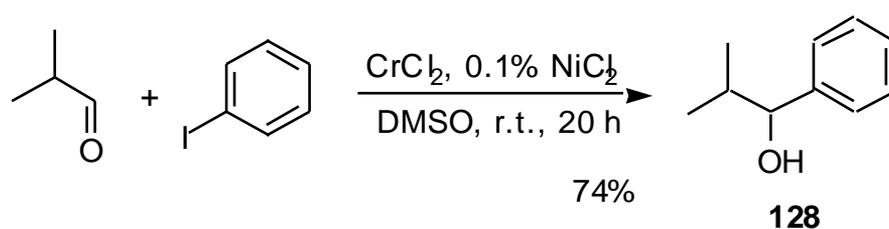


Scheme 3.8

We next took a pure sample of vinyl iodide **125** through into the Nozaki-Kishi reaction (scheme 3.8).²¹⁸ The vinyl iodide was freshly prepared, though normally had developed a pink tinge before the isobutyraldehyde was added. It is necessary to use a glove-box to weigh out and add the nickel(II) chloride and the chromium(II) chloride; the latter should be added slowly and portionwise, as the reaction can be vigorous. The nickel(II) chloride does not need to be weighed out: just a "speck" was found to be sufficient. Initially, 99.9% pure chromium(II) chloride was purchased,²³⁸ but this was found to be unnecessarily pure, and

standard laboratory grade chromium(II) chloride and nickel(II) chloride give equally good results, provided that both are scrupulously dry.

Stirring overnight in dimethyl sulfoxide under an argon atmosphere produced a dark green solution, but on work-up starting materials were routinely recovered. In order to establish whether the problem lay with the Nozaki-Kishi reaction conditions, we endeavoured to perform a straightforward reaction between isobutyraldehyde and iodobenzene; this gave a good yield of the product alcohol **128** first time (scheme 3.9),²³⁹ so we realised that the problem must lie with the vinyl iodide.

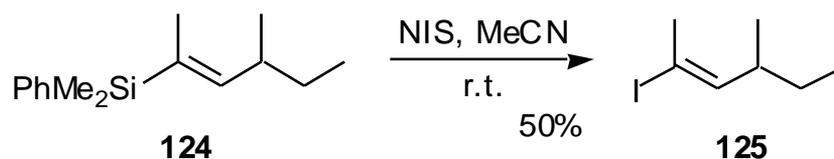


Scheme 3.9

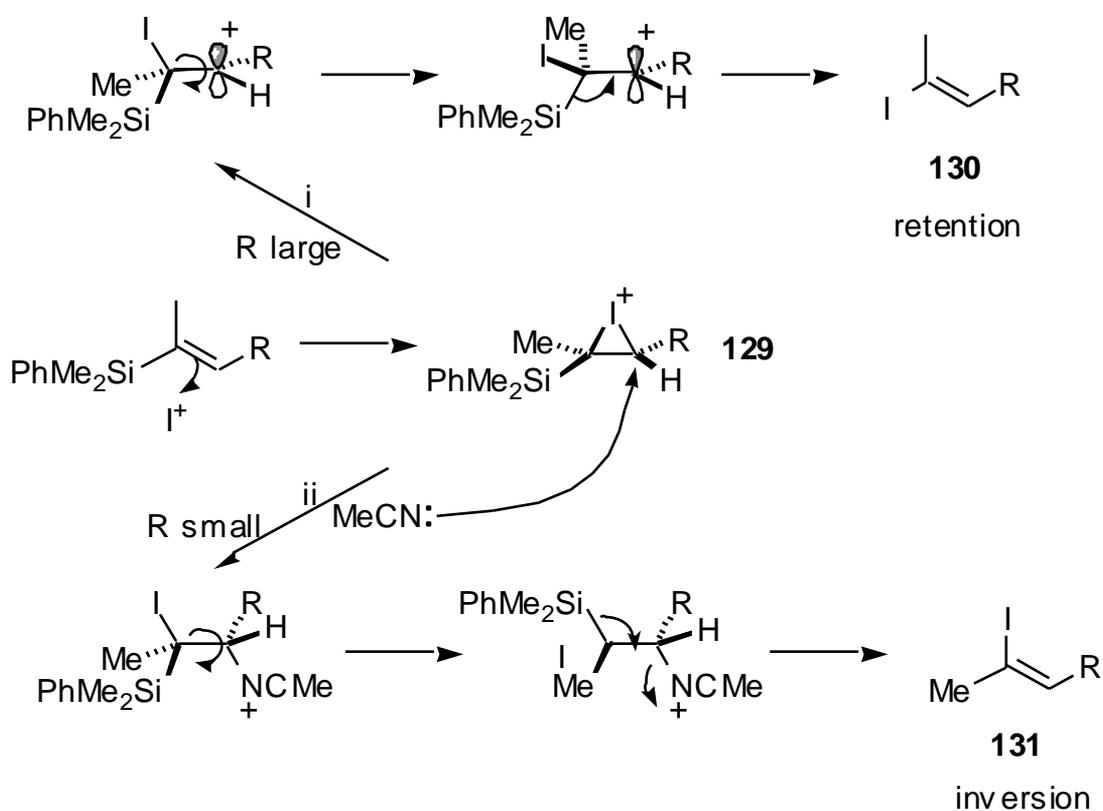
Though the columned vinyl iodide appeared pure by NMR, clearly any residues of iodine, iodine monochloride or other inorganic materials would not be revealed by this spectroscopic technique, and would be very likely to interfere with the reaction (e.g., $\text{Cr}^{2+} + \frac{1}{2} \text{I}_2 \rightleftharpoons \text{Cr}^{3+} + \text{I}^-$; $E^0 = 1.03 \text{ V}$). Further attempts to purify the vinyl iodide proved frustrating, as no sooner had apparently pure material been prepared than it began to turn pink under the influence of light and/or heat, and the Nozaki-Kishi reaction with the material failed every time.

Since Archibald did her iododesilylation investigations, Kishi has published a cleaner and superior method for many substrates, using *N*-iodosuccinimide (NIS) in acetonitrile at room temperature.²³⁵ Owing to the difficulties we were experiencing with Miller's method, and the simplicity of this much milder method, we treated our vinylsilane **124** with NIS under these conditions and obtained, in similar yield, the vinyl iodide **125** in an apparently equally pure form (NMR) but much less susceptible to turning pink (scheme 3.10). (The potential for

by-products to be formed in this much milder process is, we believe, less.) The reaction is quenched with saturated sodium sulfite solution, and vigorous stirring with this reduces any remaining iodine; washing the organic fraction twice with sodium hydroxide solution removes the succinimide by-product.



Scheme 3.10

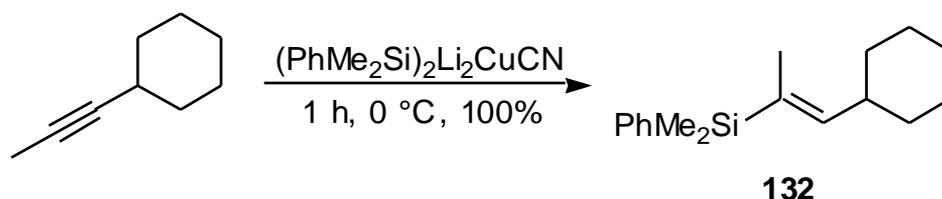


Scheme 3.11

We expected the reaction to give a good ratio of *E* (retention) to *Z* (inversion) product, since the carbon atom γ to the silicon is secondary, and Kishi found that branching here

improved this ratio. The reason for this observation is thought to be that where there is little steric bulk in that part of the molecule, solvent molecules participate in the reaction by opening the cyclic iodonium ion **129** (pathway ii, scheme 3.11), leading to overall inversion of the alkene geometry in vinyl iodide **131** (since elimination of the silyl and solvent groups takes place in an antiperiplanar fashion). In substrates where R is more bulky, solvent molecules are assumed not to be involved, and the iodonium ion **129** opens to a carbocation intermediate (pathway i). We can imagine the central C-C bond of this intermediate rotating by the smaller of the two possible angles to bring the C-Si bond parallel to the empty p-orbital, thus β -silicon stabilising it. Elimination of the silyl group in this conformation then leads to the vinyl iodide **130** with overall retention of configuration (scheme 3.11). It appeared from the NMR spectrum that only one isomer of the vinyl iodide **125** was present, and that it was identical to that formed under Miller's conditions.

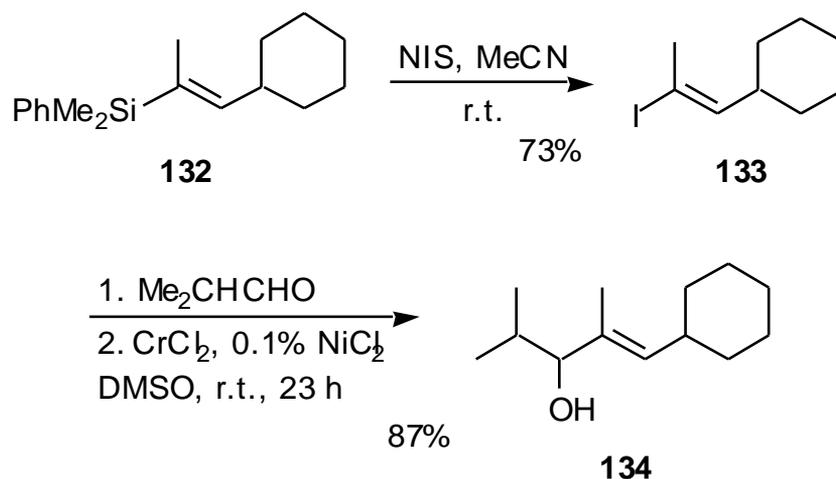
We were not able to try the Nozaki-Kishi reaction with the vinyl iodide **125** prepared by Kishi's conditions, as insufficient was obtained from the quantity of alkyne **123** brought through from the rather unsuccessful first reaction of this sequence. Instead, we found that 1-cyclohexyl-1-propyne was commercially available,²⁴⁰ and having a larger molecular mass and not possessing a stereogenic centre would make it more suitable for this sequence. (The Nozaki-Kishi reaction introduces a new stereogenic centre, and would thus lead to diastereoisomers with vinyl iodide **125**.)



Scheme 3.12

Hence we performed the silylcupration reaction on this alkyne, the reaction proceeding, as before with 3-methylpent-1-yne, in quantitative yield to give the vinylsilane **132** (scheme 3.12), again regio- and stereochemically pure (NMR). Treatment with NIS (Kishi's

conditions) gave the vinyl iodide **133** in a pure form, this time in much better yield, after chromatography. Taking this through immediately into the Nozaki-Kishi reaction with isobutyraldehyde at last led to a successful coupling from a prepared vinyl iodide, producing the allylic alcohol **134**, after a straightforward dichloromethane column, in good yield (scheme 3.13).



Scheme 3.13

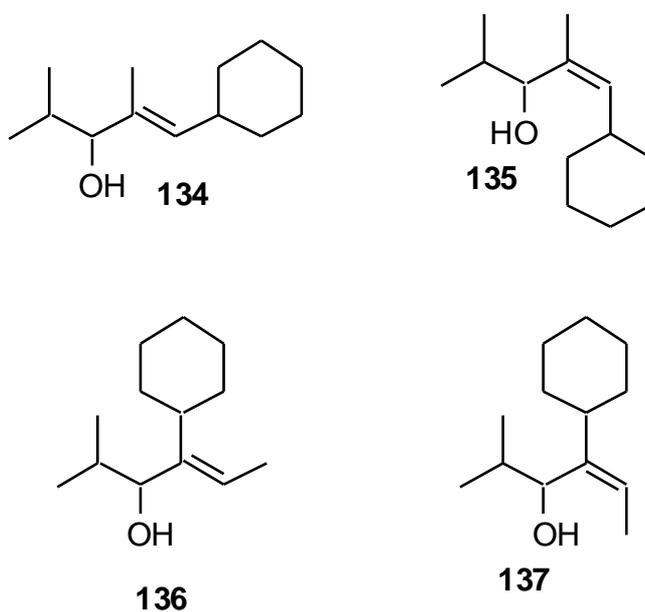


Figure 3.2

For the fragment A to fragment BC coupling, it is essential that the double bond geometry is preserved throughout these steps. The ^1H NMR spectrum showed that apparently only one isomer of alcohol **134** had been formed. Four isomers are theoretically possible (figure 3.2), however, and to verify that the one formed was the *E*-geometry in which the cyclohexyl group and the hydrogen are also on the same end of the double bond we obtained COSY and NOESY spectra of alcohol **134** (figure 3.3).

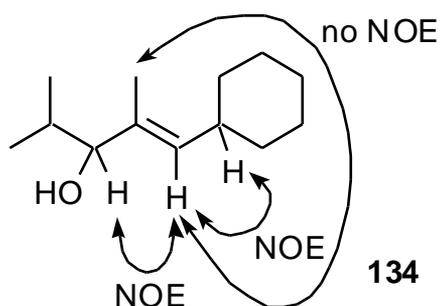
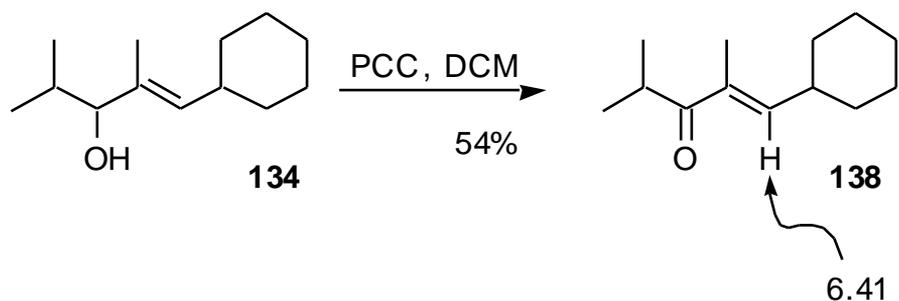


Figure 3.3

This was fairly conclusive, but to obtain further support for structure **134**, we oxidised alcohol **134** to ketone **138** with pyridinium chlorochromate in dichloromethane so that the chemical shift of the alkene hydrogen could be measured and compared with literature values for β -hydrogens in other enone systems (scheme 3.14).



Scheme 3.14

It is generally found that β -hydrogens in β -substituted *E*-enones are significantly downfield of β -hydrogens in β -substituted *Z*-enones (e.g., see figure 3.4).²⁴¹ The chemical shift of the *E*-enone β -hydrogen is less when the β -substituent is larger than a methyl group, and the value of 6.41 ppm for ketone **138** is comparable with that in similar systems (figure 3.5).^{192,242}



Figure 3.4

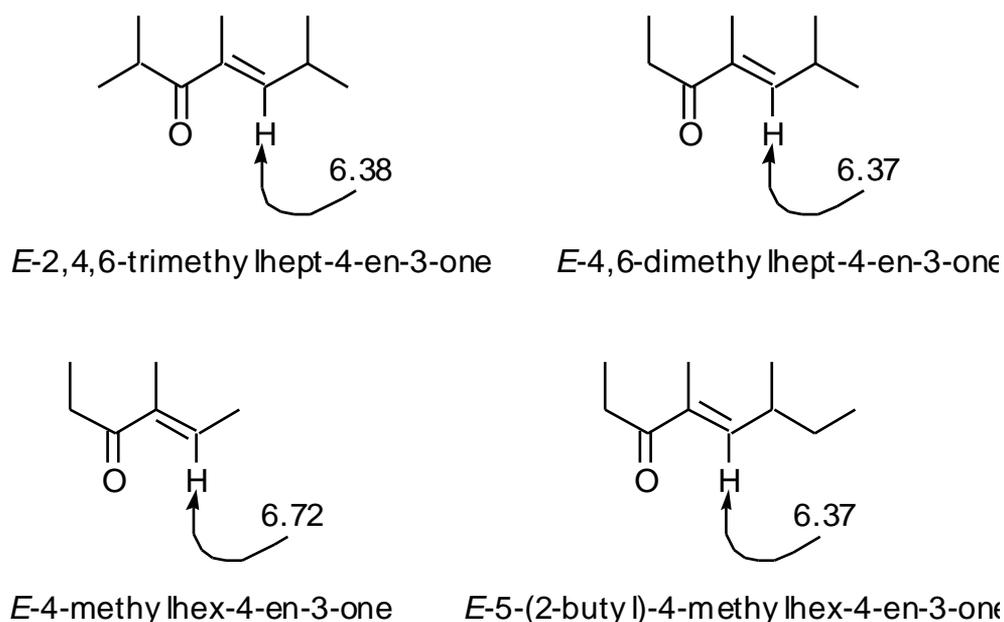


Figure 3.5

Hence, the Nozaki-Kishi reaction provides a convenient solution to the fragment A to fragment BC coupling in the model series.

3.2 Reduction of the Allylic Alcohol

3.2.1 Introduction

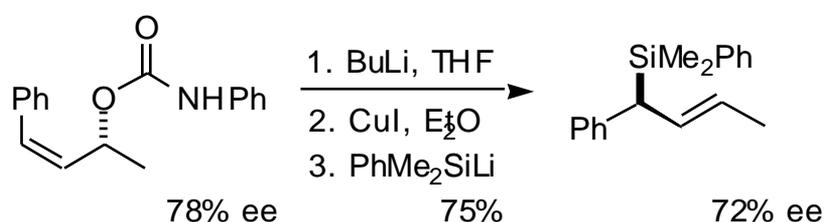
There is no standard procedure for reducing an allylic alcohol to an alkene with preservation of the regio- and stereointegrity of the double bond. (Reduction *with* allylic shift is generally easier.) Various methods have been used, such as formation of a thionoether or sulfonate derivative, followed by either radical or nucleophilic substitution of hydrogen.²⁴³ However, these are frequently substrate-specific. The Barton-McCombie reaction is probably the best-known general method, in which thionoether formation is followed by treatment with tributyltin hydride or other hydrogen atom source.²⁴⁴ Other methods include Corey's, in which the sulfate is formed from the allylic alcohol using sulfur trioxide-pyridine complex at 0 °C, and this is reduced with lithium aluminium hydride in THF.²⁴⁵ Less well-known methods which are reported not to shift or isomerise the double bond include allylic ether formation, followed by treatment with lithium triethylborohydride and palladium tetrakis(triphenylphosphine);²⁴⁶ and (for primary or secondary allylic alcohols) hydrogen with hydridopentacyanocobaltate [$\text{HCo}(\text{CN})_5^{3-}$]. These latter conditions are very mild, but even under these conditions migrations have been reported to occur.²⁴⁷

3.2.2 Silicon Methods

One appealing way of removing an allylic hydroxyl group is to substitute a silyl group for it and then protodesilylate the resulting allylsilane. It is well-established that silylcuprate reagents displace allylic acetates. In the case of tertiary allylic acetates, the reaction is completely regioselective, giving only the allylsilane with the silyl group on the less hindered end of the allylic system, and is stereospecifically *anti*.^{138,248,249} For secondary allylic acetates, it is necessary to add ether or a mixture of ether and pentane to the silylcuprate

reagent (this can be prepared only in THF), and also sometimes triphenylphosphine to make the reaction successful; by this means, Thomas was able to prepare allylsilanes in good yield from primary and secondary allylic acetates and benzoates, though with less reliable regioselectivity because of competition between S_N2' and S_N2 reaction.²⁵⁰ These methods have been successfully applied to the synthesis of the Prelog-Djerassi lactone²⁵¹ and of a prostaglandin intermediate.¹⁹⁵

Thomas has also developed a valuable route to allylsilanes from allylic carbamates, in which intramolecular delivery of the silyl group from a mixed cuprate species (e.g., species **139** in figure 3.6) leads to regioselective and *syn* stereospecific reaction (e.g., see scheme 3.15).^{192,249} This often gives good regioselectivity, even for primary and secondary allylic carbamates, although the yields are frequently low.



Scheme 3.15

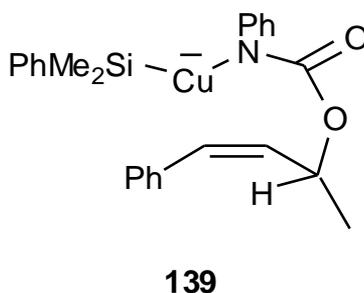
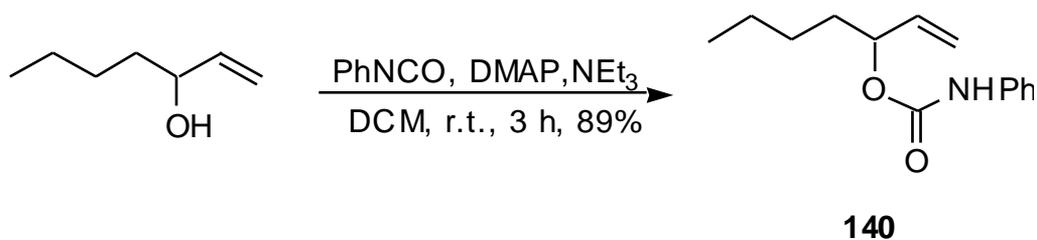


Figure 3.6

This complements the allylic acetate work, and is suitable for our system since we have a secondary allylic alcohol and want to avoid the mixture of products which we would anticipate from allylic acetate formation and silylcuprate displacement. Model work has been

carried out in the group to apply this technique to removing the allylic hydroxyl of ebelactone (see chapter 2), and this is developed further in the work described below.

3.2.3 Carbamate Methodology



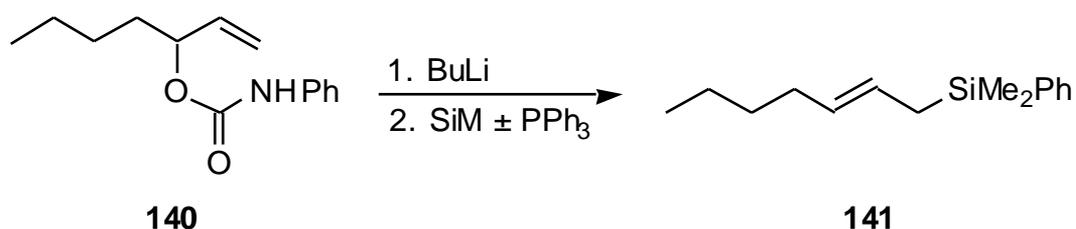
Scheme 3.16

Since quantities of the alcohol **134** were limited, we decided initially to test the carbamate methodology starting from cheap and readily available 1-hepten-3-ol. This was treated with phenyl isocyanate and 4-dimethylaminopyridine (DMAP) and triethylamine in dichloromethane for 3 hours at room temperature, and this gave the allylic carbamate **140** cleanly in very good yield after a dichloromethane column (scheme 3.16).^{192,195,252,253}

Transformation of this carbamate into the allylsilane **141** was attempted under various conditions (see scheme 3.17 and table 3.1). This type of reaction is reported to be "capricious".¹⁹⁵ However, deprotonation with *n*-butyllithium followed by addition to the silylcuprate reagent prepared from dimethyl(phenyl)silyllithium and copper(I) iodide was effective,^{192,195} the best yield being obtained when triphenylphosphine was added (to stabilise the cuprate)²⁵⁴ and the carbamate was deprotonated at 0 °C and added to the silylcuprate at the same temperature—under these conditions pure allylsilane was formed in 49% yield. The material was regiochemically pure, spectroscopic data matching literature values,²⁵⁵ with no trace of the isomer formed from direct S_N2 displacement.

The presence of triphenylphosphine in the reaction mixture frequently led to difficulties in the work-up, as it precipitated and had to be filtered off (acid could not be added to dissolve it because of the risk of protodesilylation); however, leaving it out adversely affected the

reaction. Simple addition of silyllithium by itself led to no reaction. We wondered whether another metal salt might give a better yield. Singer has reported conjugate addition of silylzincates to α,β -unsaturated carbonyl compounds,^{256,257} and on formation of dimethyl(phenyl)silylzincate and reaction with the deprotonated carbamate at $-78\text{ }^\circ\text{C}$, the allylsilane was formed in quantitative yield. Hence, the zincate would appear to be the best reagent to use, and the troublesome triphenylphosphine additive can be dispensed with.



Scheme 3.17

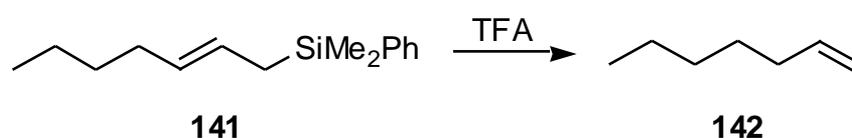
no.	equivalents				salt	method	temperature of		result
	BuLi	SiLi	salt	PPh ₃			formation of carb ⁻ / °C	addition to SiM / °C	
1	1.0	1.2	1.0	2.0	CuI	1	0	0	49%
2	1.2	1.6	1.3	2.7	CuI	2	-78	0	‡
3	1.1	6.0	3.0	6.0	CuI	1	0	0	‡
4	1.1	6.0	3.0	0.0	CuCN	1	0	0	‡
5	1.1	2.0	2.0	0.0	ZnCl ₂	1	-78	-78	100%
6	1.1	2.0	0.0	0.0	-	1	-78	0	SM

Method 1: Deprotonated carbamate (carb⁻) added to silylmetal (\pm PPh₃); Method 2: Deprotonated carbamate (carb⁻) added to salt (\pm PPh₃), and then SiLi added to this; ‡ = product formed (NMR), but in low yield and not isolated; SM = starting material recovered only; % = yield of product isolated.

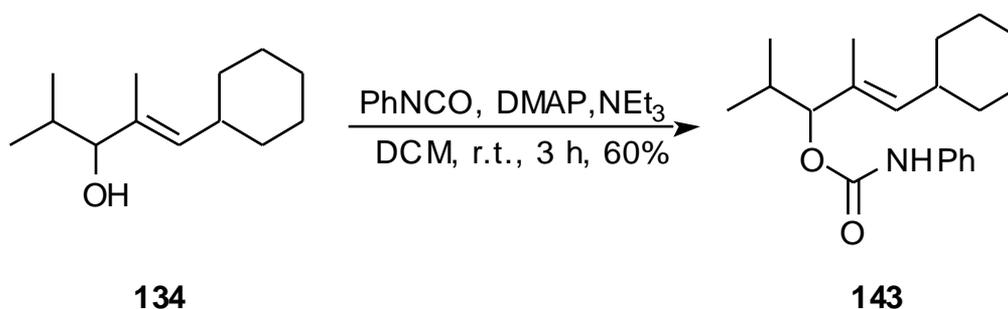
Table 3.1

Finally, addition of one drop of trifluoroacetic acid to the NMR sample of allylsilane **141** gave an NMR spectrum matching that from the literature for hept-1-ene **142**, thus verifying the feasibility of the protodesilylation step (scheme 3.18).

With this experience behind us, we turned to the model alcohol **134** itself. Once again, carbamate formation with phenyl isocyanate was efficient giving pure carbamate **143** in 60% yield (scheme 3.19). COSY and NOESY experiments on this carbamate verified that the geometry and position of the double bond was, as expected, unchanged by this reaction, and as shown in scheme 3.19.



Scheme 3.18



Scheme 3.19

On trying the various silylmetal reagents and conditions on this carbamate, however, none of them was found to lead to any of the allylsilane product **144**. In every case, starting material only was isolated (see scheme 3.20 and table 3.2); in fact, carbamate **143** appears to be an exceptionally stable compound. The most likely reason for this is that the bulky cyclohexyl ring is obscuring intramolecular attack of the cuprate on the double bond (figure 3.7).

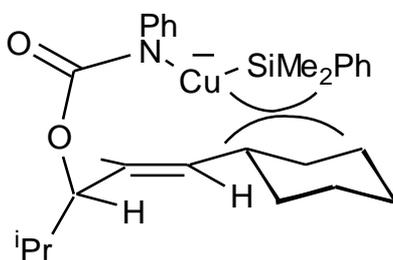
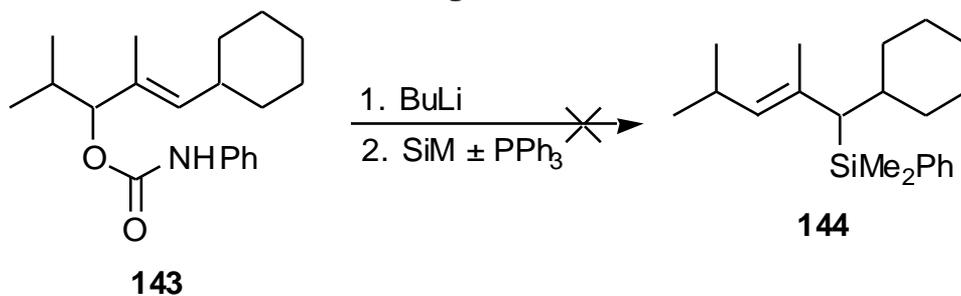


Figure 3.7



Scheme 3.20

no.	equivalents				salt	method	temperature of		result
	BuLi	SiLi	salt	PPh ₃			formation of carb ⁻ / °C	addition to SiM / °C	
1	1.0	1.2	1.0	2.0	CuI	1	0	0	SM
2	1.0	1.2	1.0	2.0	CuI	2	-78	0	SM
3	1.1	1.8	1.5	3.2	CuI	1	-78	0	SM
4	1.1	6.0	3.0	6.0	CuI	1	0	0	SM
5	1.1	6.0	3.0	0.0	CuCN	1	0	0	SM
6	1.1	2.0	2.0	0.0	ZnCl ₂	1	-78	-78	SM

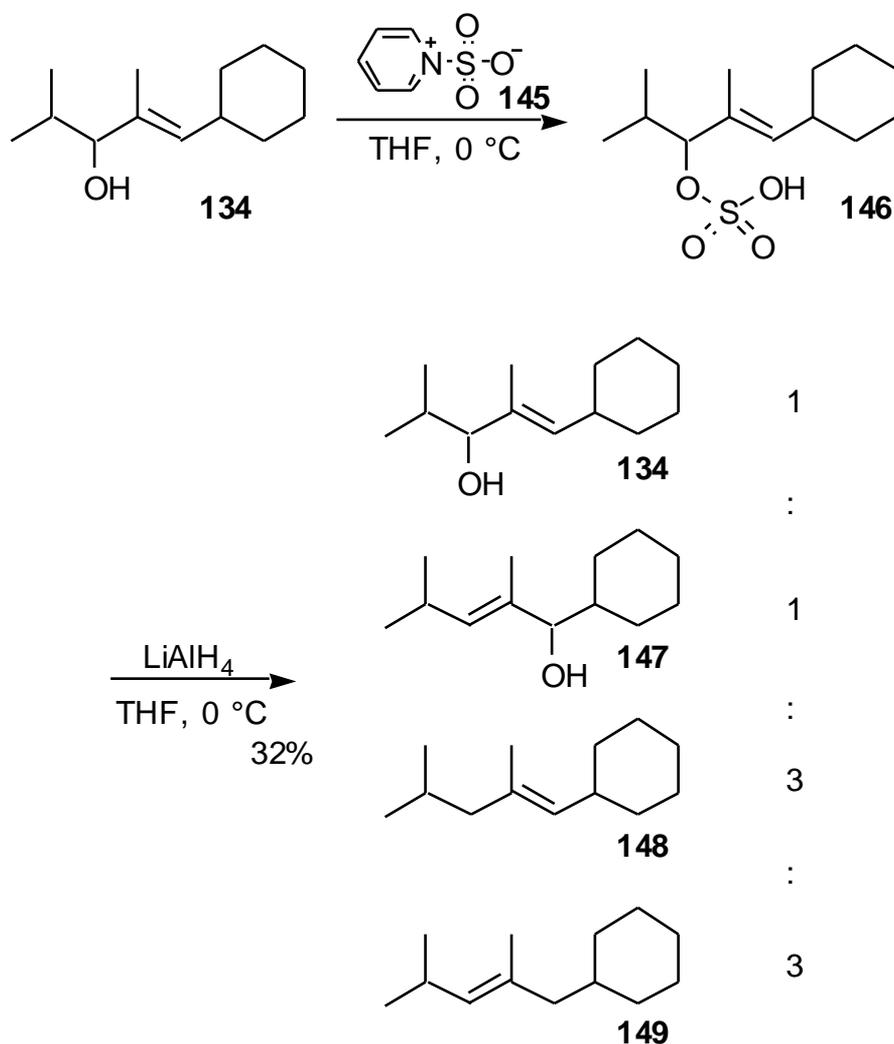
Method 1: Deprotonated carbamate (carb⁻) added to silylmetal (± PPh₃); Method 2: Deprotonated carbamate (carb⁻) added to salt (± PPh₃), and then SiLi added to this; SM = starting material recovered only.

Table 3.2

This disappointing result may mean that this methodology will not be suitable for ebelactone-a; on the other hand, if it is a result peculiar to the presence of a (six-membered) ring then it will not be a problem. Further work is needed.

3.2.4 Other Reduction Methods

Since supplies of the alcohol **134** were still available, it seemed worth seeing what product(s) would be obtained under Corey's reduction conditions.²⁴⁵ The sulfate **146** was formed by treating alcohol **134** with sulfur trioxide-pyridine complex **145** in THF at 0 °C overnight. This was not isolated, but treated again at 0 °C with lithium aluminium hydride, again overnight. After work-up and chromatography, two fractions were obtained: a mixture of inseparable alcohols **134** and **147**, and a mixture of inseparable alkenes **148** and **149** (scheme 3.21). The structures were assigned by means of COSY and NOESY spectra (see figure 3.8).



Scheme 3.21

These conditions would almost certainly be too harsh for our β -lactone-containing product of the fragment A and fragment BC coupling, and they do not seem to preserve the position of the double bond anyway.

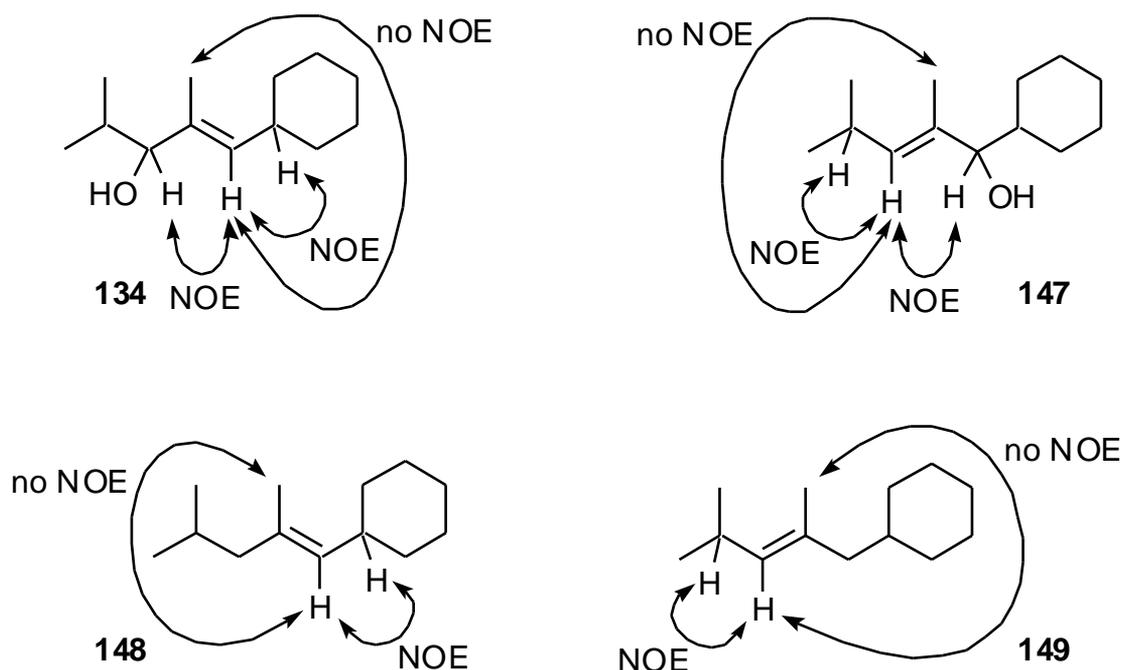
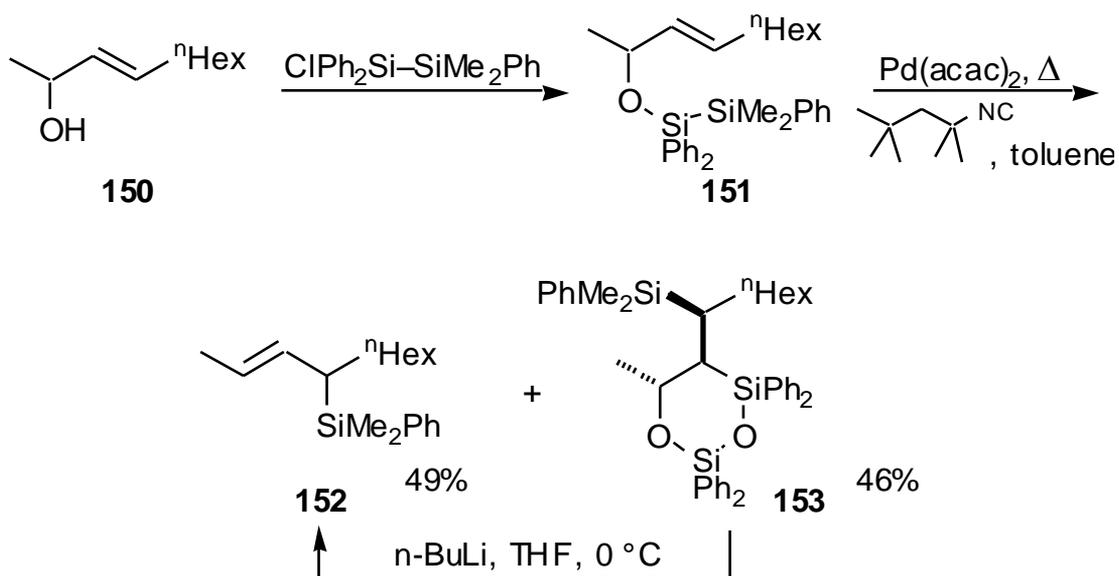


Figure 3.8

3.3 Conclusion

Hence, we have solved the problem of the fragment A to fragment BC coupling by means of the Nozaki-Kishi reaction in the model series. This needs to be tried on the real fragments (see chapter 4). The problem of reduction of the allylic alcohol to the alkene still awaits a solution. Work is currently underway in our group to find a radical method for removal of the alcohol functionality with regiocontrol. However, Ito has recently published a new method of converting allylic alcohols into allylsilanes with a high degree of stereocontrol.²⁵⁸ His procedure first forms a disilanyl ether such as **151** from the alcohol **150**

by treatment with a disilane (scheme 3.22). Heating disilanyl ether with Pd(acac)₂ and 1,1,3,3-tetramethylbutyl isocyanide gives a mixture of the desired allylsilane **152** and the six-membered cyclic siloxane **153**—this can be transformed into **152** simply by treatment with n-butyllithium in THF. In fact, this process can be carried out in one flask without separating **152** and **153**, in which case



Scheme 3.22

the yield is 93%. This method is very attractive for our purposes, and represents a possible solution to our problem.