REVIEW
PERKIN 1

# Strategies for the stereoselective synthesis of molecules with remote stereogenic centres across a double bond of fixed configuration

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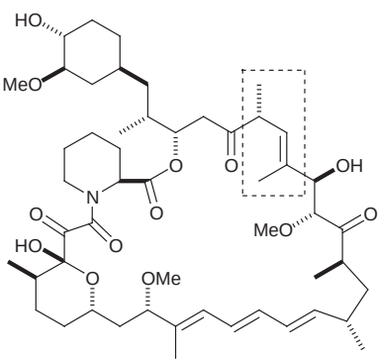
This review outlines the methods which have been used to synthesise molecules with remote stereogenic centres across a double bond of fixed configuration. The syntheses are grouped according to the underlying strategies which have been devised; the relative merits of these strategies and their usefulness in the context of the synthesis of biologically important molecules are discussed.

## 1 Introduction

One of the more challenging aspects of organic synthesis is the controlled construction of molecules with remote (*i.e.* greater than 1,3-related) stereogenic centres with high levels of diastereo- and enantioselectivity.[1] A particularly challenging goal would be the development of a *general* strategy for the control of remote stereogenic centres related across a double bond of fixed configuration.† This motif is present in many natural products, including rapamycin[2] (**1**), macbecin I[3] (**2**), precursors of epothilone A[6] (**3**) and many of the prostaglandins[11] (*e.g.* $PGF_{2\alpha}$, **4**). Alkene dipeptide isosteres (*e.g.* **5**) are intermediates in the synthesis of modified peptides **6** (a modification which does little to change the geometry of the amide backbone but greatly enhances the molecule's resistance to biodegradation) which are in demand as enzyme inhibitors.[12]

As in the more general topic of remote stereocontrol as a whole,[1] there are many different methods for the synthesis of molecules with remote stereogenic centres across a double bond, but only a few underlying strategies. In this review, we shall summarise the strategies which have been devised and concentrate on their relative merits in the context of the synthesis of biologically important molecules.



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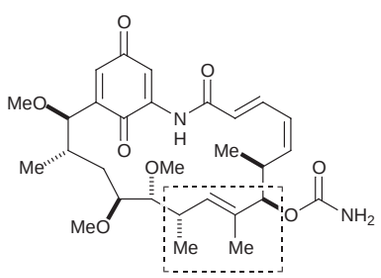

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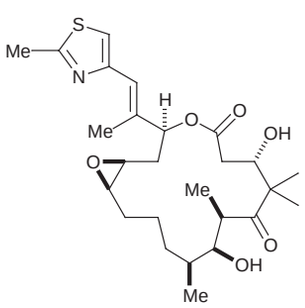

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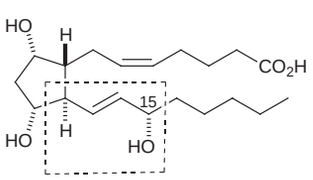

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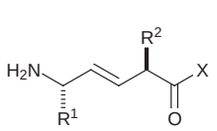

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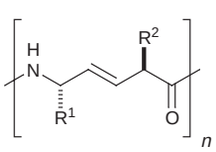
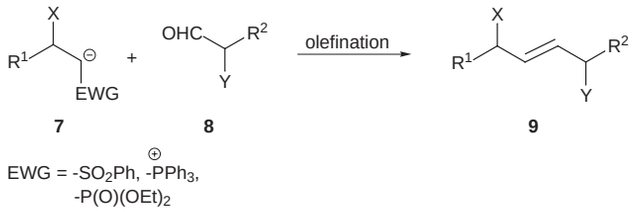


**6**

## 2 Strategy A: the coupling of chiral fragments

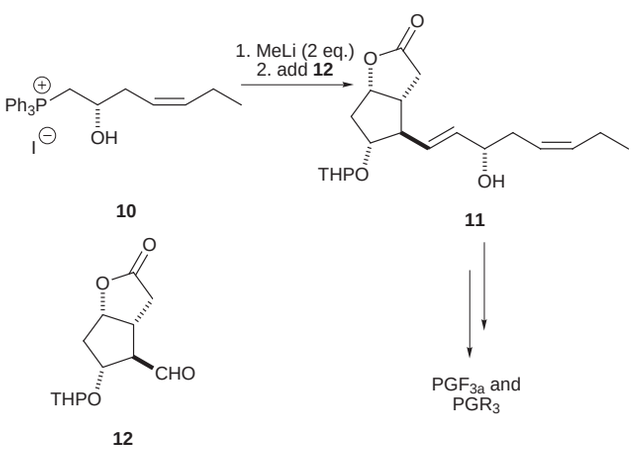
The problem of controlling remote stereochemistry across an alkene can be reduced to the problems of controlling the absolute stereochemistry of the two fragments and the geometry of the double bond required (see Scheme 1, Strategy A). Olefination reactions, such as the Wittig and Julia reactions, can provide a powerful means of coupling fragments and can render natural product syntheses, such as those of brefeldin[13] and

† This review is restricted to syntheses of molecules with chiral substituents *at both ends of an alkene.*




**Scheme 1** Strategy A: the coupling of chiral fragments.

rotaxacin,[14] highly convergent. In fact, olefination reactions are often used to couple chiral fragments even when the double bond is later removed, for example in the synthesis of *C*-(1→6′)-linked disaccharides.[15] The approach is, however, necessarily limited to the synthesis of *homochiral* molecules with remote stereochemistry. An application of the strategy to prostaglandin synthesis,[16] in which a Wittig reaction is used to couple the fragments, is shown in Scheme 2.

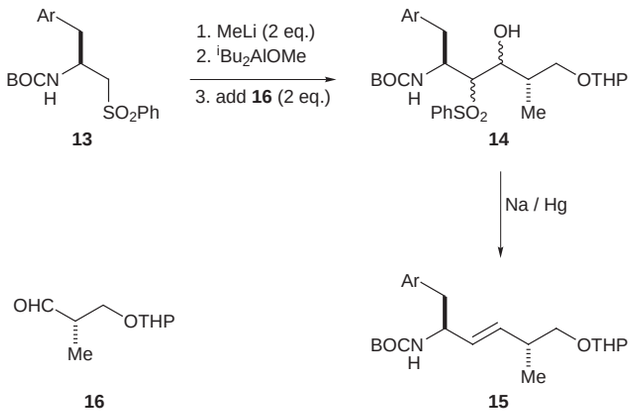



**Scheme 2**

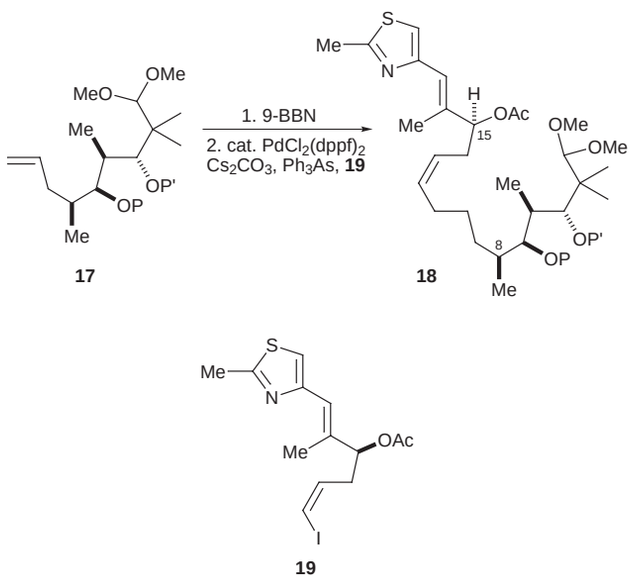
The coupling of chiral fragments is an inherently simple strategy but can be problematic in certain cases. Particular difficulties occur with olefinations which are not very stereoselective and with substrates which are susceptible to racemisation or β-elimination;[17,18] the opportunity to choose the polarity of the coupling partners can, however, often allow enough flexibility to overcome some of these problems. Hopkins' synthesis of *E*-alkene dipeptide isosteres[19] illustrates some of these issues (Scheme 3). The problem of β-elimination of the sulfone component was overcome by dilithiation of the β-amino sulfone.[13] A successful coupling was achieved in the presence of diisobutylaluminium methoxide; reduction with sodium amalgam gave the dipeptide isostere precursor **15** in respectable yield. Here, the formation of two new stereogenic centres in **14** was irrelevant; the intermediate was not purified and the formation of mixtures of diastereoisomers **14** was merely a nuisance.

Coupling of two fragments *next to* an alkene can also be a useful way to control remote stereochemistry across an alkene. For example, in his synthesis of the potential anticancer agent epothilone A, Danishefsky used a Suzuki reaction to couple the homochiral fragments **17** and **19** (Scheme 4); hydroboration of the olefin **17** with 9-BBN gave a mixed borane which was coupled with the vinyl iodide **19** under palladium catalysis to give the *Z*-alkene **18**.[7] In this way, the 1,8-stereochemical relationship between C-8 and C-15 was controlled; the last step of the synthesis involved a stereoselective epoxidation of the *Z*-double bond controlled by the conformation of the macrocyclic ring.

Epothilone A has also been prepared using olefin ring-closing metathesis to prepare the macrolactone (Scheme 5).[9,10] For example, fragments **20** and **23** were coupled to give the ester




**Scheme 3**




**Scheme 4**

**21** which was cyclised to yield the advanced epothilone intermediate **22** as a 58 : 42 mixture of geometric isomers.[9] Schinzer has synthesised epothilone A using a similar approach but, although the synthesis was more convergent, the intramolecular metathesis reaction was less stereoselective in this case.[10]

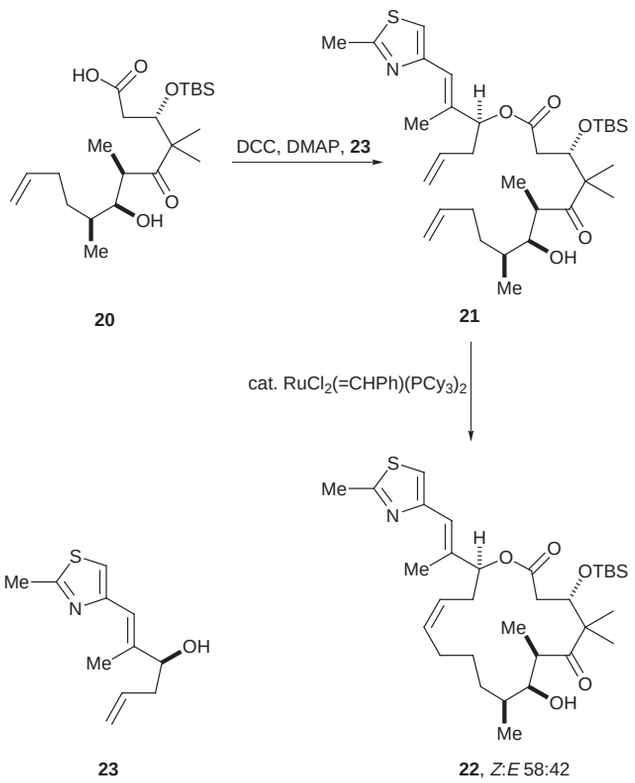
The challenge of constructing the C-29–C-30 trisubstituted double bond of rapamycin led Smith to couple the chiral fragments **24** and **28** using Julia methodology, but the β-hydroxy sulfone intermediate was converted into the ketone **25** (Scheme 6).[20] The lithium enolate of **25** was trapped with *N*-phenyltrifluoromethanesulfonimide to give the *Z*-vinyl triflate **26** with complete stereo- and regioselectivity. The synthesis was completed by coupling the vinyl triflate **26** with lithium dimethylcuprate to give the required C-27–C-32 intermediate **27**.

## 3 Strategy B: asymmetric induction by reagent control

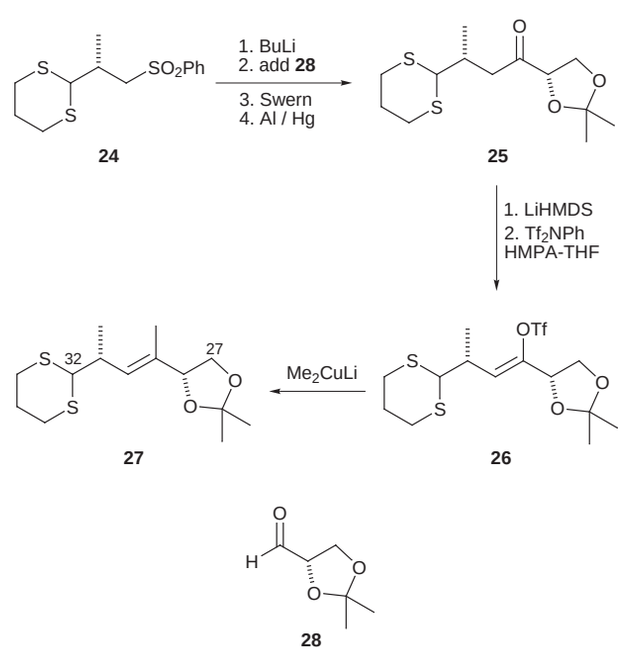
The last twenty years have seen the rapid development of many homochiral reagents which react with prochiral double bonds to generate new stereogenic centres with high and predictable enantioselectivity. Often, the stereochemical bias exerted by a chiral reagent is so great that the effect of any existing stereogenic centres in a substrate on the introduction of the new stereogenic centres can be disregarded.[21] The use of a chiral reagent is especially effective in the control of remote stereochemistry because the existing stereogenic centres in the substrate are necessarily remote from the reacting functionality (Scheme 7, Strategy B). This strategy is conceptually similar to the coupling of chiral fragments except that the order of events has changed; the introduction of one—if not both—of the

**Table 1** Stereoselective reduction of the enones **32** (Scheme 8)

| Entry | R | Chiral reducing agent and conditions | Dr (15*S*:15*R*) |
|---|---|---|---|
| 1 | *p*-$PhC_6H_4CO$ | 0.6 equiv. $BH_3$·THF, 0.1 equiv. (*S*)-**34** | 9:91 |
| 2 | *p*-$PhC_6H_4CO$ | 0.6 equiv. $BH_3$·THF, 0.1 equiv. (*R*)-**34** | 90:10 |
| 3 | THP | 3 equiv. (*S*)-**35**, −100 °C, THF | 99.5:0.5 |
| 4 | THP | 3 equiv. (*R*)-**35**, −100 °C, THF | 32:68 |

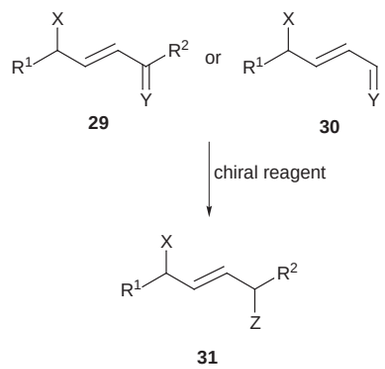



**Scheme 5**



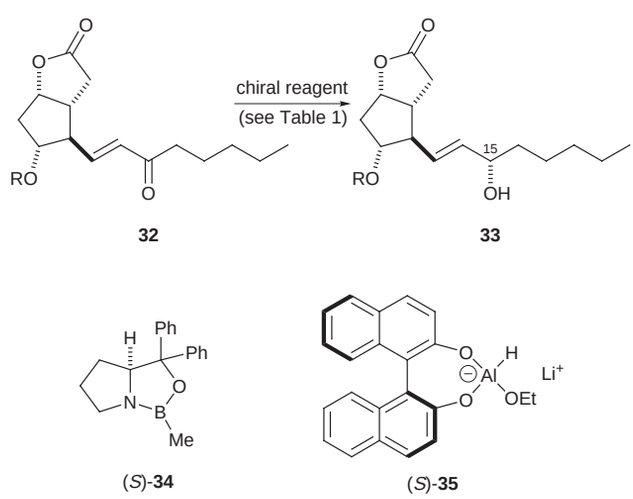

**Scheme 6**

stereogenic centres occurs *after* the backbone of the molecule has been constructed. Provided that enantiomeric (or pseudo-enantiomeric[22]) reagents are available, the approach allows *both* diastereoisomers of the product to be synthesised, though necessarily in homochiral form.




**Scheme 7** Strategy B: asymmetric induction using reagent control.

An application of asymmetric induction by reagent control to the classic problem of controlling the remote C-15 stereogenic centre in prostaglandins is summarised in Scheme 8 and Table 1. Corey's catalytic CBS reducing agent[23] **34** and Noyori's BINAL-H reagent[24] **35** have both been exploited in the reduction of enones **32**. The more expensive oxazaborolidine (*R*)-**34**, derived from the unnatural enantiomer of proline, was required to give the correct stereochemistry, although the expense was mitigated by the small quantity of catalyst required (compare entries 1–2, Table 1).[23] BINAL-H **35** exhibited a surprisingly marked match/mismatch effect[21] with enone **32** (R = THP) (compare entries 3–4, Table 1); fortunately, the more stereoselective reaction yielded the required allylic alcohol (15*S*)-**33**.[24]

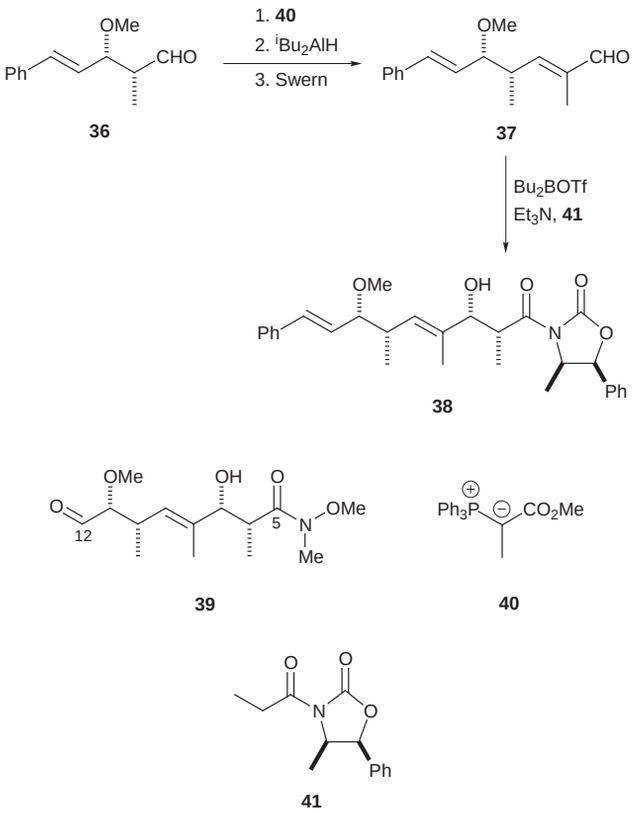



**Scheme 8**

The development of stereoselective reagent-controlled aldol methodology[25] has had a profound effect on polyketide synthesis. The attractions of this approach are obvious; the new stereogenic centres are introduced as part of a C–C bond-forming reaction and more than one stereogenic centre can be formed at the same time. The reagent control approach therefore has considerable potential in dealing with several challenges in a synthesis in the same step.

An excellent example of how these features can help to provide a concise synthesis of a natural product is Evans's synthesis

of macbecin I **2**.[5a] Here, both of the 1,2-related pairs of stereogenic centres of the C-5–C-12 fragment **39** were controlled using boron enolate methodology. In particular, addition of the boron enolate of the oxazolidinone **41** to the unsaturated aldehyde **37** gave the aldol **38** with remote stereogenic centres across a trisubstituted double bond (Scheme 9). Evans's auxiliary has been widely used in the synthesis of natural products with remote stereogenic centres related across a double bond, for example in the synthesis of zincophorin,[26] callystatin A[27] and laulimalide.[28]

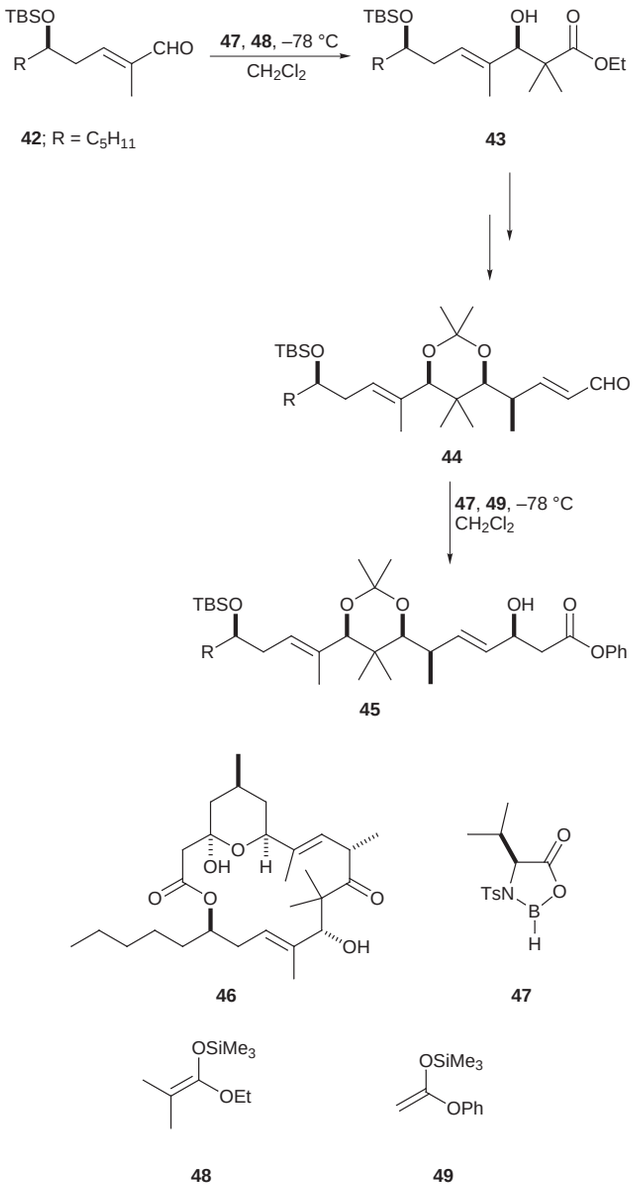



**Scheme 9**

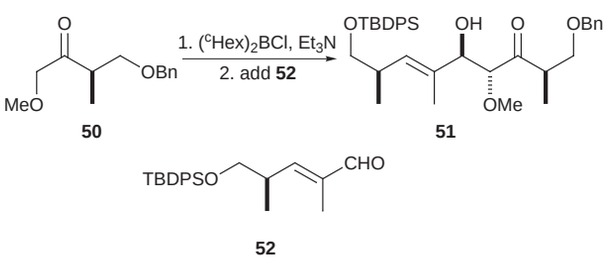
One drawback of chiral auxiliaries is that extra steps have to be used to remove the auxiliary from the product. Kiyooka, however, has used chiral oxazaborolidine promoters (such as **47**) to control all of the stereogenic centres in his proposed synthesis of acutiphycin **46**;[29] this approach avoids the need to remove a chiral auxiliary at any stage of the synthesis (Scheme 10).[30] In this concise synthesis, five Mukaiyama aldol reactions were used to control all of the stereogenic centres of **45** with 83–100% diastereoselectivity.

Another highly effective approach, which has been applied by Paterson in a synthesis of the C-24–C-32 fragment of rapamycin **1**, involved the incorporation of homochiral reagents (derived from the chiral pool) into the target molecule (Scheme 11).[31] For example, reaction of the *E*-enol boronate of the ketone **50** with the aldehyde **52** gave the aldol product **51** with remote stereogenic centres across a trisubstituted double bond. Once again, the high π-facial selectivity of the reagent dominated over the influence of a remote stereogenic centre (at C-31); the required stereochemistry introduced at C-25 was derived from the chiral ketone **50**, and the stereogenic centres flanking the new C–C bond were also both controlled.

Other C–C bond-forming reagents that are used widely in the reagent control strategy include chiral allylic boranes (such as **55**, derived from (−)-α-pinene).[32] Scheme 12 summarises the use of **55** in the synthesis of the diene **54**, an intermediate in the total synthesis of herbimycin A.[5d]



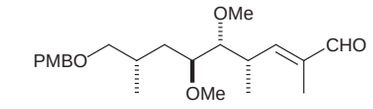

**Scheme 10**



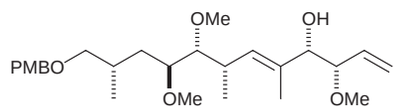

**Scheme 11**

## 4 Strategy C: asymmetric induction by substrate control

Molecules possessing remote stereogenic centres across a double bond can be divided into two categories; those which do not possess any other stereogenic centres, and those which do. Although obvious, this fact influences the way in which chemists tackle the synthesis of such molecules, especially when another stereogenic centre is close enough for more usual (*i.e.* 1,2 or 1,3) methods of stereocontrol to be applied to the problem. In this review, we shall concentrate on studies in which a *remote* stereogenic centre is used to control the stereochemical course of reactions (Scheme 13, Strategy C). An advantage of this strategy over Strategies A and B is that the approach can be




**53**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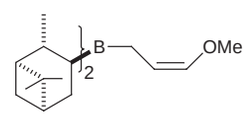
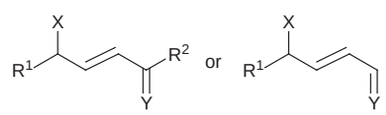
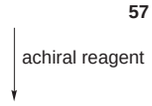


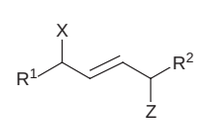

**55**

**Scheme 12**




**56** **57**



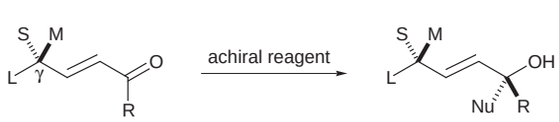




**58**

**Scheme 13** Strategy C: asymmetric induction by substrate control.

applied to the synthesis of *racemic* as well as homochiral molecules, though it is generally possible to make only one of the possible diastereoisomers.

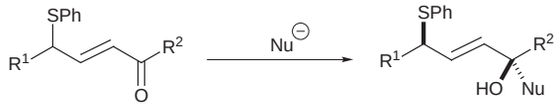
One of the most conceptually attractive—and simple—strategies in 1,4-asymmetric induction would involve the use of a vinylogous version of Cram's rule[33] (Scheme 14). Fleming has sought such a rule, in order to assess whether a remote γ stereogenic centre could transmit electronic information across an intervening double bond, but the diastereoselectivities observed were very low.[34] These low levels of diastereoselectivity were, perhaps, not entirely surprising because control of both the reactive conformation of the enone and the facial attack of nucleophilic reagents would be necessary for high stereoselectivity.




**59** **60**

**Scheme 14** A vinylogous Cram's rule?

Remarkably, however, there are several examples of high levels of 1,4-stereocontrol across an intervening *E* double bond. For example, Otera has studied the addition of organometallic nucleophiles to γ-phenylthio enones such as **61** (Scheme 15);[35] these reactions were found to proceed with remarkably high (up to 97 : 3) levels of diastereoselectivity to give the allylic alcohols **62**. The authors proposed that the enone **61** reacts *via* its s-*cis* conformation (Fig. 1).




**61**
$R^1$, $R^2$ = alkyl

**62**
dr up to 97:3

**Scheme 15**

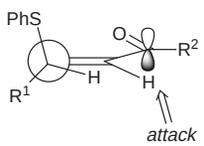



**Fig. 1**

The large size of the diphenylphosphinoyl group allows it to exert its influence over a number of carbon atoms.[36] For example, reduction of enone **62** with the bulky reducing agent L-Selectride™ gave the allylic alcohol **64** as a >85 : 15 mixture of diastereoisomers, though the reaction with sodium borohydride was markedly less selective (Scheme 16).[37] This result suggests that the origin of the stereocontrol is essentially steric. A substantial NOE effect in the $^1$H NMR spectrum of **63** suggests that the enone adopts the conformation shown in Fig. 2; attack from the opposite face to the diphenylphosphinoyl group leads to the observed diastereoisomer. The corresponding reduction of the enone **65** was similarly diastereoselective which is even more surprising in view of the fact that **65** populates both s-*cis* and s-*trans* conformations in solution.


**63**
R = $C_5H_{11}$

**64**
Li $BH^sBu_3$, dr >85:15
$NaBH_4$, dr 67:33

**Scheme 16**

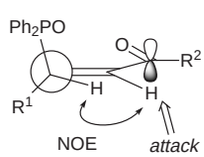
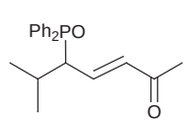



**Fig. 2**

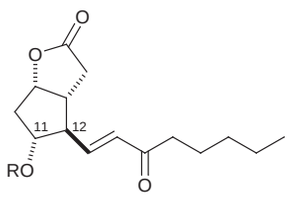



**65**

Impressive synthetic applications of 1,4-stereocontrol across an *E*-double bond were reported in the area of prostaglandin chemistry before effective homochiral reagents had been introduced (Scheme 17 and Table 2). For example, the reduction of the enone **66** (R = *p*-$PhC_6H_4CO$ or *p*-$PhC_6H_4NHCO$) with the bulky *racemic* borohydride **68** was highly diastereoselective (entries 1–2; Table 2);[38] here, the large protecting group at C-11 is thought to control the reduction by blocking one face of the enone and by forcing the enone to adopt its s-*cis* conformation (through attractive π–π interactions between the enone and the aromatic ring of the protecting group, Fig. 3). In Hayashi's examples, at least three equivalents of the alane **69** were required for good stereocontrol (entry 3; Table 2), suggesting that an *in situ* bulky "protecting group" was formed by complexation of the hydroxy group with the alane[39] and that a

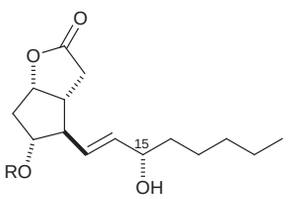
**Table 2** Stereoselective reduction of the enones **66**

| Entry | R | Reducing agent and conditions | Dr (15*S*:15*R*) |
|---|---|---|---|
| 1 | *p*-$PhC_6H_4CO$ | **68**, HMPA, THF, −120 °C | 82:18 |
| 2 | *p*-$PhC_6H_4NHCO$ | **68**, HMPA, THF, −120 °C | 92:8 |
| 3 | H | 10 equiv. **69**, toluene, −78 °C | 92:8 |

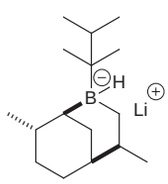



**66**

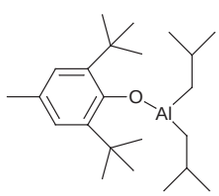
conditions (see Table 2)




**67**




**68**




**69**

**Scheme 17**

similar mechanism for the transmission of stereochemical information may be operating (Fig. 3). Although these results can be considered to be examples of 1,5 asymmetric induction, the *cis*-fused bicyclic ring system and the stereogenic centre at C-12 are likely to influence the stereocontrol considerably, not least by limiting the number of conformations populated.

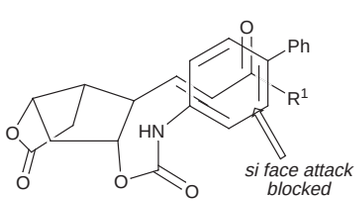
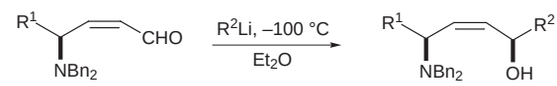



**Fig. 3**

Most of the methods which are used to synthesise molecules with 1,4- and 1,5-related stereogenic centres[1] rely on chelation control[40] or neighbouring group participation.[41] Both of these approaches might be expected to be useful in the specific case of controlling remote stereogenic centres flanking a *Z* double bond but these strategies might be difficult to use in the synthesis of molecules with an *E* double bond between the stereogenic centres.

Chelation can provide effective means of controlling 1,4 stereochemistry across an alkene.[40] For example, the addition of organocuprate reagents to *Z*-enals **70** proceeds with high levels of 1,4 asymmetric induction (Scheme 18).[42] These results can be explained in terms of the chelated transition state depicted in Fig. 4.




**70**
$R^1$ = Me, Bn or $^i$Bu

$R^2$ = Me, Bu or Ph

**71**
dr 88:12 - 97:3

**Scheme 18**

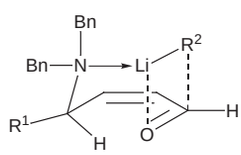
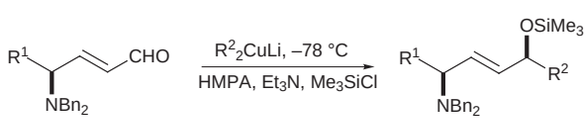



**Fig. 4**

The addition of organocuprates to *E*-enals **72** yields the [1,4]*syn*‡ silyl ethers **73** with good diastereoselectivity provided that the reaction is performed in the presence of trimethylsilyl chloride (Scheme 19);[42] the stereoselectivity observed is particularly impressive when the distance (in space) between the existing and new stereogenic centres is considered. Nakamura has reported similar behaviour in the reactions of γ-methoxymethoxy *E*-enals with cuprates in the presence of trimethylsilyl chloride.[43] Reetz[42] and Nakamura[43] have ascribed the exceptional diastereoselectivity of these cuprate additions to the ability of the reagent to complex selectively to one of the diastereotopic faces of the alkene before addition to the carbonyl group takes place (Fig. 5). The population of the s-*trans* conformation, and preference of the hydrogen atom $H^a$ to more or less eclipse the alkene, can be explained by minimisation of 1,3-allylic strain;[44] coordination to the cuprate reagent forces the organometallic reagent to be delivered selectively to the top face of the aldehyde group (Fig. 5).




**72**
$R^1$ = Me, Bn or $^i$Pr

$R^2$ = Me or Bu

**73**
dr 79:21 - 90:10

**Scheme 19**

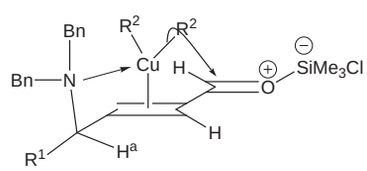
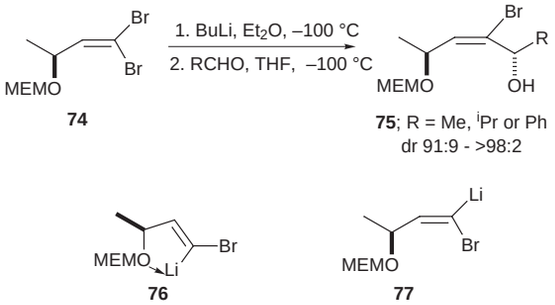



**Fig. 5**

Another successful example of the use of chelation control in 1,4-asymmetric induction across a *Z* double bond is shown in Scheme 20.[45] The vinyllithium reagent **76** was formed under

‡ We use this nomenclature to indicate that functional groups attached to two carbons with a 1,4 relationship are both above, or are both below, the plane of the illustration.




**Scheme 20**

thermodynamic conditions by using a slight excess of the starting material; the use of the MEM protecting group was important for both the stereoselectivity of this equilibration and for the diastereoselectivity of the reaction of the organolithium **76** with aldehydes. These results are explained by invoking a bicyclic chelate (Fig. 6); the aldehyde approaches the less crowded face of the chelate with the aldehyde proton occupying the more sterically demanding position. In effect, the conformation of the bicyclic chelate is controlled by, and magnifies the influence of, the existing stereogenic centre. This approach has been extended to the reactions of other electrophiles,[46] but is limited to the synthesis of *Z* $^{1,4}$*anti*-isomers such as **75**. (Not surprisingly, the additions of the vinyllithium **77** to aldehydes were not very diastereoselective.)

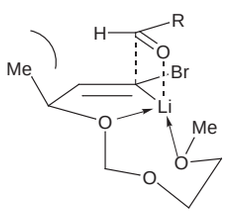
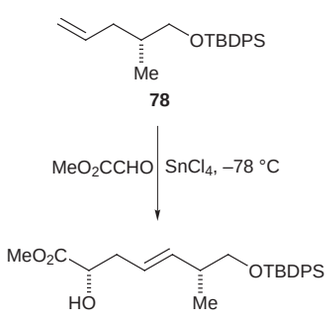



**Fig. 6**

Remarkable 1,5-asymmetric induction is possible using carbonyl "ene" reactions[47] (Scheme 21). For example, treatment of the chiral alkene **78** with methyl glyoxylate and tin(IV) chloride gave the homoallylic alcohol **79** as a 94 : 6 mixture of diastereoisomers.[48] Mikami has explained this amazing example of remote acyclic stereocontrol in terms of the extended transition state shown in Fig. 7; the stereogenic centre exocyclic to the six-membered chair-like transition state is believed to control which face of the aldehyde is attacked by minimisation of 1,3-diaxial interactions.




**Scheme 21**

In a similar vein, Thomas has developed a series of reactions which allow chiral allylic stannanes to be added to aldehydes and imines with high levels of 1,5-,[49–51] 1,6-[52] and 1,7-[53] stereocontrol across an alkene.[54] For example, transmetallation of the chiral allylic stannane **80** with tin(IV) chloride, and reaction with aldehydes, gives predominantly homoallylic alcohols **81** (*ca.* 98 : 2 diastereoselectivity) with $^{1,5}$*syn* stereogenic centres

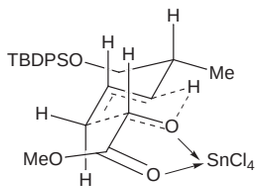
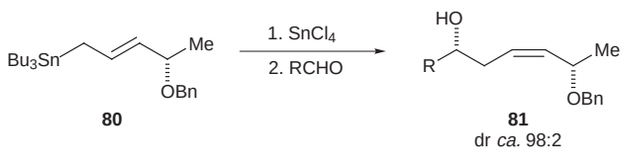
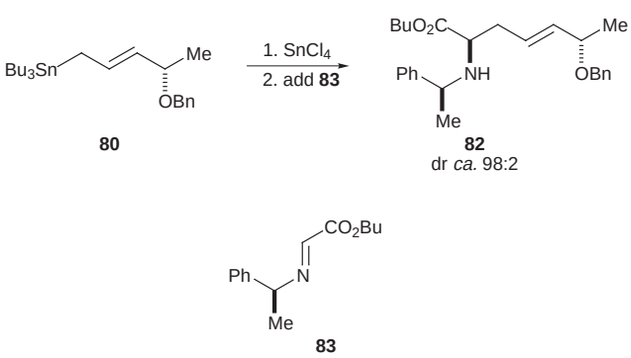



**Fig. 7**

across a *Z* double bond (Scheme 22).[49] Intriguingly, reaction of the same transmetallated stannane with the imine **83** gave the homoallylic amine **82** with high levels of diastereoselectivity but with an *E* double bond (Scheme 23).[50] The remote acyclic stereocontrol observed with allylic stannanes such as **80** is so powerful that the chiral group of the imine **83** merely perturbed the level of, but did not reverse the sense of, the 1,5-asymmetric induction.

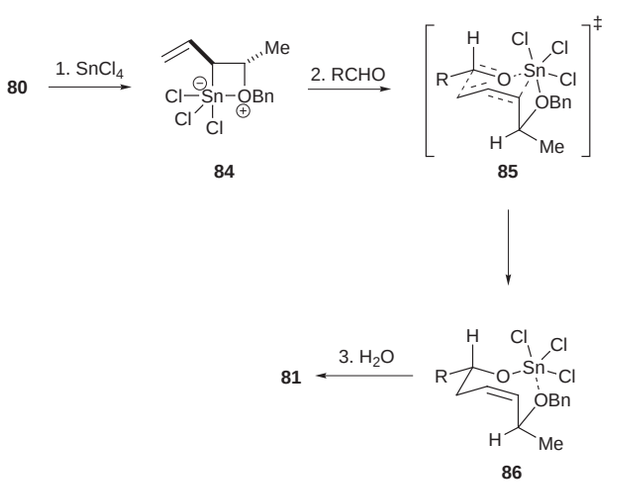



**Scheme 22**



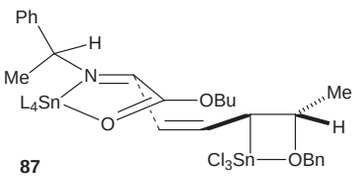

**Scheme 23**

Thomas has explained the high levels of 1,5-asymmetric induction in terms of a stereoselective transmetallation to give a tin trichloride **84** in which the methyl and vinyl groups are *trans* disposed on the chelated four-membered ring (Scheme 24);[49] the intermediate **84** has been trapped with organolithium nucleophiles, providing evidence for this suggestion.[55] The coordinated allyltin trichloride **84** is believed to react with aldehydes *via* a chair-like six-membered transition state **85** in which the R group adopts an equatorial position to minimise 1,3-diaxial interactions. The overall 1,5-asymmetric induction is a




**Scheme 24**

consequence of the stereoselectivity of the transmetallation and the stereospecificity of the allylic transposition **84**→**86**; the reaction can be considered to be a "one-pot" example of the chirality transfer strategy described in the following section. The *E*-stereoselectivity of the reaction of the allyltin trichloride **84** with imines is presumably a consequence of an open-chain transition state (**87**; Fig. 8) in this case.[50,54]



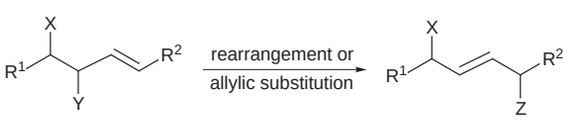

**87**

**Fig. 8**

Most of the examples of remote asymmetric induction described in this section exhibit excellent stereocontrol, but they provide a good route to only one or two of the possible stereoisomers. This lack of flexibility is a limitation of the underlying strategy; in a way, it is surprising that efficient remote acyclic stereocontrol is possible at all!

## 5 Strategy D: the chirality transfer strategy

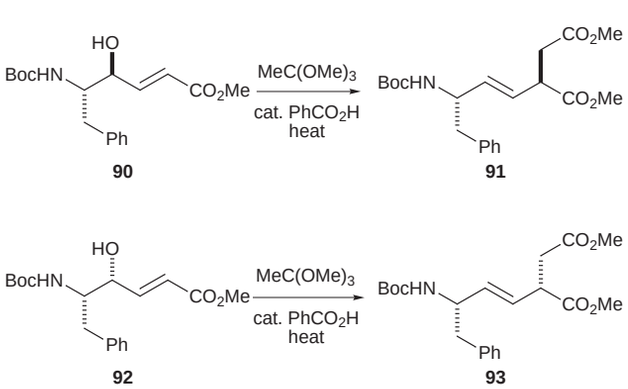
There are only a few examples of remote asymmetric induction using substrate control and all are limited in scope. In contrast there are many reliable methods for the stereoselective synthesis of molecules with 1,2-related stereogenic centres. Consequently, it is not surprising that 1,3 chirality transfer has been widely used in the synthesis of molecules with 1,4-related stereogenic centres across an alkene (Scheme 25, Strategy D). This strategy may be applied to the synthesis of both homochiral and racemic compounds.




**88** **89**

**Scheme 25** Strategy D: the chirality transfer strategy.

Sigmatropic rearrangements are a useful class of reactions for the stereospecific transposition of chirality across an allylic system. For example, a Claisen rearrangment has been used to transpose the allylic alcohols **90** and **92** in a suprafacial manner to give the amino diesters **91** and **93** (Scheme 26).[56,57] This work highlights an important feature of the chirality transfer strategy—more than one diastereoisomer can be prepared provided that the (relatively easy) problem of synthesising both diastereomeric precursors can be solved. The amino diesters **91** and **93** are protected versions of Phe-Glu *E*-alkene dipeptide isosteres.[12]

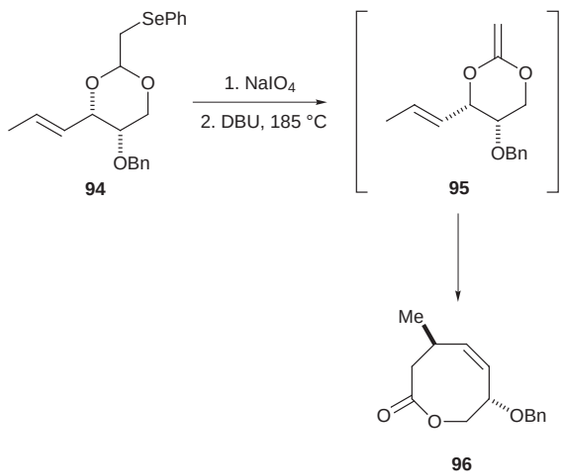



**90** **91**

**92** **93**

**Scheme 26**

An obvious limitation of the Claisen rearrangement approach would seem to be that only *E*-alkenes can be made. However, Holmes has shown that it is possible to synthesise *Z*-alkenes by constraining the rearrangement in the formation of seven- or eight-membered lactones (Scheme 27).[58] Oxidation and subsequent selenoxide elimination of **94** gave the vinyl acetal **95** which underwent [3,3]-sigmatropic rearrangement to give the eight-membered lactone **96**.




**94** **95** **96**

**Scheme 27**

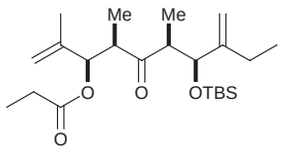
Paterson reported an exceptionally elegant application of the chirality transfer strategy (using the Claisen–Ireland rearrangement) in his total synthesis of ebelactones A and B.[59] The *E* silyl ketene acetal was prepared by enolisation of the ketoester **97** in the presence of trimethylsilyl chloride; the ketene acetal **98** rearranged highly stereoselectively to give, after hydrolysis of the silyl ester and treatment with diazomethane, the methyl ester **100** as a 96:4 mixture of diastereoisomers (Scheme 28). The 1,5-*syn* relationship across the trisubstituted double bond of the ester **100** (between C-4 and C-8) arose as a result of the highly *E*-selective enolisation[60] and the six-membered chair-like transition state **99**.

A potential precursor (**104**) of brefeldin A has two 1,5-stereochemical relationships across *E* double bonds and both of these have been established using Claisen–Ireland methodology (Scheme 29).[61] In each case, the 1,2-related stereogenic centres of the precursors **101** and **103** were transposed into 1,5-stereochemical relationships in the products **102** and **104**. The stereoselectivity of both of these processes can be understood in terms of the six-membered chair-like transition state for the rearrangement of the intermediate *Z*-ketene acetals.

Another useful aspect of the chirality transfer strategy—that *more than one* stereoisomeric product can often be made from the *same* precursor—is illustrated by the prostaglandin synthesis shown in Scheme 30.[62] Palladium-catalysed rearrangement[63,64] of the allylic acetates **106** and **108** gave the transposed allylic acetates **107** and **109** respectively. In each case, the allylic transposition was strictly suprafacial;§ rearrangement of the *Z* and the *E* allylic acetates **106** and **108** gave products which were epimeric at the new C-15 stereogenic centre.

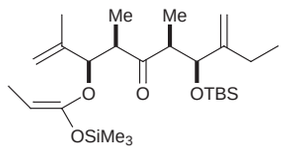
[2,3]-Sigmatropic rearrangements, too, can be exploited in the synthesis of molecules with remote stereogenic centres across an alkene. The sulfonium ylide **111**, generated from the allylic sulfide **110**, gave the homoallylic sulfide **112** in good yield (Scheme 31).[65] In addition to the stereospecific conversion of the [1,2]*syn* stereochemistry of **110** into the [1,4]*syn* stereochemistry

§ The suprafacial rearrangement of the acetate across the *Z* alkene of **106** leads to a product (**107**) in which the acetate *appears* to have migrated to the opposite face of the molecule.



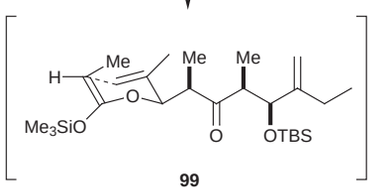

**97**

THF, –78 °C
LDA, $Me_3SiCl$, $Et_3N$



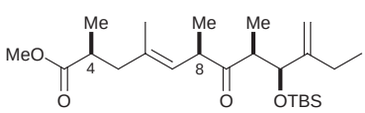

**98**

heat




**99**

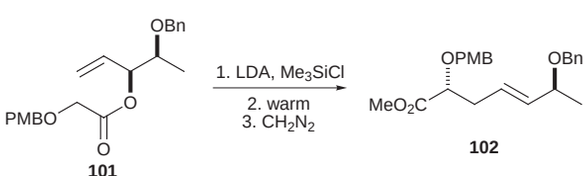
1. $H^+$
2. $CH_2N_2$

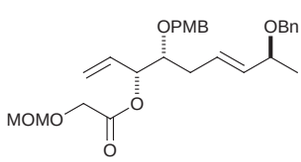



**100**

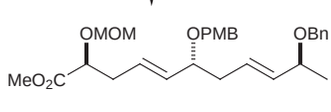
dr 96:4

**Scheme 28**



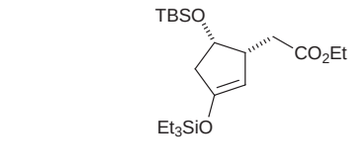




1. LDA, $Me_3SiCl$
2. warm
3. $CH_2N_2$




**Scheme 29**

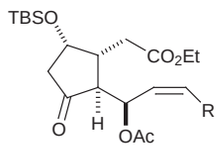
of **112**, and the completely stereoselective formation of the *E* alkene, the other stereogenic centre formed in this reaction was also controlled.



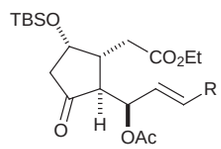

**105**

1. OHC–⁄⁄–R
$TiCl_4$
2. acetylate

1. OHC–⁄⁄–R
$TiCl_4$
2. acetylate



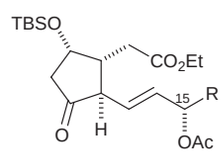

**106**



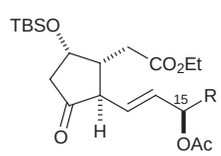

**108**

cat. $Pd(MeCN)_2Cl_2$

cat. $Pd(MeCN)_2Cl_2$

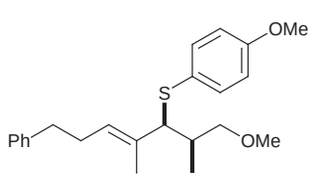



**107**



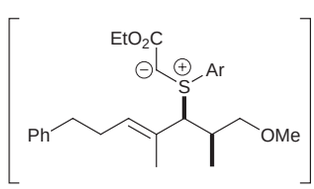

**109**

**Scheme 30**

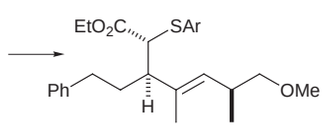



**110**

1. $N_2CHCO_2Et$ (1.6 eq.)
$HBF_4$, –50 °C
2. DBU (2.7 eq.)
3. HCl




**111**

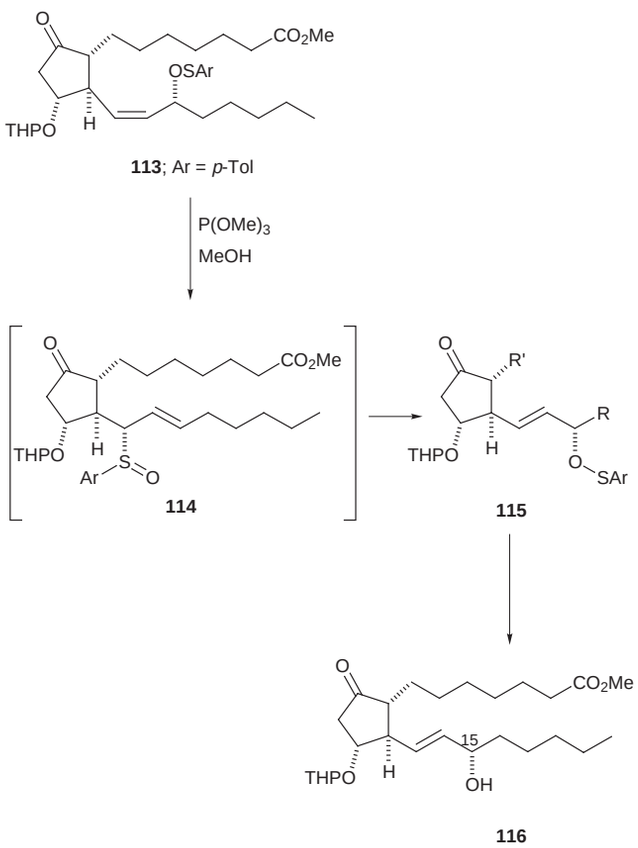



**112**

**Scheme 31**

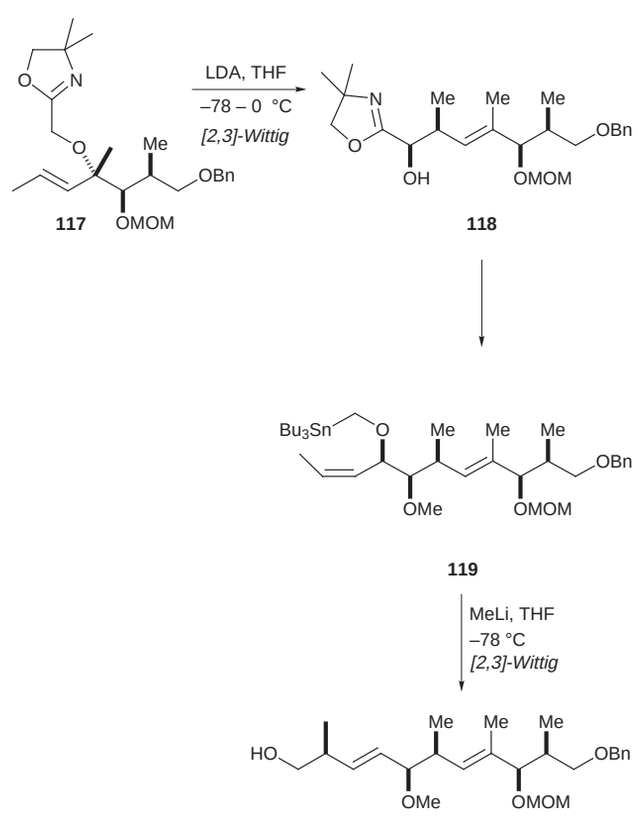
The suprafacial and *E*-selective nature of many rearrangements of *E*- and *Z*-allylically functionalised molecules can be exploited in the control of remote stereochemistry (see Scheme 32 for an example). A remarkable double rearrangement has been used to control the stereochemistry of the C-15 stereogenic centre in prostaglandins (Scheme 32); the synthesis exploits the rearrangement of the sulfenate **113** to the sulfoxide **114** and rearrangement of the sulfoxide **114** back to C-15 (→**115**→**116**).[66,67] In this series of reactions, the C-15 stereogenic centre and the geometry of the alkene are both inverted. In a sense, though, this work is peculiar; an existing 1,4 chiral relationship (in **113**) (and one across a *Z* double bond at that!) has been transformed into another 1,4 relationship across an *E* double bond (in **116**).

The most widely used [2,3]-sigmatropic rearrangement in the synthesis of molecules with 1,4-related stereogenic centres across a double bond is undoubtedly the [2,3]-Wittig rearrangement.[68] An example which involves two rearrangements and is



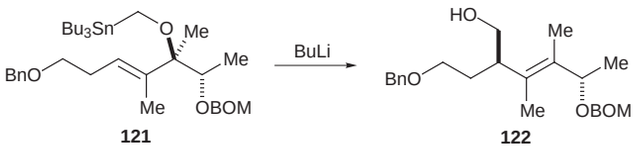

**Scheme 32**

part of a formal synthesis of macbecin I, is shown in Scheme 33.[5e,f] This methodology has also been applied in the synthesis of *E*-alkene dipeptide isosteres[69] and fragments of rapamycin,[70] herbimycin A[71] and zincophorin.[72]




**Scheme 33**

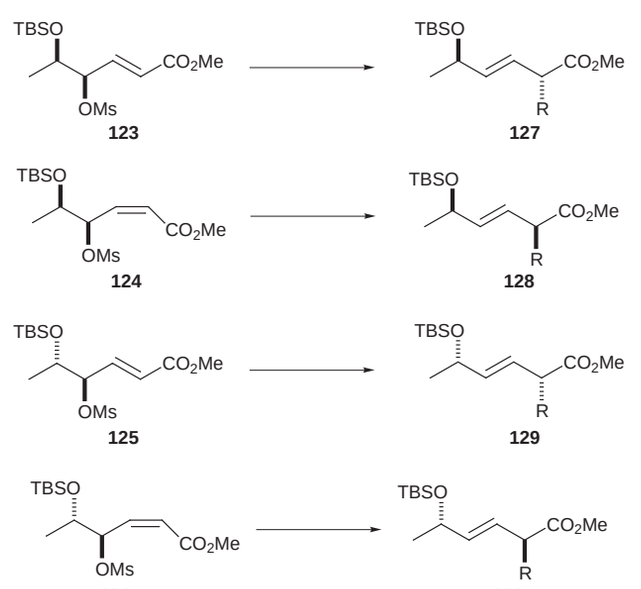
The stereocontrolled synthesis of *tetrasubstituted* double bonds is a particularly difficult challenge in organic synthesis. Kallmerten has demonstrated that, in certain cases, good levels of control of tetrasubstituted double bond geometry can be obtained in the [2,3]-Wittig rearrangement.[73] Mulzer has developed this concept one stage further in what is probably the first stereocontrolled synthesis of molecules possessing 1,4-related stereogenic centres across a tetrasubstituted double bond (Scheme 34).[74]



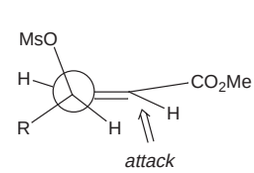

**Scheme 34**

The nucleophilic substitution reactions of organocopper and organozinc reagents generally proceed with high levels of *E*-stereoselectivity and *anti* $S_N2'$ stereospecificity and can provide a useful tool for establishing 1,4 stereochemical relationships. Considerable flexibility can be built into syntheses by careful choice of the stereochemistry of the starting materials.[75] For example, γ-mesyloxy-α,β-enoates **123**–**126** underwent highly regio- and stereoselective $S_N2'$ reactions (Scheme 35) with organocopper–$BF_3$ complexes[76] and all four stereoisomeric precursors of *E*-alkene dipeptide isosteres **127**–**130** could be prepared in this way.[77] The stereochemical course of these reactions can be explained in terms of stereospecific attack of the cuprate reagent *anti* to the leaving group on the conformation in which 1,3-allylic strain[44] is minimised (Fig. 9). This approach has been used widely in the preparation of *E*-alkene dipeptide isosteres[77–79] and β-turn promoters.[79]

A stereodivergent approach has been applied to the classic problem of controlling the C-15 stereogenic centre in prostaglandin synthesis. Addition of heptynylcerium dichloride to

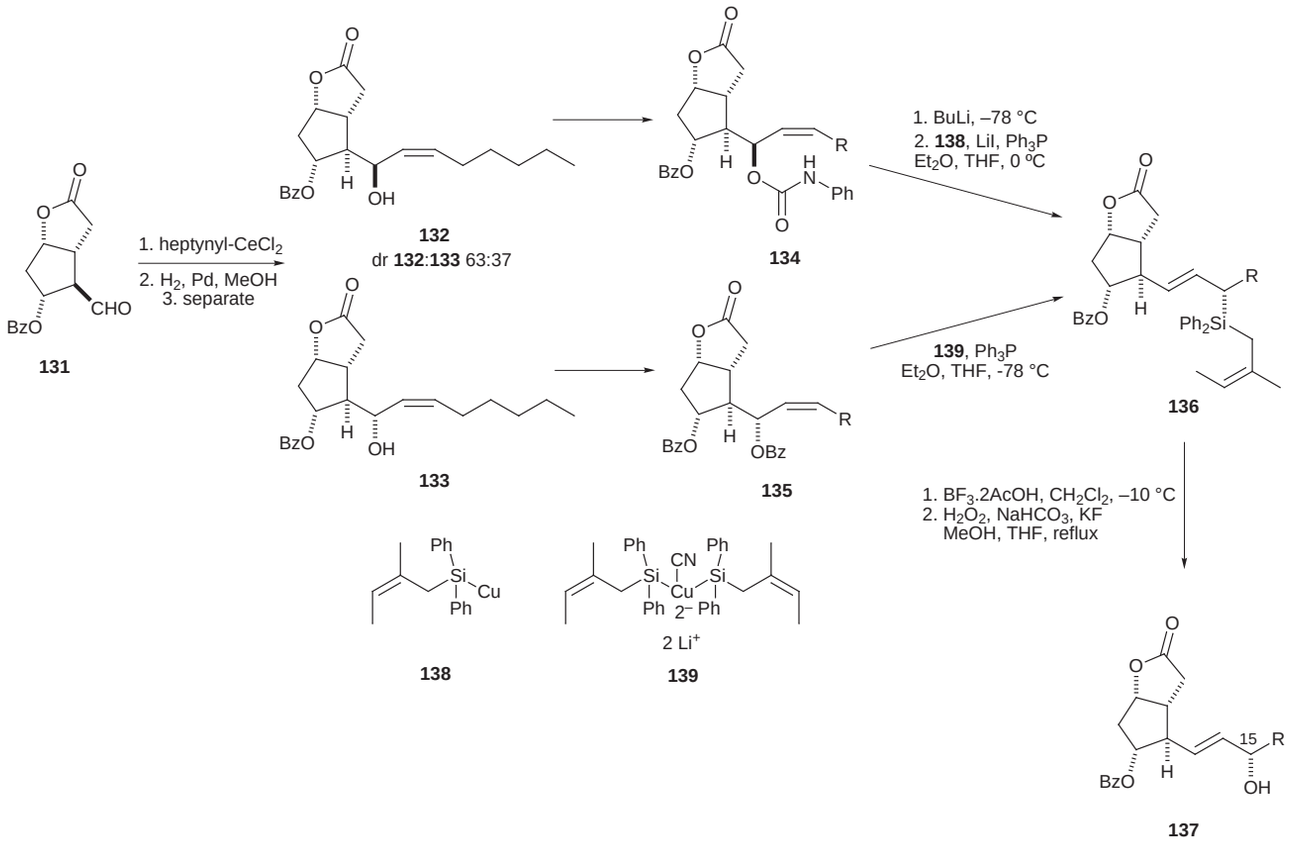



**Scheme 35**




**123** ⟶ **127**

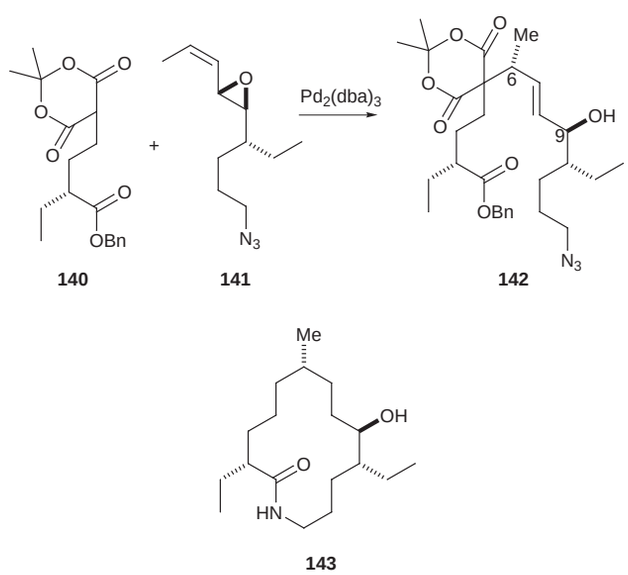
**Fig. 9**




**Scheme 36**

the aldehyde **131** was only moderately stereoselective (Scheme 36); the alkynes were reduced using Lindlar's conditions to give the alcohols **132** and **133** which were separable.[80] Fleming converted the alcohol **133** into the benzoate **135** and the alcohol **132** into the carbamate **134**; substitution of the benzoate **135** with the silyl cuprate **138** was *anti* stereospecific but the reaction of **139** with the anion of **134** was *syn* stereospecific. In this way, both diastereoisomers **132** and **133** were converted into the silane **136** and hence into the prostaglandin intermediate **137**.[81]

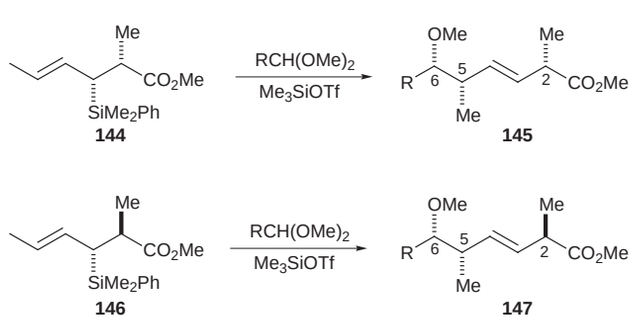
Palladium(0)-catalysed allylic substitution reactions are another valuable tool in the control of 1,4-related stereogenic centres across alkenes and these reactions generally proceed with excellent *syn* stereospecificity. For example, *syn*-stereospecific substitution of the *Z*-vinyl oxirane **141** with the malonate **140** proceeded with excellent regioselectivity to give the allylic alcohol **142**, an intermediate in the synthesis of Fluviricin B1 (**143**), with an *anti* relationship between the C-6 and C-9 stereogenic centres (Scheme 37).[82] Palladium-catalysed allylic Mitsunobu displacements have been used in the synthesis of isomers of hepoxilin $A_3$ and trioxilin $A_3$.[83]




**Scheme 37**

The *anti* stereospecificity and $S_E2'$ regiospecificity of the electrophilic substitution reactions of allylic silanes[81] have been exploited by Panek in the synthesis of homoallylic amines[84] and homoallylic ethers with remote stereogenic centres. The reaction of the allylic silanes **144** and **146** with oxonium ions proceeded with excellent *anti* stereospecifity (*anti* attack : *syn* attack 98 : 2) and with good facial selectivity ($^{5,6}$*syn* : $^{5,6}$*anti ca.* 96 : 4) on the oxonium ion (Scheme 38, Fig. 10);[85] here, the relative ease with which 1,2-stereochemistry can be controlled, and then transposed, allowed the synthesis of both $^{2,5}$*syn* and $^{2,5}$*anti* diastereoisomers **145** and **147**.

In this section, we have described a number of different 1,3 chirality transfer methods and many of these methods provide stereoselective routes to different combinations of *syn* and *anti* diastereoisomers with remote stereogenic centres across a




**Scheme 38**

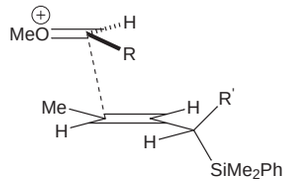
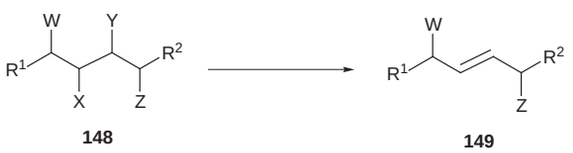



**Fig. 10**

double bond. Nonetheless, the vast majority of the methods outlined provide stereocontrolled access to *E* isomers only; the formation of *Z* isomers is possible, however, in a few exceptional—and generally—unpredictable cases.

## 6 Strategy E: the contiguous stereogenic centres strategy

The contiguous stereogenic centres strategy, like the chirality transfer strategy, relies on the fact that there are many reliable methods for 1,2 asymmetric induction. As the name suggests, the strategy involves the sterecontrolled introduction of four contiguous stereogenic centres. The middle two are then converted, typically by a stereospecific process, into a double bond of defined (and predictable) geometry (Scheme 39, Strategy E).




**Scheme 39** Strategy E: the contiguous chiral centres strategy.

An interesting example of the contiguous stereogenic centres strategy is outlined in Scheme 40.[86] The addition of Grignard reagents to the hemiacetals **150** gave the diols **151** with excellent diastereoselectivity; this reaction has been explained in terms of the chelated transition state shown in Fig. 11. Then, retro Diels–Alder reaction removed the central two stereogenic centres of **151** to give the *Z* alkene **152** with its $^{1,4}$*syn*-related stereogenic centres. A feature of the strategy was that the conditions used to synthesise **150** could be tuned, allowing the synthesis of its diastereomer **153** and hence the $^{1,4}$*anti* diol **154** as well. The products from this sequence have been used in the synthesis of (+)-pyrrolidine 197B[87] and (+)-indolizidine 195B.[88]

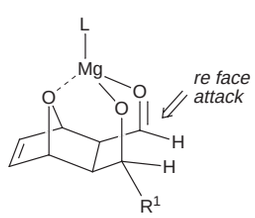
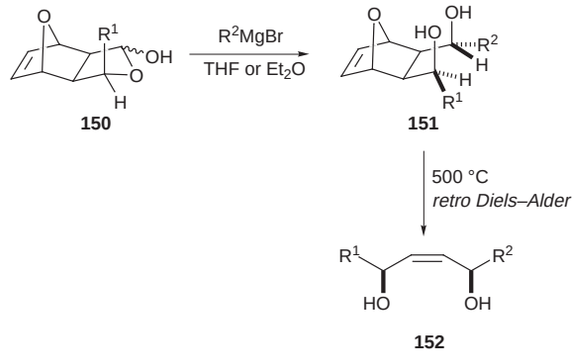
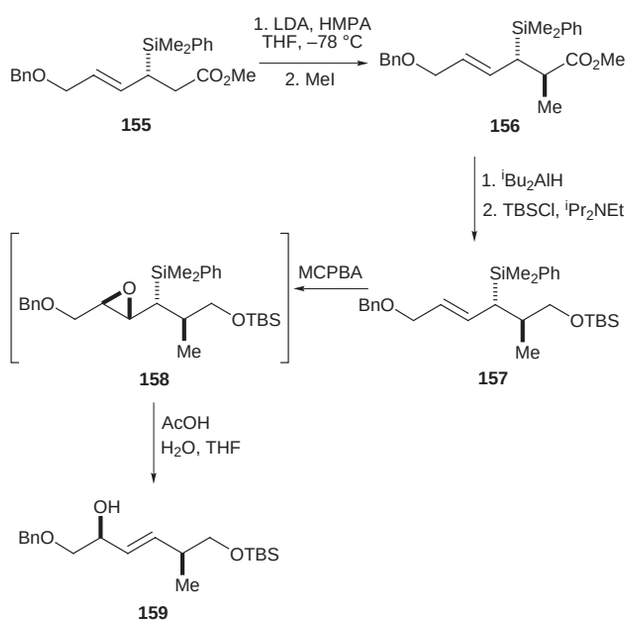



**Fig. 11**

Allylic silanes have been used widely in stereoselective synthesis in general[81] and have been expoited in the contiguous stereogenic centres strategy (Scheme 41).[89] Alkylation of the enolate of the optically-active silane **155**, *anti* to the silyl group, gave the ester **156** with high diastereoselectivity.[90] The silyl group was then used again to control the epoxidation of **157** to give the epoxide **158**. The middle two stereogenic centres of **158** were removed stereospecifically using an *anti*-stereospecific acid-catalysed Peterson elimination yielding the allylic alcohol **159**. An exceptionally useful feature of the Peterson reaction is that the elimination can often be induced in either stereochemical sense,[91] allowing *either* double bond isomer to be made from the *same* starting material.




**Scheme 40**

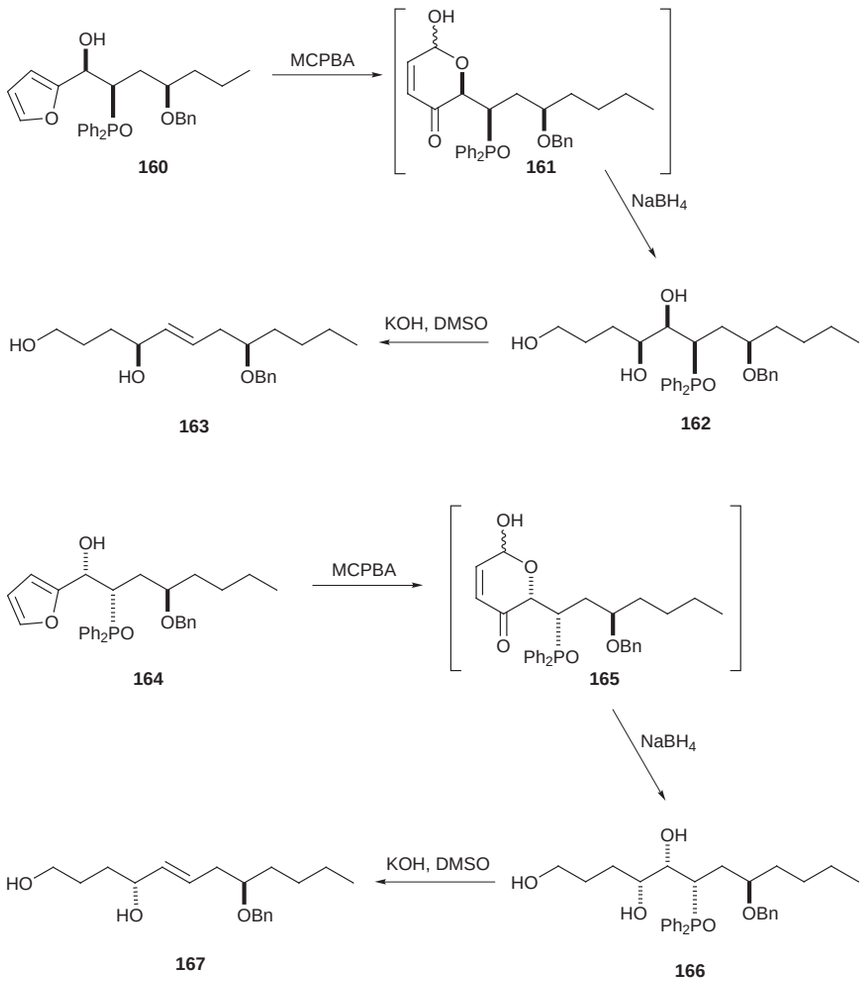



**Scheme 41**

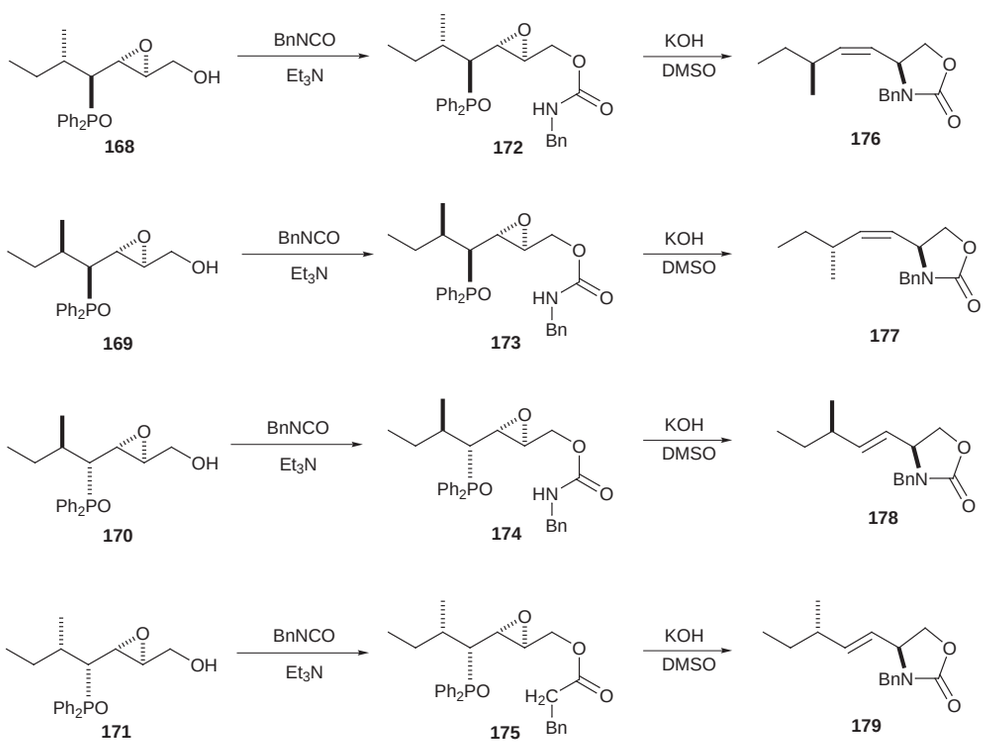
The diphenylphosphinoyl group is an exceptionally effective stereodirecting group in organic synthesis[36] and we have applied phosphine oxide chemistry to the synthesis of racemic allylic alcohols[92] and allylic sulfides[93] with 1,4-related stereogenic centres across double bonds of fixed configuration. The flexible nature of phosphine oxide chemistry allowed the synthesis of all four diastereoisomers of **160** using the Sharpless asymmetric dihydroxylation reaction[22] to introduce the asymmetry.[94] The furyl alcohols **160** and **164** were oxidised to the enones **161** and **165** and reduced to give the triols **162** and **166** as single diastereoisomers (Scheme 42). *E*-Selective Horner–Wittig elimination of **162** and **166** gave the *E*-alkenyl diols **163** and **167** with 1,5-related stereogenic centres.

The first *general* stereocontrolled synthesis of molecules bearing 1,4-related stereogenic centres across a double bond used the contiguous stereogenic centres strategy to control the remote stereochemistry (Scheme 43).¶[95] We used a combination of Sharpless kinetic resolution[96] and diastereoselective epoxidation[97] with MCPBA to synthesise the epoxides **168**–**171** stereoselectively. Then, transformation of the alcohols **168**–**171** into the urethanes **172**–**175**, and stereospecific tandem

¶ More recently, Rich has reported the stereocontrolled synthesis of all four stereoisomers of an alkene dipeptide isostere using a combination of 1,4-asymmetric induction and [2,3]-Wittig rearrangement.[69a]




**Scheme 42**




**Scheme 43**

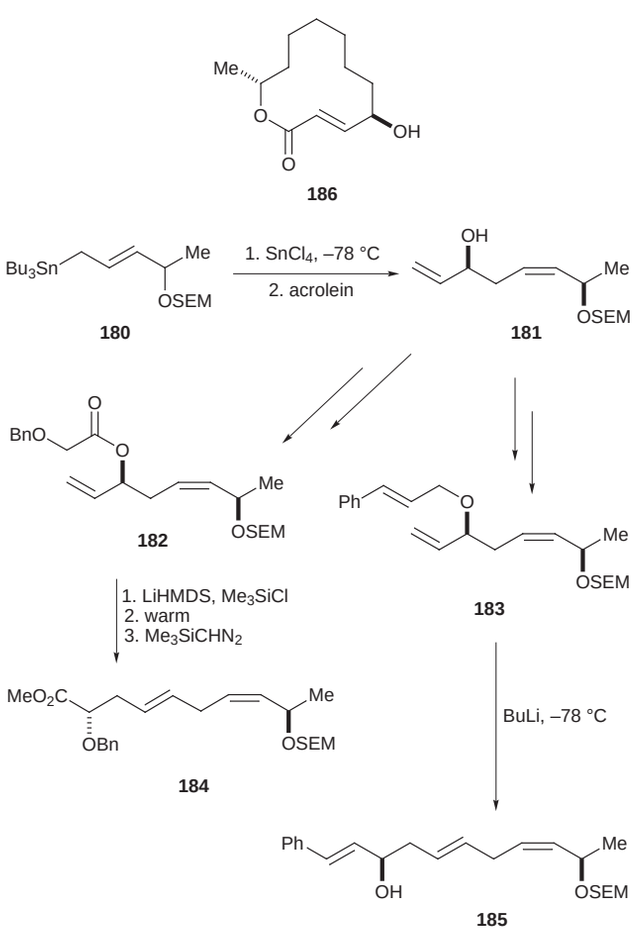
ring-opening–Horner–Wittig elimination gave the alkenyl oxazolidines **176**–**179**. In **176**–**179**, we have all four possible stereoisomers in one enantiomeric series and their enantiomers are clearly available simply by using D-(−)-dialkyl tartrate in the kinetic resolution. A weakness of this work was that an HPLC separation was needed at an early stage in the synthesis and

that kinetic resolutions can only give a 50% maximum yield of each of the products.

These examples clearly illustrate how powerful the contiguous stereogenic centres strategy can be when a flexible, stereoselective synthesis of compounds with remote stereochemistry across a double bond is required. This flexibility stems from the *stereospecific* elimination reactions which are available to remove the middle two stereogenic centres in the olefination step. The strategy can equally well be used in the synthesis of homochiral and racemic molecules.

## 7 Combined use of more than one strategy

Recently, Thomas has reported two examples of 1,8-stereocontrol across two double bonds of fixed configuration and the products were converted into the macrolactone Patulolide C (**186**) and its epimer (Scheme 44).[98] In this remarkable piece of work, *two* different strategies for remote stereocontrol—substrate control and chirality transfer—were exploited. Transmetallation of the stannane **180** and reaction with acrolein, gave the allylic alcohol **181** as a *ca*. 95 : 5 mixture of diastereoisomers. The $^{1,5}$*syn*-relationship of **181** could be transformed into either the $^{1,8}$*anti* ester **184** or the $^{1,8}$*syn* alcohol **185** (which were precursors of racemic Patulolide C and its epimer respectively) using either an Ireland–Claisen or a [2,3]-Wittig rearrangement. This study highlights both the inflexibility of remote asymmetric induction by substrate control—only the $^{1,5}$*syn* isomer **181** could be made using the tin chemistry—and the versatility offered by the chirality transfer strategy—**181** could be converted into either diastereoisomer of Patulolide.




**Scheme 44**

## 8 Summary

This review has grouped the methods available for remote asymmetric induction across double bonds of controlled geometry according to the underlying strategy used in each case. In this way, we have been able to highlight the positive and negative points of each of the strategies. Stategies A and B—the coupling of chiral fragments and the use of chiral reagents—differ only in the order of the steps; these strategies are excellent approaches to the synthesis of optically active molecules and work well provided that double bond geometry can be controlled and that good methods are available for the introduction of the stereogenic centres. It is remarkable that remote asymmetric induction by substrate control (Strategy C) is possible at all and these methods are generally limited to the only one of the possible stereoisomers. Strategies D and E—chirality transfer and the contiguous stereogenic centres strategy—both take advantage of the fact that close stereochemical relationships are easier to control than remote ones. The allylic transposition reactions exploited by Strategy D are generally *E*-selective, so it is only generally possible to make the diastereoisomers with remote stereogenic centres across an *E* double bond. The contiguous stereogenic centres strategy (Strategy E) is, on the other hand, the best approach if all possible stereoisomers (*syn*/*anti*; *E*/*Z*) are required.

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