# Stereoselective and Stereospecific Olefin Synthesis

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## 1 Introduction

The successful synthesis of many complex organic molecules often hinges on the selective introduction of a carbon–carbon double bond at a specific position and with a known configuration. The magnitude of the problem increases when more than one isolated double bond is present within the system and if the linkages are highly substituted. Such problems were highlighted by Cornforth,[1] who developed the first rational synthesis of all-*trans*-squalene (6).[2] Despite the high degree of control attained in each step of the work, the final product contained only 30—40% of the desired geometric isomer.

In recent years, a variety of new reactions have been employed to bring about the introduction of double bonds in a controlled, stereospecific or highly stereoselective manner. This Review attempts to survey these methods. Despite recent advances in the mechanistic interpretation of classical elimination reactions (*E*1, *E*2, and thermal eliminations)[3] *control* is often difficult, and therefore such reactions are excluded. Electrocyclic and sigmatropic processes have been reviewed recently,[4] and therefore only those reactions developed especially for the introduction of double bonds are exemplified.

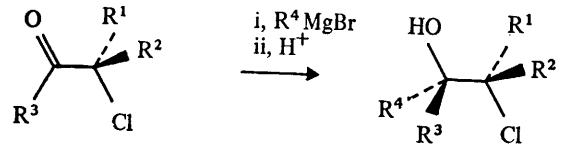
The terms stereoselective and stereospecific are used in the following sense. Stereospecific reactions are those in which stereoisomerically different starting materials each give stereoisomerically different products.[5a] Stereoselective reactions are those in which one, of two or more possible stereoisomeric products, is preferred. Thus stereospecific processes must be *completely* stereoselective.[5b] To avoid confusion of terms, eliminations are referred to as proceeding either in a *syn*- or *anti*-manner,[6] and olefin configurations are expressed as *cis* or *trans*, using the priority rules recently formulated for the *E* (entgegen, *trans*) and *Z* (zusammen, *cis*) convention.[7] Pertinent related reviews include those by Brachel

[1] J. W. Cornforth, R. H. Cornforth, and K. K. Mathew, *J. Chem. Soc.*, 1959, 112.
[2] J. W. Cornforth, R. H. Cornforth, and K. K. Mathew, *J. Chem. Soc.*, 1959, 2539.
[3] D. V. Banthorpe, 'Elimination Reactions', Elsevier Publishing Co., Inc., New York, 1963.
[4] R. B. Woodward, 'Aromaticity', Special Publication No. 21, The Chemical Society, London, 1967, p. 217; R. B. Woodward and R. Hoffmann, *Angew. Chem. Internat. Edn.*, 1969, **8**, 781; G. B. Gill, *Quart. Rev.*, 1968, **22**, 338.
[5] (*a*) H. E. Zimmerman, L. Singer, and B. S. Thyagarajan, *J. Amer. Chem. Soc.*, 1959, **81**, 108; (*b*) E. L. Eliel, 'Stereochemistry of Carbon Compounds', McGraw-Hill, New York, 1962, p. 434.
[6] W. Klyne and V. Prelog, *Experientia*, 1960, **16**, 521; *cf.* J. Sicher and J. Zavada, *Coll. Czech. Chem. Comm.*, 1968, **33**, 1278.
[7] J. E. Blackwood, C. L. Gladys, K. L. Loening, A. E. Petrarca, and J. E. Rush, *J. Amer. Chem. Soc.*, 1968, **90**, 509.

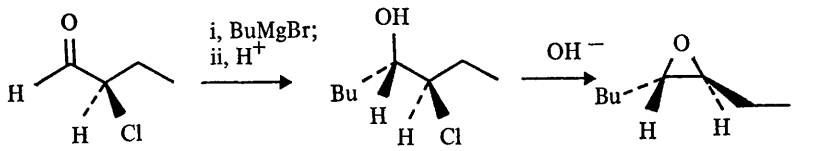
and Bahr,[8a] and Eliel.[8b] The volumes edited by Patai[8c] and Zabicky[8d] contain much useful information.

## 2 Syntheses from Carbonyl Compounds

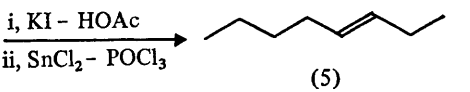
**A. The Cornforth Synthesis.**—In 1959, Cornforth[1] proposed that the most favourable conformation of α-chlorocarbonyl compounds during Grignard additions is that with the carbonyl and chlorine groups in an *anti*-periplanar disposition (1).[6] Addition would thus be expected from the least hindered side,[9] to give only one chlorohydrin (2). In fact, the chlorohydrin produced from 2-chlorobutanal (3)




(1) $R^2 > R^1$ (2)




(3) (4)

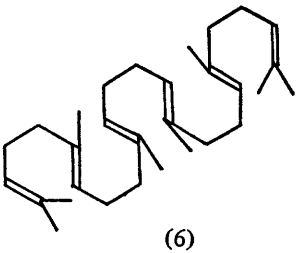



(5)

and butylmagnesium bromide gave the *trans*-epoxide (4), with over 70% selectivity, after treatment with base. The resulting epoxide could be deoxygenated completely stereospecifically to give the olefin (5) by a two-step reductive elimination. Reaction of the epoxide with sodium iodide in buffered acetic acid gave the iodohydrin, which could be reduced with stannous chloride in pyridine containing phosphorus oxychloride. The reaction was applied to a synthesis of all-*trans*-squalene (6).[2] Recently, Johnson has improved the selectivity of the

[8] (*a*) H. von Brachel and U. Bahr, 'Methoden der Organischer Chemie', 4th edn., ed. E. Müller, Georg Thieme Verlag, Stuttgart, 1970, vol. 5/1c; a chapter on the preparation of olefins is in preparation in vol. 5/1b; (*b*) E. L. Eliel, 'Stereochemistry of Carbon Compounds', McGraw-Hill, New York, 1962; (*c*) 'The Chemistry of Alkenes', ed. S. Patai, Wiley–Interscience, New York, 1962; (*d*) 'The Chemistry of Alkenes', ed. J. Zabicky, Wiley–Interscience, New York, 1970.

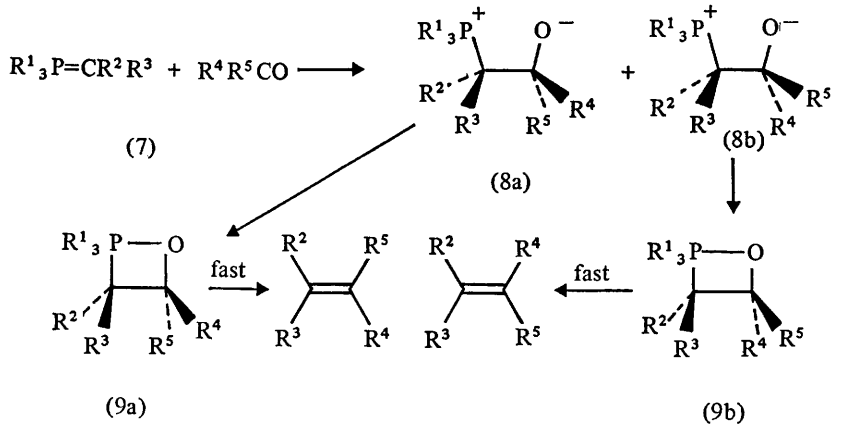
[9] D. J. Cram and F. A. Abd Elhafez, *J. Amer. Chem. Soc.*, 1952, **74**, 5828.



(6)

Cornforth Synthesis to over 90% by the simple expedient of conducting the Grignard reactions at lower temperatures (− 70 to − 90 °C).[10]

**B. The Wittig Reaction.**[11]—In its original form,[12] little steric control was possible over the Wittig reaction,[13] but subsequent investigations on the mechanism have revealed ways for controlling the selectivity of the reaction. The principal course of the reaction under various conditions is summarised in the Table. The reaction has mainly been applied to the preparation of disubstituted olefins; tri- and tetra-substituted olefins are produced in lower yields with lower selectivity. The reaction has been considered to proceed in three steps.[14] Addition of a phosphorane (7) to an aldehyde (or ketone) forms an intermediate betaine (8). Phosphorus–oxygen bond formation then occurs, followed by rapid collapse of

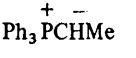



**Scheme 1**

[10] S. F. Brady, M. A. Ilton, and W. S. Johnson, *J. Amer. Chem. Soc.*, 1968, **90**, 2882.
[11] A. Maercker, *Org. Reactions*, 1965, **14**, 270; U. Schöllköpf, *Angew. Chem.*, 1959, **71**, 260; S. Trippett, *Quart. Rev.*, 1963, **17**, 406; L. L. Muller and J. Hamer, '1,2-Cycloaddition Reactions', Interscience, New York, 1967, p. 305.
[12] G. Wittig and G. Geissler, *Annalen*, 1953, **580**, 44.
[13] G. Wittig, H.-D. Weigmann, and M. Schlosser, *Chem. Ber.*, 1961, **94**, 676.
[14] A. W. Johnson, 'Ylid Chemistry', Academic Press, New York, 1966.

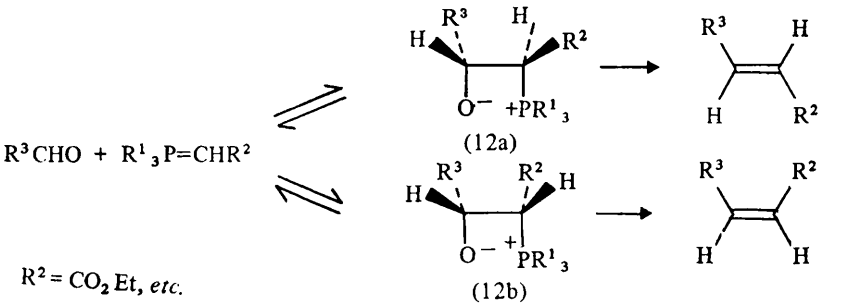
the oxaphosphetan intermediate (9) by *syn*-elimination to form the *cis*- or *trans*-olefin (Scheme 1). Certain trends of the reaction were soon established. Thus resonance-stabilised phosphoranes, *e.g.* (10), give predominantly *trans*-products.[15] In contrast, non-stabilised phosphoranes, *e.g.* (11), react to form predominantly *cis*-olefins.[16]

(10)



(11)

For resonance-stabilised alkylidenephosphoranes, kinetic studies have shown a slow, but reversible, formation of the betaine (8), hence allowing interconversion to the thermodynamically favoured form, followed by faster collapse of this intermediate to products.[17] Under these conditions, aldehydes react with preferential formation of *threo*-betaines [*e.g.* (12a), Scheme 2]. If the elimination of



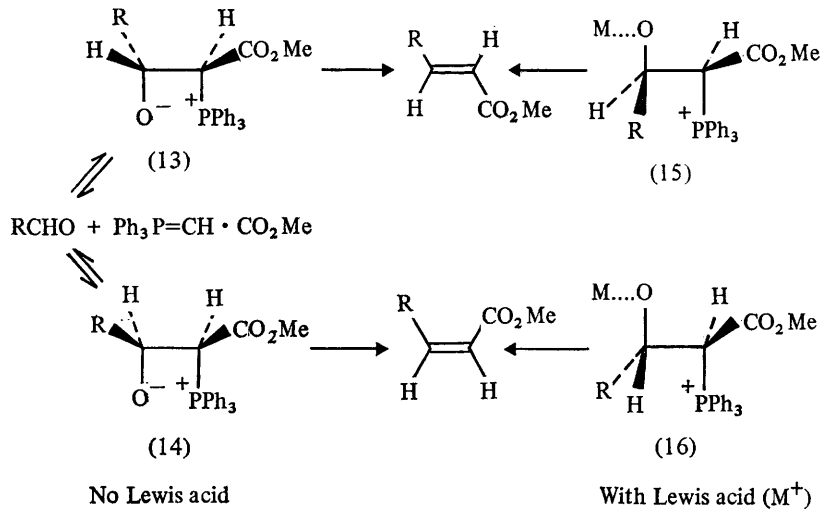
**Scheme 2**

phosphine oxide is slowed down, the intermediate betaine has a greater chance of equilibrating to the most stable isomer (12a ⇌ 12b), hence giving increased proportions of the *trans*-olefin. This has been achieved by varying the phosphorus substitution. Tricyclohexylphosphine has lower electrophilicity compared to triphenylphosphine, and greater selectivity for *trans*-alkene formation is observed.[18]

In the presence of protic solvents or Lewis acids such as lithium salts, the

[15] H. O. House and G. H. Rasmusson, *J. Org. Chem.*, 1961, **26**, 4278; R. Ketcham, D. Jambotkar, and L. Martinelli, *J. Org. Chem.*, 1962, **27**, 4666; A. W. Johnson and V. L. Kyllingstad, *J. Org. Chem.*, 1966, **31**, 334.
[16] M. Schlosser and K. F. Christmann, *Annalen*, 1967, **708**, 1.
[17] A. J. Speziale and D. E. Bissing, *J. Amer. Chem. Soc.*, 1963, **85**, 1888, 3878.
[18] H. J. Bestmann and O. Kratzer, *Chem. Ber.*, 1962, **95**, 1894.

amount of *trans*-olefin formed from stabilised alkylidenephosphoranes is decreased, more of the *cis*-isomer being produced.[19] This effect is a result of co-ordination of the oxygen atom of the intermediate betaine with the acid. One or two factors could increase the amount of *cis*-product (Scheme 3). Firstly, the

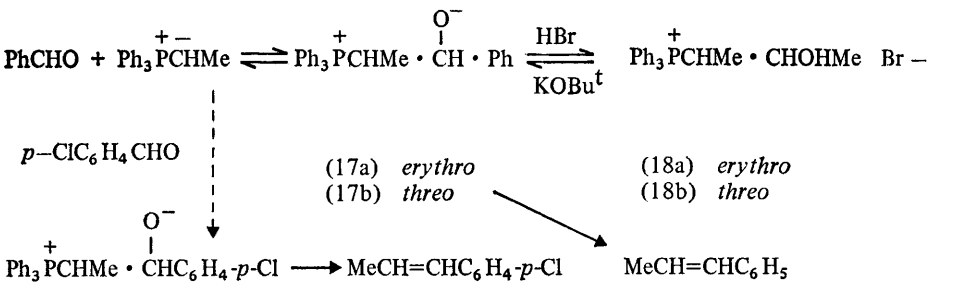



**Scheme 3**

interconversion of (15) and (16) would be slower than equilibration between the uncomplexed betaines (13) and (14), and hence, if the relative rates of decomposition of the complexed and uncomplexed betaines are similar, the reaction would be less stereoselective in the presence of Lewis acids. Furthermore, the concentration at equilibrium between (13) and (14) would not be expected to be the same as that between (15) and (16). In the uncomplexed pair, the charged groups would tend to prefer *syn*-periplanar conformations by electrostatic attraction, hence favouring the *threo*-isomer (13) and leading to *trans*-olefin. In the complexed state, an *anti*-periplanar conformation would be anticipated for (15) and (16), and little preference between these conformers would be expected, giving increased (but not favoured) formation of the *cis*-olefin.

The above arguments refer to stabilised phosphoranes only, and take no account of the effect of stereochemistry about the phosphorus atom, shown to be maintained throughout the reaction.[20] Non-stabilised phosphoranes, which constitute the majority of Wittig reagents,[13] behave in a completely different sense from stabilised phosphoranes. For these, addition to the carbonyl group is

[19] H. O. House, V. K. Jones, and G. A. Frank, *J. Org. Chem.*, 1964, **29**, 3327.
[20] A. Bladé-Font, W. McEwen, and C. A. VanderWerf, *J. Amer. Chem. Soc.*, 1960, **82**, 2646, 2396.




**Scheme 4**

rapid (Scheme 1), although still reversible, but further collapse of the betaine to give olefin is often slow. Also, the *cis*-olefin is preferred. That the formation of the betaine is reversible has been demonstrated by Schlosser and Christmann, who carried out exchange reactions with different aldehydes (Scheme 4).[21] They found that benzaldehyde reacted with the ylide (11) to give a mixture of the *threo*- and *erythro*-betaines (17). Addition of hydrobromic acid afforded the corresponding, stable, protonated betaines (18), which could be separated. The *erythro*-isomer (18a) was treated with one equivalent of potassium t-butoxide to regenerate the betaine (17a), which rapidly re-equilibrated, with the *threo*-isomer predominating. Addition of *p*-chlorobenzaldehyde to the betaine generated in this manner also afforded the *p*-chlorosubstituted methyl styrene as final product, proving reversibility of betaine formation.

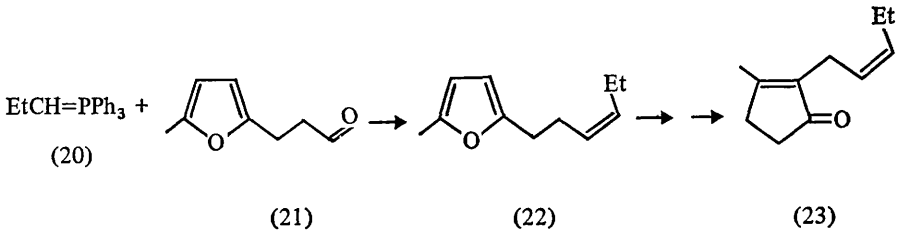
Quenching of the intermediate betaine, *e.g.* (17), could also be achieved by addition of lithium bromide to the reaction mixture, and again complexes (19)

$$\left[ Ph_3\overset{+}{P} \cdot CHR^1 \cdot CHR^2OLi \right] X^-$$

(19)

were isolated. As above, the complexes were reconverted into betaine by potassium t-butoxide. This quenching process allows considerable control of the reaction. The betaines from non-stabilised phosphoranes lose most of their reactivity (to give olefins) when lithium salts are added, whereas olefin formation is complete within a few minutes in the presence of potassium t-butoxide. When the ylides were reacted under salt-free conditions, *i.e.* no lithium bromide, *etc.* present,[22] kinetic control of the reaction was observed, and *cis*-olefins, produced *via* the *erythro*-betaine, were formed with high selectivity (> 90%). In this way,

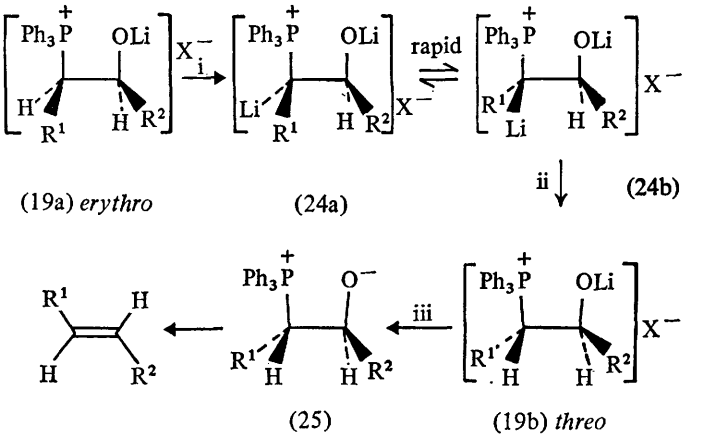
[21] M. Schlosser and K. F. Christmann, *Angew. Chem. Internat. Edn.*, 1965, **4**, 689; 1964, **3**, 636.
[22] H. J. Bestmann, *Angew. Chem. Internat. Edn.*, 1965, **4**, 583; G. Wittig, H. Eggers, and P. Duffner, *Annalen*, 1958, **619**, 10.




(21) (22) (23)

for example, the precursor (22) of *cis*-jasmone (23) could be prepared specifically from the Wittig reaction between the phosphorane (20) and the aldehyde (21).[23]

To obtain *trans*-olefins, Schlosser and co-workers adopted the following procedure (the Wittig–Schlosser reaction) (Scheme 5).[24] Lithium salts were added to inhibit elimination of the intermediate betaine to olefin. The salts formed (19) could be reacted further with butyl-lithium to form an anion (24). Although the




Reagents: i, PhLi; ii, $Bu^tOH$; iii, $KOBu^t$

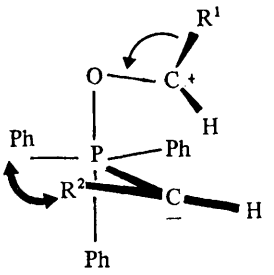
**Scheme 5**

initial *erythro*-complex (19a) was relatively stable to inversion, the anion (24) rapidly equilibrated between the two forms with the *threo*-isomer predominating. On protonation with t-butanol and reactivation with potassium t-butoxide (which is desirable but not essential) almost pure *trans*-olefin was produced from the *threo*-betaine (25).

The preferential formation of the *erythro*-betaine from non-stabilised phos-

[23] L. Crombie, P. Hemesley, and G. Pattenden, *J. Chem. Soc.* (*C*), 1969, 1016, 1024.
[24] (*a*) M. Schlosser, G. Müller, and K. F. Christmann, *Angew. Chem. Internat. Edn.*, 1966, **5**, 667; (*b*) M. Schlosser and K. F. Christmann, *ibid.*, p. 126; (*c*) see ref. 16.

phoranes under salt-free conditions requires explanation since, at first sight, this would appear to be more sterically hindered than the *threo*-isomer. Furthermore, it is observed that the *more* bulky the aldehyde component, the *greater* the selectivity for *cis*-olefin formation.[25] In order to explain these effects, Schneider[26] has considered the importance of the substituent configuration about the phosphorus atom during reaction, assuming, for unstabilised ylides, the preferential co-ordination of the carbonyl oxygen to phosphorus *before* carbon–carbon bond formation. Thus structure (26), with oxygen in the apical position and with the ylide carbon equatorial (necessary for bond formation with the aldehyde), is the one in which the aldehyde group is in the least sterically hindered position. The bulky aldehyde group $R^1$ is initially in a vertical plane away from the phosphorus substituents; $R^2$ would interact with the adjacent phenyl groups in its trisection and hence $R^2$ is distorted away from the phosphorus, as in (26). In order to



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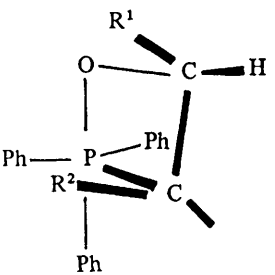
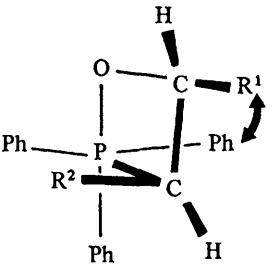
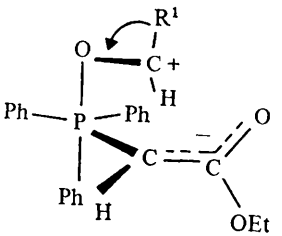


(27a)



(27b)

form the oxaphosphetan intermediate, a small rotation about the C—O bond is required. If this occurs in an anticlockwise direction, the *erythro*-configuration (27a) is achieved, in which the substituents $R^1$ and $R^2$ are eclipsed (see arrows)

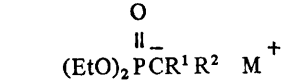


(28)

[25] U. Axen, F. H. Lincoln, and J. L. Thompson, *Chem. Comm.*, 1969, 303.
[26] W. P. Schneider, *Chem. Comm.*, 1969, 785.

but in which only one of the three phenyl groups is sterically compressed. In the alternative mode (27b) (formed by a clockwise rotation about the C—O bond), $R^1$ is not eclipsed with $R^2$, but instead serious and overriding steric compression between $R^2$ and the adjacent phenyl substituent has to be overcome and hence the former, *erythro*-form, is preferred, leading to *cis*-olefin. In the presence of polar solvents or additives which co-ordinate with the oxygen more readily than phosphorus, this mechanism need not apply. For stabilised ylides (*e.g.* with $R^2 = CO_2Et$) the aldehyde, complexed to the phosphorus, would be oriented so that the positive end would be attracted to the trisection containing the ester group, *e.g.* (28), hence leading to preferred formation of the *threo*-isomer and *trans*-olefin.

**C. Modified Wittig Reactions.**—Various extensions of the Wittig reaction have been introduced. For example, phosphonate carbanions, *e.g.* (29), also condense



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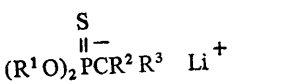
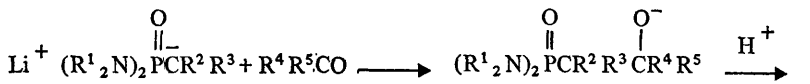


(30)

with carbonyl compounds to give olefin and phosphate ions.[27] The phosphate derivatives produced are water soluble and hence readily removed from the reaction product. *trans*-Olefins are preferentially formed.[28] Phosphonothioate esters (30) have also been used for similar purposes and again mainly give *trans*-olefins, the reactions proceeding under very mild conditions.[29] By extending these studies, the more reactive phosphonamide reagents (31) were discovered (Scheme 6).[30] These anions give adducts, *e.g.* (32), which can be easily isolated. There are several advantages of these compounds over the normal Wittig reagents, including the ability to control the stereochemistry of the intermediate $\beta$-hydroxyphosphonamide (32) by the appropriate choice of reagents for carbonyl addition. Thus, reduction of $\beta$-ketophosphonamides produced from benzoates gives the *threo*-alcohol, which yields the pure *trans*-olefin. Alternatively, the $\beta$-ketophosphonamides can be prepared by manganese dioxide oxidation of a mixture of the *threo*- and *erythro*-alcohols (32) followed by selective reduction to the *threo*-isomer. The *erythro*-adducts are obtained by crystallisation and decompose on heating to give pure *cis*-olefin. Di-, tri-, and tetra-substituted olefins can be produced by these methods as pure geometric isomers.

[27] W. S. Wadsworth and W. D. Emmons, *J. Amer. Chem. Soc.*, 1960, **83**, 1732; L. Horner, H. Hoffmann, H. Wippel, and G. Klahre, *Chem. Ber.*, 1959, **92**, 2499; H. Pommer, *Angew. Chem.*, 1960, **72**, 911; G. Wittig and U. Schöllköpf, *Chem. Ber.*, 1954, **87**, 1318.
[28] D. H. Wadsworth, O. E. Schupp, E. J. Sens, and J. A. Ford, *J. Org. Chem.*, 1965, **30**, 680.
[29] E. J. Corey and G. T. Kwiatkowski, *J. Amer. Chem. Soc.*, 1966, **88**, 5654.
[30] E. J. Corey and G. T. Kwiatkowski, *J. Amer. Chem. Soc.*, 1966, **88**, 5652, 5653; 1968, **90**, 6816; E. J. Corey and D. E. Cane, *J. Org. Chem.*, 1969, **34**, 3053.



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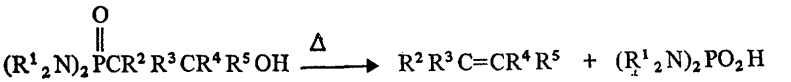

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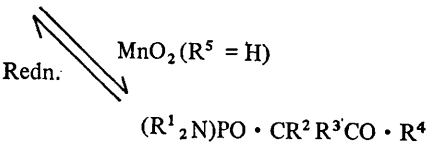
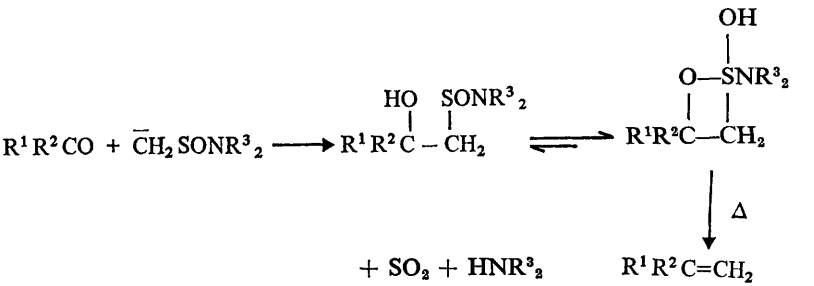


**Scheme 6**

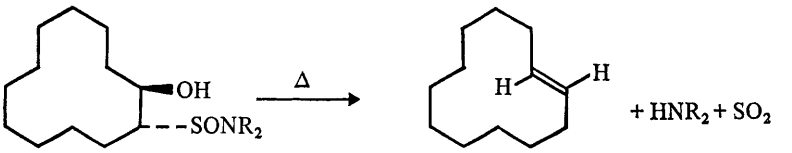


**Scheme 7**

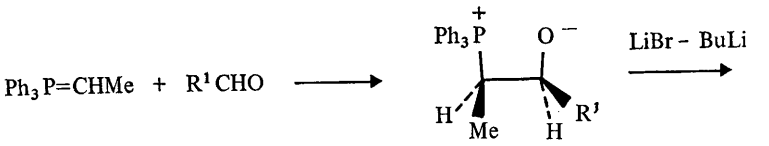
Related to the phosphonamide route is that involving sulphinamides (Scheme 7),[31] although this does not have the same synthetic scope as for phosphonamides. That *syn*-elimination occurs was demonstrated by the preparation of the *trans*-substituted hydroxysulphinamide of cyclodecane (33), which forms 95% of the *trans*-cyclodecene (34) on heating.

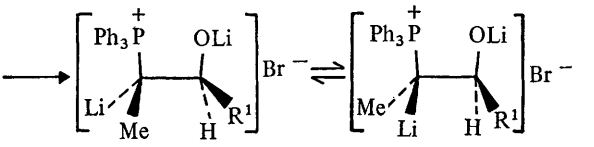
By a careful re-examination of the work of Schlosser and Christmann,[24]

[31] E. J. Corey and T. Durst, *J. Amer. Chem. Soc.*, 1966, **88**, 5656; 1968, **90**, 5548, 5553.

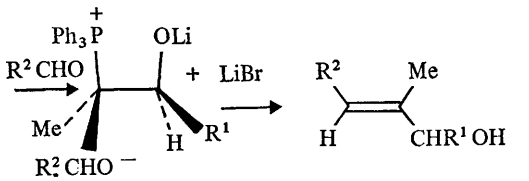



(33) (34)



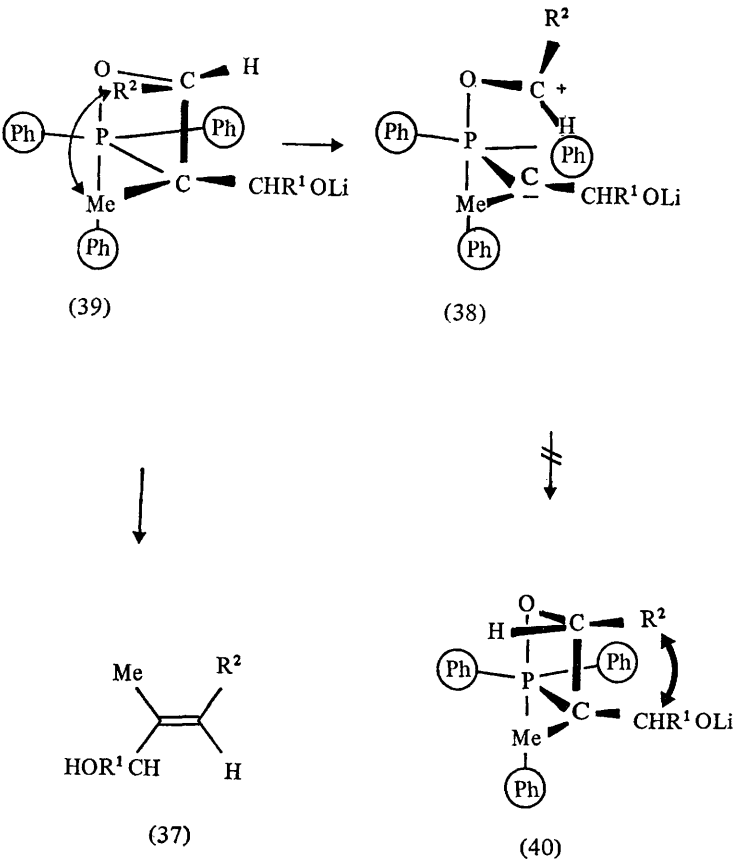

(35b) (35a)




(36)

**Scheme 8**

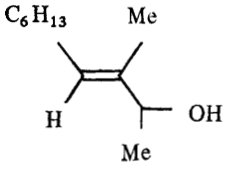
Corey has extended the normal Wittig and Wittig–Schlosser reactions to include a stereoselective method for preparing allylic alcohols. In the earlier work 'betaine ylide' intermediates (35) were made and shown to rapidly equilibrate, the *threo*-isomer (35a) predominating. Further reaction of the latter intermediate with another molecule of aldehyde gave the intermediate (36), which rapidly collapsed in a stereospecific manner to the olefin (37), in which oxygen has been lost from the *second* carbonyl moiety only (Scheme 8).[32] This addition of only the *second* aldehyde oxygen to phosphorus can also be explained in terms of



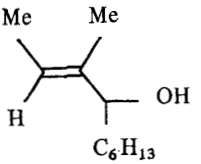

**Scheme 9**

[32] E. J. Corey and H. Yamamoto, *J. Amer. Chem. Soc.*, 1970, **92**, 226.

Schneider's mechanism,[26] in which oxygen–phosphorus bond formation precedes carbon–carbon linking to give the intermediate (38). This would prefer to react *via* formation of the oxaphosphetan (39) rather than its isomer (40) since, for the latter to form, rotation about the carbon–oxygen bond in the (clockwise) direction which compresses the substituent $R^2$ against the bulkier substituted carbon would be required (Scheme 9). The above result appears to be general. Thus reaction of the ylide (11) with acetaldehyde and then, after further betaine ylide formation, with heptanal, yields the allylic alcohol (41), whereas reaction

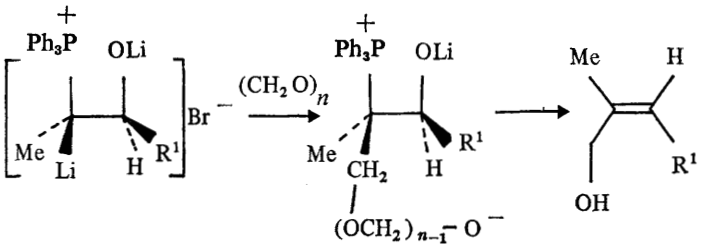



(41)




(42)

firstly with heptanal followed, in the same manner, by acetaldehyde, gave the isomeric allylic alcohol (42). The selectivity of the reaction decreases at higher temperatures. In contrast to the above cases, reaction of the betaine ylide (35) with paraformaldehyde gives mainly the product with the oxygen from the *first* aldehyde function lost. With paraformaldehyde, which doesn't contain a free carbonyl group, phosphorus–oxygen bond formation cannot occur initially, and hence it behaves rather as an alkylating agent, forming the product betaine (43),



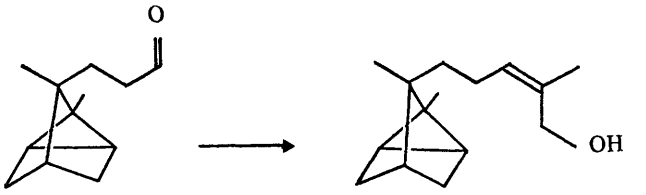

(35a) (43) (44)

**Scheme 10**

with only the oxygen from the first aldehyde moiety with which to form the oxaphosphetan intermediate and thence the olefin (44) (Scheme 10).

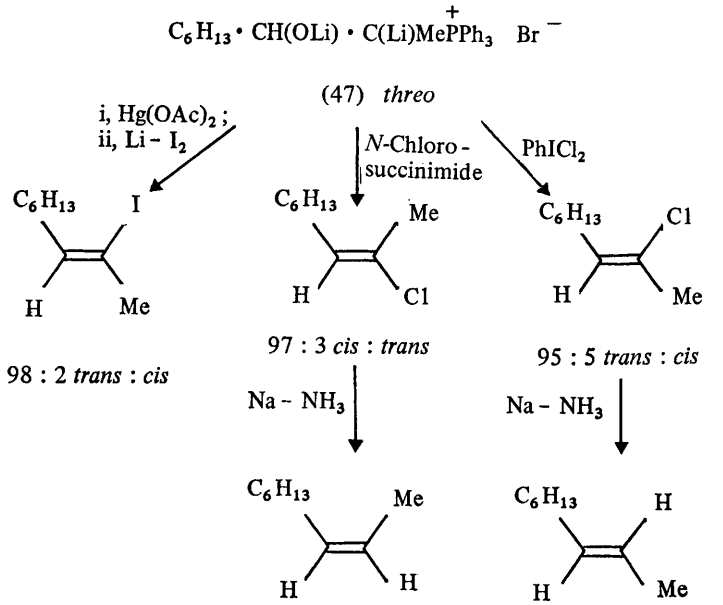
Using this reaction, α-santalol (46) was prepared in good yield from the aldehyde (45).

The betaine ylides, *e.g.* (47), are also of use for other synthetic purposes.




(45) (46)

Although alkylation with alkyl iodides is difficult, halogenation to give vinyl halides has been achieved and proceeds very selectively (Scheme 11).[33] The

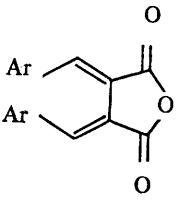



**Scheme 11**

stereochemistry of the vinyl halides was determined by their stereospecific reduction, with retention of configuration, by sodium in liquid ammonia.[34] Direct bromination and fluorination with perchloryl fluoride have also been achieved.[35] The vinyl iodides formed by this method are particularly useful for the stereospecific synthesis of trisubstituted olefins (see p. 156).

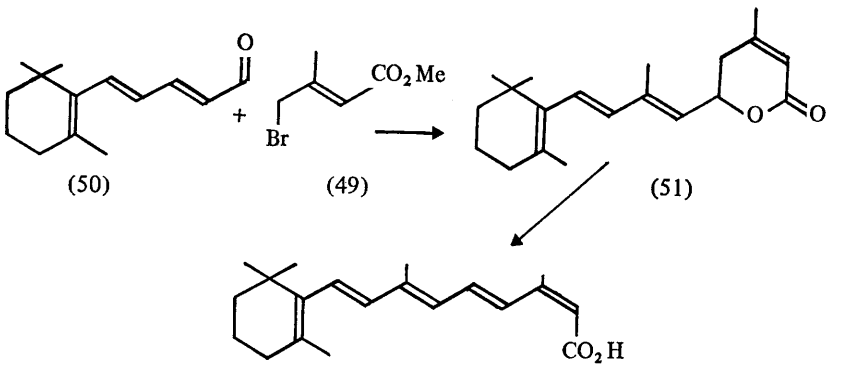
[33] E. J. Corey, J. I. Shulman, and H. Yamamoto, *Tetrahedron Letters*, 1970, 447.
[34] M. C. Hoff, K. W. Greenlee, and C. E. Boord, *J. Amer. Chem. Soc.*, 1951, **73**, 3329.
[35] M. Schlosser and K. F. Christmann, *Synthesis*, 1969, **1**, 38.

**D. Condensation Reactions.**—Reaction between a carbonyl group and an activated methylene function can give rise to conjugated olefins.[8a] These reactions almost invariably lead to *trans*-olefin formation (*i.e.* substituent *trans* to the conjugated group) and although the reactions are often stereospecific, little control over them is possible. For example, the Knoevenagel reaction between malonic acid and aromatic aldehydes gives *trans*-cinnamic acid exclusively.[36] Substituted cinnamic acids are produced as mixtures.[37] Aldol condensations,[38]




(48) Ar = 3,4-methylenedioxyphenyl

which proceed *via* a β-hydroxycarbonyl intermediate or its simple derivative, followed by elimination, also mainly form *trans*- oriented products, as in the condensations between aromatic aldehydes and ketones,[39] lactones,[40] anhydrides,[41] and heterocyclic systems.[42] Stobbe condensations also proceed similarly,[43]

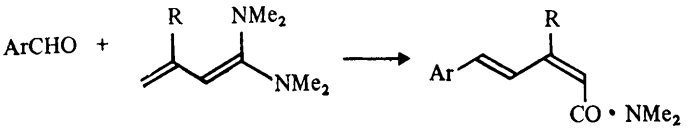



(50) (49) (51)

(52)

[36] G. Jones, *Org. Reactions*, 1967, **15**, 204.
[37] A. Foucaud, H. Person, and A. Robert, *Bull. Soc. chim. France*, 1964, 1873.
[38] C. K. Ingold, 'Structure and Mechanism in Organic Chemistry', Cornell University Press, New York, 1953, p. 680.
[39] *Cf.* D. H. R. Barton and A. J. Head, *J. Chem. Soc.*, 1956, 932; D. H. R. Barton, A. J. Head, and P. J. May, *J. Chem. Soc.*, 1957, 935.
[40] N. Baumann, M. Sung, and E. F. Ullman, *J. Amer. Chem. Soc.*, 1968, **90**, 4157.
[41] J. R. Johnson, *Org. Reactions*, 1942, **1**, 210; H. O. House, 'Modern Synthetic Reactions', Benjamin, New York, 1965, p. 236.
[42] *Cf.* K. W. Blake and P. G. Sammes, *J. Chem. Soc.* (*C*), 1970, 980.
[43] W. S. Johnson and G. H. Daub, *Org. Reactions*, 1951, **6**, 1.

even though extremely hindered products can form, *e.g.* (48).[44] However, limited control is possible in some condensations. For example, the Reformatsky reaction between the bromo-ester (49) and the aldehyde (50) forms the δ-lactone (51). Treatment with base converts this, of necessity, into 13-*cis*-vitamin A acid (52).[45] A related reaction was observed in the condensation of aromatic aldehydes with the diene-diamine (53) which gave, selectively, the *trans,cis*-amide (54).

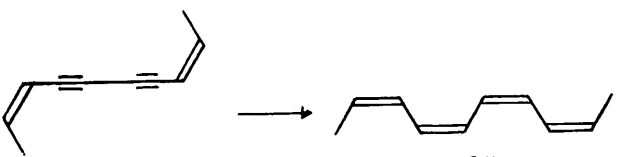



(53) (54)

$^{18}$O-Labelling experiments showed that the aldehyde oxygen ended up in the amide group, indicating a cyclic intermediate.[46]

### 3 From Acetylenes

**A. Reduction.**—Catalytic reduction of acetylenes generally affords high yields of *cis*-olefin[47] even if the product is sterically hindered, as in the reduction of the conjugated diyne (55) to the all-*cis*-tetraene (56).[48] Such reductions have been of

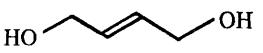


(55) (56)

great use in the preparation of carotenoids.[49] Catalytic reductions are often carried out with poisoned catalysts (*e.g.* the Lindlar catalyst[50]) in order to avoid over-reduction to the fully saturated hydrocarbon or hydrogenolysis of neighbouring groups. Under these conditions, exceptions to the *cis*-stereospecificity of reduction have been recorded. For example, the reduction of but-2-yne-1,4-diol over palladium in the presence of excess base gave mainly the *trans*-olefin (57).[51]

[44] H. G. Heller and B. Swinney, *J. Chem. Soc.* (*C*), 1967, 2452.
[45] K. Eitner, E. Truscheit, and H. Oediger, *Angew. Chem.*, 1960, **72**, 948; *cf.* U. Eisner, J. A. Elvidge, and R. P. Linstead, *J. Chem. Soc.*, 1953, 1372.
[46] D. H. R. Barton, G. Hewitt, and P. G. Sammes, *J. Chem. Soc.* (*C*), 1969, 16.
[47] K. N. Campbell and B. K. Campbell, *Chem. Rev.*, 1942, **31**, 77.
[48] D. Holme, E. R. H. Jones, and M. C. Whiting, *Chem. and Ind.*, 1956, 928.
[49] H. H. Inhoffen, H. Boldmann, and H.-J. Alday, *Annalen*, 1951, **573**, 1; *cf.* O. Isler and P. Schudel, *Adv. Org. Chem.*, 1963, **4**, 115.
[50] H. Lindlar, *Helv. Chim. Acta*, 1952, **35**, 446.
[51] F. J. McQuillin and W. P. Ord, *J. Chem. Soc.*, 1959, 2902; A. Mondon, *Annalen*, 1952, **577**, 181.

The homogeneous hydrogenation of 1,3-dienes tends to proceed by stereoselective 1,4-hydrogen addition to give *cis*-2-olefin.[52]



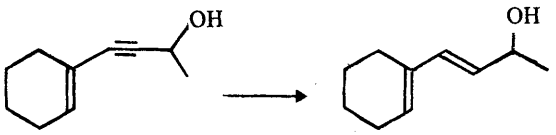
(57)

In contrast to the general mode of catalytic reduction, acetylenes are reduced by sodium in liquid ammonia in the presence of a hydrogen donor to give the *trans*-isomer.[53] Cyclodecyne (58) is converted under these conditions into *trans*-

(58) (59)

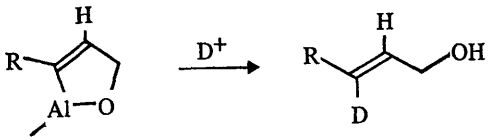
cyclodecene (59), despite the fact that the *cis*-isomer is the thermodynamically preferred product.[54] Whereas sodium gives *trans*-olefin, reduction of certain acetylenes with lithium in tetrahydrofuran at low temperatures, followed by quenching of the dianion formed with methanol, produces pure *cis*-olefin. Under these conditions the lithium salts are dimeric and appear to prefer the *cis*-configuration.[55]

Disubstituted acetylenes are slowly reduced by lithium aluminium hydride. In ether or tetrahydrofuran, specific *trans*-reduction is observed[56] whereas in toluene the *cis*-olefin is preferred, albeit with over-reduction to the saturated hydrocarbon in some cases.[57] Propargylic alcohols are also readily reduced by lithium aluminium hydride to give the corresponding *trans*-oriented allylic alcohol, *e.g.* (60) to (61)[58] *via* a complexed vinyl alane[59] which is protonated stereospecifically during workup, *e.g.* (62) to (63)[60] (see p. 156).



(60) (61)

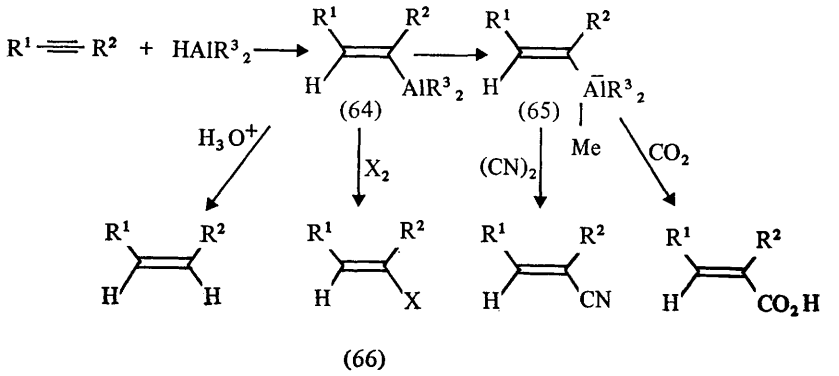
[52] E. N. Frankel and R. O. Butterfield, *J. Org. Chem.*, 1969, **34**, 3930.
[53] A. L. Henne and K. W. Greenlee, *J. Amer. Chem. Soc.*, 1943, **65**, 2020; see ref. 59, p. 27.
[54] A. T. Blomquist, L. H. Liu, and J. C. Bohrer, *J. Amer. Chem. Soc.*, 1952, **74**, 3643.
[55] G. Levin, J. Jagur-Grodzinski, and M. Szwarc, *J. Org. Chem.*, 1970, **35**, 1702.
[56] L. H. Slaugh, *Tetrahedron*, 1966, **22**, 1741.
[57] E. F. Magoon and L. H. Slaugh, *Tetrahedron*, 1967, **23**, 4509.
[58] J. D. Chanley and H. Sobotka, *J. Amer. Chem. Soc.*, 1949, **71**, 4140.
[59] For applications see R. A. Raphael, 'Acetylenic Compounds in Organic Synthesis', Butterworths, London, 1955, p. 29.
[60] (*a*) E. J. Corey, J. A. Katzenellenbogen, and G. H. Posner, *J. Amer. Chem. Soc.*, 1967, **89**, 4246; (*b*) B. B. Molloy and K. L. Hauser, *Chem. Comm.*, 1968, 1017.



(62) (63)

Activated allylic alcohols are reduced by lithium aluminium hydride with bond migration to form allenes, again in a stereospecific manner.[61]

**B. Hydroalumination and Hydroboronation.**—Di- or tri-alkylalanes add to acetylenes to give di-, tri-, or tetra-substituted olefins.[62] In a detailed examination of the reaction, it was shown that the addition could be controlled, especially the addition across disubstituted acetylenes to form, eventually, trisubstituted olefins. Dialkylalanes add across acetylenes in a stereospecific *cis*-manner (Scheme 12).[63]



(66)

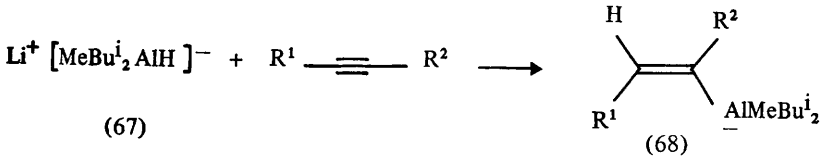
**Scheme 12**

Acid hydrolysis of the alane (64) liberates *cis*-olefin in high yield whereas reaction with halogen gives the corresponding vinyl halide,[64a] especially useful for the stereospecific preparation of vinyl iodides (66; X = I). Certain cobalt complexes behave similarly.[64b] The *cis*-alane adducts (64) react with methyl-lithium to form the corresponding *cis*-'ate' complexes (65),[65] which are also synthetically useful

[61] W. T. Borden and E. J. Corey, *Tetrahedron Letters*, 1969, 313; J. S. Cowie, P. R. Landor, and S. R. Landor, *Chem. Comm.*, 1969, 541.
[62] G. Wilke and H. Muller, *Annalen*, 1960, **629**, 222.
[63] J. J. Eisch and W. C. Kaska, *J. Amer. Chem. Soc.*, 1966, **88**, 2213.
[64] (*a*) G. Zweifel and C. C. Whitney, *J. Amer. Chem. Soc.*, 1967, **89**, 2753; (*b*) M. D. Johnson and B. S. Meeks, *Chem. Comm.*, 1970, 1027.
[65] W. Tochtermann, *Angew. Chem. Internat. Edn.*, 1966, **5**, 351.

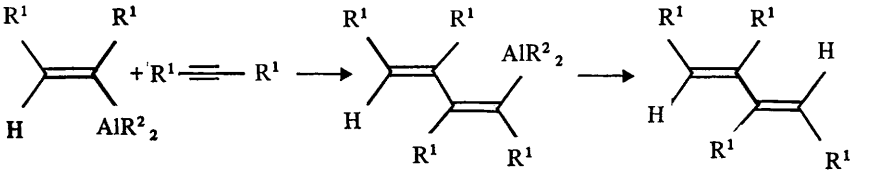
intermediates; carboxylation[66] or reaction with cyanogen[67] gives the acid or nitrile respectively, both with complete retention of configuration. Aldehydes give the corresponding allylic alcohol.[66]

Dialkylalanes themselves react with methyl-lithium to give complex hydrides, *e.g.* (67), which also add to acetylenes, but in the *anti*-mode, thus allowing the stereospecific preparation of the *trans*-'ate' complexes (68).[68]



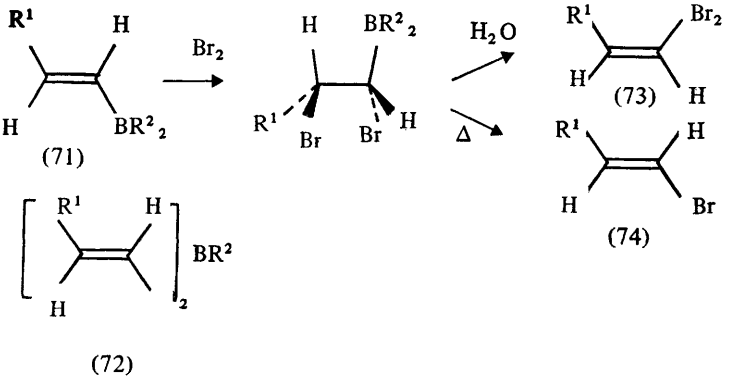

(67) (68)

Dialkylalanes can be made to react with two moles of disubstituted acetylene, the intermediate *cis*-vinylalane, *e.g.* (69), adding in a *syn*- mode to the second mole of acetylene to give, after workup, a *cis,cis*-diene (70).




(69) (70)

Hydroboronation can also be used to reduce acetylenes, the reduction occurring with *cis*-geometry. The free olefin is liberated from the intermediate vinyl-

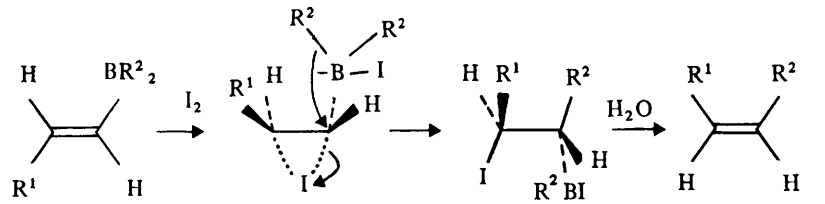



(71) (72) (73) (74)

[66] G. Zweifel and R. B. Steele, *J. Amer. Chem. Soc.*, 1967, **89**, 2754.
[67] G. Zweifel, J. T. Snow, and C. C. Whitney, *J. Amer. Chem. Soc.*, 1968, **90**, 7139.
[68] G. Zweifel and R. B. Steele, *J. Amer. Chem. Soc.*, 1967, **89**, 5085.

borane by treatment with acid. Whereas diborane itself can over-react, especially with terminal acetylenes, dialkylboranes, such as bis(3-methyl-2-butyl)borane, give the vinylborane (71) cleanly.[69] Hindered monoalkylboranes (such as 2,3-dimethyl-2-butylborane) give the corresponding divinylborane (72).[70]

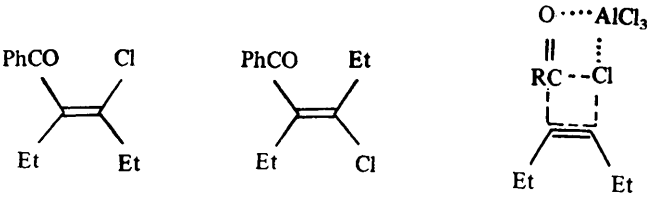
The complexes (71; $R^1$ = alkyl) add bromine in an *anti*-manner, and the adducts can be decomposed selectively to the vinyl bromide, hydrolysis giving the *cis*-compound (73) and thermal decomposition the *trans*-isomer (74).[71] In contrast, iodination does not produce vinyl iodides since an alkyl shift from



(71) (75) (76) (77)

boron to carbon occurs, presumably *via* the iodonium intermediate (75), which collapses to the iodide (76). Hydrolysis then gives the alkyl-substituted *cis*-olefin (77).[72] Hydroboronation of iodo-acetylenes proceeds normally to form the *cis*-vinyl iodide.[73]

**C. Addition to Acetylenes.**—Additions of acids across acetylenes often occur stereospecifically in a *trans*-manner.[74] However, in polar solvents, or with very strong acids, formation of the vinyl cation intermediate is favoured, and these

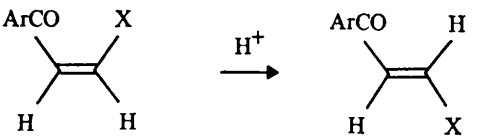


(78) (79) (80)

[69] H. C. Brown and G. Zweifel, *J. Amer. Chem. Soc.*, 1961, **83**, 3834.
[70] G. Zweifel, N. L. Polston, and C. C. Whitney, *J. Amer. Chem. Soc.*, 1968, **90**, 6243.
[71] H. C. Brown, D. H. Bowman, S. Misumi, and M. K. Unni, *J. Amer. Chem. Soc.*, 1967, **89**, 4531.
[72] G. Zweifel, H. Arzoumanian, and C. C. Whitney, *J. Amer. Chem. Soc.*, 1967, **89**, 3652.
[73] G. Zweifel and H. Arzoumanian, *J. Amer. Chem. Soc.*, 1967, **89**, 5086.
[74] R. C. Fahey and D.-J. Lee, *J. Amer. Chem. Soc.*, 1967, **89**, 2780.

can give either *cis*- or *trans*-adducts.[75] Conditions during addition are of prime importance in these reactions, and this is exemplified by the reaction of hex-3-yne with benzoyl chloride catalysed by aluminium trichloride.[76] In dichloromethane at low temperatures, the *cis*-addict (78) is predominant, with only small amounts of the *trans*-product (79). On increasing the temperature or by increasing the polarity of the solvent, the *trans*- isomer is preferred. The *cis*- adduct forms by addition of the donor complex (80), whereas *trans*-addition proceeds *via* free oxocarbonium ions. Other reagents also add in a *cis*-manner to acetylenes, such as with mercuric acetate.[77]

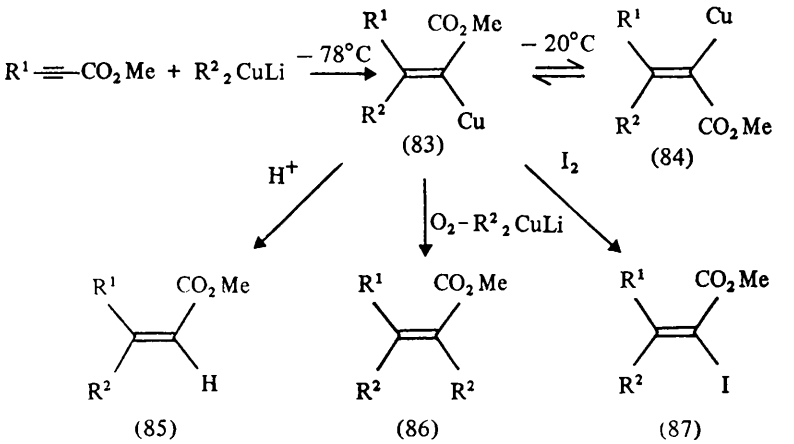
Conjugate addition to ethynyl ketones also occurs stereospecifically in an *anti*-manner.[78] However, for the addition of halogen acids, the initial *cis*-product (81)




(81) (82)

is readily rearranged by excess acid into the thermodynamically stable *trans*-adduct (82). It is pertinent that substitution of the halogen by a nucleophile, *e.g.* thiophenol, also occurs stereospecifically with *retention* of configuration.

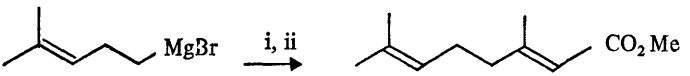
The conjugate addition of alkyl groups across $\alpha\beta$-acetylenic esters has also




Scheme 13

[75] D. S. Noyce, M. A. Matesich, M. D. Schiavelli, and P. E. Peterson, *J. Amer. Chem. Soc.*, **87**, 2295.
[76] H. Martens and G. Hoornaert, *Tetrahedron Letters*, 1970, 1821.
[77] G. Drefahl, G. Heublein, and A. Wintzer, *Angew. Chem.*, 1958, **70**, 166.
[78] B. Cavalchi, D. Landini, and F. Montanari, *J. Chem. Soc.* (*C*), 1969, 1204.

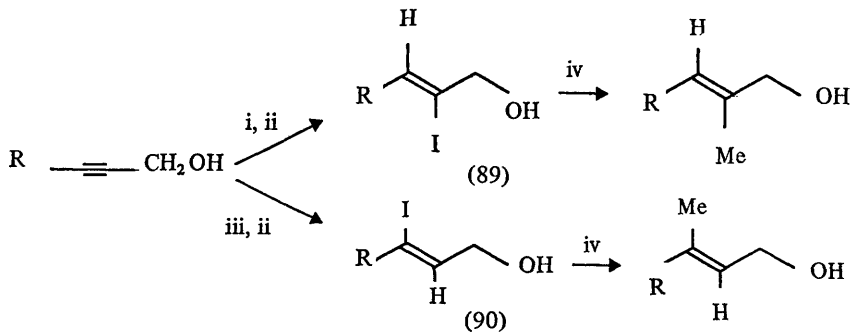
been achieved.[79] Alkylcopper lithium complexes have been used. By operating at low temperatures (− 78 °C) a very high *cis*-selectivity was observed. The reaction (Scheme 13) proceeds *via* the enolate (83), which loses its stereochemical integrity at − 20 °C to equilibrate with the isomeric enolate (84). Quenching of the intermediate (83) with water yields the unsaturated ester (85). Oxidation with air in the presence of an excess of the alkylcopper lithium reagent effects coupling to give the dialkylated product (86). Reaction with iodine forms the iodide (87). All the reactions proceed stereospecifically. The method has been applied to the preparation of trisubstituted isoprenoid olefins, *e.g.* (88).[80] The copper enolate




Reagents: i, CuI $(Bu_3P)_4$ - $Bu_3P$; ii, Me —≡—$CO_2Me$ (88)

intermediate was stabilised by the presence of excess tributylphosphine as a ligand. Pyrrolidine could also be used as a stabilising ligand, in which case the alkylations approached 99% stereoselectivity for the *trans*-isomer formed by *syn*-addition. The reaction is general, but phenylpropiolic acid gave, with dimethylcopper lithium, a mixture of isomers. With the free acid, it was better to use methylcopper as the reagent. The resulting enolate then maintains its configuration even at room temperature, and protonates to give *cis*-β-methylcinnamic acid. Addition of methyl-lithium to this enolate catalysed the equilibration.[81]

**D. Vinyl Iodides.**—Reduction of propargylic alcohols with lithium aluminium



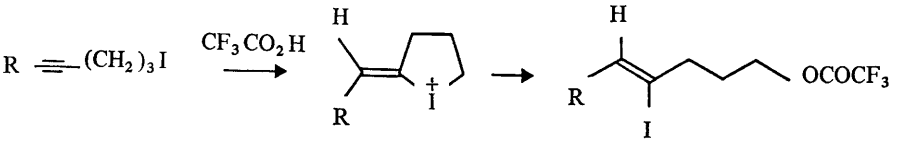

Reagents: i, 60 : 1 $LiAlH_4$ - $AlCl_3$; ii, $I_2$; iii, 1 : 2 $LiAlH_4$- NaOMe; iv, $Me_2CuLi$

Scheme 14

[79] E. J. Corey and J. A. Katzenellenbogen, *J. Amer. Chem. Soc.*, 1969, **91**, 1851.
[80] J. B. Siddall, M. Biskup, and J. H. Fried, *J. Amer. Chem. Soc.*, 1969, **91**, 1853.
[81] J. Klein and M. Turkel, *J. Amer. Chem. Soc.*, 1969, **91**, 6186.

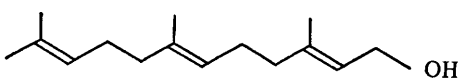
hydride forms an alane complex (see p. 151), *e.g.* (62). Quenching of this intermediate with iodine instead of with protons produces vinyl iodides.[60a] The direction of addition of the iodine can be controlled in a regiospecific manner by the appropriate choice of reducing conditions (Scheme 14) to give either of the *trans*-vinyl iodides (89) and (90). The presence of methoxide increases the rate of formation of the alcohol aluminate complex and catalyses the internal delivery of hydrogen in the sense observed.[60b] Presumably the presence of Lewis acid catalyses external addition of hydride by the more usual Markovnikov orientation.

Vinyl iodides can also be prepared stereospecifically *via* alanes[64] and betaine ylides.[33] An alternative method is by using controlled 1,4-halogen shifts (Scheme 15).[82] The vinyl iodides so formed can be alkylated with lithium dialkylcopper

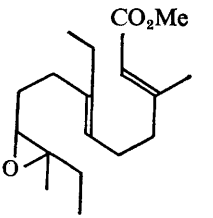



Scheme 15

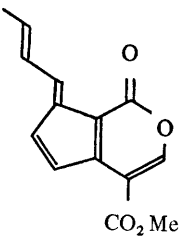
complexes, with displacement of the iodine occurring with complete retention of configuration.[83] This stereospecific preparation of trialkylated olefins has been applied to the preparation of all-*trans*-farnesol (91)[60] and the racemic *Cecropia*




(91)




(92)



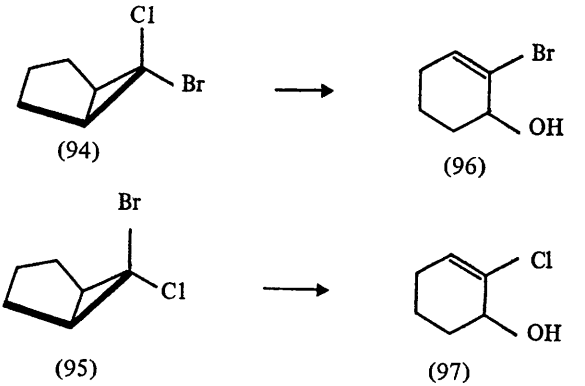

(93)

[82] R. E. Peterson, B. J. Bopp, and M. M. Ajo, *J. Amer. Chem. Soc.*, 1970, **92**, 2834.
[83] E. J. Corey and G. H. Posner, *J. Amer. Chem. Soc.*, 1967, **89**, 3911; 1968, **90**, 5615; E. J. Corey and G. H. Posner, *Tetrahedron Letters*, 1970, 315.

juvenile hormone (92).[84] A related reaction was used in the synthesis of fulvoplumierin (93).[85]

## 4 Rearrangement Reactions

**A. Halogenocyclopropanes.**—The halogenocyclopropanes are readily prepared by addition of a halogenocarbene to an olefin. The pyrolysis or solvolysis of halogenocyclopropanes is very dependent on the stereochemistry of these adducts. Thus, for the bicyclo[3,1,0]-adducts (94) and (95), solvolysis catalysed by silver

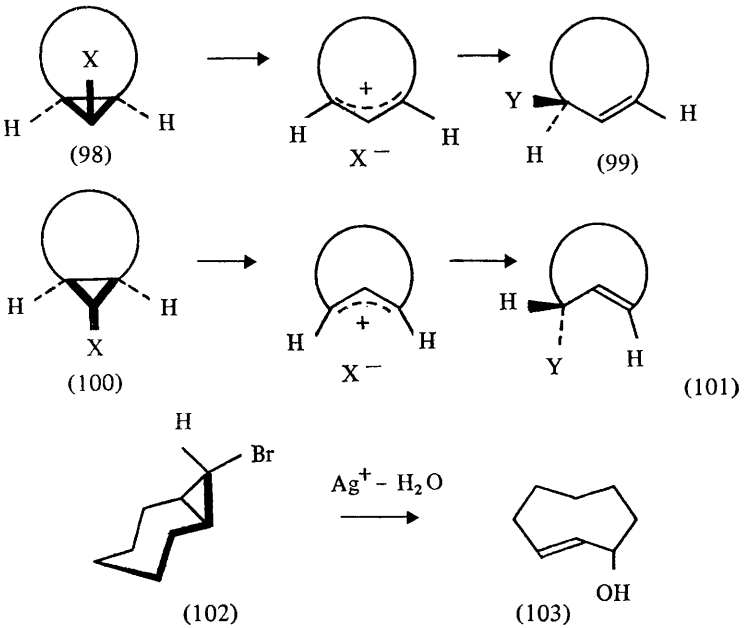



(94) (96)

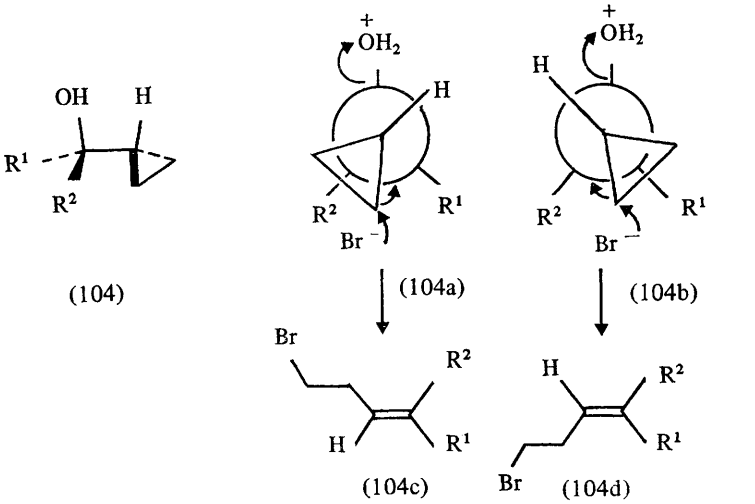
(95) (97)

ion loses the *endo*-oriented halogen only, to produce the ring-expanded alcohols (96) and (97) respectively.[86] Pyrolysis also reflects the orientation of the substituents, and again only the *endo*-halogens rearrange.[87] The stereochemistries of these reactions are a consequence of the symmetry-controlled orientation of the rearrangement of cyclopropyl cations to allyl cations.[88] In summary, these predict that the routes of ring opening are restricted to those shown in (98) to (99) and (100) to (101). Thus, in cyclic derivatives, *endo*-halogenocyclopropanes form *cis*-olefins and *exo*-substituted compounds form *trans*-olefins. In this way, medium-ring *trans*-cycloalkenes have been prepared, *e.g.* (102) to (103).[89] The synthetic usefulness of this process should grow since stereoselective methods for the reduction of dihalogenocyclopropanes are being developed.[90]

[84] E. J. Corey, J. A. Katzenellenbogen, N. W. Gilman, S. A. Roman, and B. W. Erickson, *J. Amer. Chem. Soc.*, 1968, **90**, 5618.
[85] G. Büchi and J. A. Carlson, *J. Amer. Chem. Soc.*, 1968, **90**, 5336.
[86] P. S. Skell and S. R. Sandler, *J. Amer. Chem. Soc.*, 1958, **80**, 2024.
[87] M. S. Baird, D. G. Lindsay, and C. B. Reese, *J. Chem. Soc.* (*C*), 1969, 1173; C. B. Reese and A. Shaw, *J. Amer. Chem. Soc.*, 1970, **92**, 2566; C. W. Jefford and R. Medary, *Tetrahedron Letters*, 1966, 2069; C. W. Jefford, E. Huang Yeu, and R. Medary, *Tetrahedron Letters*, 1966, 6317; C. W. Jefford and W. Wojnarowski, *Tetrahedron Letters*, 1968, 193, 199.
[88] See ref. 4; R. B. Woodward and R. Hoffmann, *J. Amer. Chem. Soc.*, 1965, **87**, 395; H. C. Longuet-Higgins and E. W. Abrahamson, *J. Amer. Chem. Soc.*, 1965, **87**, 2046.
[89] G. H. Whitham and M. Wright, *Chem. Comm.*, 1967, 294.
[90] *Cf.* K. Hofmann, S. F. Orochena, S. M. Sax, and G. A. Jeffrey, *J. Amer. Chem. Soc.*, 1959, **81**, 992; D. Seyferth, H. Yamazaki, and D. L. Alleston, *J. Org. Chem.*, 1963, **28**, 703; C. L. Osborn, T. C. Shields, B. A. Shoulders, J. F. Krause, H. V. Cortez. and P D. Gardner, *J. Amer. Chem. Soc.*, 1965, **87**, 3158.

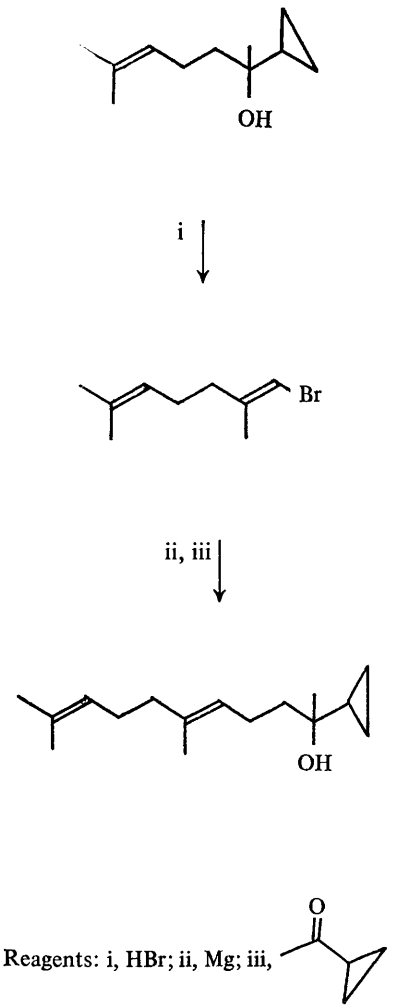



**B. The Julia Synthesis.**[91]—α-Cyclopropylcarbinols are cleaved by acid in a stereoselective *trans*-manner (Scheme 16).[92] Although the preparation of disubstituted olefins occurs essentially selectively, extension to the preparation of



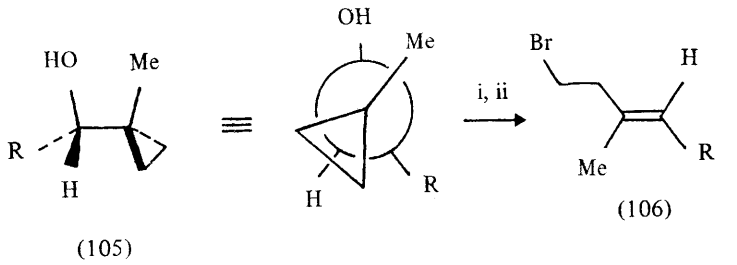

[91] M. Julia, S. Julia, and R. Guegan, *Bull. Soc. chim. France*, 1960, 1072.
[92] See ref. 10.

trisubstituted olefins also gave quantities of the *cis*-olefin (5—10%). Considering the Newman projection of the α-cyclopropylcarbinol (104) in its transition states (104a) and (104b) it is apparent that, unless there is a large difference in the steric requirements of the groups $R^1$ and $R^2$, there will be little preference for either conformer (104a) or (104b). This is true if one of the groups is hydrogen [*e.g.* (104; $R^2$ = H)], in which conformer (a) is preferred to conformer (b), leading to the *trans*-olefin (104c).




**Scheme 16**

Johnson has extended the Julia synthesis to include the stereospecific synthesis of trisubstituted olefins by placing the extra substituent next to the cyclopropyl function rather than by the alcohol group, *e.g.* (105).

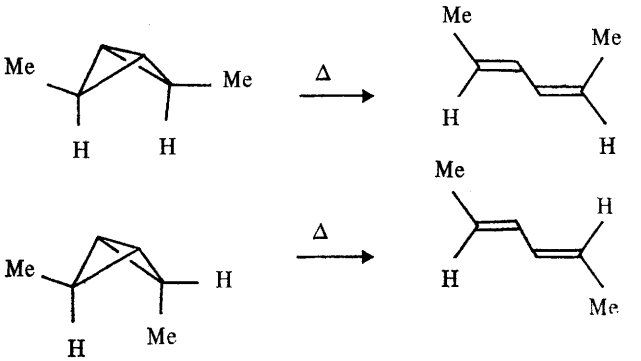



(105) (106)

Reagents: i, $PBr_3$ – LiBr – Collidine; ii, $ZnBr_2$

Prior conversion of the carbinol (105) into its corresponding bromide, followed by rearrangement catalysed by zinc bromide, gave only the *trans*-olefin (106). This modified procedure was employed in a total synthesis of steroids[93] and in a synthesis of the racemic juvenile hormone (92).[94]

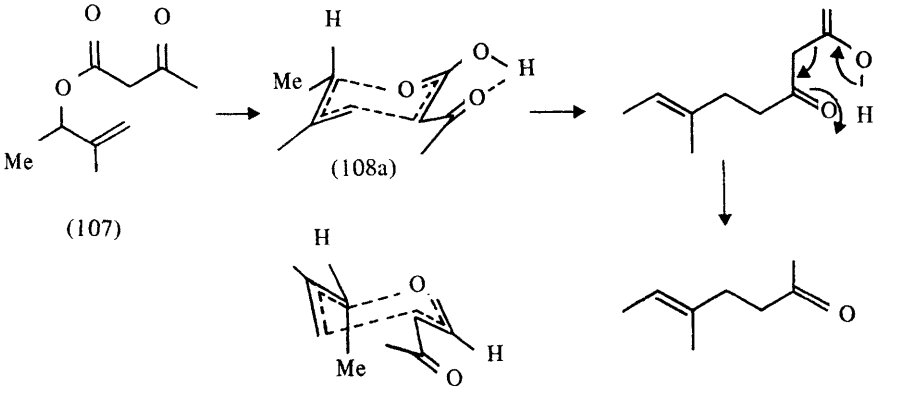
**C. Thermal Rearrangements.**—Stereospecific olefin formation often results from thermal electrocyclic processes,[4] *e.g.* Scheme 17.[95] However, two interesting




**Scheme 17**

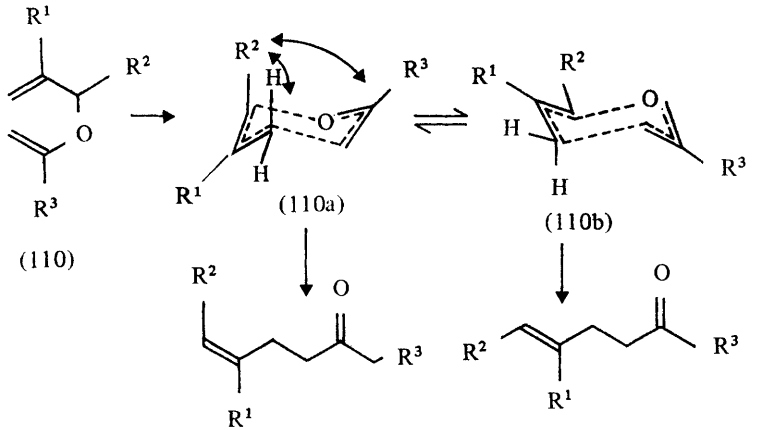
[93] W. S. Johnson, M. F. Semmelhack, M. U. S. Sultanbawa, and L. A. Dolak, *J. Amer. Chem. Soc.*, 1968, **90**, 2994.
[94] W. S. Johnson, T. Li, D. J. Faulkner, and S. F. Campbell, *J. Amer. Chem. Soc.*, 1968, **90**, 6225.
[95] G. L. Closs and P. E. Pfeffer, *J. Amer. Chem. Soc.*, 1968, **90**, 2452.

methods have recently been adapted for use in the stereospecific preparation of trisubstituted olefins. These are the rearrangements of allyl acetoacetates, the Carroll reaction,[96] *e.g.* (107) to (109); and the transformation of allyl vinyl ethers, the Claisen rearrangement,[97] *e.g.* (110) to (111).



(107) (108a) (108b) (109)

The Carroll reaction has been shown to involve a cyclic transition state.[98] Recently, the steric requirements for the reaction have been determined.[99] A



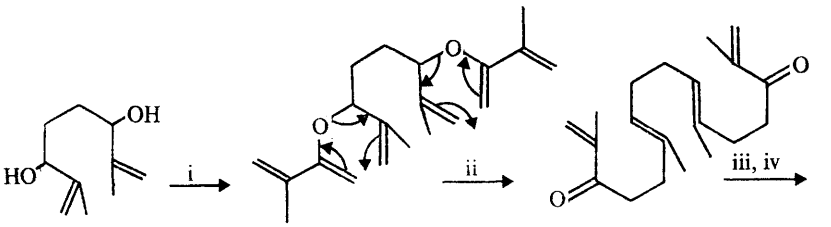
(110) (110a) (110b)

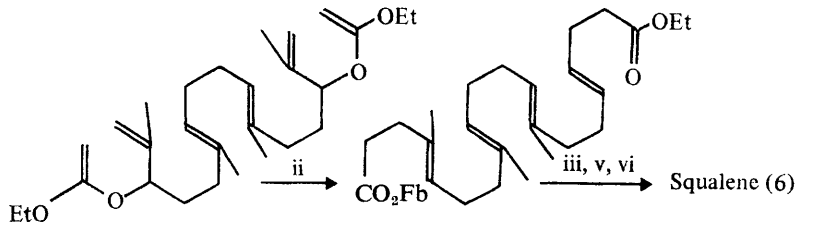
(111a) Minor product (111b) Major product

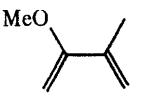
[96] M. F. Carroll, *J. Chem. Soc.*, 1940, 704, 1266; 1941, 507; J. Dreux and J. Cologne, *Bull. Soc. chim. France*, 1955, 1312.
[97] D. L. Dalrymple, T. L. Kruger, and W N. White 'The Chemistry of the Ether Linkage', ed. S. Patai, Wiley–Interscience, New York, 1964, p. 635.
[98] W. Kimel and A. C. Cope, *J. Amer. Chem. Soc.*, 1943, **65**, 1992.
[99] N. Wakabayashi, R. M. Waters, and J. P. Church, *Tetrahedron Letters*, 1969, 3253.

chair-type conformation is adopted in the transition state (108), and as a consequence high selectivity is observed if one of the two possible chair-conformers is preferred, *e.g.* (108a) > (108b). For derivatives in which there is no preference, mixtures are obtained.

The Claisen rearrangement gives predominantly *trans*-olefins.[100] Again, a




Reagents: i,  $-H^+$; ii, Heat; iii, $LiAlH_4$;

iv, $MeCH(OEt)_3$; v, $CrO_3$– pyridine; vi, $Ph_3P{=}C(Me)_2$

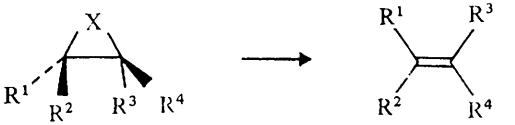
**Scheme 18**

[100] K. C. Brannock, *J. Amer. Chem. Soc.*, 1959, **81**, 3379.

chair-type transition state (110a and 110b) is adopted.[101] As for the Carroll reaction, the greater the preference for one of the two possible transition-state conformers, the higher the selectivity of the reaction. This can be achieved by increasing the bulk of the substituent [$R^2$ in (110)]. The synthetic value of this reaction is illustrated in Scheme 18, a very stereoselective route to squalene.[102]

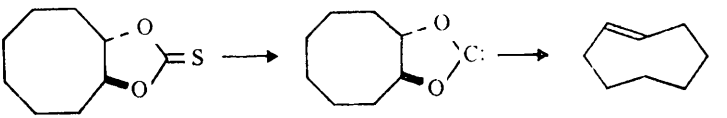
## 5 Elimination Reactions

**A. Cyclic Elimination Reactions.**—Symmetry-controlled extrusions of the type (112) to (113), *i.e.* cheletropic reactions,[4] often occur in a completely stereospecific manner, as do retrograde Diels–Alder reactions.



(112) (113)

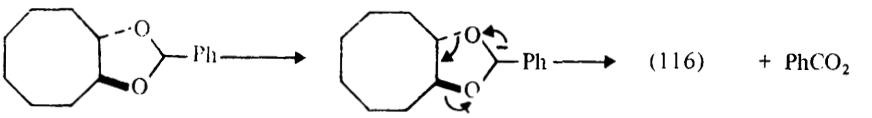
Corey has recently developed the elimination of cyclic thionocarbonates for the controlled formation of olefins.[103] Thus, treatment of the 1,2-*trans*-cyclooctanediol ester (114) with trivalent phosphorus[104] produces the carbene (115), which eliminates carbon dioxide to form the *trans*-olefin (116). Trithiocarbonates



(114) (115) (116)

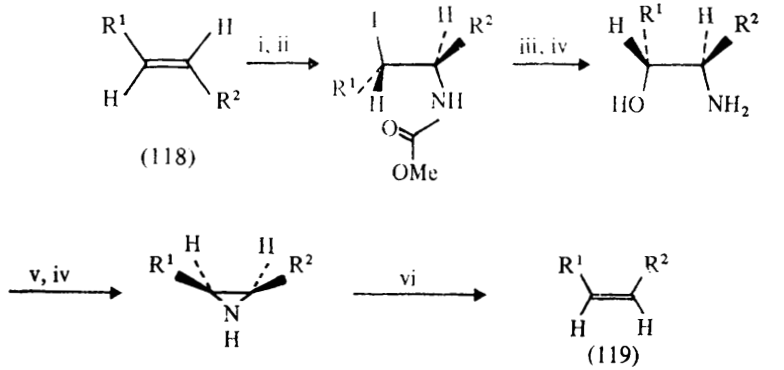
behave similarly.[105] A related reaction has been developed by Whitham.[106] 2-Phenyldioxolidines react with base to form olefin and eliminate benzoate anion.[107] By treating the benzylidene acetal (117) with butyl-lithium, *trans*-cyclooctene (116) was formed; an example of a symmetry-allowed, reversed 1,3-dipolar addition reaction.[108]

[101] D. J. Faulkner and M. R. Peterson, *Tetrahedron Letters*, 1969, 3243; C. L. Perrin and D. J. Faulkner, *ibid.*, 1969, 2783.
[102] W. S. Johnson, L. Werthemann, W. R. Bartlett, T. J. Brocksom, T. Li, D. J. Faulkner, and M. R. Peterson, *J. Amer. Chem. Soc.*, 1970, **92**, 741.
[103] E. J. Corey and J. I. Shulman, *Tetrahedron Letters*, 1968, 3655; E. J. Corey and R. A. E. Winter, *J. Amer. Chem. Soc.*, 1963, **85**, 2677.
[104] E. J. Corey, *Pure Appl. Chem.*, 1967, **14**, 19.
[105] E. J. Corey, F. A. Carey, and R. A. E. Winter, *J. Amer. Chem. Soc.*, 1965, **87**, 934.
[106] J. N. Hines, M. J. Peagram, G. H. Whitham, and M. Wright, *Chem. Comm.*, 1968, 1593.
[107] P. S. Wharton, G. A. Hiegel, and S. Ramaswami, *J. Org. Chem.*, 1964, **29**, 2441; R. L. Letsinger and D. F. Pollart, *J. Amer. Chem. Soc.*, 1956, **78**, 6079.
[108] R. Huisgen, *Angew. Chem. Internat. Edn.*, 1963, **2**, 565.




(117)

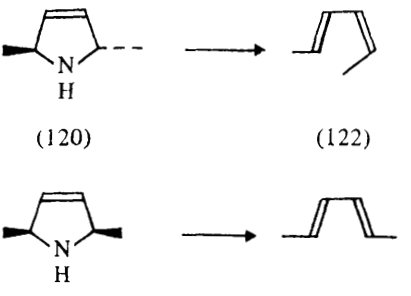
Synthetic applications of the above methods depends on the availability of pure *trans*- or *cis*-diols. Since these are readily made by the oxidation of an olefin, a route for the interconversion of *cis*- and *trans*-olefins is apparent. A similar process, *i.e.* (118) to (119) (Scheme 19) has been described involving aziridine in-




Reagents: i, INCO; ii, MeOH; iii, Heat; iv, $OH^-$; v, $H_2SO_4$; vi, BuONO

**Scheme 19**

termediates.[109] Dienes can be produced in a similar manner from the corresponding 3-pyrrolines (120) and (121), which are deaminated stereospecifically to the

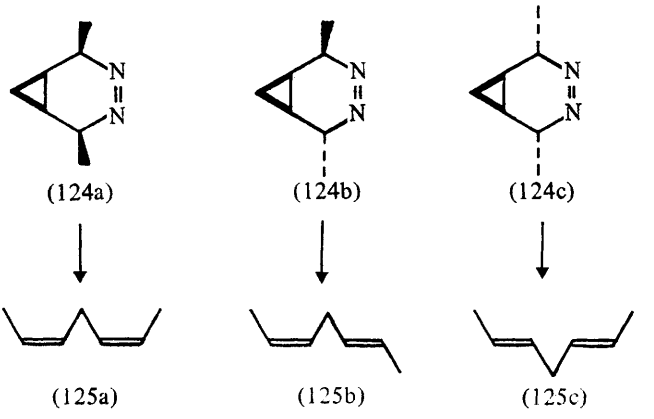


(120) (122)

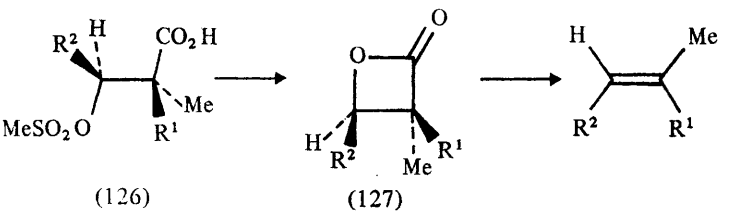
(121) (123)

[109] R. M. Carlson and S. Y. Lee, *Tetrahedron Letters*, 1969, 4001.

corresponding dienes (122) and (123).[110] Sulpholenes behave similarly.[111] The synthesis has recently been extended to the stereospecific preparation of all three 1,4-dienes. The cyclopropyl derivatives (124) lose nitrogen on heating to

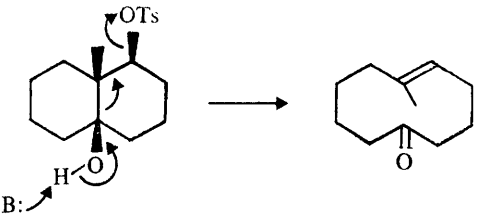



give only one diene (125) each.[112] Trisubstituted double bonds can also be prepared stereospecifically by the elimination of carbon dioxide from β-lactones, *e.g.* (127), themselves readily prepared by the cyclisation of β-methanesulphonyl oxyacids (126).[113]



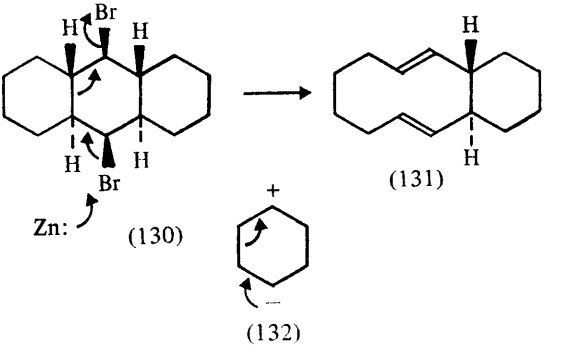

**B. Fragmentations and Non-cyclic 1,2-Eliminations.**—Fragmentation reactions[114] are very useful for the preparation of medium-ring cyclic derivatives.[115] Thus, the hydroxytosylate (128) is cleaved by base in a specific manner to give the *trans*-cyclodecenone (129).[116] The process is general for 1,4-disubstituted systems – even

[110] D. M. Lemal and S. D. McGregor, *J. Amer. Chem. Soc.*, 1966, **88**, 1335.
[111] S. D. McGregor and D. M. Lemal, *J. Amer. Chem. Soc.*, 1966, **88**, 2858; W. L. Mock, *ibid.*, 1966, **88**, 2857.
[112] J. A. Berson and S. S. Olin, *J. Amer. Chem. Soc.*, 1969, **91**, 777.
[113] M. U. S. Sultanbawa, *Tetrahedron Letters*, 1968, 4569.
[114] C. A. Grob and P. W. Schiess, *Angew Chem. Internat. Edn.*, 1967, **6**, 1.
[115] J. A. Marshall, *Rec. Chem. Progr.*, 1969, **26**, 4781.
[116] P. S. Wharton, *J. Org. Chem.*, 1961, **26**, 4781.



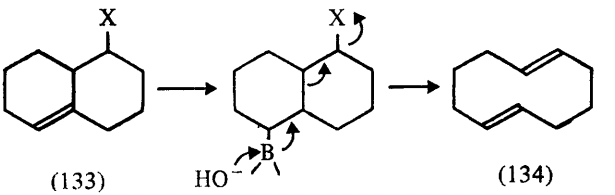

(128) (129)

dibromides can undergo elimination of bromine, *viz.* (130) to (131),[117] – and depends on the potential formation of carbanionic and carbonium ion (132)




(130) (131) (132)

centres. The anion can be generated as above, from a hydroxy-group, or from amines,[118] and even by treatment of an alkylborane with base, *e.g.* (133) to (134).[119] The disposition of the substituents determines the geometry of the

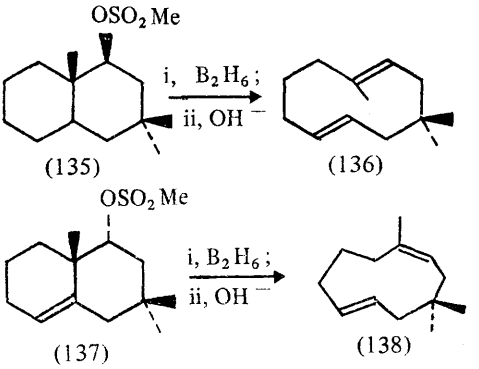



(133) (134)

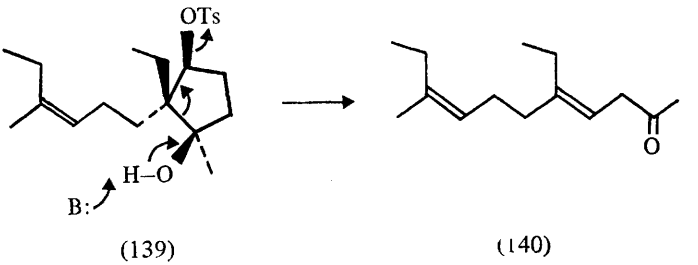
olefinic bonds formed, allowing considerable control of the processes, such as in the reactions (135) to (136) and (137) to (138).[115]

A related reaction was used to introduce double bonds stereospecifically in an

[117] P. S. Wharton, Y. Sumi, and R. A. Kretchmer, *J. Org. Chem.*, 1965, **30**, 234.
[118] C. A. Grob, H. R. Kiefer, H. J. Lutz, and H. J. Wilkens, *Helv. Chim. Acta*, 1967, **50**, 416.
[119] J. A. Marshall and G. L. Bundy, *Chem. Comm.*, 1967, 855.




approach to the juvenile hormone (92). The hydroxytosylate (139) fragmented when treated with base to give the corresponding ketone (140).[120]




1,2-Reductive eliminations have also been used to prepare olefins. In a detailed mechanistic study, it was found that bromine could be eliminated from 1,2-dibromides, *e.g. dl*-stilbene dibromide, in a stereospecific *anti*-manner, but only with a few two-electron reductants.[121] Most reducing agents led to a mixture of *cis*- and *trans*- olefins. These include one-electron reductants such as chromium(II) complexes.[122] As detailed above (Section 2A), the reduction of iodohydrins to olefins required strict control in order to maintain complete stereospecificity, and only after trying a large number of conditions were the appropriate reagents found, namely, the use of stannous chloride and phosphoryl oxychloride in pyridine.[1]

The authors thank Professors Barton, Cornforth, and Sutherland for their interest and encouragement.

[120] R. Zurflüh, E. N. Wall, J. B. Siddall, and J. A. Edwards, *J. Amer. Chem. Soc.*, 1968, **90**, 6224.
[121] I. N. Mathai, K. Schug, and S. I. Miller, *J. Org. Chem.*, 1970, **35**, 1733.
[122] J. K. Kochi, D. M. Singleton, and L. J. Andrews, *Tetrahedron*, 1968, **24**, 3503.

**Table** *Selectivity of Wittig reactions.*

| *Conditions* | *Stabilised phosphoranes* | *Non-stabilised phosphoranes* |
|---|---|---|
| *Polar solvent* | | |
| *a*) Aprotic | Low selectivity but mainly *trans* | Low selectivity |
| *b*) Protic | *cis*-Isomer selectivity increased | *trans*-Isomer selectivity increased |
| *Non-polar solvent* | | |
| *a*) Salt-free | High selectivity for *trans*-Isomer | High selectivity for *cis*-Isomer* |
| *b*) With salt | *cis*-Isomer selectivity increased | *trans*-Isomer selectivity increased |

* Major *trans*-isomer by Wittig–Schlosser procedure, *i.e.* prior treatment with BuLi or PhLi and then reprotonation.[24]