# Saturated and unsaturated hydrocarbons

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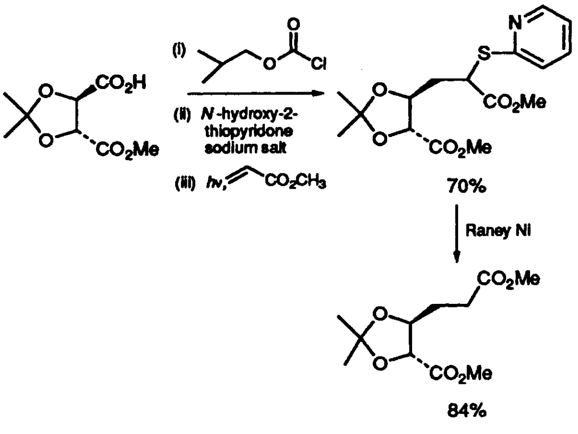
## 1 Saturated hydrocarbons

Further developments of radical deoxygenation methodology have included approaches to dideoxygenations, as well as dehalogenation and deamination,[1-4] whilst an electroreductive deoxygenation of $\alpha$-methylsulfonyloxyesters *via* a catalytic selenation–deselenation sequence has also been reported.[5] Radical decarboxylation procedures allow stereoselective alkylations with activated olefins of tartaric acid derived radicals, with retention of configuration (**Scheme 1**).[6]

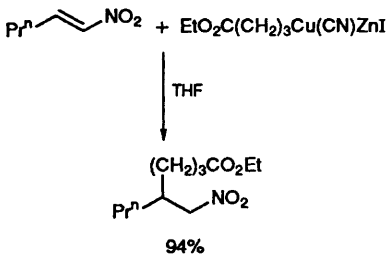


**Scheme 1**

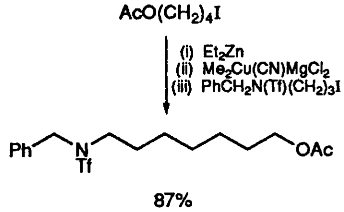
Direct desulfonylations using magnesium in ethanol with catalytic mercuric chloride proceed in excellent yield,[7] and a mild procedure for the decarbonylation of aldehydes at room temperature in the presence of catalytic $Rh(PPh_3)_3Cl$ and stoichiometric diphenylphosphorylazide has been reported.[8]

The selective reduction of the double bond in $\alpha\beta$-unsaturated carbonyl compounds has been achieved using an oxygen-activated palladium catalyst for ketones,[9] $SmI_2$-HMPA for esters, acids, amides, and anhydrides,[10] and with CO and $H_2O$ in the presence of $Rh_6(CO)_{16}$ for esters and ketones.[11]

The additions of copper-zinc reagents to a variety of nitro olefins produce polyfunctional nitroalkanes in high yields (**Scheme 2**),[12] and functionalized dialkylzinc reagents treated with $Me_2Cu(CN)(MgCl)_2$ in DMPU have been shown to undergo cross-coupling reactions with alkyl iodides in excellent yields (**Scheme 3**).[13]

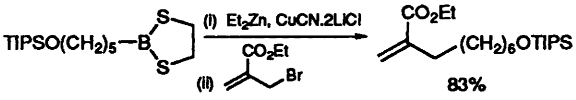


**Scheme 2**



**Scheme 3**

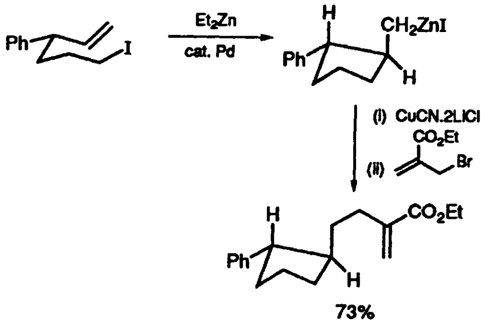
A new procedure for the transmetallation of organoboron derivatives with $Et_2Zn$ or $Me_2Zn$ allows access to the corresponding dialkylzinc reagents, which are not readily available by standard methods (**Scheme 4**).[14]



**Scheme 4**

In addition, a method allowing the insertion of zinc dust into primary alkyl chlorides, bromides, sulfonates, or phosphates has been reported with a variety of adducts prepared under copper catalysis;[15] $Pd^{II}$

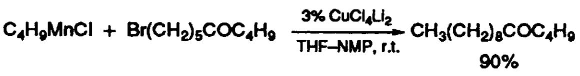
catalysis enables the facile formation of alkyl zinc iodides in the synthesis of cyclopentylmethyl zinc iodides, which were then subsequently further derivatized (**Scheme 5**).[16]



**Scheme 5**

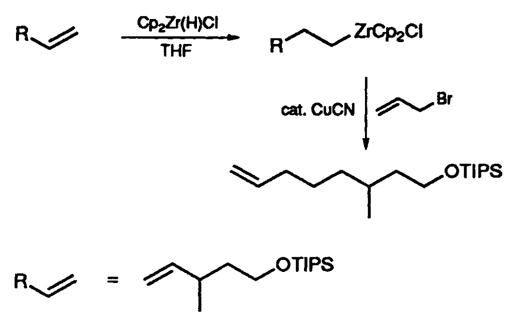
The application of alkenyl zinc reagents in the preparation of functionalized carbocycles has also been reported,[17] as has the use of ω-alkenylalkyllithiums derived from the corresponding methyl selenide for the preparation of cyclopentanes.[18]

Organomanganese chloride reagents have been found to be chemoselective and high yielding when applied under copper catalysis at room temperature to the preparation of a range of functionalized alkanes, and minimal β-elimination was observed (**Scheme 6**).[19] Alkylzirconium derivatives obtained from the hydrozirconation of olefins have been alkylated in the presence of catalytic CuCN with activated halides or phosphonates (**Scheme 7**).[20]



$$C_4H_9MnCl + Br(CH_2)_5COC_4H_9 \xrightarrow[\text{THF–NMP, r.t.}]{3\%\ CuCl_4Li_2} \underset{90\%}{CH_3(CH_2)_8COC_4H_9}$$

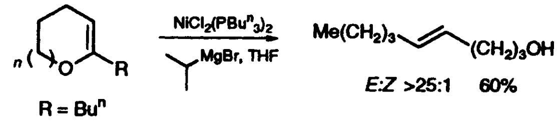
**Scheme 6**



**Scheme 7**

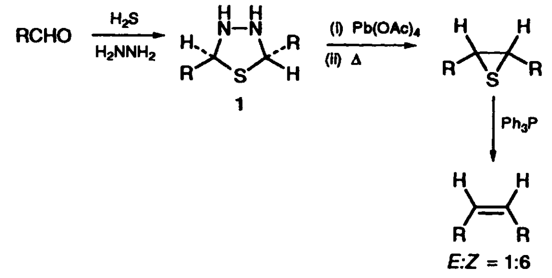
## 2 Olefinic hydrocarbons

Transfer hydrogenations of alkynes in the presence of a $Pd^0$ catalyst have been shown to proceed in a highly stereoselective manner to afford *Z*-alkenes,[21] as do new catalysts under standard hydrogenation conditions.[22,23] The nickel-catalysed reductive cleavage of cyclic enol ethers with a Grignard reagent, however, produces the corresponding *E*-alkenes (**Scheme 8**).[24]



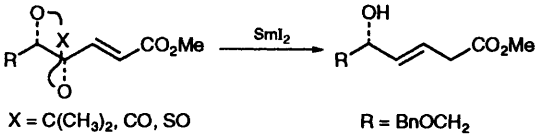
**Scheme 8**

A number of elimination procedures have been published during the period of this review, including the dehydration of benzylic and tertiary alcohols using molybdenum acetylacetonate,[25] and a two-fold extrusion reaction of 1,3,4-thiadiazolines **1** which provides stereoselectively unhindered *Z*-olefins (**Scheme 9**).[26]



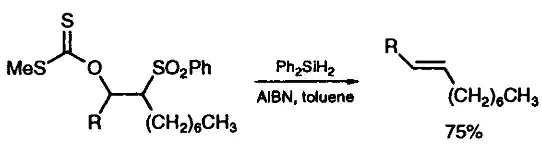
**Scheme 9**

An efficient decarbonylation–dehydration of aliphatic carboxylic acids using Pd- and Rh-based catalysts provides terminal olefins,[27] and the conversion of *cis-vicinal* dimethanesulfonates with alkali metal tellurides or selenides leads to the corresponding olefin.[28] Acetonides, together with cyclic carbonates or sulfites of γ, δ-dihydroxy-*E*-αβ unsaturated esters undergo reductive cleavage with $SmI_2$ to give δ-hydroxy-*E*-βγ-unsaturated esters in good yield (the use of magnesium affords the fully saturated ester) (**Scheme 10**).[29]



**Scheme 10**

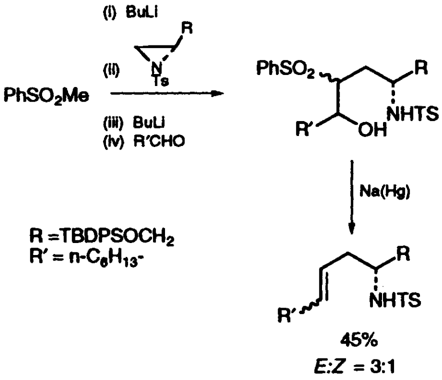
Methyl xanthate derivatives of β-hydroxy sulfones have been shown to undergo radical deoxygenation to yield the corresponding olefin in a modified Julia olefination, where the reductive elimination of the sulfone moiety can often be problematic (**Scheme 11**).[30]



**Scheme 11**

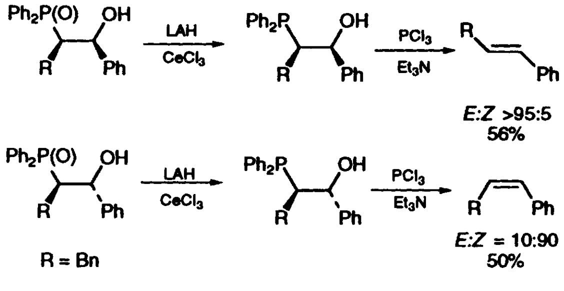
Enantiomerically pure *N*-tosyl homoallylic amines are obtained *via* a three component coupling reaction between a (phenylsulfonyl)-methane, enantiomerically pure *N*-tosylaziridines, and aldehydes to give

$\beta$-hydroxysulfones, which yield the corresponding olefins under Julia reductive elimination conditions (**Scheme 12**).[31]



**Scheme 12**

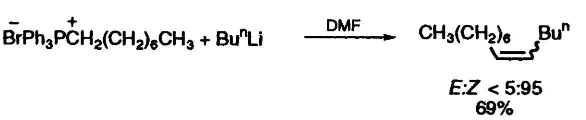
Horner–Wittig eliminations of $\beta$-hydroxyphosphine oxides in a variety of substrates has permitted the stereoselective synthesis of allylic and homoallylic amines, and non-conjugated unsaturated carboxylic acids;[32-34] and *erthyro-* and *threo*-phosphinyl alcohols provide *E*- and *Z*-alkenes, respectively, by an *anti*-elimination under acidic conditions, in contrast to the Horner–Wittig *syn*-eliminations (**Scheme 13**).[35]



**Scheme 13**

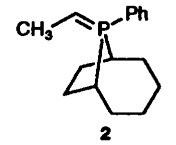
The use of $K_2CO_3$ and MeCN in Horner–Wadsworth–Emmons olefinations involving $\beta$-ketophosphonates prevents racemization of chiral centres in base sensitive phosphonates.[36]

The Wittig olefination reaction continues to be among the most popular methods for preparing alkene double bonds, but control of stereochemistry remains the key issue. A new one-pot, three-component procedure where the carbonyl moiety is derived from DMF has been reported to proceed with variable stereocontrol, but the best results were obtained with stabilized ylides and phosphonate esters (**Scheme 14**).[37]



**Scheme 14**

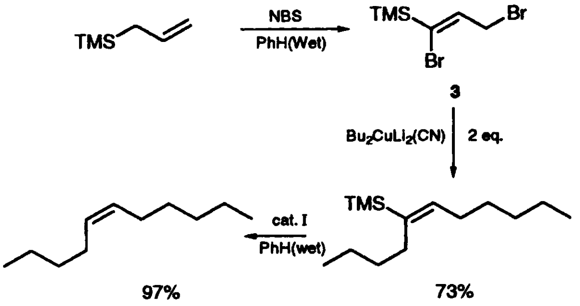
The bicyclic non-stabilized ylide **2** reacts with aldehydes to afford *E*-alkenes with high stereoselectivity; however, an inexpensive source of **2** is required before it becomes a general reagent.[38]



**2**

The application of cyclodextrin to the olefination reactions of aromatic aldehydes leads to only limited stereocontrol,[39] but tris(2-methoxy-methoxyphenyl)-phosphine has given good selectivities when employed with stabilized, $\alpha$-heterosubstituted ylides.[40,41]

A new method for the construction of geometrically pure alkene double bonds has been reported where, having prepared the key dibromide **3** exclusively as the *Z*-isomer, selective functionalization of both the bromide and the silicon atoms allowed elaboration to a number of derivatives (**Scheme 15**).[42]

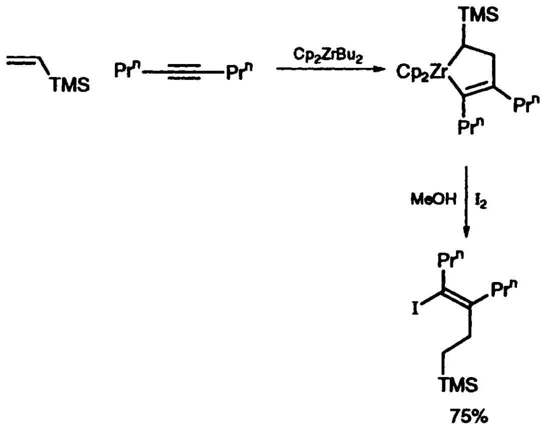


**Scheme 15**

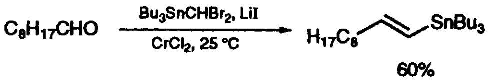
The number of procedures that utilize transition metals in the synthesis of double bonds continues to increase, including the isomerization of endocyclic double bonds to an *exo* position *via* a palladium-catalysed hydrogenolysis of allylic formates, sulfones, and nitro compounds,[43] the palladium-catalysed coupling of organoboron-derivatives with 1-alkenyl-triflates[44] and the development of a $Pd^0$ water soluble catalyst enabled Heck, boronic acid, and alkynyl coupling reactions, as well as allylic substitutions, to be carried out in aqueous media.[45]

The preparation of stereo-defined, functionalized olefins has become increasingly important because of their application in transition metal mediated couplings, and a number of new procedures for the preparation of these useful intermediates have been published; for example, the cross-coupling of alkynes and alkenes in the presence of Zr-complexes leads to the formation of zirconacyclopentenes which, following alcoholysis and iodination, afford stereoselectively trisubstituted alkenyl iodides · (**Scheme 16**).[46,47]

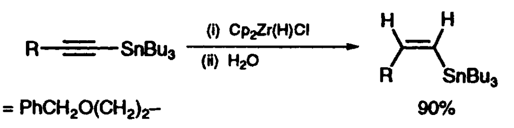
The conversion of aldehydes into *E*-alkenyl stannanes, including a facile one-pot procedure using chromium chemistry (**Scheme 17**),[48,49] of acyltins to vinyltins with phosphorus ylides,[50] and of tin-alkynes to *Z*-alkenyl stannanes using zirconium chemistry (**Scheme 18**),[51] have all been reported. Stannyl-cupration of acetylenes followed by quenching with a suitable electrophile affords substituted vinyl stannanes (**Scheme 19**).[52]



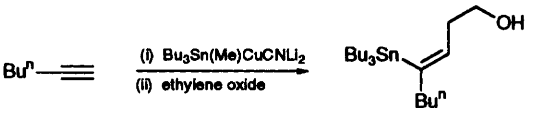
Scheme 16



Scheme 17

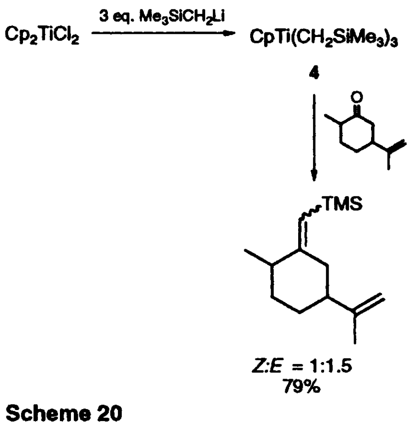


Scheme 18

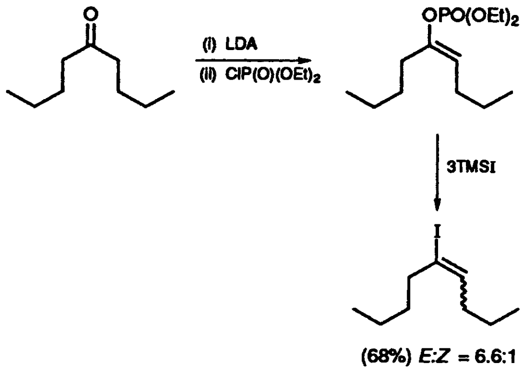


Scheme 19

Vinyl silanes have been prepared from a range of carbonyl compounds with the titanium (IV) reagent 4 (**Scheme 20**),[53] and a series of vinyl iodides are available through the action of TMSI on the appropriate vinyl phosphate which in turn are obtained from the corresponding ketones (**Scheme 21**).[54]



Scheme 20

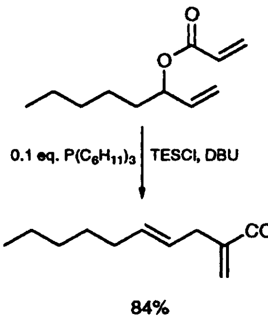


Scheme 21

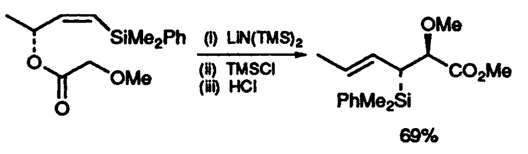
## 3 Stereoselective simultaneous formation of $sp^3$ and $sp^2$ centres

### 3.1 Claisen rearrangements

The synthetic utility of the Claisen rearrangement is further demonstrated this year in its application to the preparation of a number of different classes of compounds, including $\gamma$, $\delta$-unsaturated-aldehydes,[55] $\gamma$, $\delta$-unsaturated-trifluoromethylketones,[56] bicyclic lactones,[57] branched chain D-*myo*-inositols,[58] and cembranoids;[59] as well as its application in a general method of iterative cyclopentannulation.[60] The Ireland–Claisen rearrangement of allylic acrylates *via* phosphonium-substituted ester enolates has been achieved using only catalytic trialkylphosphine (**Scheme 22**),[61] and optically active *Z*-vinylsilanes rearrange to *anti*-$\alpha$-alkoxy-$\beta$-silyl-*E*-hexanoates with high diastereoselectivity (**Scheme 23**).[62]

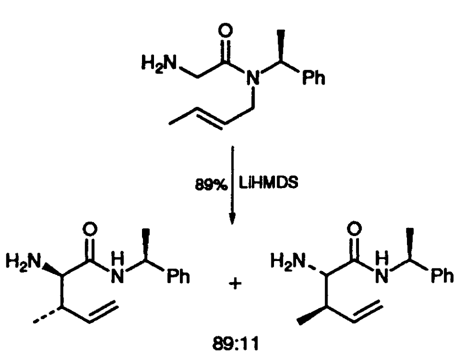


Scheme 22



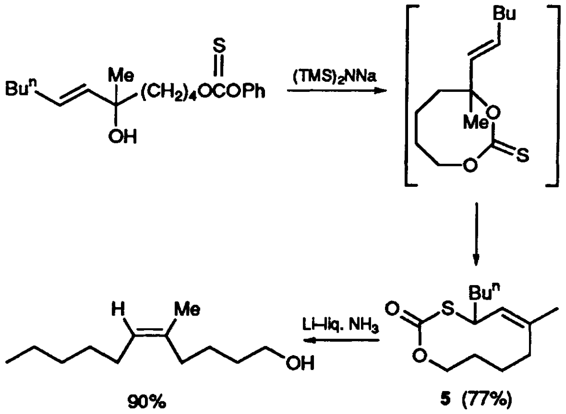
Scheme 23

The aza-Claisen rearrangement of enolates of the *N*-crotyl derivatives of glycolamide and glycinamide proceeds with high *syn*:*anti* selectivity, and the procedure has been developed using a chiral auxiliary to enable the synthesis of $\alpha$-hydroxy and $\alpha$-amino acids (**Scheme 24**).[63]



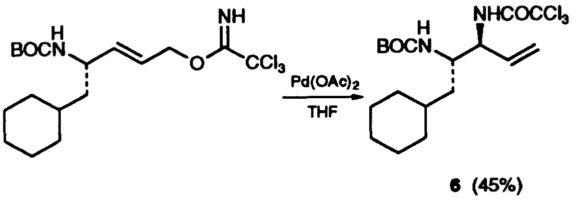
Scheme 24

Very mild, essentially neutral, conditions are reported to enable the 3-aza-Claisen rearrangement of *N*-allyl amides, using $I_2$, $P(OEt)_3$, and $Et_3N$.[64] The stereoselective construction of the *Z*- or *E*-double bond in the ten-membered thiolcarbonates **5** can be achieved by controlling chair-like transition states in the [3,3]-sigmatropic rearrangement of eight-membered thionocarbonates. The subsequent reductive desulfurization of **5** then affords tri- or tetra-substituted olefins (**Scheme 25**).[65]

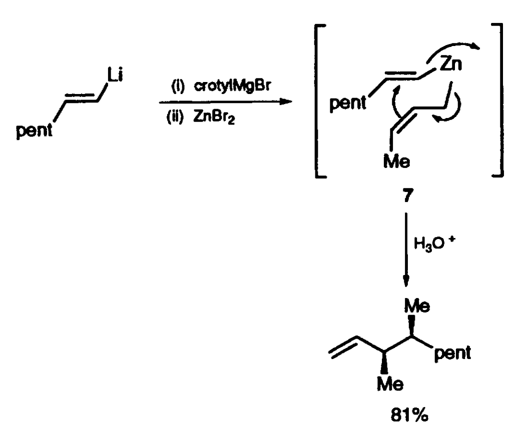


Scheme 25

Further studies on the thio-Claisen rearrangement illustrated that modest diastereoselectivity can be achieved.[66–68] A study of the [3,3]-sigmatropic rearrangement of chiral trichloroacetimidic esters has found that palladium catalysis enables stereoselective synthesis of the dipeptide bioisostere **6** (**Scheme 26**).[69] The interesting metalla-Claisen rearrangement involving **7** has enabled the stereoselective preparation of compounds with two adjacent stereocentres under very mild conditions (**Scheme 27**).[70]



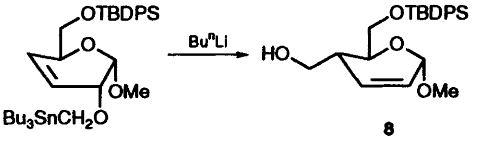
Scheme 26



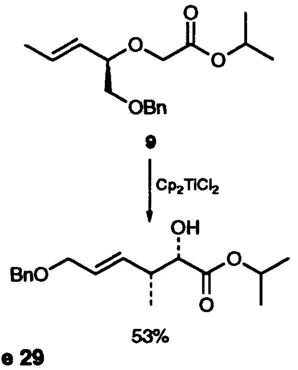
Scheme 27

### 3.2 Wittig rearrangements

The [2,3] Wittig rearrangement has been applied to a number of different targets, including subunits of herbimycin A[71] and rapamycin,[72] both from D-glucose, and to the preparation of the 4C-hydroxymethyl-hex-2-enopyranoside **8** (**Scheme 28**),[73] as well as to the synthesis of the racemic Ireland alcohol where the key reaction was a titanium-mediated rearrangement of **9** (**Scheme 29**).[74]

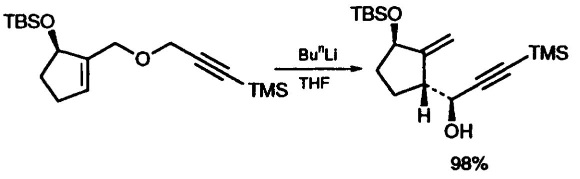


Scheme 28



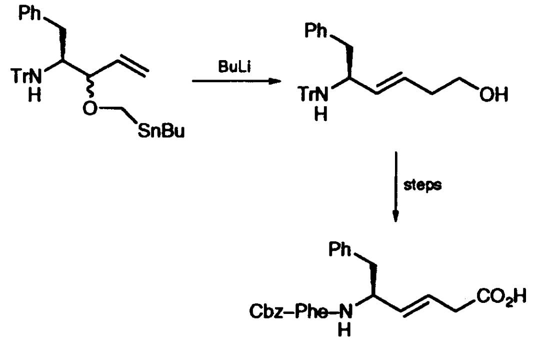
Scheme 29

The use of a tandem [2,3]-Wittig rearrangement followed by an anionic oxy-Cope rearrangement of propargyl ethers has enabled the synthesis of key precursors to (+)-faranal and (−)-antirhiene.[75] The application of [2,3]-Wittig rearrangement to (1-cyclopentenyl)methyl propargyl ethers was found to proceed with good stereocontrol (**Scheme 30**).[76]

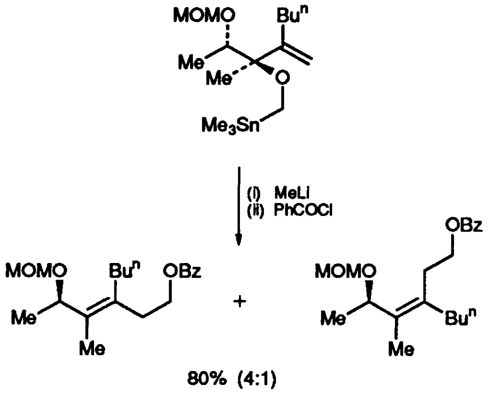


Scheme 30

A series of alkene dipeptide isosteres has been prepared using a Wittig–Still rearrangement (**Scheme 31**),[77] and the application of the rearrangement to tertiary allylic ethers has allowed the preparation of geometrically defined tetrasubstituted olefins with modest stereocontrol (**Scheme 32**).[78]

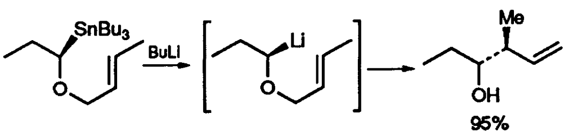


**Scheme 31**



**Scheme 32**

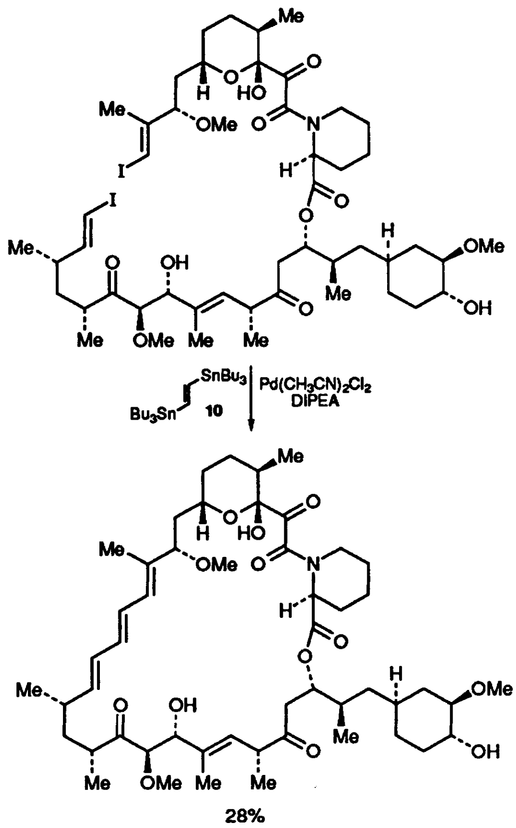
Further studies on the mechanism of the Wittig rearrangement suggest that the lithium-bearing terminus undergoes inversion rather than retention, as demonstrated by the use of enantiomerically defined α-(allyloxy)stannanes (**Scheme 33**).[79]



**Scheme 33**

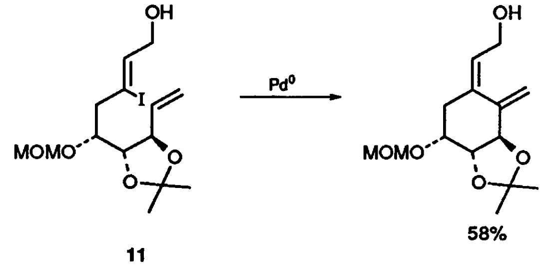
## 4 Conjugated dienes

Further extensions of the Stille methodology have been reported in the synthesis of 1,3-dienes, such as the stereocontrolled synthesis of enantiomerically pure dienylsulfoxides[80] or the use of alkenyl(phenyl)iodonium salts in cross-coupling reactions.[81] Two examples of macrocyclizations have been published using in one case a direct intramolecular Stille coupling in a synthesis of the polyene macrolactam leinamycin,[82] and in the other an insertion of the enedistannane **10** in a synthesis of rapamycin (**Scheme 34**).[83]



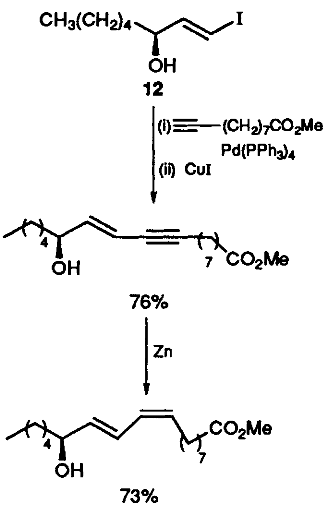
**Scheme 34**

An interesting communication has demonstrated that intramolecular coupling reactions of vinyl stannanes and vinyl halides can be achieved with just stoichiometric $Cu^I$ Cl in DMF, without any palladium catalyst.[84] A palladium-catalysed coupling reaction of β-stannylenoates with β-triflylenoates provides electron-deficient 1,3-dienes,[85] and the successful coupling of 2,2-difluorovinylboranes and vinyl halides to afford 1,1,-difluoro-1,3-dienes has been reported.[86] The synthesis of the chiral A-ring synthon for 1α,2β,25-trihydroxyvitamin $D_3$ was achieved using a palladium-catalysed cyclization of the *Z*-vinyl iodide **11** derived from D-mannitol (**Scheme 35**).[87]



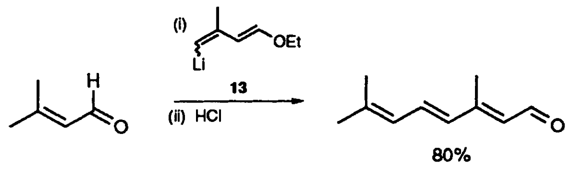
**Scheme 35**

The Pd–Cu catalysed reaction of the chiral vinyl iodide **12** with methyl dec-9-ynoate followed by selective reduction has afforded methyl coriolate (**Scheme 36**).[88]

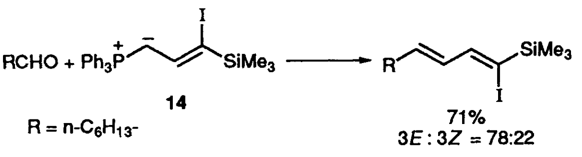


Scheme 36

A number of procedures involving the conversion of carbonyl moieties into 1,3 dienes, including the use of lithiodienol ethers **13** (**Scheme 37**)[89] and 3-iodo-3-trimethylsilylallylic phosphonium ylide **14** to furnish 1-iodo-1-trimethylsilyl-1,3-dienes with high stereoselectivity (**Scheme 38**),[90] have been reported.



Scheme 37

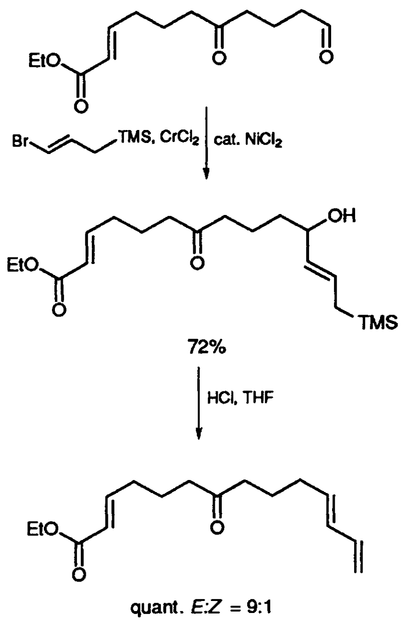


Scheme 38

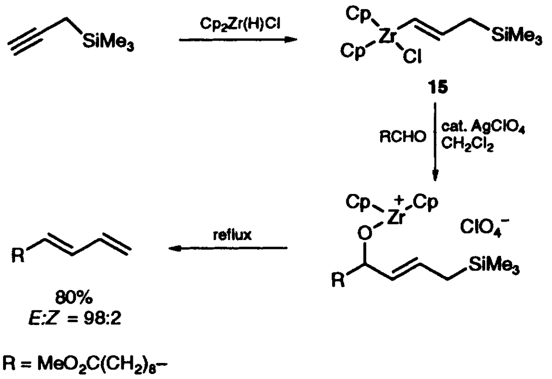
Two methodologies utilizing vinologous Peterson olefination of aldehydes were reported, one in which a chromium-mediated coupling reaction of 1-bromo-3-trimethylsilylpropene affords allylic hydroxysilanes and subsequently 1,3-dienes. This approach takes advantage of the chemoselectivity of chromium organometallics (**Scheme 39**).[91] Similarly, the coupling of trimethylsilyl-1-propenyl-zirconocene chloride **15** with aldehydes in the presence of $AgClO_4$ followed by 1,4-eliminations has provided 1,3-dienes (**Scheme 40**).[92,93]

γ-Trimethylsilyl crotonaldimine **16** enables a fluoride-mediated four-carbon homologation of aldehydes (**Scheme 41**),[94] and the condensation of the allylborane **17** with heterocyclic aldehydes followed by base induced Peterson olefination leads to 1,3-diene derivatives (**Scheme 42**).[95]

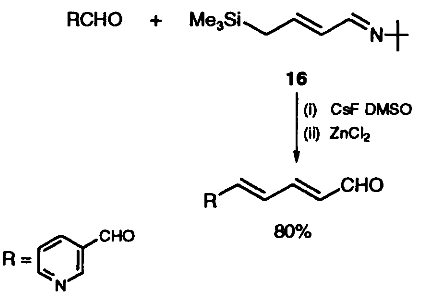
A variety of 2-phenylthio-1,3-dienes have been prepared through the palladium-catalysed



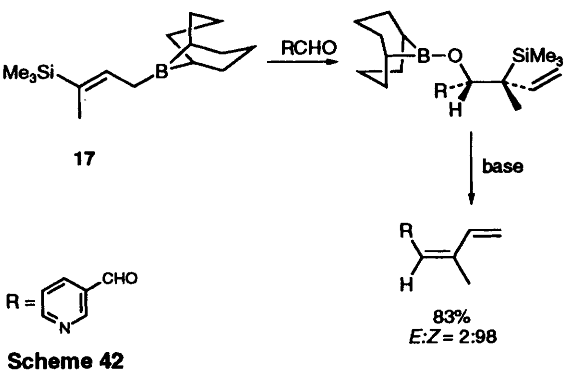
Scheme 39



Scheme 40



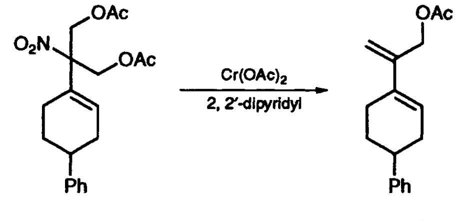
Scheme 41



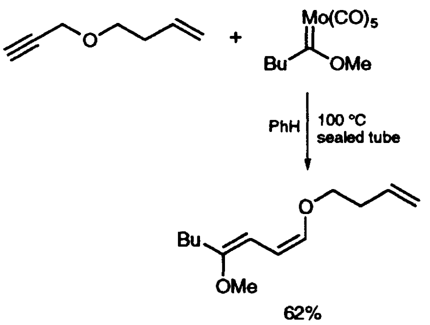
Scheme 42

cross-coupling reaction of $\alpha$-allenyl acetates under nonbasic conditions.[96]

Substituted 1,3-dienes are also prepared by the reductive elimination of allylic nitro derivatives (**Scheme 43**),[97] and 1,4-dialkoxy-1,3-dienes can be prepared stereoselectively by the thermolysis of molybdenum carbene complexes in the presence of propargyl ethers instead of the expected cyclic ethers (**Scheme 44**).[98] A range of 2,3-disubstituted-1,3-butadienes have been prepared from organotin and butadienyl-lithium reagents.[99]

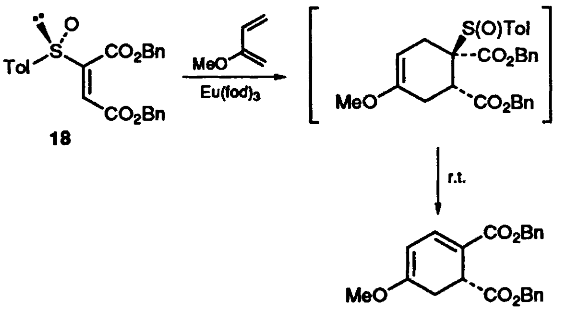


**Scheme 43**



**Scheme 44**

Several 1,3-cyclohexadienedicarboxylate esters of high stereopurity have been prepared with the new dienophile benzyl methyl-(*S*)-2-(*p*-tolylsulfinyl)-maleate **18** through a $TiCl_4$ promoted Diels–Alder reaction, followed by spontaneous sulfinyl elimination (**Scheme 45**).[100]

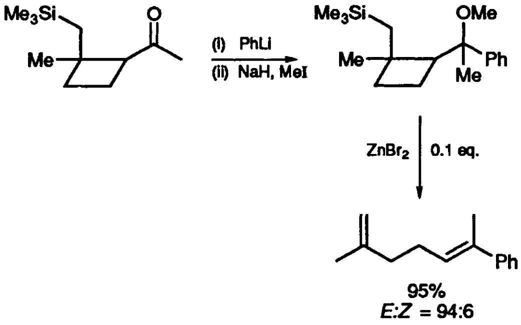


**Scheme 45**

## 5 Non-conjugated dienes

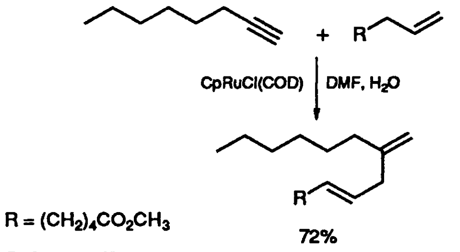
A typical approach to the synthesis of non-conjugated diene systems is illustrated in the synthesis of eicopentaenoic acid where ozonolysis, selective reduction, and Wittig reactions are used to produce the required *Z*-skipped diene.[101] Another example is the preparation of a sex pheromone through the alkylation of a terminal acetylene and subsequent selective reduction to give an *E,Z*-1,6-diene system.[102]

Newer approaches that have been published include the 1,4-elimination of 1-methoxymethyl-2-(trimethylsilylmethyl)cyclo-butanes, promoted with catalytic $ZnBr_2$, to furnish 1,2,5-trisubstituted-1,5-dienes stereoselectively (**Scheme 46**).[103]

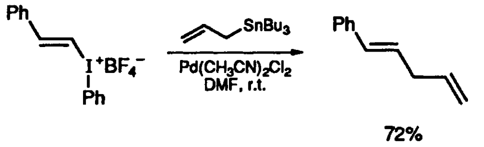


**Scheme 46**

Additions of alkenes to acetylenes in the presence of catalytic Cp(COD)RuCl affords 1,4-dienes (**Scheme 47**)[104] and the cross-coupling under palladium catalysis of alkenyl(phenyl)iodonium salts with allyl stannanes (**Scheme 48**) also leads to 1,4-dienes.[81]



**Scheme 47**

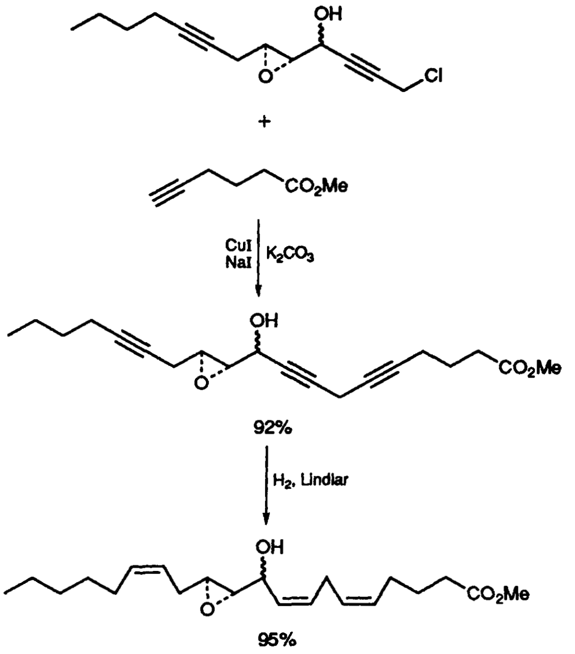


**Scheme 48**

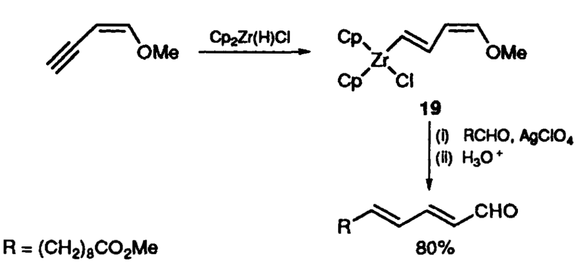
## 6 Polyenes

The use of acetylenic coupling reactions with vinyl halides leading to 1,3-enynes and subsequent stereoselective reduction is illustrated well in a new synthesis of lipoxin $B_4$.[105] The coupling reaction between a terminal acetylene and a propargyl chloride under mild conditions in the presence of only CuI, NaI, and $K_2CO_3$ has allowed the preparation of hepoxilin $B_3$ epimers (**Scheme 49**) using the same overall strategy.[106]

The straightforward derivatization of aldehydes with preformed reagents is a common approach, and is demonstrated in the use of the $\delta$-alkoxydienyl zirconocene complex **19** which enables a four-carbon homologation reaction which can be used in an iterative manner (**Scheme 50**).[107] The development of

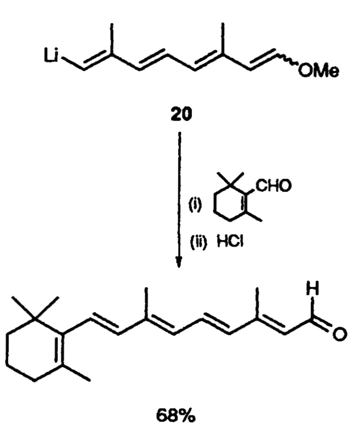


**Scheme 49**



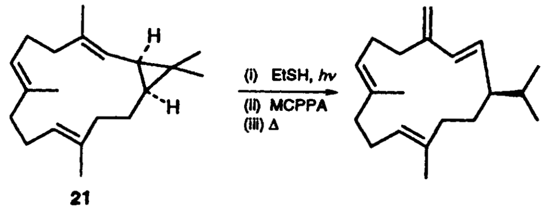
**Scheme 50**

a synthetic equivalent to ω-lithio dehydrocitral **20** has enabled the expedient preparation of retinoid aldehydes (**Scheme 51**),[108] and a reaction sequence involving Arbuzov rearrangement of allyl phosphites followed by Horner–Wadsworth–Emmons olefination provides substituted trienes and tetraenes stereoselectively from aldehydes.[109] Straightforward Wittig olefinations have also been used in the preparation of polyene oligomers.[110,111]

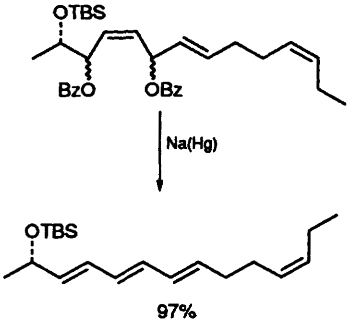


**Scheme 51**

The synthesis of carotenoid alkylidene butenolides has now been developed, utilizing sulfone chemistry in order to avoid the more drastic reaction conditions required by Wittig chemistry.[112] The use of alternative radical ring-opening reactions of vinylcyclopropanes has allowed the stereocontrolled elaboration of the diterpene casbene **21** into a number of different cembranes.[113]

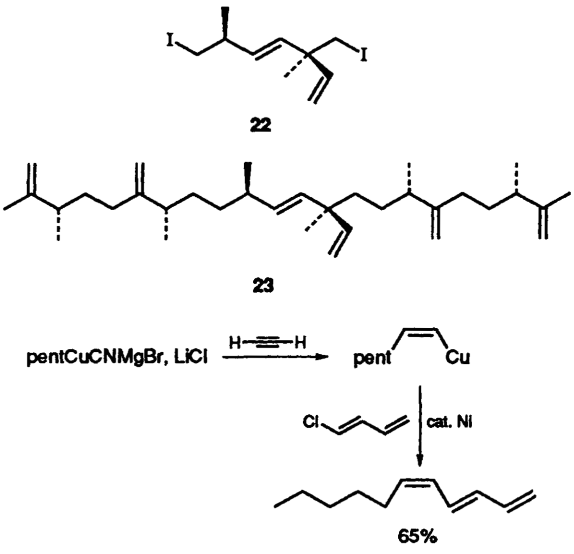


A stereoselective synthesis of conjugated all-*E* trienes uses Na(Hg) amalgam for a reductive elimination of 1,6-dibenzoate-2,4-dienes instead of low-valent titanium and is thus more tolerant of other functional groups present (**Scheme 52**),[114-117] has been described.



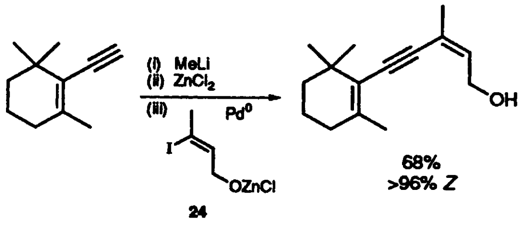
**Scheme 52**

A cuprate coupling reaction with the alkyl diiodide **22** has formed the key step in a synthesis of ( − )-$C_{34}$-botryococcene **23**,[118] and the carbocupration of acetylene followed by *in situ* coupling with chlorobutadiene in the presence of catalytic $NiCl_2(PPh_3)_2$ has facilitated the stereoselective addition of a triene unit onto a Grignard reagent (**Scheme 53**).[119]



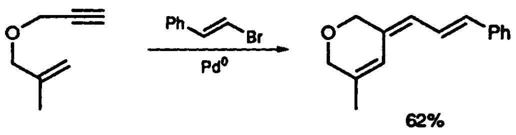
**Scheme 53**

The palladium-catalysed cross-coupling reaction of the organozinc **24** without protecting groups has been used in an approach to the synthesis of carotenoids and retinoids (**Scheme 54**).[120]



**Scheme 54**

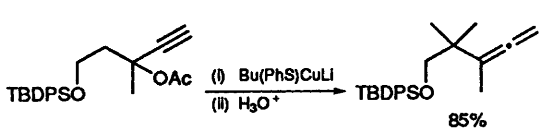
An extension of intramolecular cyclizations of 1,6-eneynes containing a terminal acetylene has afforded triene units stereoselectively when the reactions are carried out in the presence of a vinyl halide under palladium catalysis (**Scheme 55**).[121] The importance of Stille coupling methodology in polyene synthesis is further demonstrated in a syntheses of the C-1–C-14-tetraene nitrile unit of calyculin A[122, 123] and for stable linear polyenes.[124]



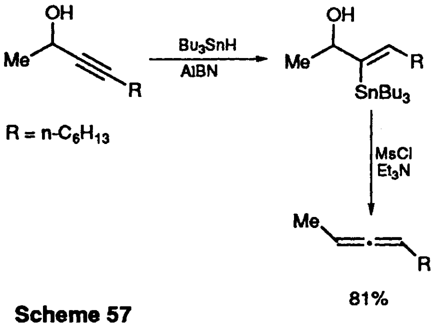
**Scheme 55**

## 7 Allenes

The use of propargylic derivatives as precursors to allenic moieties is further illustrated by the synthesis of terminal allenes from the action of lithium butyl(phenylthio)cuprate on propargylic acetates (**Scheme 56**).[125] The hydrostannation of propargylic alcohols, and subsequent deoxystannylation, produces allenes in a two-step, one-pot operation (**Scheme 57**).[126]

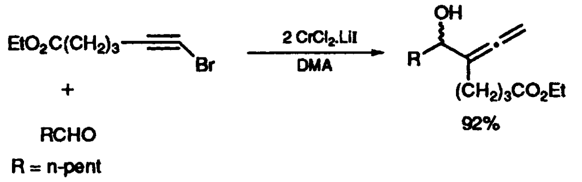


**Scheme 56**



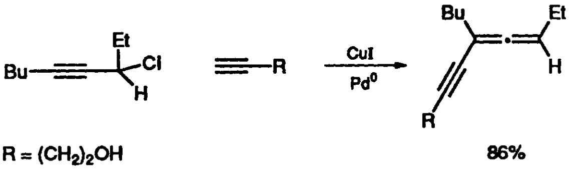
**Scheme 57**

The additions of functionalized propargylic halides to aldehydes or ketones have been accomplished in the presence of $CrCl_2$ to give functionalized allenic derivatives not normally accessible by this type of approach (**Scheme 58**).[127]

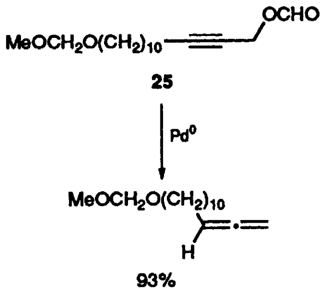


**Scheme 58**

Simple additions of propargylic halides, tosylates, and acetates to terminal alkynes in the presence of $Pd^0$ lead efficiently to conjugated allenynes (**Scheme 59**),[128] and a series of allenol lactones have been prepared from propargylic acetates and 4-pentynoic acid, also using palladium catalysis.[129] The palladium-catalysed conversions of terminal propargylic formates **25** into terminal allenes have also been reported (**Scheme 60**).[130]

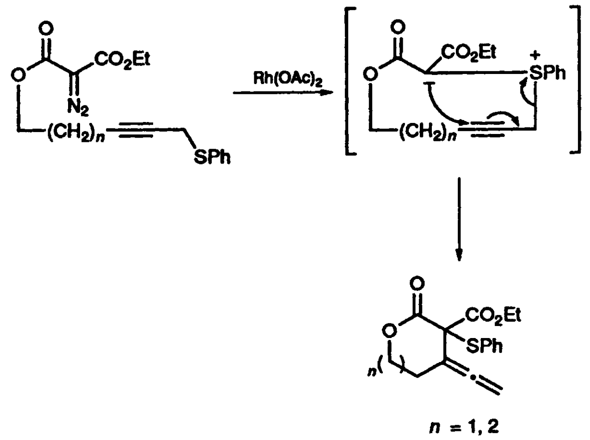


**Scheme 59**

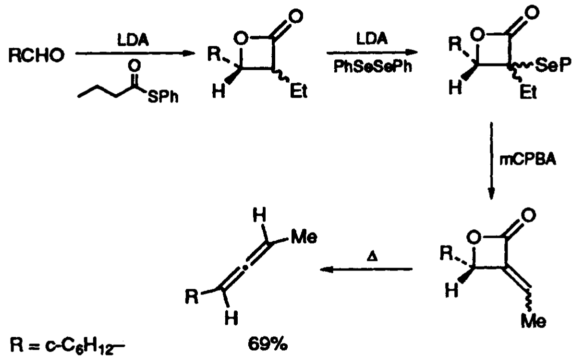


**Scheme 60**

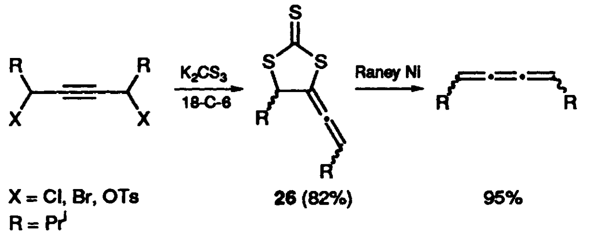
Two examples of the synthesis of allenes using [2,3]-sigmatropic rearrangements have been published. One example uses cyclicpropargylsulfonium ylides and affords terminal allenic lactones (**Scheme 61**),[131] and another utilized a dienylselenide to furnish an allenic system which was then applied in a synthesis of an anti-fungal agent.[132]
A [2 + 2] cycloreversion reaction involving $\alpha$-alkylidene-$\beta$-lactones has allowed the preparation of substituted allenes (**Scheme 62**),[133] and a procedure for the synthesis of isocyanate substituted allenes has been published.[134] The use of Raney nickel for the desulfurization of dithiolanes such as **26** has extended this approach to 1,3-butatrienes, to include alkyl substituted systems (**Scheme 63**).[135]



**Scheme 61**



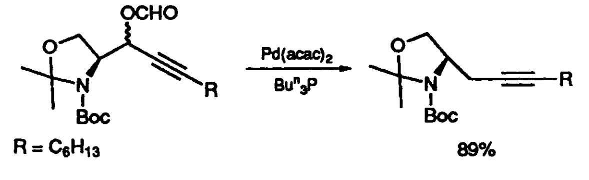
**Scheme 62**



**Scheme 63**

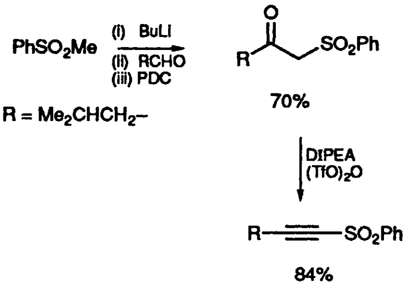
## 8 Alkynes

The preparation of 1,2-disubstituted alkynes by decarboxylation–hydrogenolysis of propargyl formates is of great synthetic importance given the ease of formation of the latter (**Scheme 64**).[130]



**Scheme 64**

Synthetic procedures for the preparation of a number of acetylene derivatives have been published, including: chloroacetylene,[136] 1-(phenylsulfonyl)-1-alkynes from aldehydes or $\varepsilon$-caprolactone *via* $\beta$-ketosulfones (**Scheme 65**),[137] unsymmetrical 1,2-bis-(perfluoro)ethynes *via* dehydroiodination,[138] chiral propargylic amines by the conversion of optically active amine aldehydes using dimethyl diazophosphonate,[139] 3-acetoxy-3-alkoxy propynes through hypervalent iodine oxidation of alkoxy allenes.[140]



**Scheme 65**

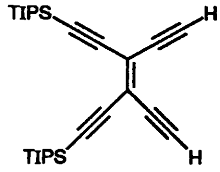
Homopropargylic alcohols have been synthesized from the allenylboration of aldehydes and ketones,[141] whereas $\gamma$-hydroxy alkynes are derived from the dichloromethylene derivatives of lactones by reductive elimination with lithium metal.[142] Alkynyl alcohols have been produced from $\alpha$-chloroenones which are themselves derived from the aldol condensation of 1-bromo-1-chloro ketones followed by dehydration.[143]

The preparation of ethyl arylpropiolates is possible using palladium-catalysed cross-coupling reactions of terminal alkynes with aryl iodides.[144] In a number of other studies success without palladium catalysis was reported such as the coupling between aryl- or vinyl-halides and terminal alkynes using catalytic CuI–2PPh$_3$.[145] Similarly, the condensation of terminal functionalized alkynes with propargylic tosylates or chlorides using $K_2CO_3$, NaI, and CuI at room temperature,[146] and with CuI, $Na_2CO_3$, and $Bu_4NCl$ at room temperature have been reported.[147] The potential use of these last two routes as a convenient stereoselective route into skipped diynes, triynes, dienes, and trienes cannot be ignored.

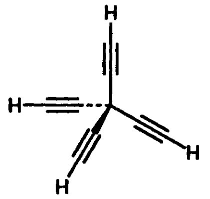
The synthesis of a range of cyclic dialkynes using the dilithium salts of terminal alkynes has been reported, along with the preparation of a series of symmetrically disubstituted diacetylenes with polychlorophenyl rings as side groups, and linear polyether chains as spacers.[148,149] There is much interest in the properties of polyacetylenic compounds and this is reflected in the growing number of preparations reported, such as the synthesis of hexabutadiynylbenzene *via* palladium-catalysed coupling of terminal alkynyl units,[150] whereas copper catalysis proved much more successful in the synthesis of tribenzocyclotriyne.[151] The successful synthesis of a series of selectively protected tetraethynylethenes, such as **27**, has allowed the preparation of [18]- and [12]-annulenes to be completed *via* oxidative cyclization, and also of mono cross-conjugated compounds.[152,153]
The synthesis of stable tetraethynyl-butatriene has been described, along with the total synthesis of tetraethynyl-methane **28**, which is quite an

achievement considering the steric demands of the quarternary centre.[154,155] The syntheses of diethyl-dipropargyl- and tetrapropargyl-methane have also been published.[156]

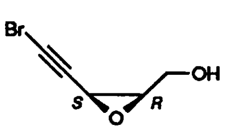
A general asymmetric approach towards the synthesis of *cis*-epoxy polynes, which are naturally occurring antifeedants, has been described and uses optically pure (2*R*,3*S*)-5-bromo-2,3-epoxy-4-pentyn-1-ol **29** as the key intermediate in a copper-catalysed cross-coupling reaction with terminal alkynes.[157,158]



**27**



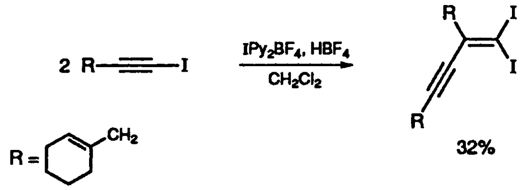
**28**



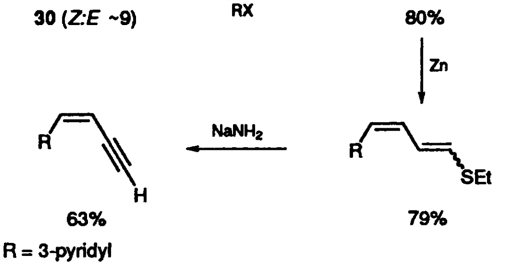
**29**

## 9 Enynes

The direct coupling of terminal alkynes with vinyl iodides using catalytic CuI-PPh$_3$ in the presence of K$_2$CO$_3$ affords eneynes with retention of configuration and without the need for palladium catalysis.[159] Similarly, the derivatization of l-iodoalkynes, mediated with catalytic IPy$_2$BF$_4$–HBF$_4$, affords head to tail eneynes (**Scheme 66**).[160] The enyne sulfide **30** is readily converted into 1,3-diene derivatives which lead to *Z*-enyne products following the elimination of ethanethiol with excess sodamide (**Scheme 67**).[161]



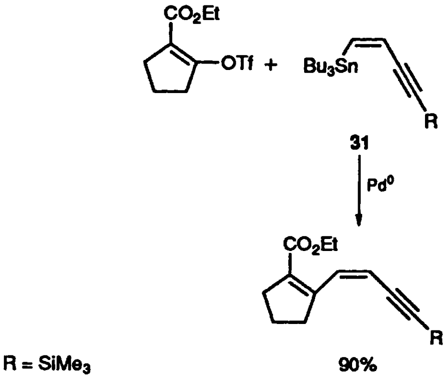
**Scheme 66**



**Scheme 67**

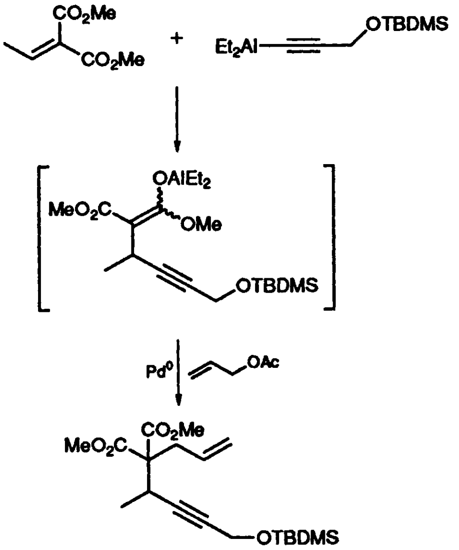
Disubstituted propynyl alcohols can be dehydrated using PdCl$_2$(PPh$_3$)$_2$ and SnCl$_2$ under neutral conditions to afford *Z*-but-3-en-1-ynes.[162]

*E*-Conjugated eneynes bearing an acetal function on the allylic, propargylic, homoallylic, or homopropargylic position were prepared by the facile palladium-catalysed coupling of the corresponding vinyl tins with 1-bromo-alk-1-ynes.[163] Elaboration of eneyne linchpins such as **31** using palladium catalysis and enol triflates has enabled the rapid building of polyenyne structures (**Scheme 68**).[164]



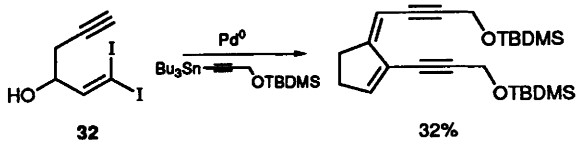
**Scheme 68**

The preparation of a range of skipped cyclic ene- and diene-diynes by the addition of dilithium salts of diterminal enediynes to the appropriate dihalogenides has been reported.[165] The addition of alkynylalanes to alkylidene-malonates followed by palladium-catalysed allylation allows the construction of 1,6-eneynes in a single operation (**Scheme 69**).[166]



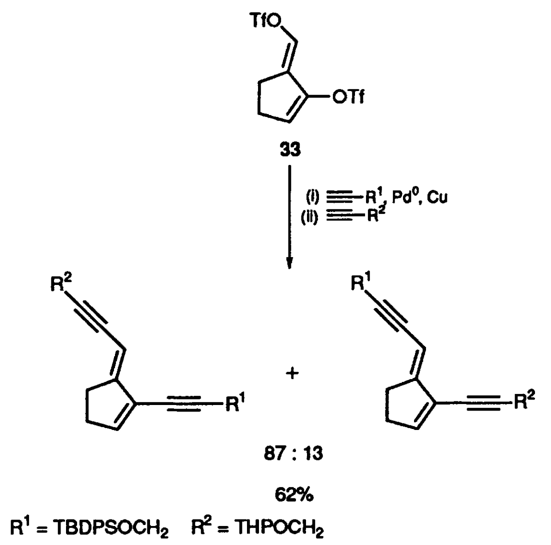
**Scheme 69**

The discovery of powerful anti-tumour antibiotic enediyne natural products has stimulated considerable interest, since their complex structures and mode of action are novel and their biological activity is potent. There has been an ever increasing number of publications about these exquisite molecules, ranging from model studies to total synthesis. Thus, the synthesis of enediynes by the reaction of bicycloalkenyldiiodinium salts with lithiumalkynyl cuprates,[167] and the conversion of the diiodide **32** into enediynes using palladium-mediated chemistry has been reported (**Scheme 70**),[168] along with an analogous approach using a dibromide.[169]

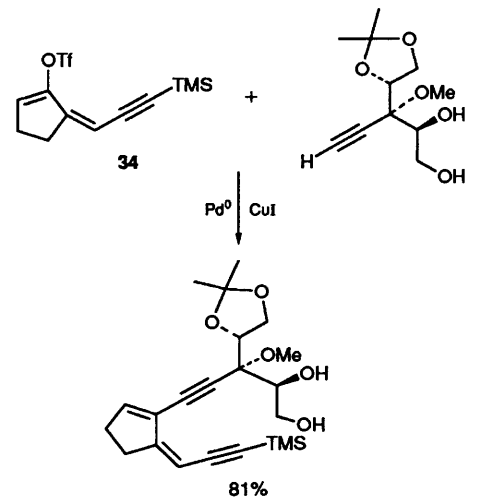


**Scheme 70**

The consecutive palladium-catalysed coupling reactions of the *E*-bis(enoltriflate) **33** with two different alkynes in a one-pot reaction have afforded mixtures of dienediynes with some degree of selectivity (**Scheme 71**),[170] and application of this approach with *Z*-enoltriflate **34** has realized the successful synthesis of chiral dienediynes (**Scheme 72**).[171]

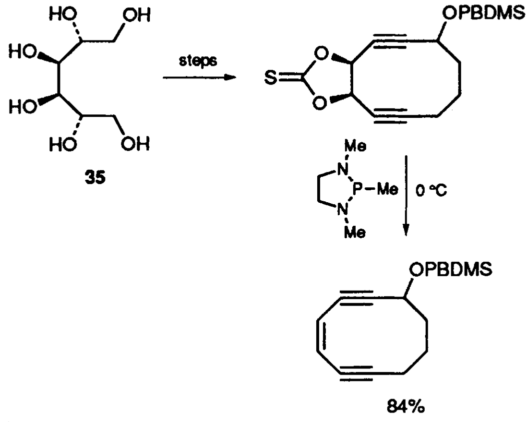


**Scheme 71**



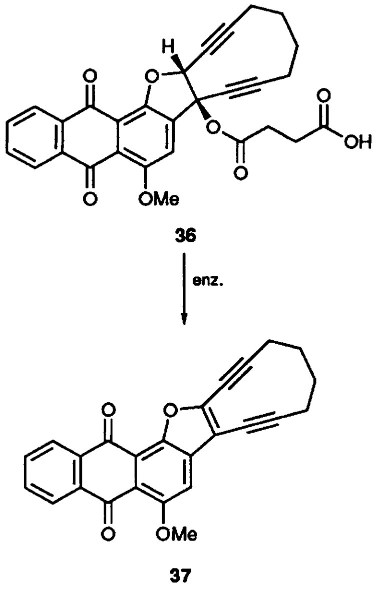
**Scheme 72**

An interesting conversion of dulcitol **35** into the *Z*-hex-3-ene-1,5-diyne unit has been published. It uses a Corey–Winter reaction involving the elimination of thionocarbonate for the introduction of the ene unit (**Scheme 73**).[172]

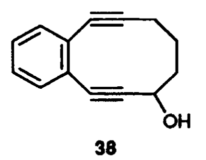


**Scheme 73**

The enzymatic conversion of the anthraquinone **36** into the enediyne **37** has been reported (**Scheme 74**),[173] as has the conversion of *o*-dibromobenzene, using palladium catalysis, into the diyne **38** which was eventually elaborated to CDPI$_3$-enediyne.[174]



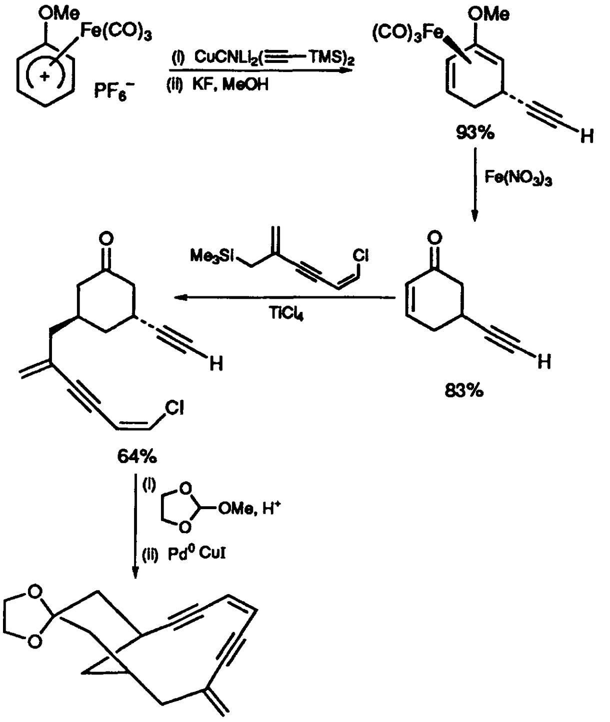
**Scheme 74**



**38**

The first total synthesis of calicheamicin $\gamma_1$I has been reported,[175] and a number of different approaches to the core structures of these molecules have been published. An allylic diazene rearrangement was used in a synthesis of the tricyclic core of dynemicin,[176] and a [2,3]-Wittig rearrangement of a cyclic enediyne ether was used in a synthesis of a bicyclic core.[177]

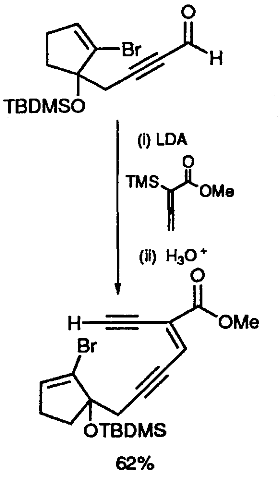
An intramolecular [3,4]-ene reaction has provided a bicyclic subunit of these anti-tumour agents,[178] and a preparation of the bicyclic enediyne **39** has been achieved using a series of iron-, copper-, titanium-, silicon-, and palladium-mediated reactions (**Scheme 75**).[179]



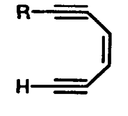
**39** (20%)

**Scheme 75**

The conversion of propargylic aldehydes into acyl substituted enediynes has been achieved using enolates derived from $\alpha$-trimethylsilyl-$\alpha$-allenyl carbonyl compounds (**Scheme 76**),[180] and enediyne synthons like **40** have been utilized in the preparation of a new class of enediyne compound, where the final cyclization was mediated by chromium salts (**Scheme 77**).[181]

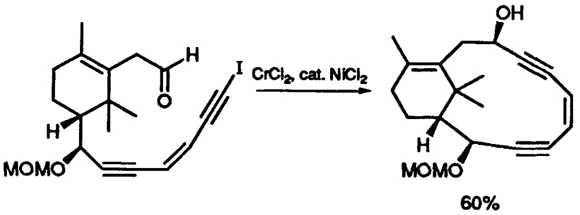


**Scheme 76**



R = Bu$^t$Ph$_2$Si, Pr$^i_3$Si

**40**



**Scheme 77**

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