Saturated oxygen heterocycles

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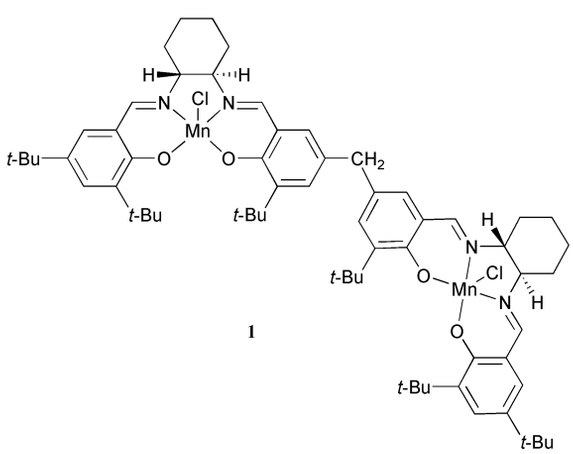
1 Introduction

As with previous reviews in this series, the recent literature on three to nine-membered oxygen heterocycles has been surveyed. Only those systems with a single heteroatom have been covered, with the exclusion of cyclic acetals and ketals. Again, while sugar derivatives have not been generally included, there are inevitably examples of pyran synthesis which owe much to this rich area of chemistry.

Given the large number of publications in this area, no attempt has been made at comprehensive coverage. We have elected to focus on short communications for the most part, with full papers describing work covered in the previous reviews merely being cited, and not discussed in detail. Where previous work has been alluded to without citation, these references can be found in the previous reviews.

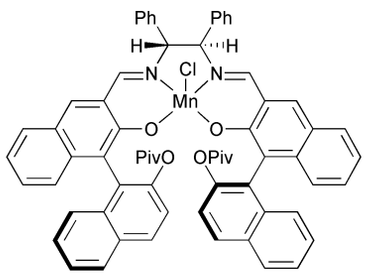
2 Three-membered rings

Dimeric catalyst **1** has been used in the Jacobsen–Katsuki epoxidation. While this system offers no obvious advantage for the enantioselectivity, it can be used at lower catalyst loadings than is usual, and is readily precipitated from the reaction mixture by addition of hexane, allowing ready recycling.[2] Furthermore, urea–hydrogen peroxide can be used as terminal oxidant with this catalyst.[3]



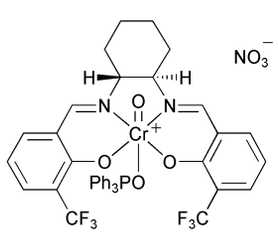
1

Katsuki has previously reported particularly hindered salen ligands featuring axial chirality at the aromatic rings. New developments along these lines have provided easily accessible complexes such as **2**, prepared from BINOL, which give enantioselectivities comparable or in some cases superior to the "standard" Jacobsen catalysts.[4]



2

While the oxomanganese-salen intermediate in such epoxidations has never been isolated, the corresponding oxochromium species is readily accessible. Enantiomeric excesses of greater than 90% have now been obtained using complex **3** stoichiometrically, while lower selectivities were obtained in the catalytic reaction. It is noteworthy that this system performs better in the epoxidation of *trans*-alkenes, and that bulky substituents on the aromatic ring are not required for high selectivity.[5] There are two distinct differences between chromium and manganese-salen complexes which must be borne in mind. In the former case, enantioselectivity is better for *trans*-alkenes, and bulky substituents on the aromatic rings are not essential. However, as a result of a systematic study of substituent effects, it is proposed that two different trajectories of alkene approach may be operative, both giving rise to the same enantiomer. It seems likely that chromium-salen complexes are less planar than their manganese counterparts, and this may account for the differences between the two systems.[6] Recent computational studies have provided further insight into this aspect.[7]



3

Molecular oxygen is the ultimate clean oxidant! For the first time, Gaillon and Bedioui have demonstrated the electrochemically assisted activation of molecular oxygen by a manganese salen complex in an ionic liquid. However, scant mention of alkene epoxidation was made in this initial report.[8]

Supported chiral catalysts often give lower enantioselectivity than their homogeneous counterparts. However, in the case of a polymer-supported salen ligand, prepared from a

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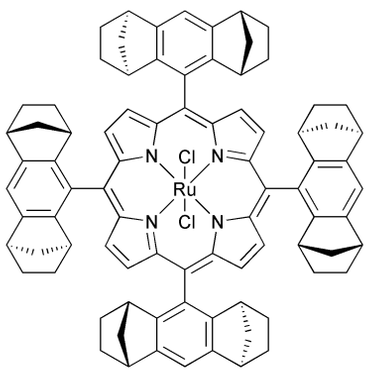
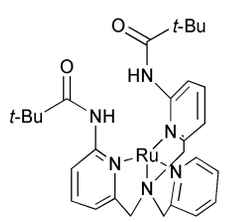
styryl-substituted salen (including dendrimers) the enantioselectivities obtained are only marginally lower in optimal cases.[9] Other work in this area includes the development of phenylacetylene-substituted[10] and perfluoroalkyl-substituted[11] manganese-salen complexes, while a full account of the development of ruthenium-salen complexes for the photoactivated asymmetric epoxidation of alkenes has recently appeared.[12]

Ruthenium-porphyrin **4**, with D_4 symmetry, has been shown to be effective for the asymmetric epoxidation of a range of conjugated alkenes, with superior enantioselectivity being observed for *cis*-olefins (up to 80% ee).[13]



4

Complementarity between epoxidation and C–H oxidation was observed in the case of ruthenium complexes **5** and **6**. While **5**, with electron-withdrawing substituents at two of the pyridine 6-positions, proved better for epoxidation, **6** gave higher chemoselectivity in C–H oxidation reactions.[14]



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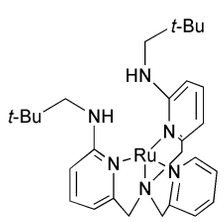
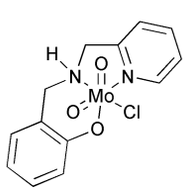


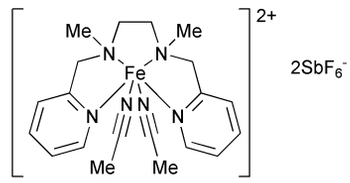
6

Epoxidation with Mo(VI) species often exhibits complex kinetics, so that the mechanism has been the source of much debate. One postulated mechanism involves the simultaneous coordination of the alkene and alkyl hydroperoxide, followed by rearrangement to a metallacycle. Complexes such as **7**, featuring tridentate ligands, should not accommodate such additional coordination, and yet still function as effective catalysts, supporting a mechanism involving direct oxygen transfer.[15] A DFT study of the biphasic epoxidation of alkenes by oxomolybdenum species shows that acid catalysis is a factor in this epoxidation, while suggesting that dimeric catalysts do not play a significant role.[16] Further computational studies on the epoxidation of allylic alcohols by methyltrioxorhenium have also been reported.[17]



7

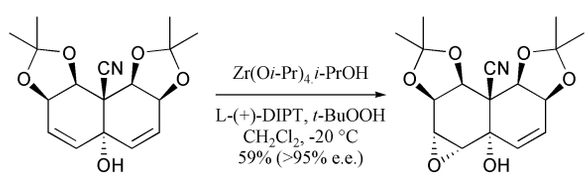
The effective use of hydrogen peroxide as a terminal oxidant is still an important goal. Iron complex **8** functions well in this regard, allowing epoxidation of a range of simple alkenes within 5 minutes. It was shown that the complex is oxidised under the reaction conditions to give a bridged dimer reminiscent of the active site of methane monooxygenase.[18]



8

Manganese(II) sulfate (1 mol%) in a mixture of aqueous sodium carbonate and DMF also provides an efficient catalytic system, although a large excess of hydrogen peroxide is required. This combination of reagents is environmentally friendly, and can be used on a large scale. Cyclooctene oxide was formed in 67% yield on a 1 molar scale by this method.[19] With trifluoroethanol as solvent, no catalyst is even needed, although a small amount of phosphate buffer proved beneficial![20]

In studies directed towards hypoglaunine B and related natural products, Spivey *et al.* have demonstrated the desymmetrisation of a *meso* doubly allylic alcohol using Sharpless methodology. Thus, epoxidation of **9** gave **10** with excellent enantioselectivity and good yield. The use of zirconium proved critical with the hindered tertiary alcohol, facilitating the formation of eight contiguous stereogenic centres in a single step (Scheme 1).[21] Kinetic resolution of racemic allylic alcohols

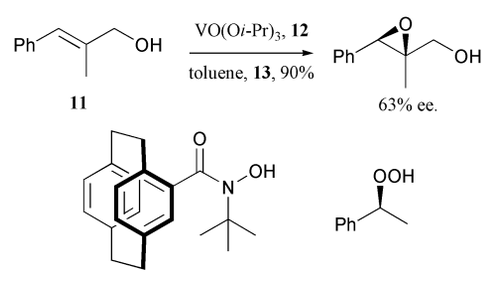


9 **10**

Scheme 1

under Jacobsen–Katsuki epoxidation conditions has also been reported.[22]

In a further example, this time showing double stereodifferentiation, the beneficial effect of using the matched enantiomer of a chiral hydroperoxide was demonstrated. Using (*R*)-hydroxamic acid **12** in conjunction with (*S*)-hydroperoxide **13**, alkene **11** was epoxidised with 63% ee (Scheme 2). However,



11 63% ee.

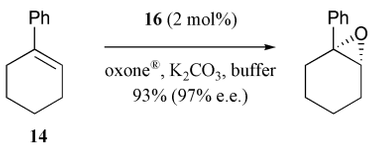
12 **13**

Scheme 2

with this hydroperoxide the enantiomeric (*S*)-hydroxamic acid gave only 33% ee, while the racemic hydroperoxide gave 49% ee. Nevertheless, *tert*-butyl hydroperoxide still provided the best enantioselectivity at 72% ee.[23]

The use of nonmetal catalysts for the oxidation of organic substrates has been reviewed, with a significant emphasis on the use of dioxiranes and oxaziridines in epoxidation.[24] Shu and Shi have presented a detailed account of their use of hydrogen peroxide in acetonitrile as terminal oxidant for asymmetric

dioxirane-mediated epoxidations.[25] The same group have investigated the Baeyer–Villiger oxidation of their standard catalyst **15**, and as a result developed ketone **16** which can be used in much lower catalyst loadings. For instance, in the epoxidation of **14**, excellent enantioselectivity and conversion was obtained with only 2 mol% catalyst, compared to the 20–30 mol% required with ketone **15** (Scheme 3).[26] The structurally related ketone **17** has also been demonstrated to be effective for the epoxidation of terminal olefins (up to 85% ee).[27]



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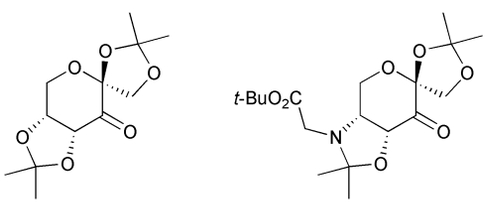
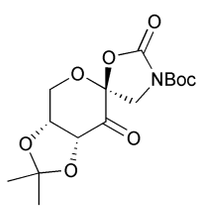


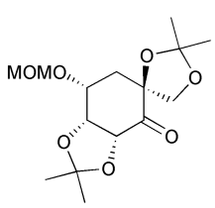
15 **16**

Scheme 3



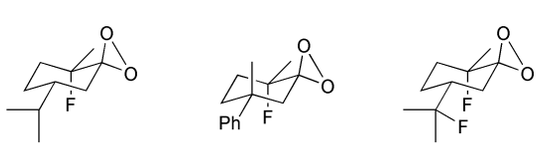
17

A range of carbocyclic analogues of **15** have been studied. While these are marginally less effective for the asymmetric epoxidation of *trans*-alkenes, compound **18** gives higher enantioselectivity than **15** (31% compared to 15%) in the epoxidation of styrene.[28]



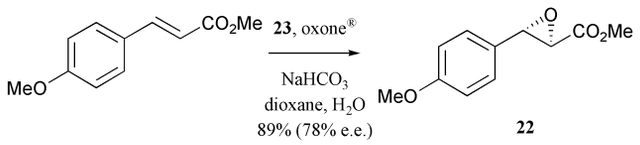
18

Dioxiranes derived from such ketones can in principle transfer either oxygen atom to an alkene. The consequences of this can be seen in a recent study by Solladié-Cavallo *et al.* using α-fluorocyclohexanones. While delivery of the equatorial oxygen in **19** is believed to be favoured, further hindrance to the axial oxygen as in **20** leads to a 30% increase in ee for the epoxidation of *trans*-stilbene. Even more surprisingly, the addition of a remote fluorine as in **21** leads to an identical increase in enantioselectivity.[29]



19 **20** **21**

Biaryl ketone **23** is effective for the epoxidation of electron deficient alkenes. The preparation of **22** by this method (Scheme 4) is an excellent demonstration of the utility of these



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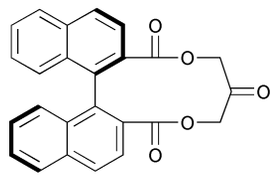
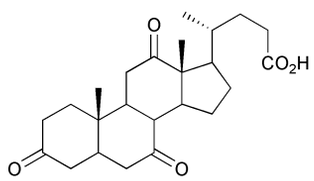


23

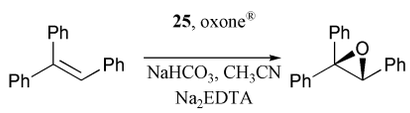
Scheme 4

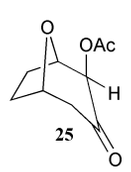
compounds, providing 93 g of epoxide of 78% ee in a single run! This epoxide is an important intermediate in the synthesis of diltiazem.[30] A further approach to the use of dioxiranes in the epoxidation of electron-deficient alkenes features dehydrocholic acid **24** as oxygen transfer agent. Enantioselectivities were typically in the range 30–40%, although in one case 75% ee was observed.[31] A recent computational study has investigated the activation barriers to dioxirane epoxidation of alkenes, and it was concluded that dioxirane can act as either an electrophilic or nucleophilic oxidant depending on the electronic nature of the substrate.[32]



24

Armstrong and co-workers have previously reported the use of **25** in dioxirane-mediated asymmetric epoxidation. A survey of related aromatic esters has shown that in fact **25** is still the optimal ester to date. A particularly impressive 98% ee was obtained in the epoxidation of phenylstilbene (Scheme 5).[33]

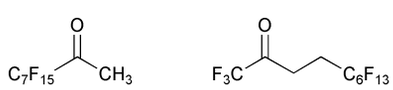




25

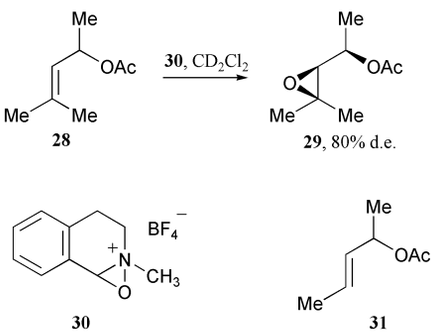
Scheme 5

Fluorous catalysts are attractive due to their easy removal and recovery from the reaction medium. While ketones **26** and **27** are both effective as dioxirane precursors, only **27** can subsequently be recovered. Under optimal conditions, using hexafluoroisopropanol (hexafluoropropan-2-ol) as solvent, catalytic quantities of **27** could be used, in conjunction with only a small excess of terminal oxidant.[34]



26 **27**

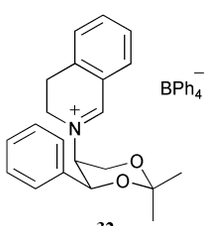
Allylic strain has been found to exert a key influence on diastereoselectivity in the epoxidation of allylic acetates with oxaziridinium salt **30**. Thus, while acetate **28** gives the *threo*-isomer **29** with 80% de, the less substituted double bond in **31** gives a 1 : 1 diastereomeric mixture (Scheme 6). A transition



Scheme 6

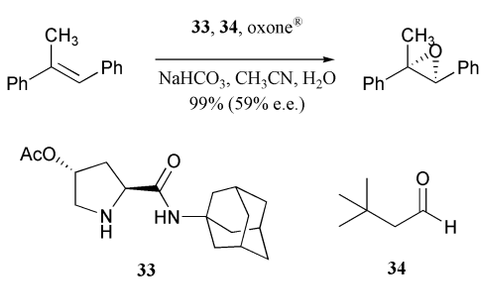
state involving electrostatic interaction between the acetate and the charged nitrogen is consistent with lower stereoselectivities obtained with trifluoroacetates. Epoxidation of geranyl acetate, however, takes place regioselectively at the 6,7-double bond.[35]

In other related work, an improved iminium salt **32** has been reported which permits the epoxidation of phenylstilbene with 59% ee. Compound **32** presumably exists predominantly in the conformation shown, so that oxaziridinium ion formation is highly diastereoselective, removing the possibility of less selective oxygen transfer due to a diastereomeric mixture of oxaziridinium ions.[36]



32

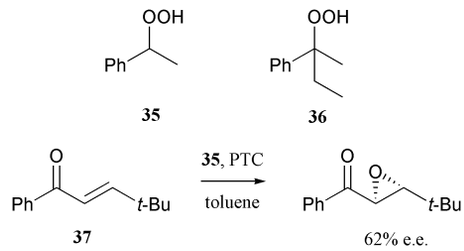
Oxaziridinium salts are presumably intermediates in the enantioselective epoxidation shown in Scheme 7, catalysed (50 mol%) by a combination of amine **33** and aldehyde **34**.[37]



Scheme 7

The diastereoselective intramolecular oxygen transfer from chiral oxaziridinium ions reported by Armstrong and Draffan in 1999 has now been described in detail. Little diastereoselectivity was observed in the analogous attempted intramolecular transfer of oxygen from a dioxirane, an observation ascribed to competing direct epoxidation by oxone®.[38]

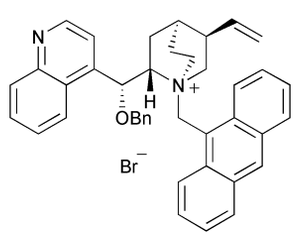
The use of epoxyketones as building blocks in synthesis has been reviewed.[39] The use of chiral racemic hydroperoxides **35** and **36** in the Weitz–Scheffer epoxidation of chalcones such as **37** in the presence of cinchona-derived phase-transfer catalysts has been demonstrated. In this particular case both of these hydroperoxides gave higher enantioselectivity than cumyl and *tert*-butyl hydroperoxides, although the limited number of examples presented makes it difficult to see if this result is general (Scheme 8). Both the recovered hydroperoxide and its



Scheme 8

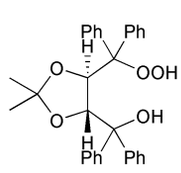
derived alcohol were found to be slightly enantiomerically enriched.[40]

In a detailed study of epoxidation conditions using **38** as phase-transfer catalyst, a number of trends were observed. Increasing either the polarity of the solvent or concentration of substrate was detrimental to enantioselectivity, leading to the suggestion that these effects are effectively one and the same. The reaction was also limited by solubility of the catalyst, so that no advantage was seen in increasing the catalyst loading beyond 5 mol%. As a result of this study, conditions have been found which allow high yielding and highly enantioselective epoxidation of chalcones with as little as 1 mol% catalyst at room temperature.[41]



38

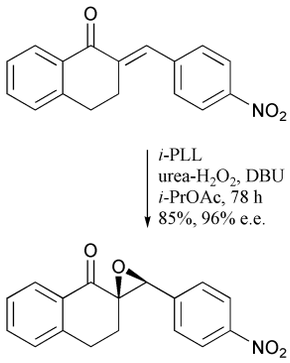
Aoki and Seebach have described a chiral hydroperoxide **39** derived from TADDOL, which epoxidises chalcone with up to 97% enantiomeric excess.[42]



39

The Juliá–Colonna epoxidation of electrophilic alkenes using poly-L-leucine as catalyst has long been restricted to the epoxidation of *trans*-disubstituted olefins. Improved conditions using poly-L-leucine immobilised on a polystyrene support (*i*-PLL) allow epoxidation of trisubstituted alkenes in a biphasic system. For instance, epoxide **40** was produced with 96% ee under these conditions (Scheme 9).[43] While this reaction is normally carried out in a biphasic manner due to low solubility of the poly-L-leucine, a variant has been reported in which the leucine is immobilised on polyethylene glycol, thus allowing a homogeneous reaction to be carried out in THF.[44]

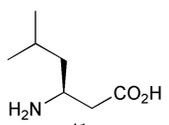
Further evidence has been provided that amino acid residues close to the *N*-terminus have the most profound effect in such epoxidation reactions. For instance, in the epoxidation of chalcone, a peptide consisting of 2 L-leucine residues followed by 5 D-leucine and a further 13 L-leucine gives a slight excess of the same enantiomer as would be provided using a poly-D-leucine catalyst. Moving the D-leucine grouping one residue closer to the terminus increases the ee dramatically.[45] A polymer derived from β^3-leucine **41** also gives high enantioselectivity in



40

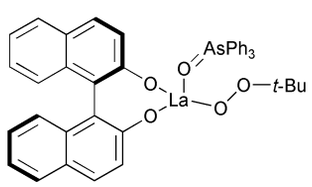
Scheme 9

this process.[46] Surprisingly the same polymer immobilised on TentaGel has been reported to be ineffective, while the importance of α-helices to the catalytic activity has been emphasised.[47] A number of applications of this reaction to the synthesis of useful building blocks have been reported.[48]



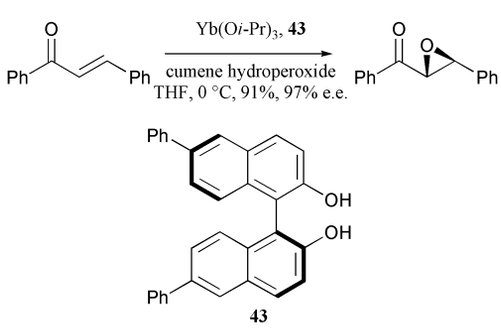
41

The use of lanthanum-BINOL complexes in the asymmetric epoxidation of enones has been discussed in previous reviews in this series. A catalyst consisting of equimolar lanthanum tri-*iso*-propoxide, BINOL and triphenylarsine has been found to be particularly effective at catalytic loadings as low as 5 mol%. As a result of detailed studies, the structure of the active catalyst is proposed to be **42**, although nonlinear optical effects



42

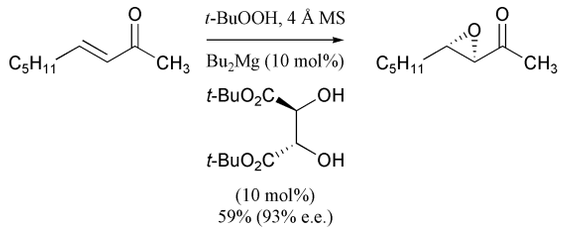
show that complex equilibria are involved in the generation of this species.[49] A range of unsaturated acid derivatives have been epoxidised with good selectivity using this system.[50] In other recent work, Chen, Qian and de Vries have shown that 6,6′-disubstituted BINOL ligands are more effective. For lanthanum and gadolinium complexes there is little difference in selectivity between bromo and phenyl substitution,[51] while the best results were obtained with the ytterbium complex of ligand **43** (Scheme 10).[52]



43

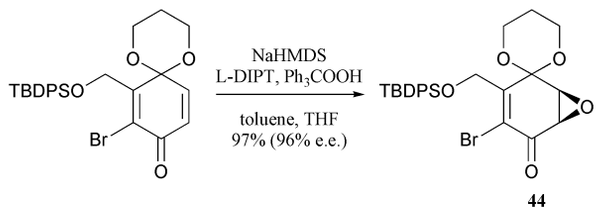
Scheme 10

The asymmetric epoxidation of alkyl-substituted enones is still a significant challenge. However, recent work has shown that a catalyst derived from dibutylmagnesium and di-*tert*-butyl tartrate is effective in this case (Scheme 11).[53a] Quinone epoxide



Scheme 11

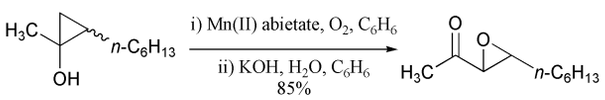
44, an intermediate in the synthesis of (−)-cycloepoxydon, was prepared by a related method (Scheme 12).[53b–d]



44

Scheme 12

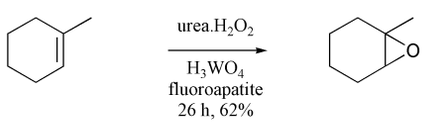
A less obvious method for the preparation of acyloxiranes is shown in Scheme 13, in which cyclopropanols undergo radical



Scheme 13

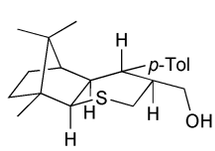
fragmentation in the presence of oxygen followed by ring closure.[54]

Heterogeneous epoxidation can offer advantages due to the shape selectivity of the catalysts, typically zeolites, used. For instance, titanosilicate Ti-MWW shows good selectivity for the epoxidation of *trans*-alkenes in a *cis–trans* mixture.[55] Formation of diols at acidic sites within the catalyst can be a significant competing reaction which can be suppressed by ion exchange with quaternary ammonium salts.[56] Other highlights in heterogeneous epoxidation during 2001 include the efficient epoxidation of propene using molecular oxygen as oxidant.[57] The use of X-ray absorption fine structure (XAFS) methods for the study of titanium–silica epoxidation catalysts has been reviewed.[58] One final method is particularly attractive since it uses no solvent, and proceeds in extremely high yield. Simply mixing solid urea–H_2O_2 complex, tungstic acid powder and fluoroapatite with a liquid alkene gives rise to the epoxide in good yield (Scheme 14).[59]



Scheme 14

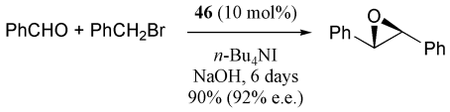
Sulfide **45** gives rise to moderate enantioselectivity (typically 60–75% ee) for the Corey–Chaykovsky reaction of aromatic aldehydes with benzyl bromides.[60]

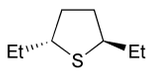


45

Metzner and co-workers had previously reported the use of C_2-symmetric cyclic sulfides in such reactions. Reaction times in the catalytic reaction, which were of the order of a month,

have been substantially reduced by the addition of tetra-*n*-butylammonium iodide to effect halide exchange, thus increasing the rate of initial attack of the sulfide (Scheme 15). Sulfide



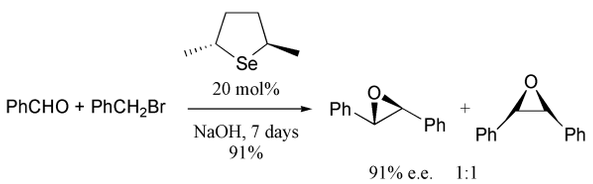


46

Scheme 15

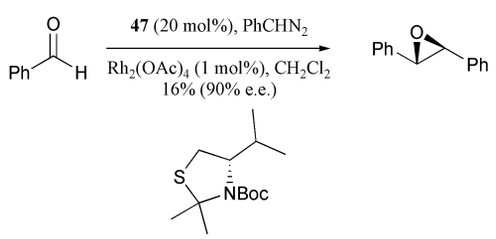
46, with ethyl groups at the stereogenic centres, was shown to give higher enantioselectivity than the previously reported methyl analogue.[61]

Similarly, the first report of the catalytic use of chiral selenides in such an epoxidation has appeared, although in this case a 1 : 1 mixture of *cis* and *trans*-epoxides was obtained (Scheme 16). Clearly this result has mechanistic implications.[62]



Scheme 16

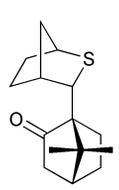
The use of diazo compounds as precursors to sulfur ylides has become prominent in recent years, and while camphor-derived sulfides are currently the most successful, a new valine-derived thiazolidine **47** gives comparable enantioselectivity for the formation of stilbene oxide (Scheme 17).[63]



47

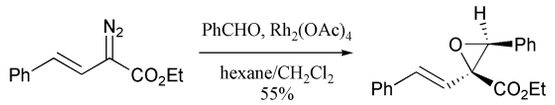
Scheme 17

However, while these sulfides give high enantioselectivity, they generally give poor yields in the case where phenyldiazomethane is generated *in situ*. A detailed study of a particularly wide range of sulfides highlights the conformational changes within these systems and provides a new sulfide **48** which gives high yields and enantioselectivity in these reactions.[64] Further development of this reaction has shown that it is even possible to generate the tosylhydrazone (precursor to the diazo compound) *in situ*, so that this reaction is now a catalytic asymmetric coupling of two different aldehydes to give the corresponding epoxide.[65]



48

In some cases synthetically useful yields of epoxides can be obtained by the direct carbene transfer to aldehydes. For instance, epoxide **49** was obtained in this way (Scheme 18), while

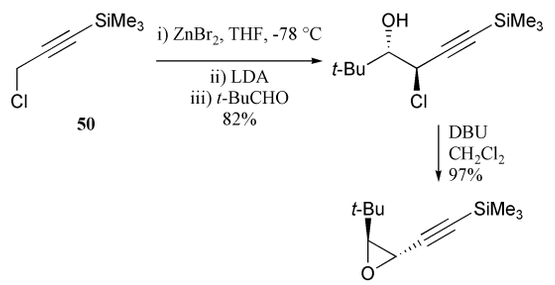


49

Scheme 18

a more conventional epoxidation would require oxygen transfer to the least nucleophilic double bond of a diene.[66]

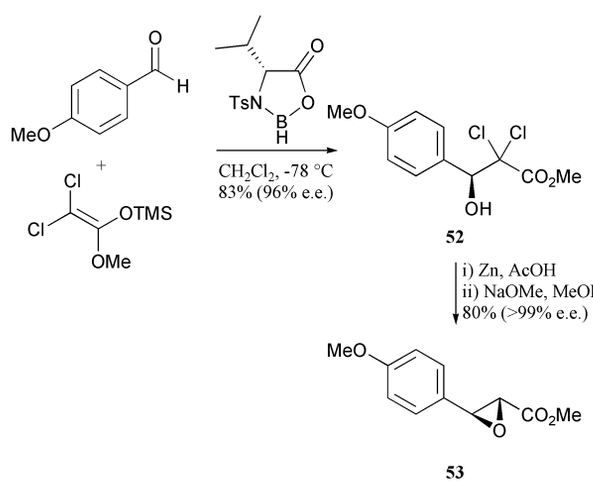
The diastereoselective Darzens' condensations of chloromethyloxazolines reported by Florio and co-workers have now been described in full, including a computational study.[67] A related procedure utilises propargylic chlorides (prop-2-ynyl chloride) such as **50** as carbenoid precursors. Reaction with aldehydes proceeds with moderate to good diastereoselectivity, followed by stereospecific ring closure to give the alkynyloxirane **51** (Scheme 19).[68]



51

Scheme 19

As an alternative to this, the asymmetric Mukaiyama aldol reaction can be used (Scheme 20). Thus, the aldol reaction was followed by partial dechlorination and cyclisation to give the enantiomerically pure *trans*-epoxide **53** (*via* a single recrystallisation of **52**).[69]



52

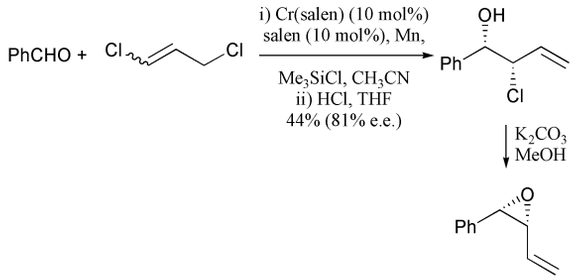
53

Scheme 20

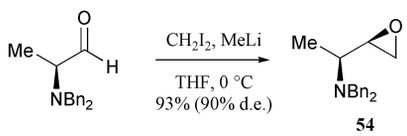
A related procedure uses an asymmetric variant of the Nozaki–Hiyama coupling to provide the intermediate chlorohydrin. An excess of ligand to metal is required in order for good *syn*-diastereoselection to be obtained (Scheme 21).[70]

An improved protocol for the reaction of iodomethyllithium with carbonyl compounds has been reported as an efficient entry into epoxides such as **54** *en route* to 1,3-diamines. The iodomethyllithium is generated *in situ*, and a range of aldehydes and ketones can be used (Scheme 22).[71]

The use of selenium compounds in carbenoid transfer has already been discussed. Further improvements have been made in the arylseleninic acid catalysed epoxidation of aliphatic alkenes. This method is more attractive than peracid epoxid-



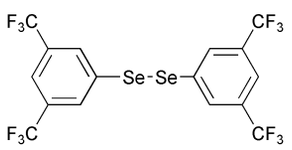
Scheme 21



54

Scheme 22

ation since it uses hydrogen peroxide as oxidant, and with diselenide **55** as catalyst precursor, loadings as low as 0.5 mol% are effective under optimal conditions (2,2,2-trifluoroethanol as solvent, 0.2 mol% NaOAc as base).[72]

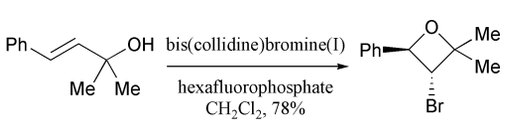


55

This method is less effective for the epoxidation of monosubstituted alkenes. However, in this case benzenearsonic acid is an effective catalyst, with a fluorinated solvent, 1,1,1,3,3,3-hexafluoropropan-2-ol, proving critical to the success of the method.[73]

3 Four-membered rings

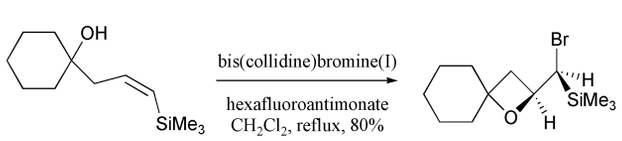
Fleet and co-workers have described the synthesis and folding of hexapeptides containing oxetane-β-amino acids.[74] Halocyclisation reactions have been widely applied to the synthesis of five-membered and larger rings. However, a formal 4-*endo-trig* cyclisation of tertiary cinnamyl alcohols does permit the formation of oxetanes in this manner (Scheme 23).



Scheme 23

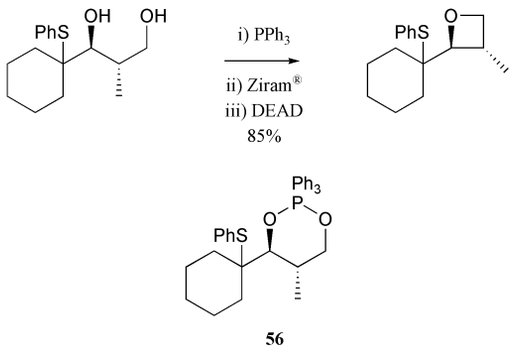
Unfortunately the reaction is not tolerant to increased substitution of the double bond.[75]

The related 4-*exo* cyclisations were troublesome due to competing 5-*endo* reaction, so that addition of silicon functionality was required in order to realise the desired regioselectivity (Scheme 24).[76]



Scheme 24

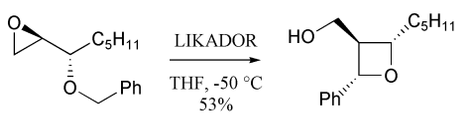
In 1996 Eames and Warren reported a modified Mitsunobu reaction for the formation of oxetanes. A more detailed study now examines the scope and limitations of the reaction as well as providing mechanistic information. For instance, in the absence of ziram® (zinc *N,N*-dimethyldithiacarbamate) intermediate **56** is formed which ultimately leads to tetrahydrofuran formation. Presumably this additive slows or prevents this reaction, allowing oxetane formation to become competitive (Scheme 25).[77]



56

Scheme 25

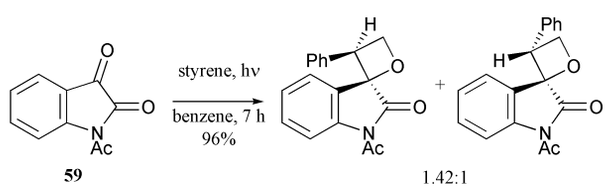
Cyclisation of benzyl glycidyl ether **57** gives the oxetane **58** as the sole product (Scheme 26). However, the corresponding allyl glycidyl ether gives only the oxepane as a result of 7-*endo* ring closure.[78]



57 **58**

Scheme 26

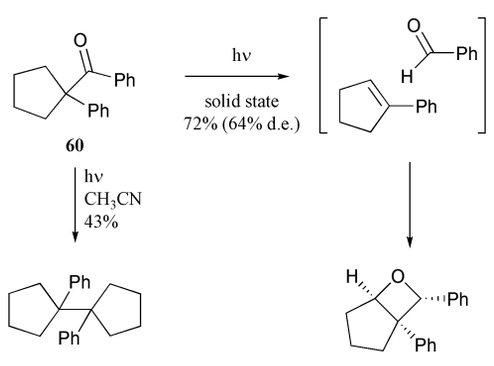
Paternò–Büchi reactions of *N*-acetylisatin **59** with styrene derivatives provide high yielding access to spirocyclic oxetanes with high regioselectivity (Scheme 27).[79] Bach has published detailed accounts of his group's earlier work in this area.[80]



59

Scheme 27

Recent work by Kang and Scheffer highlights a profound difference between solution phase and solid state behaviour of ketone **60**. While Norrish type I cleavage and subsequent dimerisation to give **61** was observed upon photolysis of **60** in acetonitrile, oxetane **62** was obtained from the solid state reaction, presumably *via* hydrogen abstraction to form the aldehyde and alkene followed by Paternò–Büchi reaction (Scheme 28).[81]

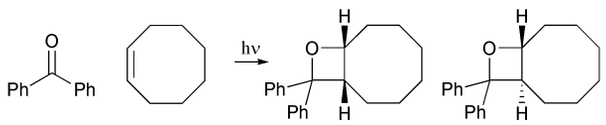


60 **61** **62**

Scheme 28

The intricate mechanistic details of the Paternò–Büchi reaction are beyond the scope of this review (and this reviewer!). Singlet and triplet electronic states are involved, and the

exo–endo selectivity can be affected by a number of factors, including temperature, concentration and solvent viscosity.[82] An unusual observation has recently been documented in the case of the reaction of benzophenone with *cis*- and *trans*-cyclooctene. With *cis*-cyclooctene **63**, reactions at higher temperature actually led to an increase in the proportion of the less stable *trans*-cycloadduct **65** (Scheme 29). The analogous

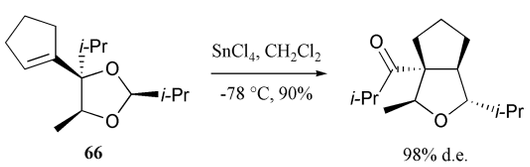


Scheme 29

reaction of *trans*-cyclooctene gives predominantly the *trans*-cycloadduct over a wide range of temperatures. These results have been interpreted in terms of the conformations of the short-lived triplet diradical intermediates.[83]

4 Five-membered rings

The approaches of Overman and Paquette to the synthesis of sclerophytin A were discussed in the previous review in this series. A full account of these studies has now been presented.[84] In other work from Overman's group, the factors affecting stereoselectivity in the Prins-pinacol reaction (used in the Irvine synthesis of this natural product) have shown a subtle stereoelectronic effect. Thus, while *syn*-acetals rearrange to give the 2,5-*cis* THF with high selectivity, this trend can be reversed in the *anti*-series, *e.g.* **66**, by placement of a bulky substituent at the allylic position or increased substitution of the double bond (Scheme 30).[85]



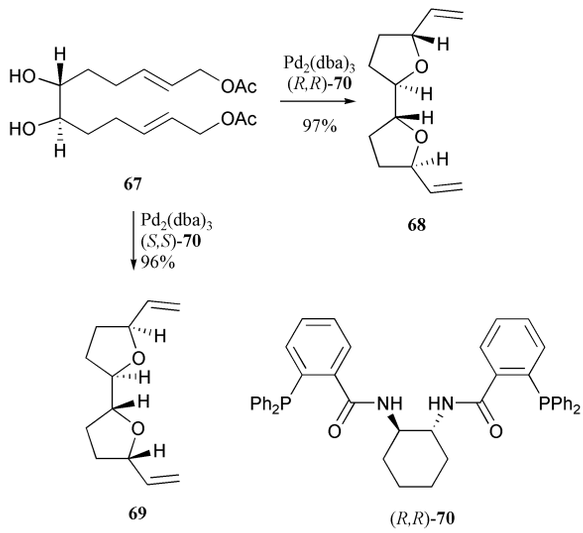
Scheme 30

Excellent stereocontrol has been demonstrated in a formal synthesis of the annonaceous acetogenin uvaricin. Palladium-catalysed cyclisation of **67** in the presence of ligand (*R,R*)-**70** gave the *trans*/*threo*/*trans*-isomer **68** cleanly. This was elaborated to give an advanced intermediate converging with the 1998 total synthesis reported by Yazbak, Sinha and Keinan. However, use of the enantiomeric ligand provided the *cis*/*threo*/*cis* isomer **69** with the correct stereochemistry for other members of this class of natural products (Scheme 31).[86]

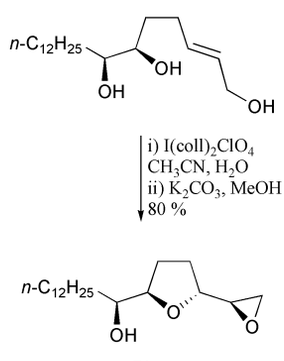
In the first total synthesis of mosin B, the tetrahydrofuran ring was formed by iodocyclisation followed by ring closure of the resulting halohydrin to give the epoxide **71** (Scheme 32).[87] Other publications in this area include full accounts of the syntheses of tonkinecin and annonacin from Hu *et al.*,[88] and of quinone-acetogenin hybrids from the group of Koert.[89]

Oxidative cyclisation of 1,5-dienes is a particularly effective strategy for the synthesis of tetrahydrofurans found in a number of natural products, particularly the acetogenins which often contain oxygen functionality adjacent to the oxacyclic ring. An acyclic precursor **72** was cyclised in this manner in the total synthesis of rollidecin C (Scheme 33).[90]

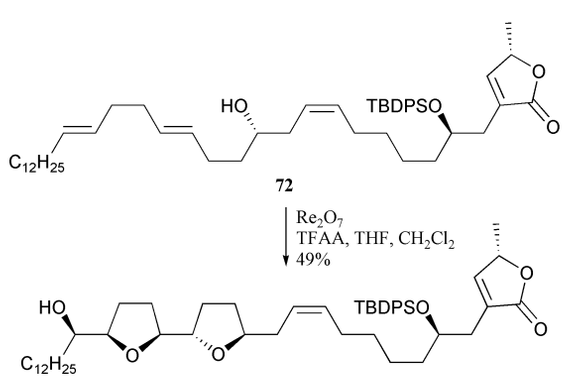
Consideration of the likely transition state for the reaction has led Brown and Keily to develop an enantioselective version of this process using cinchona-based phase transfer catalyst **38** (Scheme 34).[91]



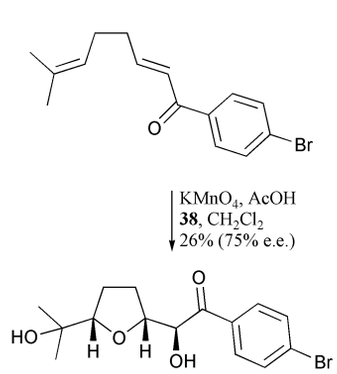
Scheme 31



Scheme 32

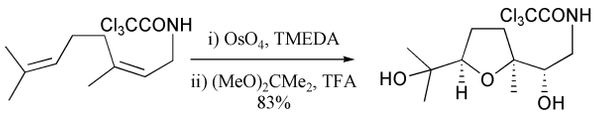


Scheme 33



Scheme 34

During an investigation of the effect of hydrogen bonds in directing double-bond dihydroxylation, the cyclisation shown in Scheme 35 was observed. While this reaction uses stoichio-

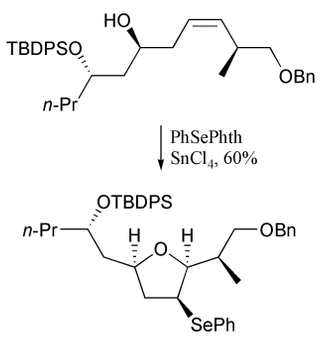


Scheme 35

metric osmium tetraoxide, it is still attractive since the yields are generally superior to those obtained with rhenium and manganese oxidants.[92] Improved yields have been recently reported in a ruthenium-catalysed process.[93]

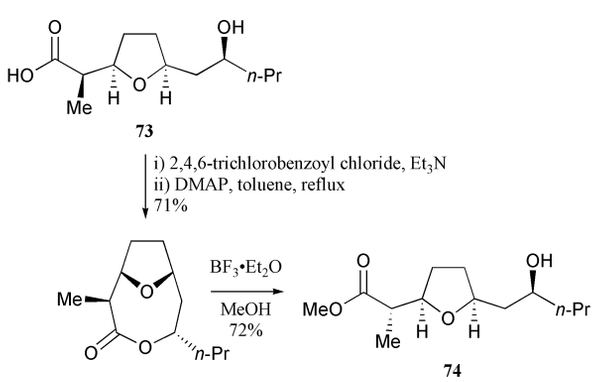
A related non-directed oxidation of 1,4-dienes has also been reported using a number of oxidants, including osmium tetraoxide, in catalytic amounts.[94]

The pamamycin natural products have been much studied, and two total syntheses of pamamycin 607 were reported in 2001. In the first, all three tetrahydrofuran rings were formed using electrophile-initiated cyclisation reactions such as the one shown in Scheme 36.[95]



Scheme 36

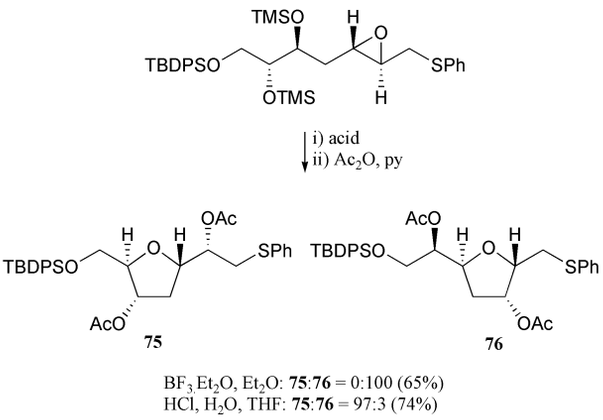
The THF-forming reactions used in the second total synthesis[96] have been discussed in previous reviews, and so will not be repeated here. However, a serendipitous epimerisation during the lactonisation of **73** (a precursor to the bis-THF fragment of this natural product) provided **74**, with the same stereochemistry as the smaller portion of these compounds (Scheme 37).[97]



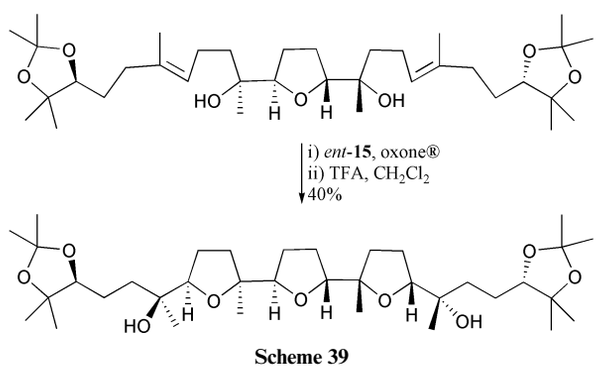
Scheme 37

Halo- and selenocyclisations are mechanistically related to epoxide opening reactions, so it is worth considering these reactions together. Where possible during epoxide opening, the 5-*exo*-*tet* pathway is generally preferred. However, a number of factors can favour alternative modes of cyclisation. Perhaps the most striking is the switching between 5-*exo* and 5-*endo* pathways under the conditions shown in Scheme 38. In fact, compound **76** does not arise from direct 5-*endo* cyclisation, but by the formation and 5-*exo* cyclisation of a thiiranium ion.[98] Similar reactions of thiiranium ions from the Warren group have also been reported in full.[99]

The double asymmetric epoxide formation–opening shown in Scheme 39 was used in the asymmetric synthesis of (−)-longlilene peroxide, as a result of which the absolute stereochemistry of the natural product was established.[100] Other hydroxy-epoxide cyclisations have been reported.[101]

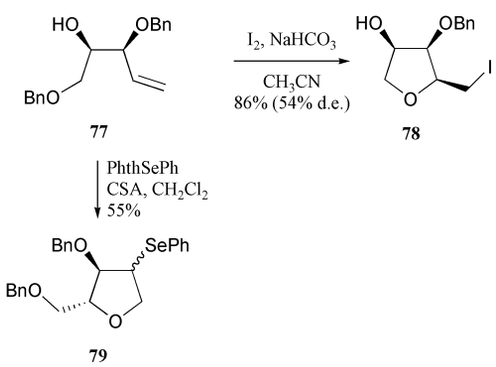


Scheme 38



Scheme 39

One issue to consider during electrophile-initiated cyclisation reactions is protecting group lability. For instance, in the reaction of **77** with iodine, only 5-*exo* cyclisation products **78** were obtained, with loss of one of the benzyl protecting groups. However, selenocyclisation gave the 5-*endo* product **79** exclusively, but as a 1 : 1 mixture of diastereoisomers (Scheme 40).[102]



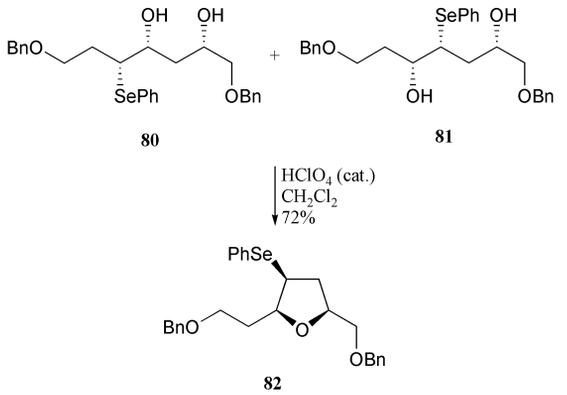
Scheme 40

In related competition studies, tetrahydrofurans were formed in preference to piperidines.[103]

The seleniranium ions intermediate in these reaction types can also be generated by acid-catalysed ring-closure of hydroxyselenides. A full account of previous work has been published,[104] and also a study of the cyclisation of substrates such as **80** and **81** (an 80 : 20 mixture was used with the major regioisomer not being assigned) to give **82** (Scheme 41).[105]

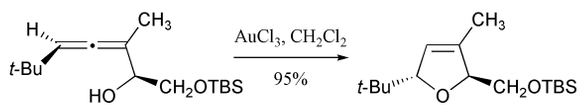
Finally for this reaction type, Wirth's group have previously reported success in the use of chiral selenium reagents. These work well when attached to polystyrene as a solid support, including examples of tetrahydrofuran formation with up to 80% enantiomeric excess.[106]

It is often preferable to use a proton as an electrophile, rather than introducing and then removing a halide. However,



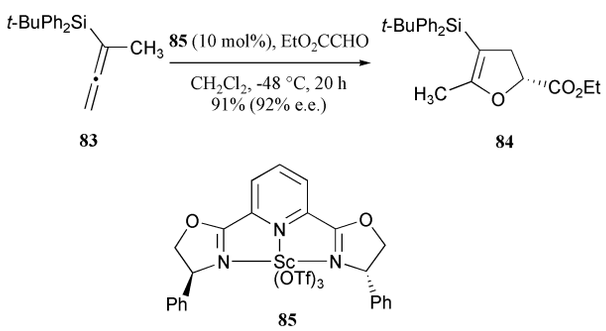
Scheme 41

acid lability of substrates can be a problem, so that the use of gold(III) chloride as shown in Scheme 42 should find broad applicability.[107]



Scheme 42

Intermolecular annulation of allenes has also been used to prepare dihydrofurans. Reaction of **83** with ethyl glyoxylate catalysed by **85** gave **84** with high enantioselectivity (Scheme 43).[108]



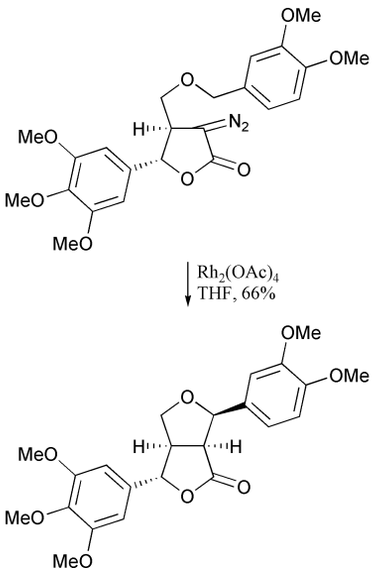
Scheme 43

Diazo compounds have long been used as precursors to a range of oxygen heterocycles. A number of new developments and improvements were reported during 2001. Benzylic C–H insertion was used as the key step in a total synthesis of the lignan epimagnolin (Scheme 44).[109] Anomalous insertion products have been obtained from similar reactions. Kinetic isotope effects were used to narrow down the mechanistic possibilities, although a definitive mechanism is not available at this time.[110]

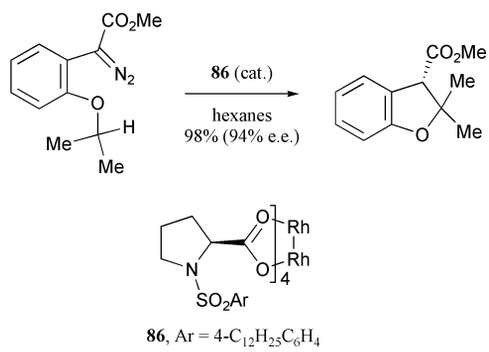
Enantioselective C–H insertion reactions are possible as shown in Scheme 45, although the enantioselectivity increases with C–H bond type in the order methyl < methylene < methine.[111]

Oxonium ylides, formed from metallocarbenoids can also give rise to enantiomerically enriched tetrahydrofurans. For example, use of rhodium phosphate catalyst **88** allowed formation of **87** with 62% ee (Scheme 46).[112] Asymmetric 1,2-rearrangements of oxonium ylides have also been reported.[113]

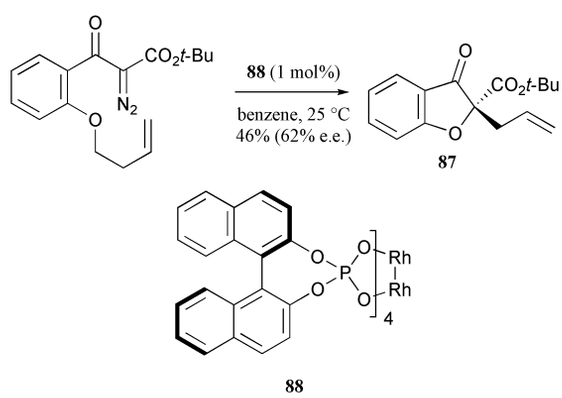
In a diazo-decomposition not involving rhodium, reaction of protected β-hydroxyaldehyde **89** with benzyl diazoacetate gave **90**. Unfortunately an excess of the diazo ester (2–6 equivalents) was required (Scheme 47).[114] Diazosulfones have also been used successfully in this process.[115]



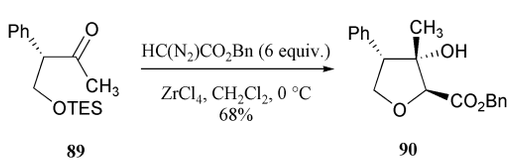
Scheme 44



Scheme 45

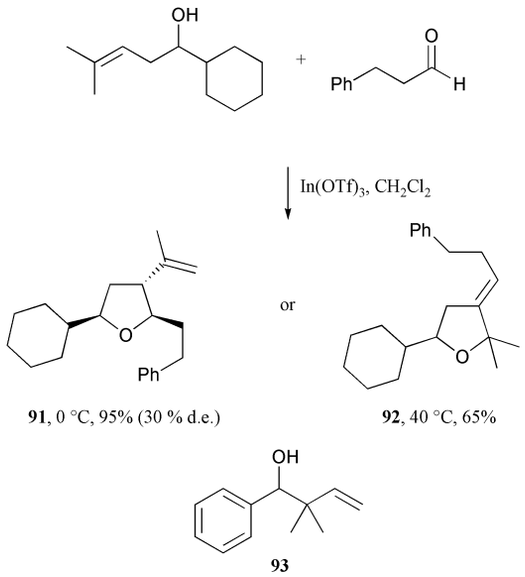


Scheme 46



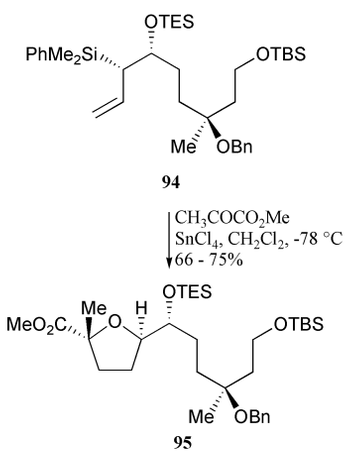
Scheme 47

Changing the temperature of a reaction can have a profound effect on the product distribution. For example, in the reaction of homoallylic alcohols with aldehydes catalysed by indium triflate, **91** was formed at low temperature, while **92**, formed by a 1,3-rearrangement, was the sole product at higher temperature (Scheme 48).[116] Related work shows that isomeric homoallylic alcohols such as **93** can also give rise to products similar to **92** in a reaction which involves rearrangement prior to cyclisation.[117]



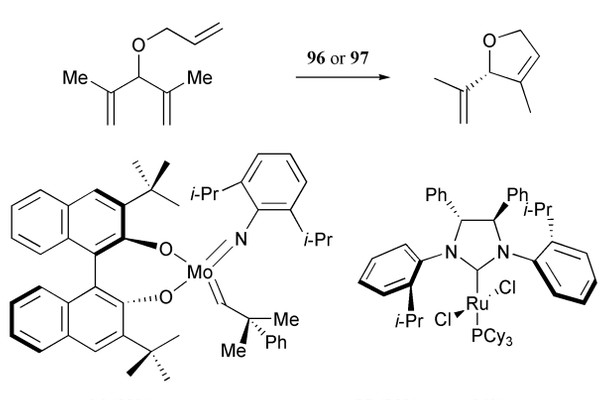
Scheme 48

A [3 + 2] annulation of allylsilanes with aldehydes has now been used to install quaternary stereogenic centres in an approach to pectenotoxin II. For example, reaction of **94** with methyl pyruvate gave **95** essentially as a single diastereoisomer (Scheme 49).[118]

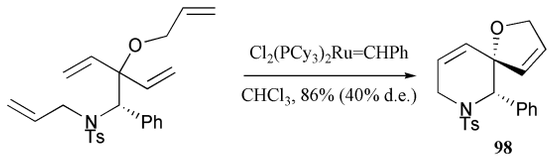


Scheme 49

Two new catalysts, **96**[119] and **97**,[120] have been reported for the asymmetric ring-closing metathesis shown in Scheme 50. Although **97** gives lower enantioselectivity in this particular reaction, addition of a second methyl group *cis* to the first on the double bonds increases the ee to 90%.

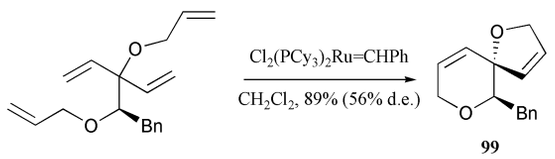


Scheme 50



Scheme 51

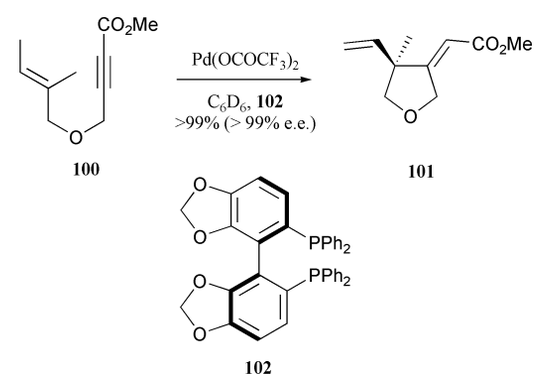
The double ring-closing metathesis shown in Scheme 51 was mentioned in the previous review. Further work has shown that formation of the five-membered ring precedes that of the six-membered ring, although some stereochemical equilibration was observed with one diastereoisomer of the monocyclic intermediate.[121] Due to conformational differences, the opposite stereochemical outcome was observed in the formation of the oxygen analogue **99** (Scheme 52).[122] Enyne metathesis has



Scheme 52

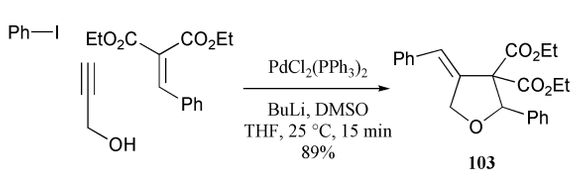
also been used to prepare five-membered rings, with an improved catalytic system being recently reported.[123] Compounds similar to **98** have also been prepared by cyclisation of the corresponding diol.[124] A number of other diol cyclisations have been reported, the main difference between them being the method of preparation of the cyclisation precursor.[125]

Palladium catalysis has been used in a number of different ways in the formation of tetrahydrofurans. For instance, the ene-type reaction of substrate **100** in the presence of ligand **102** gave rise to the formation of a single enantiomer **101** (Scheme 53).[126]



Scheme 53

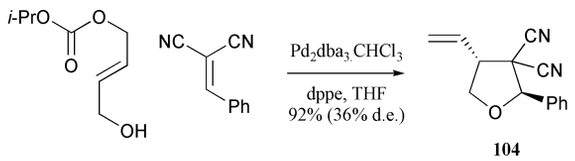
Structurally related oxacycles have also been synthesised by two similar approaches. For instance, the three-component coupling shown in Scheme 54 provided **103** in high yield.[127]



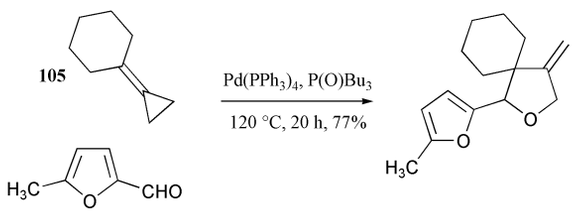
Scheme 54

Alternatively, final cyclisation onto a π-allylpalladium intermediate gave **104** (Scheme 55).[128]

One further [3 + 2] annulation which appears to be reasonably general is the reaction of methylenecyclopropanes such as **105** with aldehydes (Scheme 56). Unfortunately, for unsymmetrically substituted methylenecyclopropanes essentially no diastereoselectivity was observed.[129]



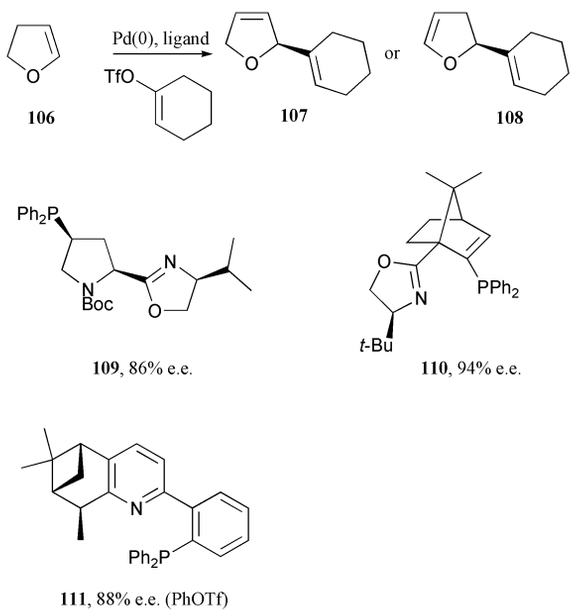
Scheme 55



Scheme 56

The use of palladium-catalysed alkoxycarbonylation in tetrahydrofuran synthesis has been discussed in previous reviews in this series. A full account of some of this work has been published,[130] as well as improved experimental conditions.[131]

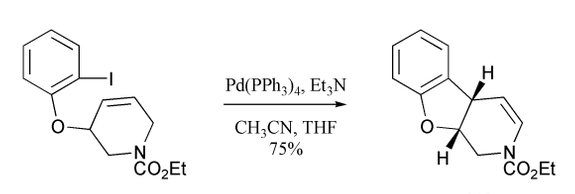
Asymmetric Heck reactions can be used to enantioselectively functionalise 4,5-dihydrofuran **106** (Scheme 57). A number of



Scheme 57

new ligands have been reported for this process, including **109**,[132] **110**[133] and **111**.[134] All of these ligands, featuring P,N-donor atoms, give isomer **107** predominantly, while P,P-ligands tend to lead to further isomerisation favouring product **108**. These results have been examined computationally, in addition to the observation of intermediates by NMR and ligand dissociation prior to rearrangement is believed to be the driving force for the formation of **107**.[135]

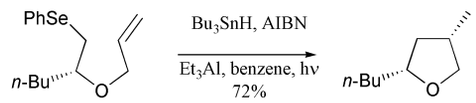
Further applications of the Heck reaction in tetrahydrofuran synthesis include that shown in Scheme 58. Again, due to the *syn* addition to the double bond, the only possible reductive



Scheme 58

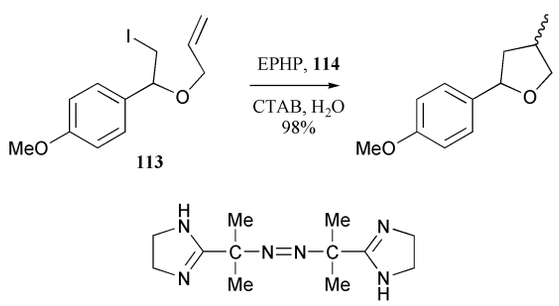
elimination of the palladium hydride results in isomer **112** in which the double bond has been transposed from its original position.[136]

As an alternative to the Heck reaction, free-radical cyclisation was also used in this case. As expected, a number of other free-radical approaches to tetrahydrofurans were reported during 2001. Reversal of the usual diastereoselectivity in such cyclisations was observed upon addition of triethylaluminium as shown in Scheme 59. In the absence of this reagent, the diastereomeric excess was 64% favouring the *trans*-isomer.[137]



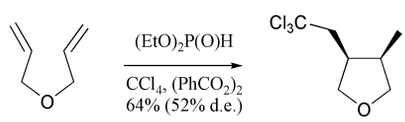
Scheme 59

The actual 5-*exo*-*trig* cyclisation step is so well established that most of the advances are in the development of improved conditions, notably those which do not require the use of toxic tin hydride reagents. One new method which scores well on a number of counts is the cyclisation of hydrophobic substrates such as **113** in water, in the presence of a water-soluble radical initiator **114**, 1-ethylpiperidine hypophosphite (EPHP) and cetyltrimethylammonium bromide (CTAB) (Scheme 60).[138]

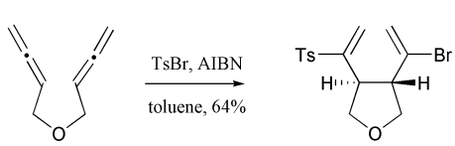


Scheme 60

A further use of phosphites as radical precursors is shown in Scheme 61.[139] This reaction, and the one shown in Scheme 62,[140] feature generation of the cyclising radical by addition to an unsaturated system. One further method features single electron oxidation using ceric ammonium nitrate to introduce oxygen functionality adjacent to the tetrahydrofuran ring.[141]

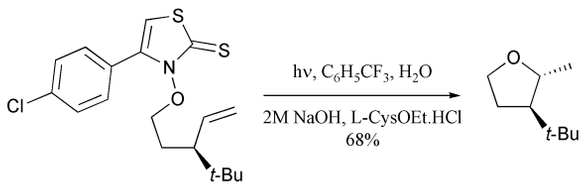


Scheme 61



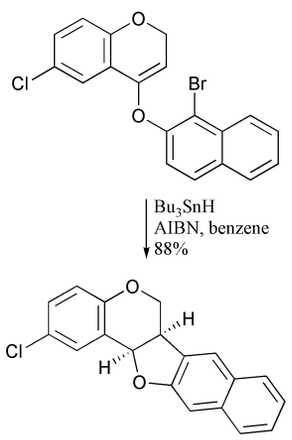
Scheme 62

Free radicals adjacent to carbonyl groups can be formed by oxidation with manganese(III) acetate. Recent work has shown that these reactions are more efficient, as well as producing less waste, when carried out in a mixed solvent system of dichloromethane and an ionic liquid.[142] Oxygen-centred radicals are less frequently used than their carbon-centred counterparts. A novel biomimetic process uses L-cysteine ethyl ester hydrochloride as hydrogen donor in such reactions (Scheme 63).[143] A short review of oxygen-centred radicals has also been published.[144]



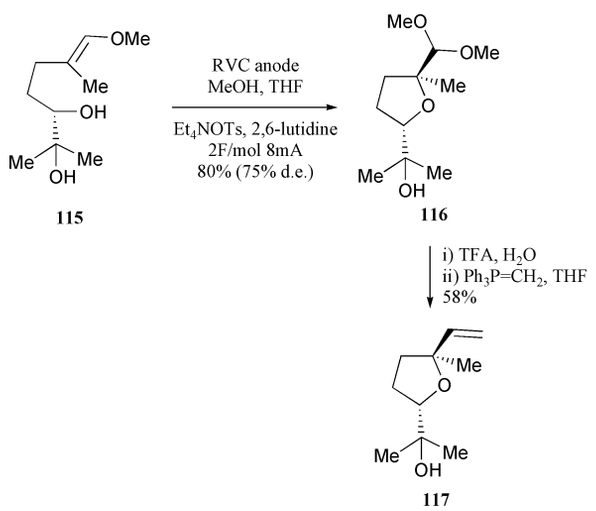
Scheme 63

While the most common, 5-*exo*-*trig* cyclisations are not the only free-radical reactions to form tetrahydrofurans. For instance, a 5-*endo* cyclisation has been used to prepare pterocarpan derivatives (Scheme 64).[145] In other free-radical work, the full account of Kilburn's total synthesis of paeonilcatone B has appeared.[146]



Scheme 64

Anodic oxidation can be an efficient method for reversing the polarity of enol ethers. For example, oxidation of **115** gave good selectivity for diastereoisomer **116** with the formation of a quaternary stereogenic centre. Simple transformations then provided (+)-linalool oxide **117** (Scheme 65).[147]



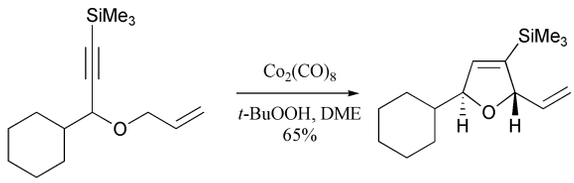
115 **116** **117**

Scheme 65

Similar oxidation reactions of ketene dithioacetals,[148] have been reported including a total synthesis of nemorensic acid.[149]

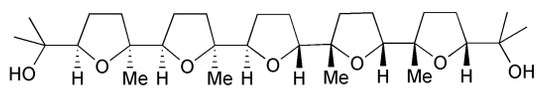
The Pauson–Khand reaction of enynes with dicobalt hexacarbonyl is so widespread that the rearrangement reaction shown in Scheme 66 is perhaps a little surprising. However, replacement of the trimethylsilyl group with methyl led to the formation of the Pauson–Khand adduct as the only product.[150]

The initially-proposed structure of glabrescol was revised to **118** as a result of total synthesis. However, elegant computational work by Bellenie and Goodman showed that the correct



Scheme 66

C_2-symmetric stereoisomer can be predicted by consideration of the energies of various isomers with metals incorporated.[151]

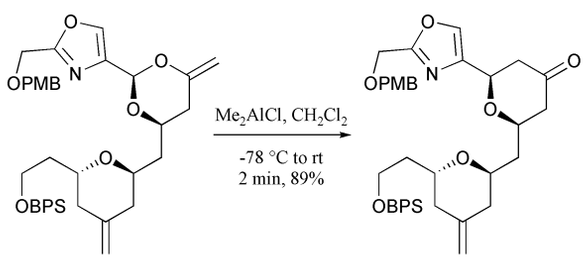


118

Domino reactions of 1,3-dicarbonyls giving 2-alkylidenetetrahydrofurans were discussed in the previous review. Full papers on this topic have been published by two groups.[152]

5 Six membered rings

Two of the most noteworthy total syntheses involving tetrahydropyrans reported in 2001 come from the group of Smith at Pennsylvania. While most of the chemistry used to prepare the pyran rings of phorboxazole A has been discussed in previous reviews in this series, it is worth reproducing the key Petasis–Ferrier rearrangement of **119** into **120** which was used to prepare the bis-oxane fragment (Scheme 67).[153] The total synthesis

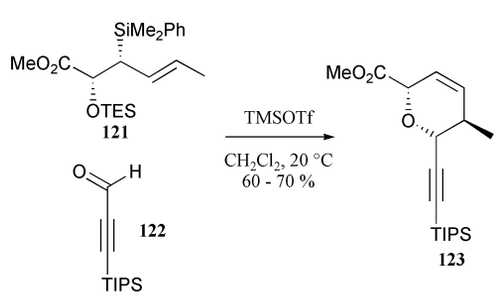


119 **120**

Scheme 67

of spongistatin 2 and formal synthesis of spongistatin 1 have also been described, using building blocks reported previously.[154] The same rearrangement has been used in the total synthesis of the cytotoxic macrolide (+)-zampanolide.[155]

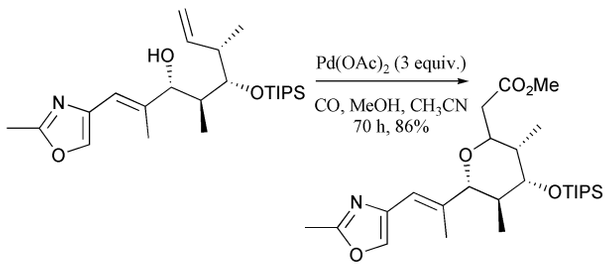
Two other approaches to the tetrahydropyran rings found in phorboxazole A have also been reported. In what is essentially a Prins reaction, allylsilane **121** was allowed to react with aldehyde **122** to give **123**. The enhanced nucleophilicity of the triethylsilyl ether compared to trimethylsilyl proved critical in obtaining an acceptable yield (Scheme 68).[156] Intramolecular



121 **122** **123**

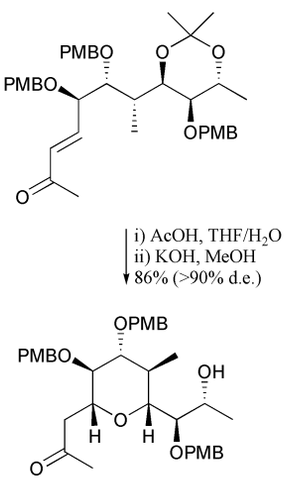
Scheme 68

alkoxycarbonylation provided both oxane rings in the synthesis of an advanced intermediate also containing two of the oxazoles found in this natural product. The first such cyclisation is shown in Scheme 69.[157]



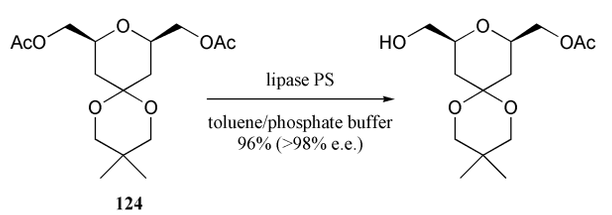
Scheme 69

Two approaches to the F ring of spongistatin 1 have been reported recently, the former making use of an enol ether precursor *via* epoxidation and ring opening,[158] while the latter uses the ring-opening of a known bicyclic acetal to prepare this portion.[159] A further total synthesis of spongistatin 1, making extensive use of aldol chemistry, features the cyclisation step shown in Scheme 70. Initially a 1 : 1 mixture of epimers was formed, but treatment with base gave clean equilibration to the stereoisomer shown.[160]



Scheme 70

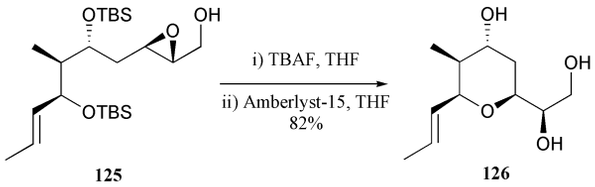
In recent studies towards the synthesis of the bryostatins, Yadav *et al.* used conjugate addition of an alkoxide anion to form the tetrahydropyran ring.[161] A further approach from the Hoffmann group uses enzymic desymmetrisation of a *meso*-tetrahydropyran **124** formed by ozonolysis of an oxabicyclo-[3.2.1]octene (Scheme 71).[162]



124

Scheme 71

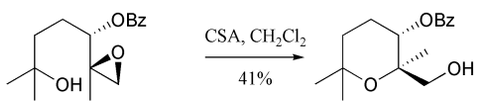
The antifungal polyketide ratjadone has been the subject of two relatively similar approaches. The first total synthesis provided the naturally occurring enantiomer in a highly convergent approach. For the tetrahydropyran portion, substrate **125** was prepared by Evans' aldol chemistry followed by a vinylogous Mukaiyama aldol reaction to introduce the complete carbon skeleton with all requisite stereochemistry. Minimal functional group manipulation provided **125** which was cyclised in high yield to give **126** (Scheme 72).[163] The second total synthesis provided the enantiomer of the natural product, in which the tetrahydropyran ring was prepared by an essentially identical epoxide opening, after a similar opening gambit.[164]



125 **126**

Scheme 72

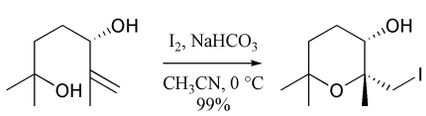
In such epoxide-opening reactions, protecting groups may in fact be far more than passive partners. For instance, anchimeric assistance by the benzoyl group in **127** results in overall retention of stereochemistry to give **128** as the major product, albeit in relatively low yield, while the benzyl protecting group gives clean inversion as expected, as well as significantly higher yields (Scheme 73).[165] While problems were found in the



127 **128**

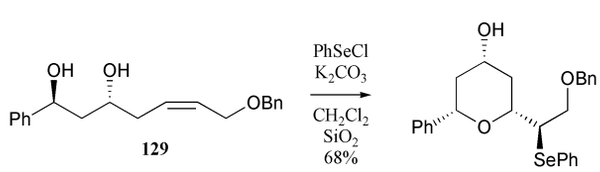
Scheme 73

preparation of 2,2,6,6-tetrasubstituted oxanes by opening of vinyloxiranes, a halocyclisation related to that shown in Scheme 73 was found to be particularly effective (Scheme 74).[166]



Scheme 74

Cyclisation onto seleniranium ions is well-documented, although a striking substituent effect has recently been observed. Treatment of **129** with phenylselenyl chloride gave little cyclisation in the absence of silica gel (Scheme 75). Replacement of the benzyloxy group with propyl led to a much more rapid cyclisation, leading the authors to propose stabilisation of the intermediate by the adjacent oxygen.[167]

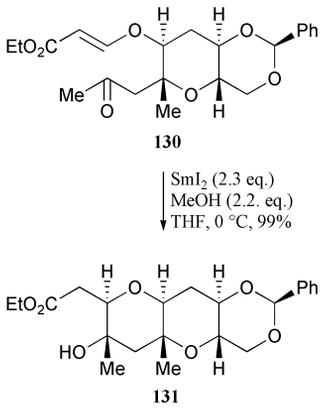


129

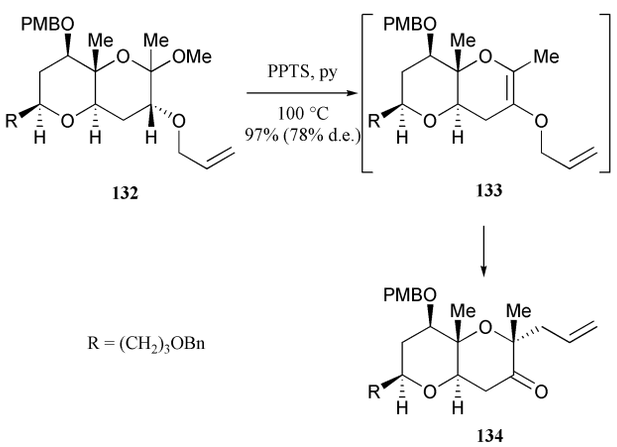
Scheme 75

The brevetoxins and related natural products are discussed in some detail in the following section. However, as these natural products also contain tetrahydropyran rings, some discussion here is also warranted. Many of the approaches use combinations of existing methodologies, and so will only be mentioned briefly, while newer or more efficient combinations of methods will be discussed in more detail. Nakata and co-workers have prepared a tris-tetrahydropyran corresponding to the C′D′E′ fragment of maitotoxin using epoxide-opening and samarium iodide induced reductive cyclisation, both reactions allowing the stereoselective introduction of quaternary centres. For instance, treatment of **130** with SmI_2–MeOH in THF gave **131** in essentially quantitative yield (Scheme 76).[168] Yamamoto's group have used this[169] and other[170] reactions to prepare fragments of gambierol.

A tetracyclic fragment of the same natural product has been prepared using a combination of methods, including the Claisen rearrangement shown in Scheme 77 to convert lactol ether **132**, *via* **133**, into **134**. Asymmetric hetero-Diels–Alder



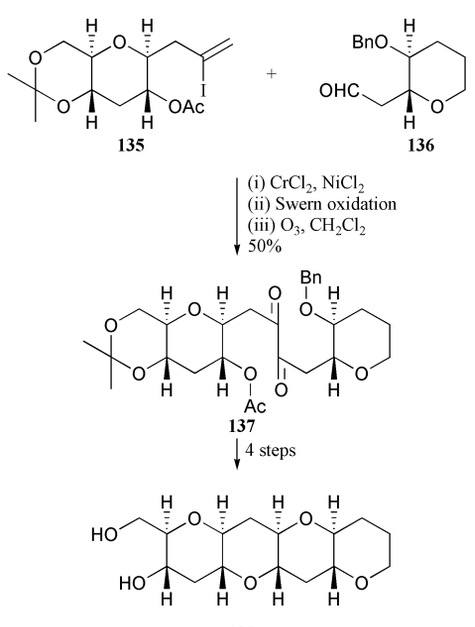
Scheme 76



Scheme 77

methodology (see also Schemes 92 to 94) and enol-ether metathesis also figured in this synthesis.[171]

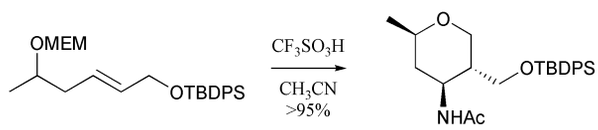
While many approaches to the *trans*-fused oxanes found in these natural products have been developed, the remaining problem given the size of these targets is efficient linking of such oxanes. For targets of this size, linear synthesis is not viable. Coupling of **135** and **136** followed by Swern oxidation and ozonolysis gave diketone **137** which was subsequently elaborated (4 steps) into **138** (Scheme 78).[172] A related cyclisation of an α-dicarbonyl followed by reduction of the resulting



Scheme 78

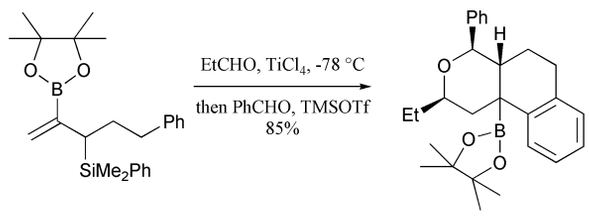
lactol was used to prepare a tetracyclic fragment of the prymnesins, another group of marine toxins.[173]

Prins cyclisations remain popular for the formation of tetrahydropyrans. Recent studies have extended this utility in several directions. While it is usual to form a 4-halotetrahydropyran in this type of reaction, use of trifluoroacetic acid followed by hydrolysis of the resulting ester allows efficient introduction of oxygen functionality. Furthermore, use of triflic acid† in acetonitrile allows the introduction of nitrogen at this position (Scheme 79).[174]



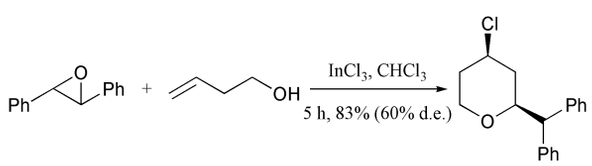
Scheme 79

Carbon functionality, in the form of an aromatic ring, can also be used as the carbenium ion trap (Scheme 80) in a reaction in which the boron functionality exerts stereochemical control as well as providing potential for further elaboration.[175]



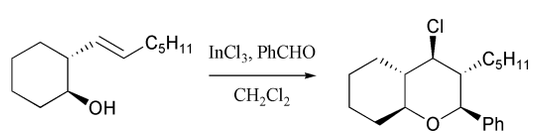
Scheme 80

While generation of the initial carbenium ion from an aldehyde or acetal is still the most common approach, epoxides can also serve as precursors in a ring-opening rearrangement process (Scheme 81).[176] The same group have also reported



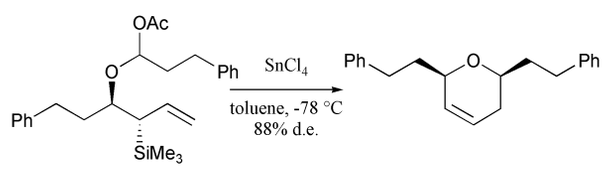
Scheme 81

more conventional indium chloride-mediated Prins cyclisations, including the stereoselective formation of a pentasubstituted tetrahydropyran shown in Scheme 82.[177]



Scheme 82

Elegant studies from Roush and Dilley were able to establish that the reaction shown in Scheme 83, as well as related intermolecular reactions, proceeds *via* a boat transition state. Various stereochemical arguments were used, as well as the

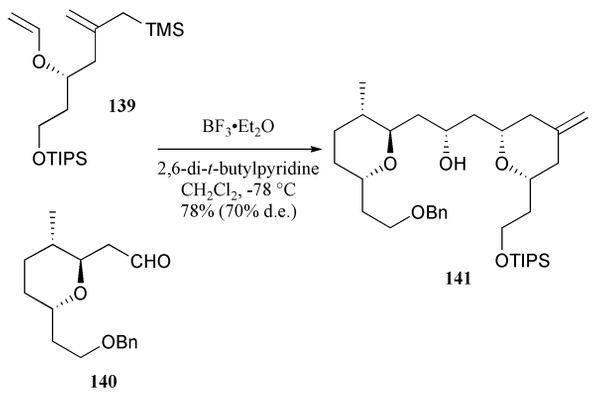


Scheme 83

† The IUPAC name for triflic acid is trifluoromethanesulfonic acid.

isolation of several unexpected products, to reach this conclusion, in which [3,3]-sigmatropic rearrangements play a significant role.[178]

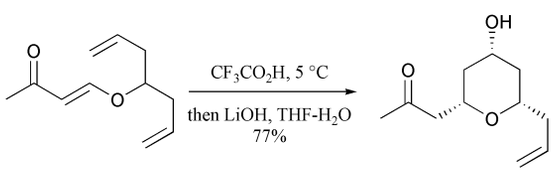
A novel cascade process has been developed in which the oxacarbenium ion intermediate in such a process is generated by Mukaiyama aldol reaction. Thus, reaction of enol ether **139** with aldehyde **140** gave bis-tetrahydropyran **141** with good stereoselectivity and yield (Scheme 84). Intermediate **141** was elaborated to provide a formal total synthesis of leucascandrolide A.[179] Related cyclisations, albeit lacking the cascade aspect, have been reported using bismuth triflate as catalyst.[180]



Scheme 84

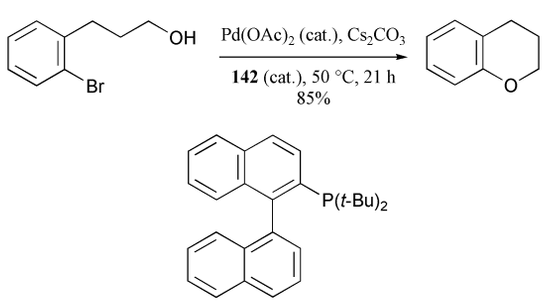
Improved conditions for Prins cyclisations utilising heterogeneous catalysts have also been reported over the last 12 months.[181]

In other studies towards leucascandrolide A, a similar enol ether cyclisation was used to prepare the same tetrahydropyran, with trifluoroacetic acid as catalyst/nucleophilic trap, followed by hydrolysis of the resulting ester (Scheme 85).[182]



Scheme 85

Buchwald's group have developed efficient methods for the formation of carbon–heteroatom bonds using palladium catalysis. In order to simplify the application of any synthetic methodology to new systems, a detailed account presenting optimal conditions and outlining scope and limitations is always welcome! In this particular case, one of the key factors appears to be use of ligand **142** (Scheme 86). Although not

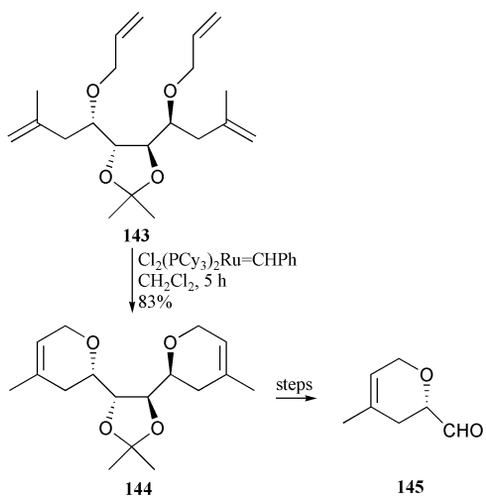


142

Scheme 86

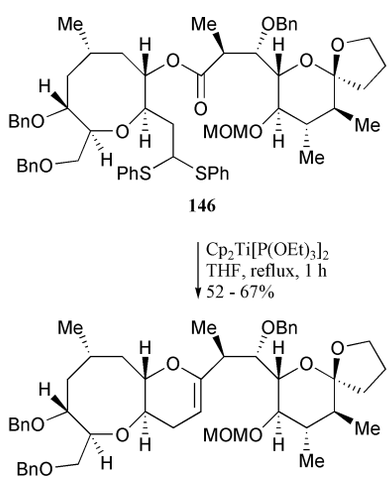
explicitly discussed for chroman formation, racemisation during cyclisation of secondary alcohols was also discussed, and suitable conditions outlined which circumvent this problem.[183]

The microtubule-stabilising agent laulimalide has attracted significant synthetic interest. The group of Davidson at Utah have used ring-closing metathesis to prepare both tetrahydropyran rings, although an asymmetric oxa-Diels–Alder reaction was shown to be a viable alternative.[184] A double ring-closing metathesis was also used to provide the key tetrahydropyranyl aldehyde **145** used in this approach. Treatment of **143** with the Grubbs' catalyst provided **144** as the sole metathesis product. Deprotection and oxidative cleavage of the diol then provided **145** (Scheme 87).[185] Ghosh's work on the same natural product was discussed in the previous review in this series. In 2001, both Ghosh[186] and Paterson[187] reported macrolactonisation approaches to this target starting with known dihydropyran precursors.



Scheme 87

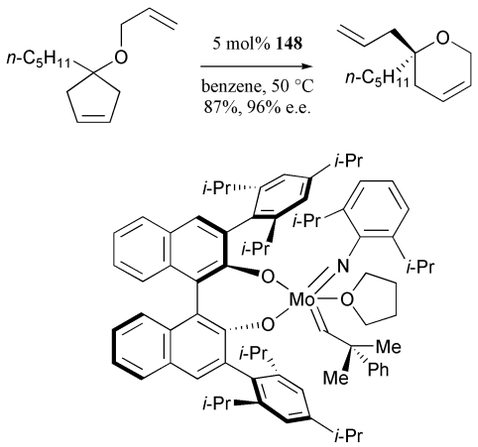
Hirama and co-workers have noted a lack of reproducibility in the Tebbe methylenation/ring-closing metathesis approach to the six-membered J ring of ciguatoxin CTX3C, and have developed an alternative approach based on metal alkylidene formation from dithioacetal **146** to give **147** (Scheme 88).[188]



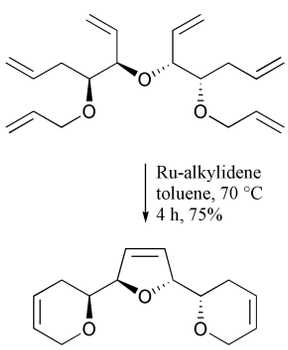
Scheme 88

The development of efficient catalysts has led to an increase in the applications of asymmetric ring-closing metathesis. Catalyst **148** allows the highly selective formation of quaternary stereogenic centres as shown in Scheme 89.[189]

Formation of multiple rings in a single step is possible (Scheme 90). In this report, both five and six-membered rings were formed.[190] A further double metathesis will no doubt find use in the synthesis of marine polyethers. Treatment of **149**, prepared from *cis*-3,4-dichlorocyclobutene, with a ruthenium

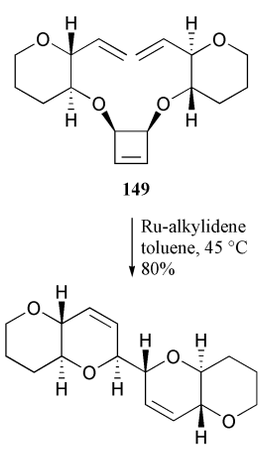


Scheme 89



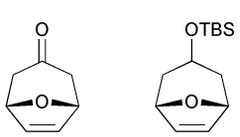
Scheme 90

alkylidene catalyst allowed the high-yielding formation of **150** (Scheme 91).[191] Other applications of ring-closing metathesis include the stereoselective preparation of the tetrahydropyran core of the pseudomonic acids.[192]



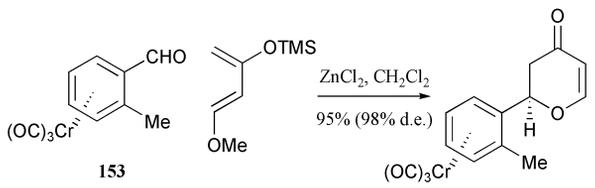
Scheme 91

A surprising difference is observed in the ring-opening metathesis of bicyclic ethers **151** and **152** to give disubstituted tetrahydropyrans. Compound **152** is much more reactive, and prone to polymerization, than **151**, with this reaction being independent of the stereochemistry of the OTBS group.[193]



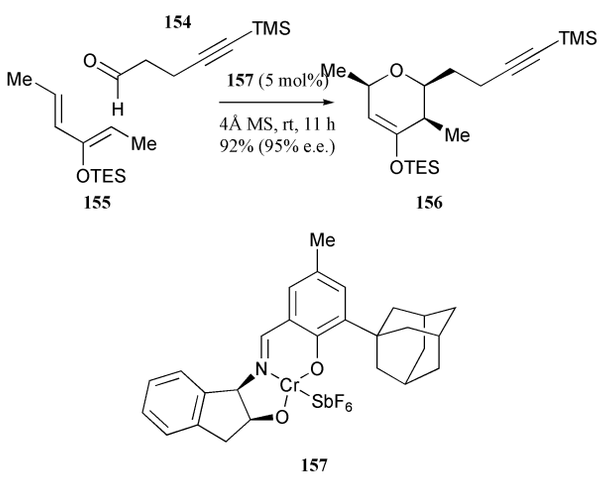
For enol ether metathesis, giving rise to cyclic enol ethers, the less stable tungsten and molybdenum catalysts have generally proved more successful. However, a recent report shows that ruthenium alkylidenes with an additional carbene ligand are equally successful in this reaction.[194]

As a readily removed chiral auxiliary, the planar chiral chromium tricarbonyl moiety has much to offer given its ease of removal from an aromatic ring. Essentially complete diastereocontrol was observed in the zinc chloride-catalysed oxa-Diels–Alder reaction of **153** with the Danishefsky diene (Scheme 92).[195]



Scheme 92

Jacobsen has done much to demonstrate the utility of this reaction in total synthesis. For instance, the reaction of **154** with **155** catalysed by **157** allowed highly enantioselective formation of **156** which was used in the total synthesis of the cytotoxic natural product FR901464 (Scheme 93).[196] Other



Scheme 93

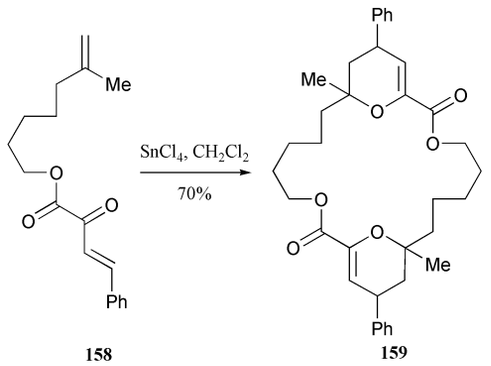
applications of this methodology include the synthesis of (+)-ambruticin,[197] while copper-bisoxazoline complexes were used in the total synthesis of (−)-malyngolide, forming a quaternary stereogenic centre albeit with modest stereocontrol.[198]

Bolm and Simié have described a new bidentate bis-sulfoximine ligand which is particularly effective for oxa-Diels–Alder reactions of cyclohexadiene.[199]

The conformational preference of α-keto esters was used to good effect in preventing the intramolecular oxa-Diels–Alder reaction of **158**, allowing the formation of macrocycle **159** as the sole product (Scheme 94).[200]

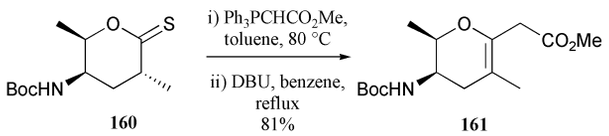
FR901464 and ambruticin have also been prepared by other methods. In the case of the former, the Garner aldehyde was elaborated to provide thiolactone **160**, which was subjected to a seldom-used sequence involving Wittig homologation and deconjugation to provide **161** (Scheme 95).[201] For the latter natural product, one of the pyran rings was formed using metathesis, while the other was prepared by intramolecular Michael addition under thermodynamic conditions as shown in Scheme 96.[202]

Intramolecular conjugate addition has been further used in the synthesis of the unusual triterpene natural products testudinariols A and B. Treatment of **162** with potassium *tert*-butoxide gave a mixture of isomers including **163**.



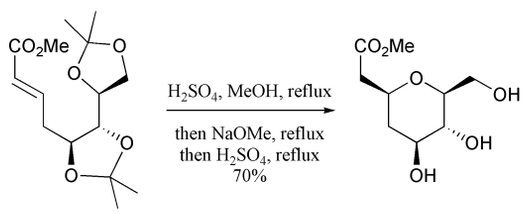
158 159

Scheme 94



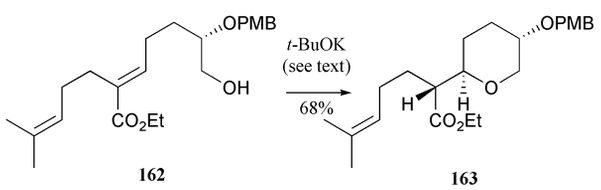
160 161

Scheme 95



Scheme 96

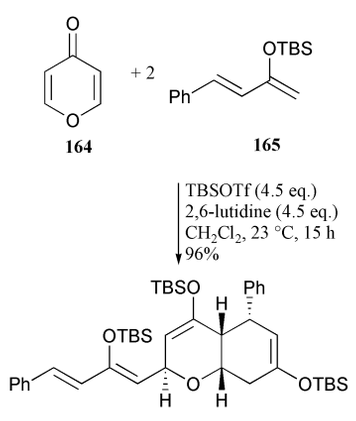
The unwanted isomers were separated and re-subjected to the cyclisation conditions to obtain, after three iterations, the desired isomer in 68% yield (Scheme 97).[203]



162 163

Scheme 97

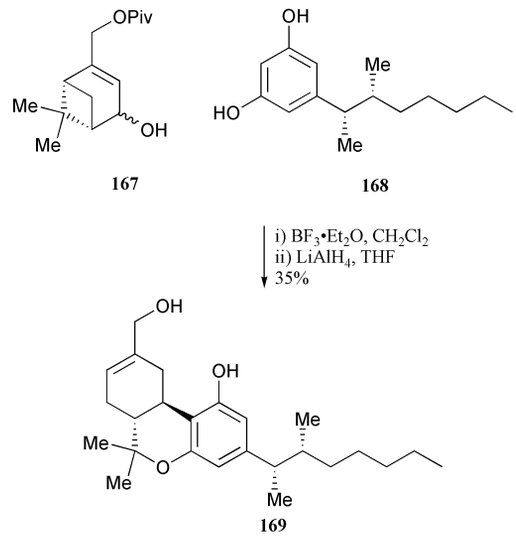
Domino reactions of pyran-4-one **164** allow a rapid increase in molecular complexity. For instance, with siloxydiene **165**, fused tetrahydropyran **166** is produced in spectacular yield (Scheme 98).[204]



164 165 166

Scheme 98

In the final method for this section, a synthesis of potent cannabinoid **169** has been disclosed. In an unusual rearrangement, addition of boron trifluoride–diethyl ether to a mixture of **167** and **168**, followed by reductive removal of the pivalate ester, gave **169** (Scheme 99).[205]

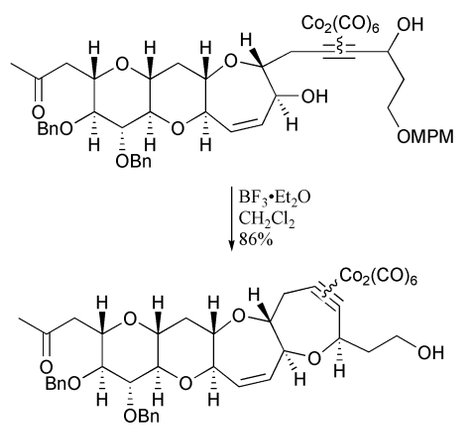


167 168 169

Scheme 99

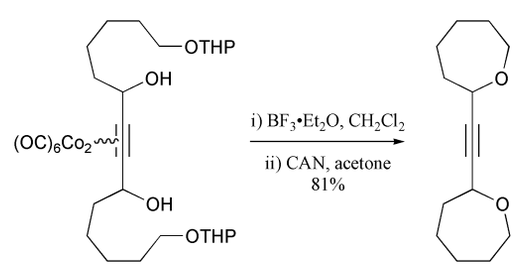
6 Medium sized rings

The group of Isobe continue to pursue a total synthesis of ciguatoxin 1B using intramolecular Nicholas reactions to provide the medium-sized rings. In their latest work, a BCDE ring fragment was prepared using two iterations of this methodology. The final annulation is shown in Scheme 100.[206]



Scheme 100

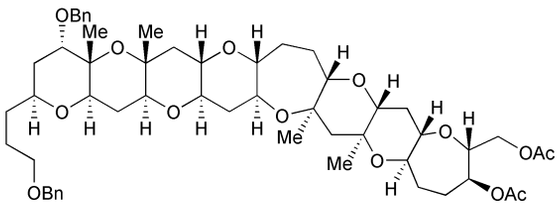
The simultaneous formation of two oxepanes (and other ring sizes) by this method has also been accomplished (Scheme 101).[207]



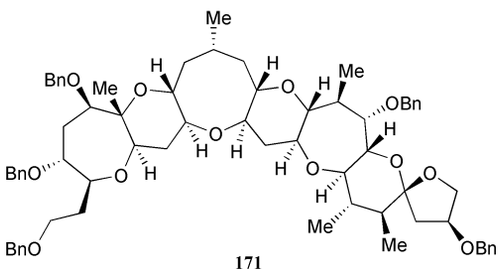
Scheme 101

The preparation of the FGH rings of gambierol using alkylborane cross-coupling was described in the previous review. This work has now been described in full, including a modification of the method of introduction of the required angular methyl group.[208] Further work has provided compound **170** containing all eight oxacyclic rings of this compound.[209] This

methodology has also been applied to the synthesis of **171**, containing 7 of the 13 rings of ciguatoxin 1B,[210] while elaboration of an ester followed by ring-closing metathesis was used in the synthesis of a tetracyclic portion of the same natural product.[211]

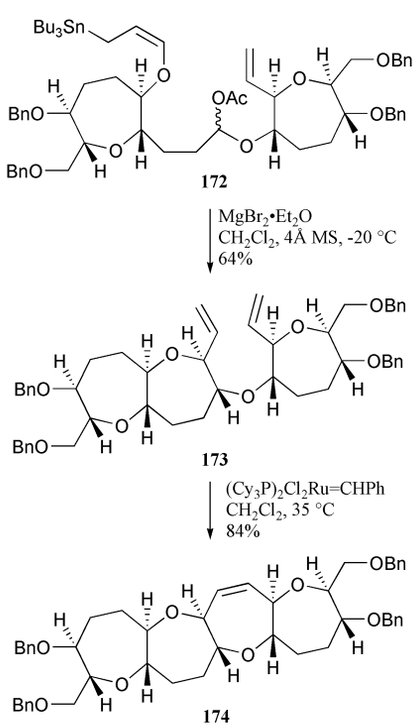


170



171

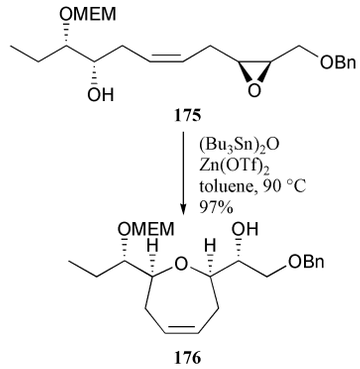
Given the complexity of such compounds, there is a need for efficient methods for bridging oxacycles. A recent report from the group of Yamamoto has shown that it is possible to link two fragments and form a further two oxacyclic rings in short order. Thus, cyclisation of **172**, derived by reduction–acetylation of the corresponding ester, gave **173**, which subsequently underwent ring-closing metathesis to give **174** (Scheme 102).[212]



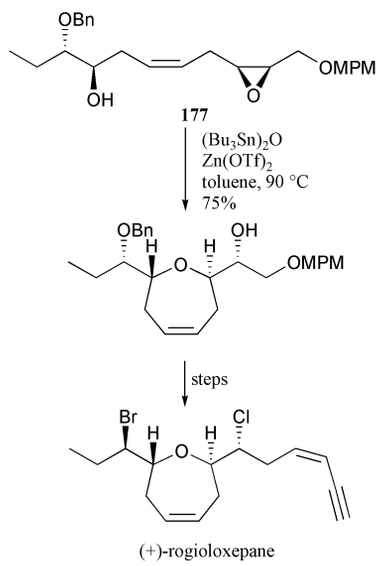
Scheme 102

A formal total synthesis of (+)-isolaurepinnacin has been achieved using an efficient intramolecular epoxide opening of **175** to give **176** (Scheme 103).[213] A slightly lengthy sequence of functional group transformations then allowed convergence with Overman's total synthesis.

A similar route was used to provide the first total synthesis of (+)-rogioloxepane, in which the diastereomeric alcohol **177** was used to provide the required 2,7-*trans* substitution pattern (Scheme 104).[214]

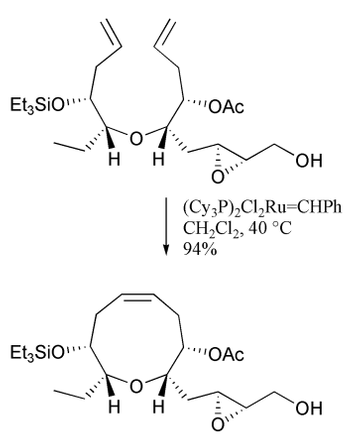


Scheme 103



Scheme 104

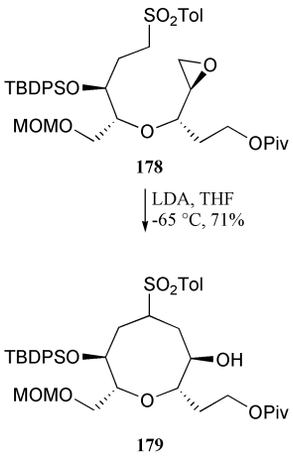
A structurally related natural product, (−)-isolaurallene, has been prepared by a route in which the oxonane ring was formed by the metathesis step shown in Scheme 105. Installation of the stereochemistry on the acyclic precursor is, in the opinion of the reviewer, a far more effective approach than relying on diastereoselective elaboration of a conformationally flexible nine-membered ring.[215]



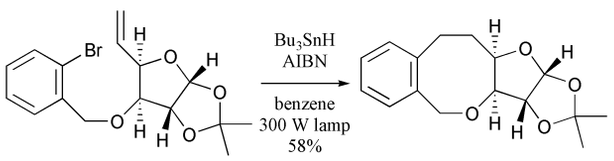
Scheme 105

Similarly-substituted eight-membered rings such as **179** have been prepared by intramolecular epoxide-opening (Scheme 106). The stereochemistry in the precursor **178** was installed by way of a diastereoselective hetero-Diels–Alder reaction.[216]

Free radical cyclisations to give medium sized rings are relatively uncommon. While the reaction shown in Scheme 107 takes place in good yield, formation of the *trans*-ring junction is much less efficient.[217]

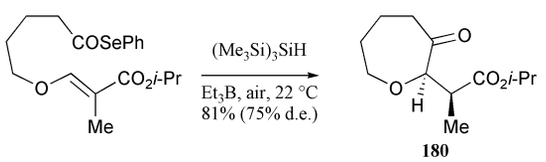


Scheme 106



Scheme 107

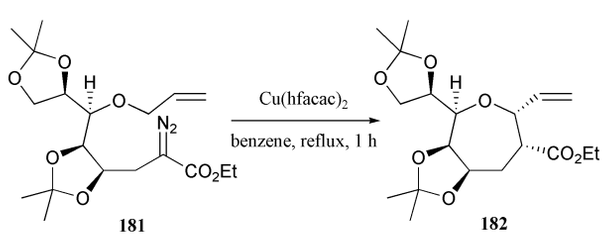
The extent of stereoselectivity in acyl radical cyclisations was found to depend on the size of oxacycle formed. For instance, while moderate diastereocontrol was observed in the formation of **180** (Scheme 108), higher selectivity was achieved in the



Scheme 108

formation of the corresponding pyran, while surprisingly five-membered ring formation gave the weakest stereochemical control of all.[218]

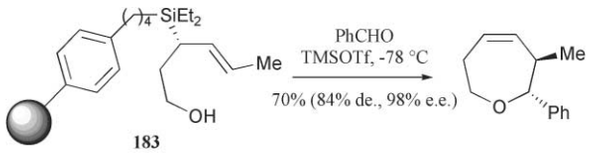
Diazo-decompositions to give medium-ring ethers have focused mainly on O–H insertion and formation and rearrangement of oxonium ylides. More recently it has been shown that treatment of **181** with copper(II) hexafluoroacetylacetonate gives **182** chemoselectively. However, other catalysts and conditions gave alternative products, highlighting the sensitive nature of the metal-bound carbene (Scheme 109).[219]



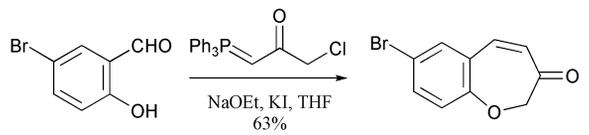
Scheme 109

A range of polymer-bound reagents have been successfully developed over the last few years, often rivalling solution phase reactions in their selectivity. One recent addition is a polystyrene-bound allylsilane **183** which undergoes efficient condensation with aldehydes, with concomitant release from the support (Scheme 110).[220]

The simple but efficient annulation of an oxepane onto a substituted salicylaldehyde has provided the first total synthesis of pterulone (Scheme 111).[221]

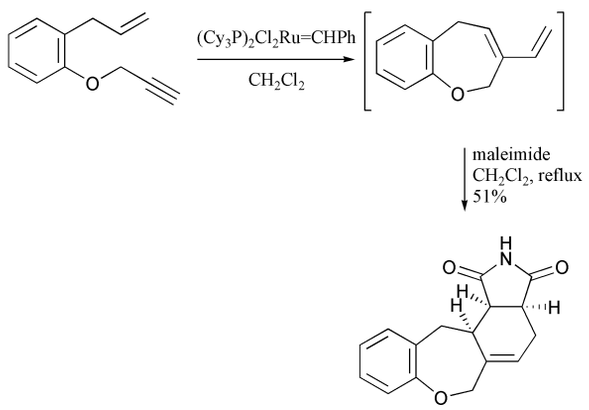


Scheme 110



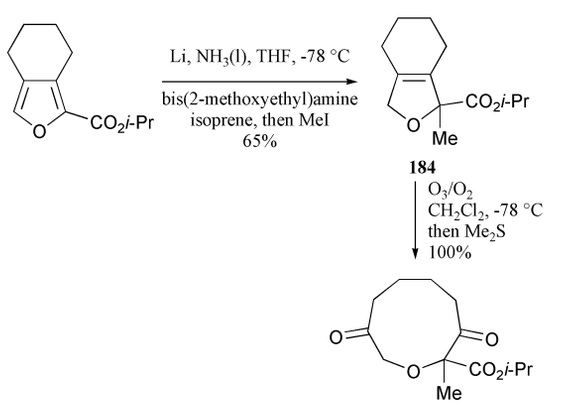
Scheme 111

A further route to benzo-fused oxepanes utilises enyne metathesis followed by a Diels–Alder reaction, allowing a rapid efficient increase in molecular complexity (Scheme 112).[222]



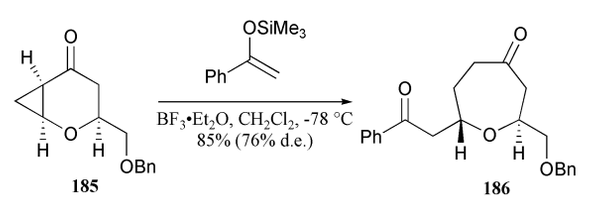
Scheme 112

Ring expansion has long been used as a method for the preparation of medium and large ring ethers. A recent variation on this theme uses the Birch reduction of furans to generate a substrate **184** for ozonolysis (Scheme 113).[223]



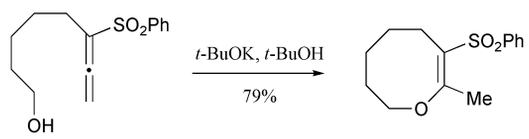
Scheme 113

A one-carbon ring expansion of cyclopropanated pyranones such as **185** with subsequent nucleophilic trapping gives predominantly the 2,7-*trans* oxepane **186**. A range of enol ethers were used with generally good yields and moderate diastereoselectivity (Scheme 114).[224]



Scheme 114

One final method allows the preparation of 5 to 8-membered rings, but is particularly effective for the formation of medium-sized rings and so has been included in this section. Treatment of allenylsulfone **187** with potassium *tert*-butoxide gave oxocane **188** in good yield (Scheme 115). Cyclisation of the



187 **188**

Scheme 115

corresponding sulfoxide failed, although this method was applicable to the smaller ring sizes.[225]

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