REVIEW

Novel methods for the synthesis of three-, four-, five-, six- and seven-membered, saturated and partially unsaturated carbocycles

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Reviewing the literature from May 1998 to April 1999.

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1 Introduction

The aim of this review is to give an overview of the newest methods in carbocyclic synthesis. We concentrate on reactions that form a single ring, although we include intramolecular reactions that lead to the formation of two rings. Methods are chosen for their novelty and we only discuss very significant developments and improvements to known reactions. Occasionally, where our criteria would cause us to ignore an important method of constructing a particular ring size, a single example of the reaction type is included. We also reference some relevant reviews that have appeared during the last two years.

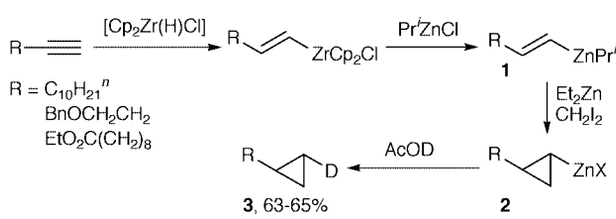
The term "[X + Y] annulation" is used to describe any method that combines two fragments that provide X and Y carbon atoms to the final carbocycle, regardless of the mechanism and the number of steps involved. Reactions that lead to the formation of only one endocyclic bond (single or double) of a five- or six-membered carbocycle are grouped together, as most such reactions can be used for either ring size. The ring expansions in Section 7.4 can be used to make six-membered as well as seven-membered carbocycles, but we feel that they will find greater application for the latter, hence their position in the review.

2 Three-membered carbocycles

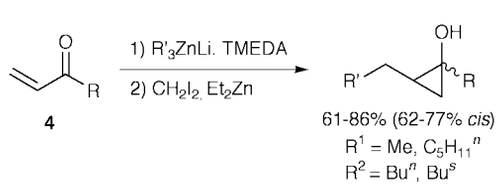
2.1 [2 + 1] Annulations

2.1.1 Metal carbenoids derived from dihalo compounds

Zinc carbenoids are efficiently made by the action of diethylzinc on diiodomethane and are some of the most commonly used cyclopropanating reagents. Cyclopropanation of vinylzincs **1** proceeds faster than cyclopropanation of other vinylmetals, and the resulting cyclopropylzincs **2** react smoothly with acetic acid to give cyclopropanes **3** (Scheme 1).[1] Allylation proceeds in the presence of CuCN·2LiCl, but in modest yield. Zinc enolates can also be cyclopropanated to give cyclopropanols in 34–93% yield.[2] The enolates are made either from α-iodoaldehydes and α-iodoketones or by addition of lithium trialkylzincates to α,β-unsaturated ketones **4** (Scheme 2).



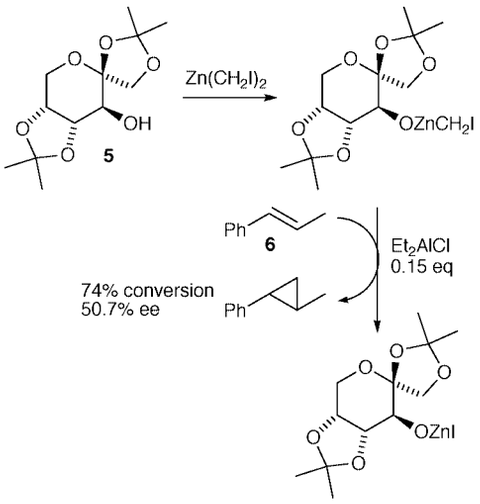
Scheme 1



Scheme 2

When $Zn(CH_2I)_2$ is modified with trifluoroacetic acid to give $CF_3CO_2ZnCH_2I$, it cyclopropanates alkenes, without directing groups, in 70–99% yield and much more rapidly than without

the modifier. When alcohol **5** is used as the modifier and a Lewis acid is added, cyclopropanation of *trans*-β-methylstyrene **6** occurs enantioselectively (Scheme 3).[3]

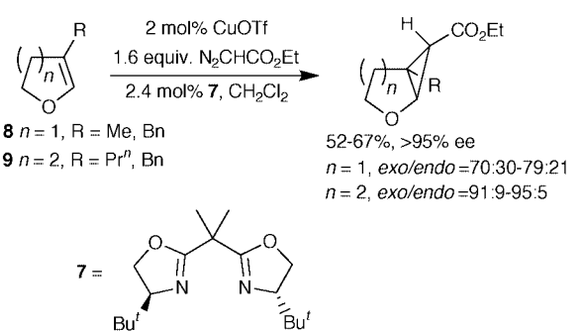


Scheme 3

2.1.2 Carbenes and metal carbenoids from diazocarbonyl compounds

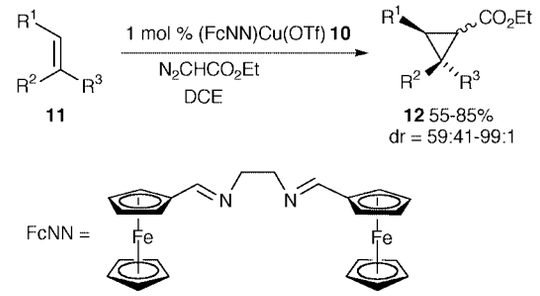
Transition-metal catalysed reactions of diazo compounds with alkenes have been widely used to make cyclopropanes.[4] Copper complexes and dirhodium(II) tetracarboxylates have been the most common catalysts.

Copper(I)-catalysed enantioselective cyclopropanation of alkenes is now well established[5] and bisoxazoline ligands (*e.g.* **7**) are probably the most widely used ligands. Dihydrofurans **8** and dihydropyrans **9** have been cyclopropanated enantioselectively using this type of catalyst with ethyl diazoacetate (Scheme 4).[6] Ferrocenyl ligands are becoming popular. Copper complex **10** catalyses reactions of ethyl diazoacetate with alkenes **11** to give cyclopropanes **12** in high yield with modest to excellent diastereoselectivity (Scheme 5).[7] The bisazaferrocene ligand **13** is the first of a new class of bidentate, C_2-symmetric ligands based on planar-chiral heterocycles (Scheme 6).[8] Copper(I)-catalysed, *trans*-selective cyclopropanation of aryl-, alkyl- and silyl-substituted alkenes **14** gives cyclopropanes **15** in 87–96% ee using this ligand. Combinatorial chemistry has been applied to the search for new, cheap, readily available and highly stereoselective cyclopropanation catalysts. Asymmetric synthesis of 3-phenyl-2,3-methanophenylalanine has been developed by panning catalysts in a library format.[9] The protocol was estimated to increase the rate of screening by one or two orders of magnitude relative to a conventional screening of 2–3 reactions at a time.

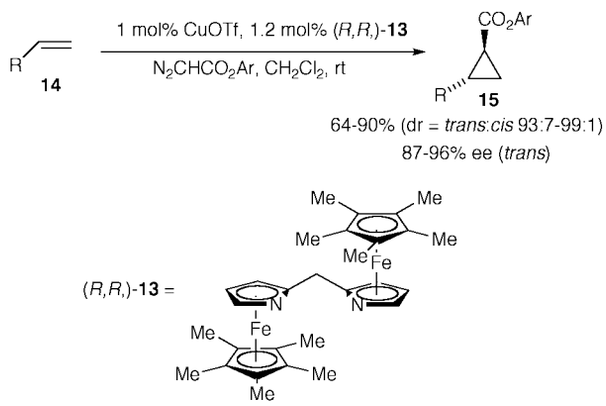


Scheme 4

Dirhodium(II) tetracarboxylates are also popular catalysts for diastereoselective and enantioselective cyclopropanations. A phosphonate tether has been used in rhodium-catalysed diastereoselective intramolecular cyclopropanations (Scheme 7).[10]

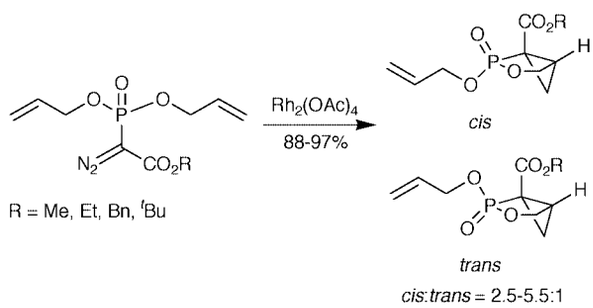


Scheme 5

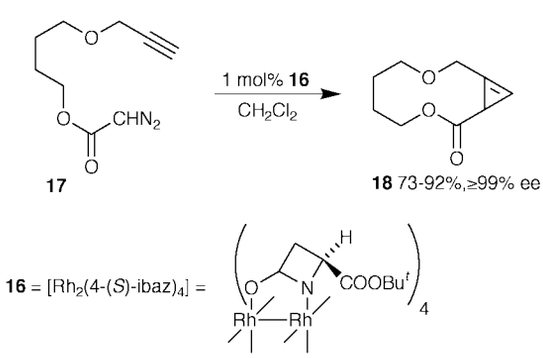


Scheme 6

Chiral dirhodium catalyst **16** cyclises diazoacetate **17** to give macrocyclic cyclopropene **18** in 73–92% isolated yield and ≥99% ee without the need for high-dilution techniques (Scheme 8).[11]



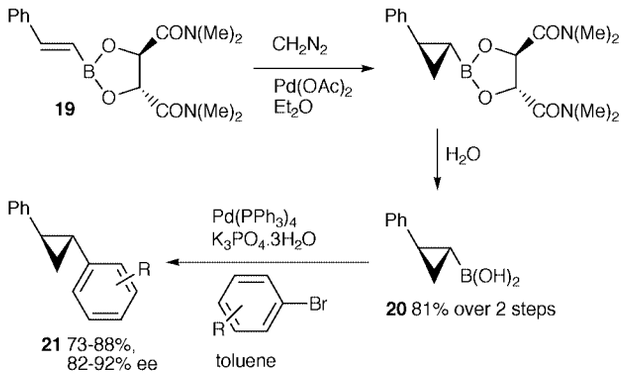
Scheme 7



Scheme 8

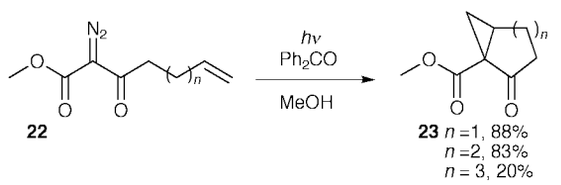
The complexes of other metals also catalyse cyclopropanation. Ruthenium(II) complexes containing diamine-based ligands [RuCl(*p*-cymene)(TsN-NR_2)] catalyse (0.5 mol%) the reaction of alkyl diazoacetate with alkenes to give cyclopropanes in good yield and with modest to good stereoselectivity.[12] Palladium-catalysed cyclopropanation of the enantiopure (*E*)-

1-vinylboronic ester **19**, followed by hydrolysis to the boronic acid **20** and Suzuki cross-coupling gave cyclopropanes **21** in high ee (Scheme 9).[13]

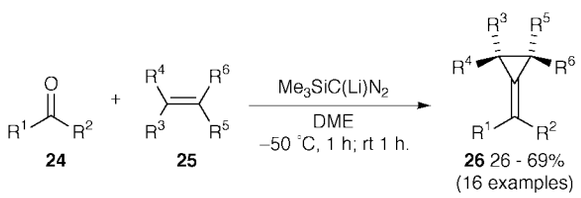


Scheme 9

Carbenes can be generated by photochemical or thermal decomposition of diazo compounds without using a catalyst. Wolff rearrangement is the main reaction of singlet dicarbonylcarbenes but triplet dicarbonylcarbenes, generated by sensitised photolysis of diazo compounds **22**, cyclise to give cyclopropanes **23** in good yield (Scheme 10).[14] However, the reaction cannot be used to make lactones. Lithiation of commercially-available trimethylsilyldiazomethane followed by reaction with an aliphatic ketone **24** and an alkene **25** gives methylenecyclopropane **26**, *via* a thermally-generated, singlet alkylidene carbene (Scheme 11).[15]



Scheme 10

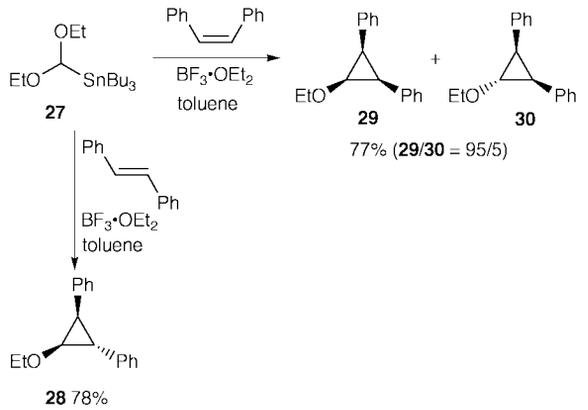


Scheme 11

2.1.3 Other methods of [2 + 1] annulation

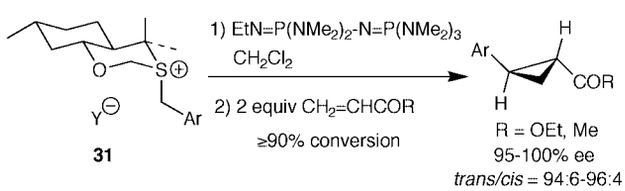
Stannyl-substituted acetals react with alkenes and boron trifluoride to give alkoxycyclopropanes in 28–89% yield. The reaction of diethoxyacetal **27** with *trans*-stilbene gives ethoxycyclopropane **28**, while reaction with *cis*-stilbene gives a 95:5 mixture of ethoxycyclopropanes **29** and **30**, showing that the reaction is stereospecific with respect to the alkene geometry (Scheme 12).[16] An intramolecular version of the reaction is also effective.[17] Alkoxycyclopropanes are also readily prepared in 43–65% yield by reaction of an orthoformate with an alkene in the presence of TMSCl and zinc (*e.g.* Scheme 13).[18] The latter method obviates the need for handling toxic α-halo or α,α-dihalo ether precursors or the multistep procedures involved in the preparation of stoichiometric Fischer carbenoids.

Nucleophilic addition to electron-deficient double bonds is the first step in many two step cyclopropanation methods. Sulfonium ylides, generated by the action of a phosphazene super base on chiral sulfonium salt **31**, cyclopropanate α,β-unsaturated ketones and esters in about 90% yield and 95–100% ee (Scheme 14).[19] Both the chiral auxiliary and the base can be



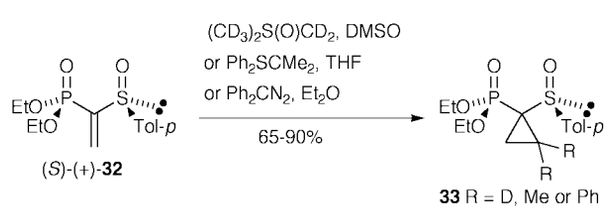
Scheme 12

Scheme 13

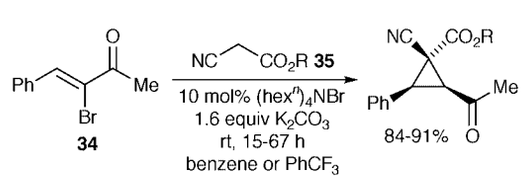


Scheme 14

recovered in high yield. Sulfoxide **32** reacts with sulfoxonium ylides or diphenyldiazomethane to give enantiopure cyclopropanes **33** with complete diastereoselectivity in 65–90% yield (Scheme 15).[20] 1,2,3-Trisubstituted cyclopropanes, including those that contain a quaternary carbon, have been made in excellent yield and with moderate to total diastereoselectivity using enolate chemistry.[21] Of particular interest is the total diastereoselectivity in reactions of acyclic enone **34** with cyanoacetates **35** in benzene or benzotrifluoride (Scheme 16). In a related double displacement reaction, enantiopure glycidyl nosylate **36** was transformed in one pot to cyclopropanolactones **37** in 41–70% yield and with high enantiomeric purity. The use of caesium fluoride allows the reaction to proceed under almost neutral conditions (Scheme 17).[22]

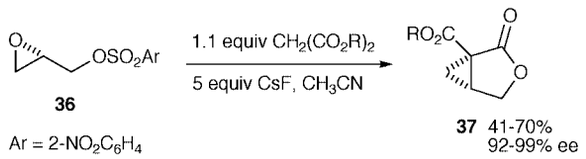


Scheme 15

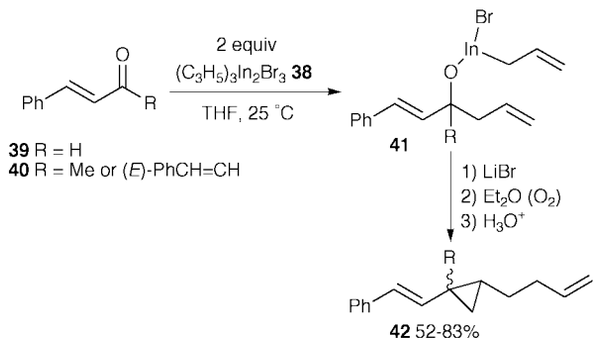


Scheme 16

Cyclopropanes can also be formed by double addition to carbonyl compounds. Allylindium sesquibromide **38** reacts with α,β-unsaturated aldehyde **39** and ketones **40** to give homoallylic indium alkoxides **41** (Scheme 18). Addition of

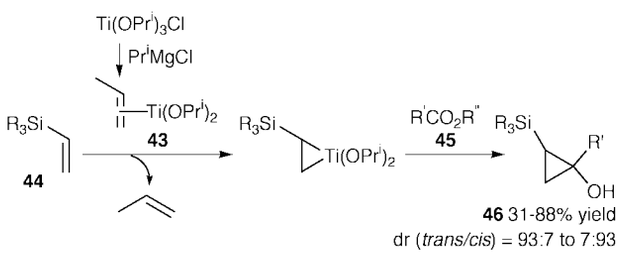


Scheme 17

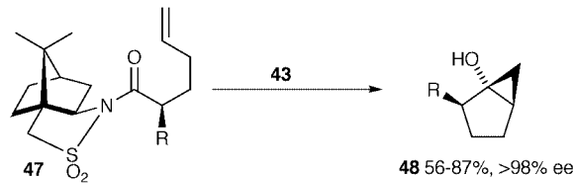


Scheme 18

lithium bromide generates ate complexes, and aerobic work-up then leads to the formation of vinylcyclopropanes **42** in 52–83% yield.[23] A titanium(II) species **43**, which is prepared *in situ* from $Ti(OPr^i)_3Cl$ and isopropylmagnesium bromide, couples vinylsilanes **44** and esters **45** to give silylcyclopropanols **46** (Scheme 19).[24] Cyclisation of unsaturated acylsulfonamides **47**, derived from Oppolzer's camphorsultam, with the same titanium(II) species **43** gives cyclopropanols **48** in good yield, high ee, and with a dr of 92 : 8–>99 : 1 (Scheme 20).[25]



Scheme 19



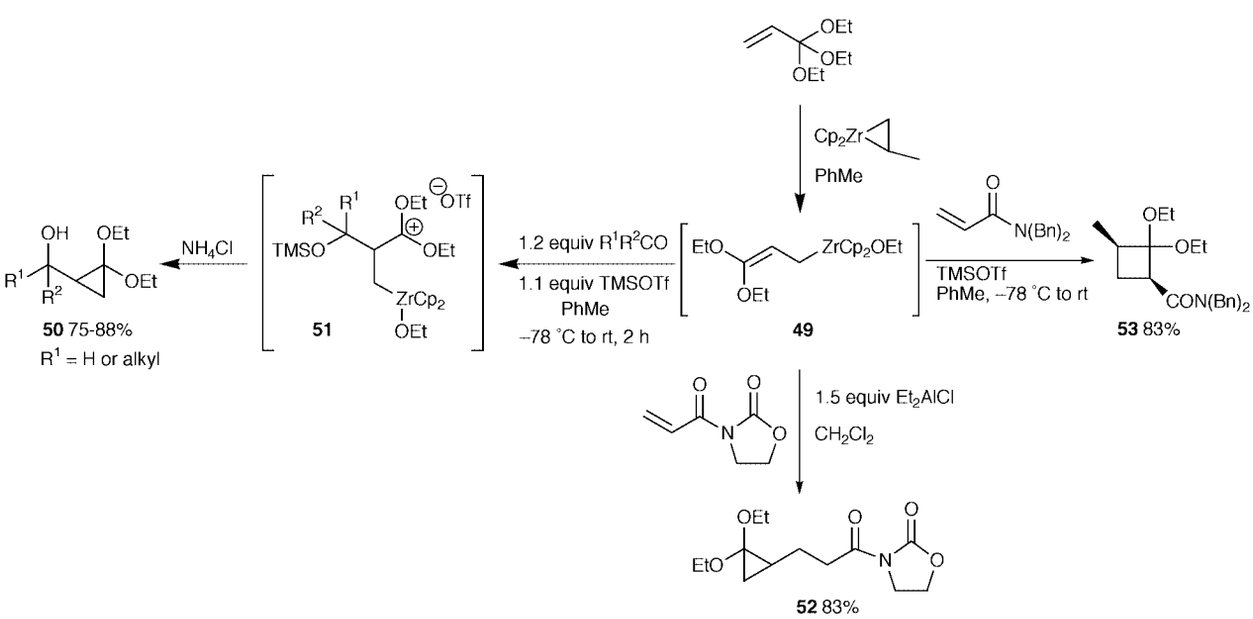
Scheme 20

2.2 Other methods of synthesis

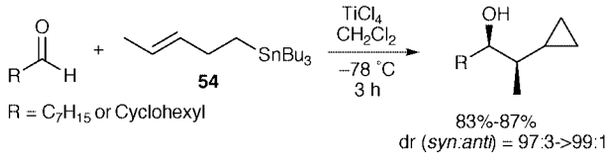
Related zirconium chemistry has been used to generate a γ,γ-dialkoxyallylic zirconium species **49**, which reacts with ketones and aldehydes to give *gem*-dialkoxycyclopropanes **50** in 75–88% yield (Scheme 21).[26] The first step is an aldol-type reaction and the resulting oxonium ion **51** then reacts with the alkylzirconium. Reaction of the same reagent with α,β-unsaturated carbonyl compounds can be controlled to give either cyclopropanes[27] **52** or cyclobutanes[28] **53** in high yield. Homoallylic stannanes also react with carbon electrophiles such as acetals, acid halides and aldehydes in the presence of Lewis acids to give cyclopropanes in 76–87% yield.[29] The reaction of *E*-homoallylic stannane **54** proceeds with high diastereoselectivity (Scheme 22).

Aryl-substituted α-halo epoxides **55** react with samarium(II) iodide in the presence of HMPA to give cyclopropanols **56** (Scheme 23).[30] Elimination occurs in the absence of HMPA.

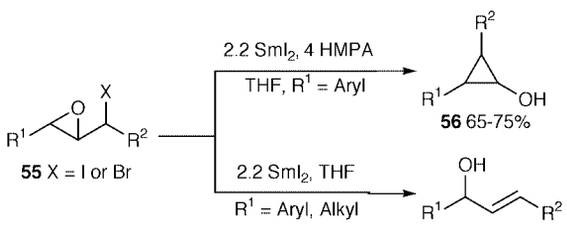
Cyclopropanes can be formed by reductive elimination of transition metals. Neutral complexes, derived from cationic η^3-allylpalladium–pyridinylpyrazole[31] **57** or η^3-allylpalladium–pyridinylimidazole[32] complexes, catalyse cyclopropanation of ketene silyl acetals with allylic acetates (*e.g.* Scheme 24). In an asymmetric version of this reaction using oxazolidinylpyrazole complexes **58**, cinnamyl acetate **59** is converted into a mixture of cyclopropane **60** and unsaturated ester **61** in 34–56% yield and with modest enantioselectivity. (Scheme 25).[33] Cyclobutanone **62** undergoes a rhodium-catalysed domino sequence in which C–C and C–O bonds are successively cleaved. The length of the carbon tether between the two phosphorus atoms of the ligand determines what product is formed: ethylene, trimethylene and tetramethylene give ring opening, recyclisation to cyclopentanone **63** and decarbonylation to give cyclopropane **64**, respectively (Scheme 26).[34]



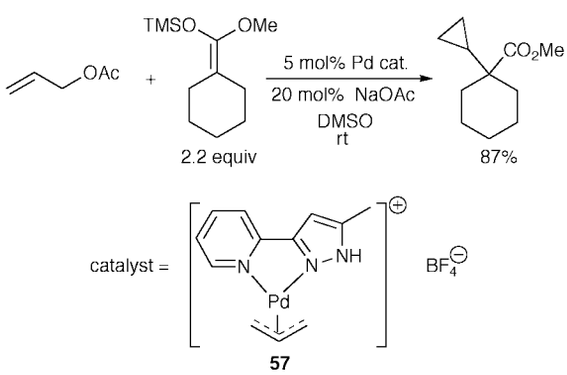
Scheme 21



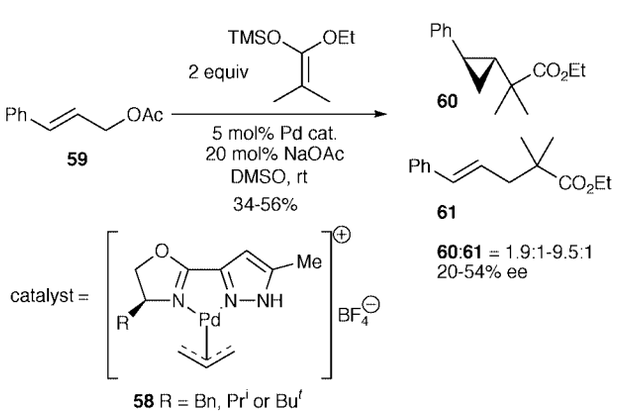
Scheme 22



Scheme 23



Scheme 24



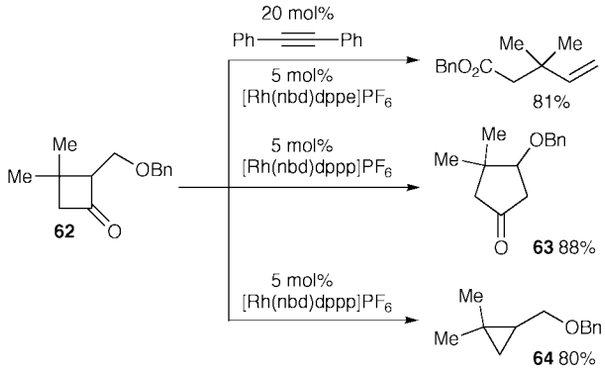
Scheme 25

3 Four-membered carbocycles

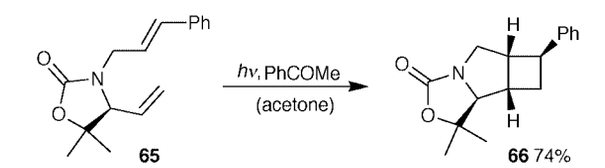
3.1 [2 + 2] Annulations

Photochemical [2 + 2] cycloadditions are commonly employed to synthesise cyclobutanes.[35] Diastereoselectivity with respect to chiral centres already present in the alkenes is of primary importance. Total diastereoselectivity was achieved in the intramolecular cycloaddition of chiral carbamate **65** to give *exo*-product **66** (Scheme 27).[36] One way of enhancing face selectivity in intermolecular cycloadditions is to use a cleavable dimer. C_2-Symmetric bis-butenolide **67** is easily made from D-mannitol, and undergoes photocycloaddition with ethylene to give bis-cyclobutane **68** with more facial differentiation than for simple γ-hydroxymethyl-α,β-butenolide derivatives (Scheme 28).[37] The bis-adduct can then be cleaved to give the *anti* compound **69** with an overall dr >98 : 2.

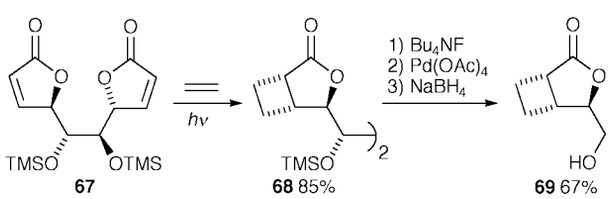
Photolysis of chromium alkylidene complexes **70** generates ketenes that react with racemic vinyltins **71** to give cyclobutanones **72** in good yields as single diastereomers (stereochemistry unknown) (Scheme 29).[38] Elimination of the β-oxazolidinone group from cyclobutanone **72** ($R^1 = R^2 = Me$, $R^3 = Bn$) gives cyclobutenone **73**, which undergoes palladium(0)/copper(I) catalysed cross-coupling with iodobenzene to give cyclobutenone **74**. This chemistry should provide a general route to chiral 3-substituted cyclobutenones.



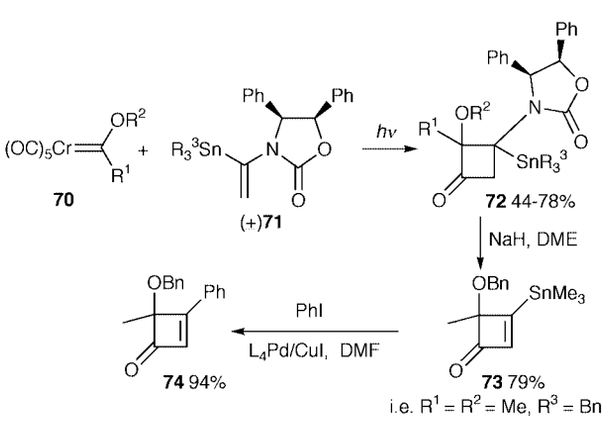
Scheme 26



Scheme 27

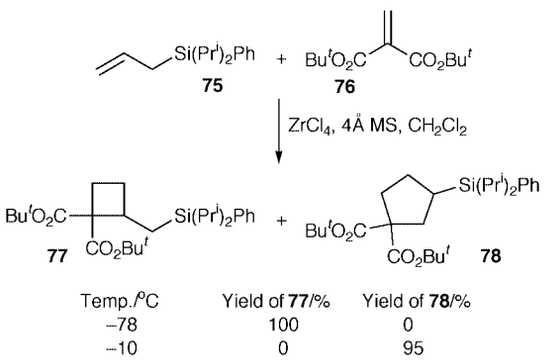


Scheme 28

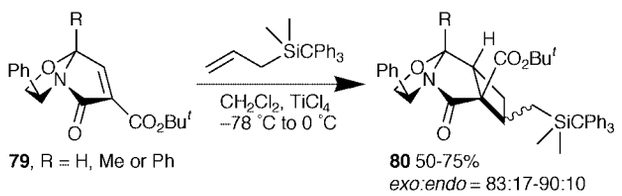


Scheme 29

At low temperature allyldiisopropylphenylsilane **75** reacts with α,β-unsaturated diester **76** to give cyclobutane **77** in a zirconium tetrachloride-mediated [2 + 2] annulation (Scheme 30).[39] The course of the reaction is temperature dependant with diester **76** giving cyclopentane **78** at higher temperature. Chiral bicyclic lactams **79** reacted with allyldimethyltritylsilane under similar conditions to give exclusively cyclobutanes **80** in 50–75% yield with total face selectivity and good *exo* diastereoselectivity (Scheme 31).[40] Oxidising silanes *exo*-**80** gave primary alcohols in 53–69% yield. γ,γ-Dialkoxyallylic zirconium species



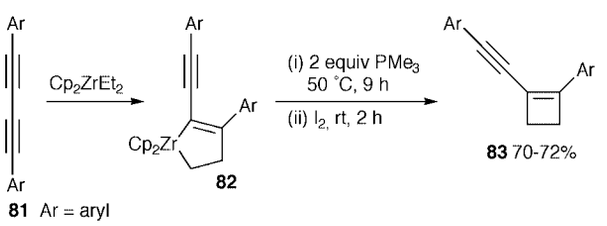
Scheme 30



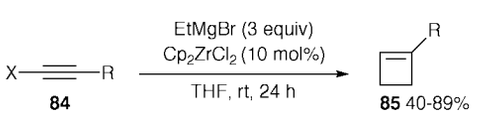
Scheme 31

49 undergo related [2 + 2] annulations with α,β-unsaturated amides to give cyclobutanes **53**[28] in high yield (Scheme 21).

Reductive elimination of α-alkynyl substituted zirconacyclopentenes **82**, prepared from diaryldiynes **81** and diethylzirconocene, gives alkynylcyclobutenes **83** in 62–70% yield upon heating in the presence of trimethylphosphine (Scheme 32).[41] A related zirconium-catalysed reaction of alkynyl halides **84** with ethylmagnesium bromide produces cyclobutenes **85** in 40–89% yield (Scheme 33).[42] Two C–C bonds are formed on the ethyl moiety of the ethylmagnesium bromide.

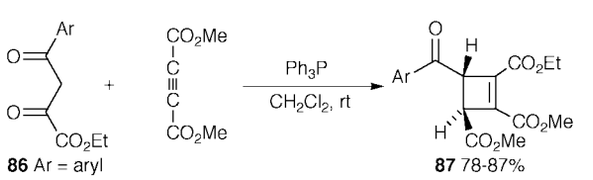


Scheme 32



Scheme 33

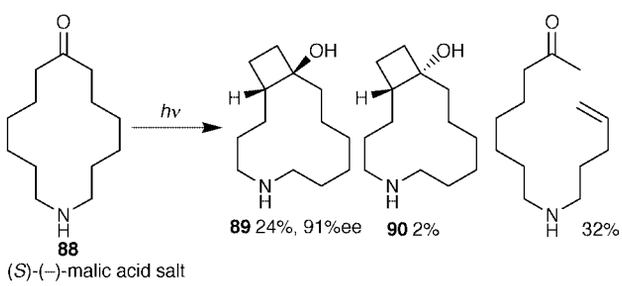
Ethyl 4-aryl-2,4-dioxobutanoates **86** can be converted into cyclobutenes **87** in 78–87% yield *via* a one pot addition–cyclisation procedure (Scheme 34).[43] The cyclobutenes undergo electrocyclic ring opening to give highly electron-deficient 1,3-dienes.



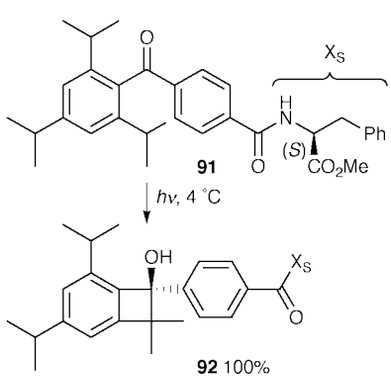
Scheme 34

3.2 Cyclisations forming one endocyclic bond and rearrangements

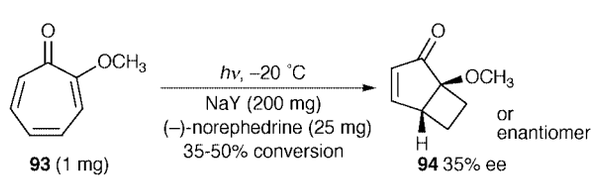
Excellent stereoselectivity can be induced in photocyclisations by carrying out the reactions in the solid state. Irradiation of a benzene solution (*S*)-(−)-malic acid salt of amine **88** gives a 2 : 1 mixture of cyclobutanols **89** and **90** as racemates (Scheme 35).[44] However, irradiation of the crystalline material gave cyclobutanol **89** in 24% yield and 91% ee following basic work-up (Norrish/Yang type II photochemistry). Similarly, when irradiation of crystalline ketone **91** was performed at >350 nm through a cut-off filter, it underwent solid-state photocyclisation to give a single diastereomer **92** in quantitative yield (Scheme 36).[45] The same reaction carried out in benzene solution showed no diastereoselectivity at all. The concept of controlling electrocyclisation using chirally modified zeolites has also been demonstrated. Upon irradiation, tropolone methyl ether **93**, included within NaY zeolite modified by (−)-norephedrine, yields the bicycle **94** in 35–50% yield and up to 50% ee (Scheme 37).[46]



Scheme 35



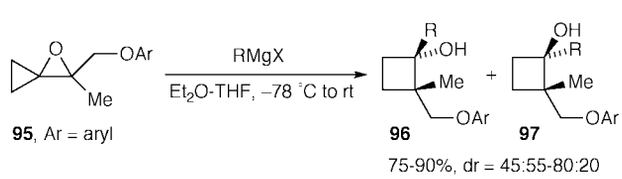
Scheme 36



Scheme 37

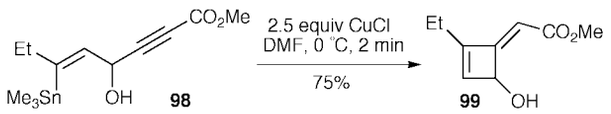
Lewis acid-induced ring expansion of oxaspiropentanes to give cyclobutanones is well established. In a new variant of this reaction, Grignard reagents efficiently ring expand and alkylate oxaspiropentanes **95** to give cyclobutanols **96** and **97** in good yield (Scheme 38).[47]

A method utilises copper–tin transmetalation of vinyltins (*e.g.* **98**) and 4-*exo-dig* conjugate addition onto α,β-alkynic



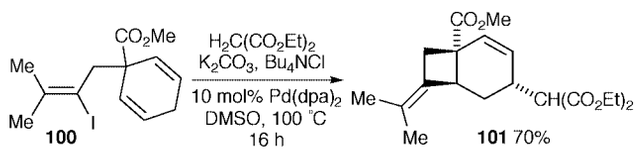
Scheme 38

esters to give cyclobutanes or cyclobutenes (*e.g.* **99**) in 73–95% yield (7 examples) (Scheme 39). The conditions are exceptionally mild and tolerate unprotected hydroxy groups.[48]

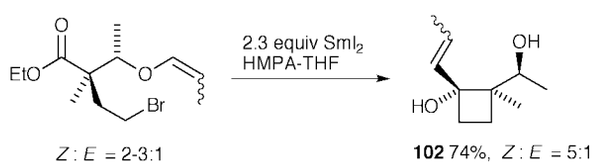


Scheme 39

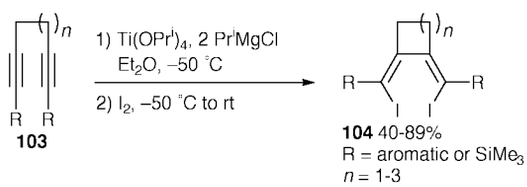
Cyclisations that are not ring-size specific and efficiently form five- and six-membered rings are often much less effective when used to make four-membered rings. However, aryl and vinyl iodides bearing a cyclohexa-2,5-dienyl moiety undergo intramolecular Heck reaction to give four-membered carbocycles; cross-coupling with carbon and heteroatom nucleophiles then gives diastereomerically pure polycyclic alkenes in good yield, *e.g.* vinyl iodide **100** gave bicycle **101** in 70% yield (Scheme 40).[49] Alkylsamariums will undergo 4-, 5-, 6- and 7-*exo-trig* cyclisation onto esters and have been used to make cyclobutanol **102** in a three step cascade reaction sequence (Scheme 41).[50] Another reaction sequence that is effective for four-membered as well as five- and six-membered rings is the formation of bicyclic titanacyclopentadienes from diynes **103** and their reaction with iodine to give exocyclic 1,4-diiodobutadienes **104** in 40–89% yield (Scheme 42).[51] The more traditional cyclisation of δ-halovaleronitrile **105** to cyclobutyl cyanide **106** has now been achieved using sodium hydroxide and phase-transfer catalysis in a solid–liquid phase system (Scheme 43).[52] The absence of solvent makes this method both clean and atom efficient.



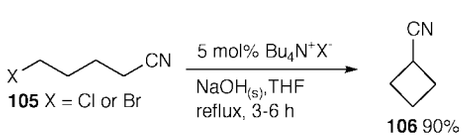
Scheme 40



Scheme 41



Scheme 42

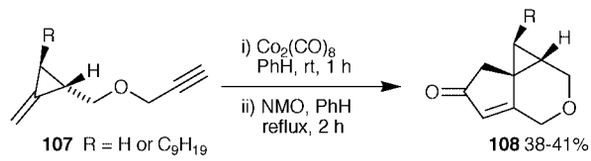


Scheme 43

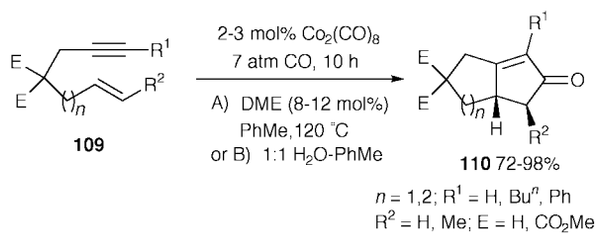
4 Five-membered carbocycles

4.1 [2 + 2 + 1] Annulations

The Pauson–Khand reaction is one of the most important methods of making cyclopentenones.[53] Even methylenecyclopropanes **107** undergo intramolecular Pauson–Khand reactions to give highly strained tricyclic systems **108** in modest yield (Scheme 44).[54] An important discovery is that both 1,2-dimethoxyethane and water promote catalytic Pauson–Khand reactions of enynes **109** to give α,β-unsaturated ketones **110** (Scheme 45).[55] The intermolecular Pauson–Khand reaction of reactive alkenes such as norbornene† and norbornadiene occurs in >90% yield under the same conditions.

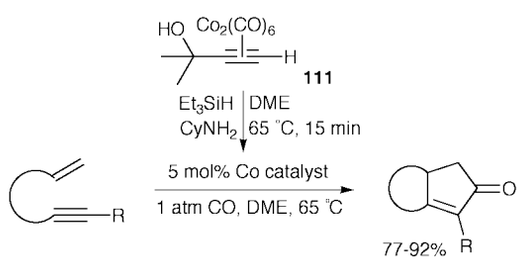


Scheme 44



Scheme 45

A number of convenient substitutes for the labile $Co_2(CO)_8$ catalyst have been reported. Methylidynetricobalt nonacarbonyl cluster, $Co_3(CO)_9(\mu^3\text{-CH})$, is an excellent air-stable catalyst precursor that catalyses (2 mol%, toluene, 120 °C, 7 atm CO, 10–20 h) both intramolecular and intermolecular Pauson–Khand reactions, generally in 83–98% yield (14 examples).[56] The hexacarbonyldicobalt–alkyne complex **111** of 2-methylbut-3-yn-2-ol is also a convenient catalyst precursor and has been used for novel, thermal, intramolecular Pauson–Khand reactions under 1 atmosphere of carbon monoxide (Scheme 46).[57] A similar protocol involves the generation of hexacarbonyldicobalt–alkyne complexes using sub-stoichiometric amounts of cobalt(II) bromide (0.4 equiv) and zinc (0.43 equiv) under 1 atmosphere of carbon monoxide. The resulting complexes react with norbornene (67–88% yield) and cyclopentene (30–35% yield).[58]

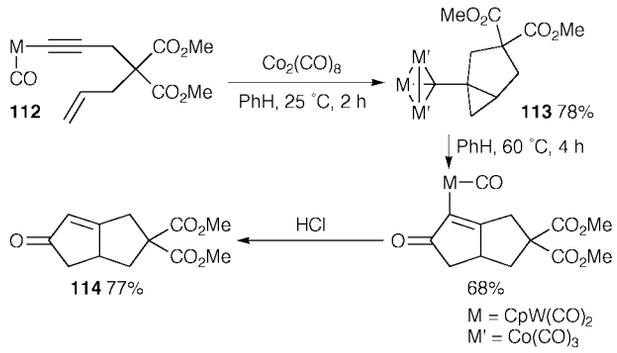


Scheme 46

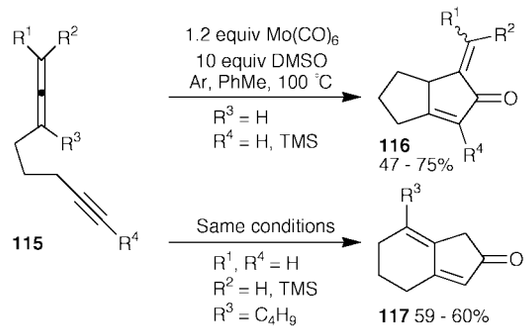
When alkynyltungsten complex **112** is complexed with $Co_2(CO)_8$, it undergoes an intramolecular reaction, *via* a carbenoid intermediate, to give cyclopropane **113** (Scheme 47). Heating in benzene followed by treatment with acid gives cyclopentenone **114**. This novel variant, unlike the standard Pauson–Khand reaction, is successful for electron-deficient olefins having a β-hydrogen and for styrene derivatives.[59]

Other metals can be used in [2 + 2 + 1] cyclisations. Molybdenum hexacarbonyl-induced cyclisation of monosubstituted alkynyl allenes **115** gives α-methylenecyclopentenones **116** or bicyclo[4.3.0]nonanes **117**, depending on the substitution pattern of the allene (Scheme 48).[60] Diastereomerically pure heterobimetallic complex **118** undergoes stereospecific cyclisation to give a single diastereomer **119** (Scheme 49). Such

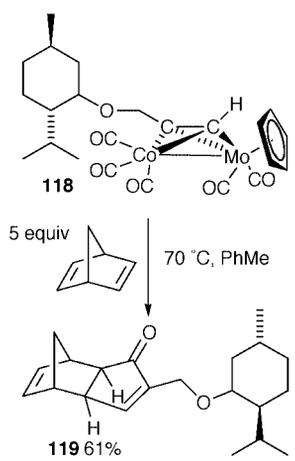
† The IUPAC name for norbornane is bicyclo[2.2.1]heptane.



Scheme 47

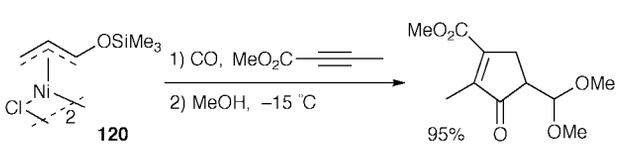


Scheme 48



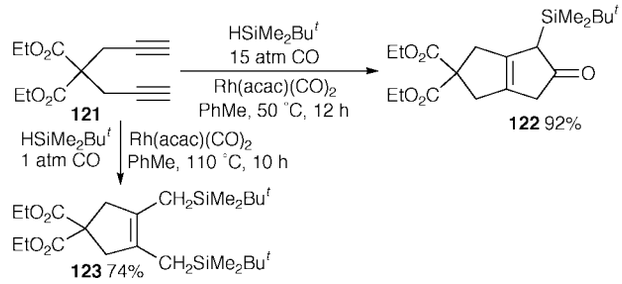
Scheme 49

compounds have not previously been used to produce organic products.[61] Until now nickel-mediated cyclocarbonylation has lacked popularity because of the toxicity of nickel(0) carbonyl. However, π-allyl nickel complexes (*e.g.* **120**, Scheme 50) have been shown to react with alkynes and carbon monoxide at low temperature to give cyclopentenones in 37–98% yield.[62] Under a high pressure of carbon monoxide, rhodium-catalysed silyl carbocyclisation–hydrosilylation of diyne **121** also gives a cyclopentenone **122** in 92% yield (Scheme 51). Cyclopentene **123** is the sole product when the reaction is carried out under 1 atm of carbon monoxide.[63]



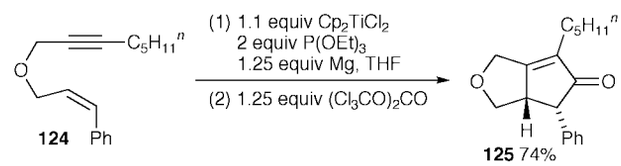
Scheme 50

Carbon monoxide is not the only possible one carbon donor. Titanacycles generated from enynes using low-valent titanocene can be trapped with bis(trichloromethyl) carbonate to give

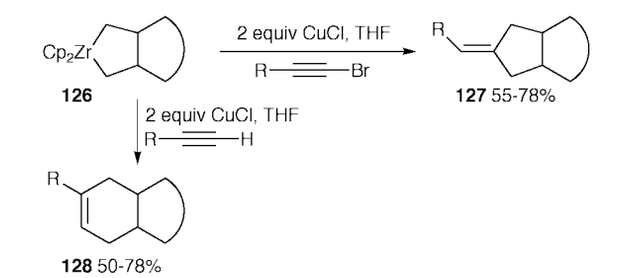


Scheme 51

bicyclic cyclopentenones in 30–85% yield (Scheme 52).[64] The reaction is stereospecific with *Z*-enyne **124** giving cyclopentenone **125** and the corresponding *E*-enyne giving the opposite diastereomer. Similarly, in the presence of copper(I) chloride, zirconacyclopentanes **126** react with alkynyl bromides to give cyclopentanes **127** (Scheme 53).[65] Cyclohexenes **128** are formed when terminal alkynes are used instead of alkynyl bromides.



Scheme 52

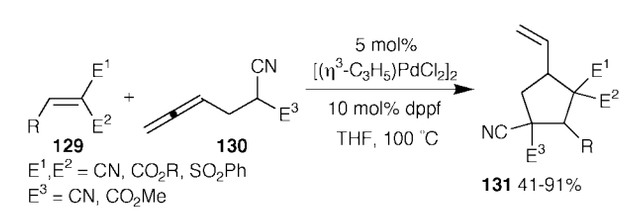


Scheme 53

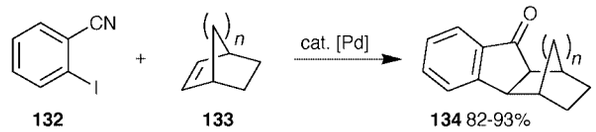
4.2 [3 + 2] Annulations

Zirconium tetrachloride mediated [3 + 2] annulation of allyldiisopropylphenylsilane with α,β-unsaturated diesters proceeds in 54–68% yield and with high diastereoselectivity (>96 : 4) to give, after oxidative cleavage of the C–Si bond, cyclopentanols. The course of the reaction is temperature dependent with diester **76** giving cyclopentane **78** at −10 °C and cyclobutane **77** at −78 °C (Scheme 30).[39] Cyclopentanols can also be made from α,β-unsaturated ketones using the same reagent.[66]

A palladium-catalysed, formal [3 + 2] cycloaddition between electron-deficient alkenes **129** and allenyl malonitriles **130** provides a novel route to cyclopentanoids **131** under neutral conditions (Scheme 54).[67] The mechanism proposed involves a C–H insertion at the activated methine followed by a carbopalladation–hydropalladation sequence. Palladium(0) also catalyses the reaction of 2-iodobenzonitrile **132** with bicyclic alkenes **133** to give bicyclic aryl ketones **134** (Scheme 55).[68]

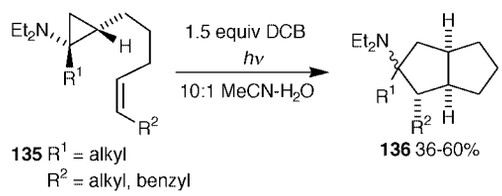


Scheme 54



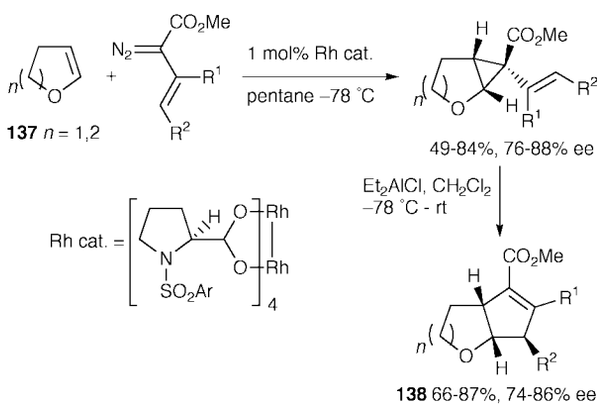
Scheme 55

Cyclopropylamine cation radicals can be generated by photosensitised oxidation of cyclopropylamines **135** and rearrange to give β-iminium carbon radicals. These radicals then undergo two 5-*exo* cyclisations to give bicyclic amines **136** (Scheme 56).[69]



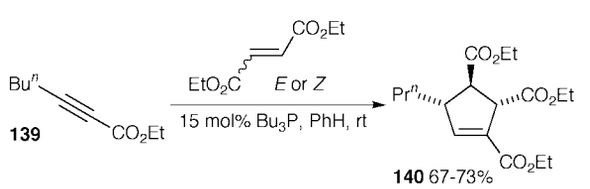
Scheme 56

A two step, asymmetric [3 + 2] annulation between vinylcarbenoids and vinyl ethers **137** gives fused cyclopentenes **138** in 74–86% ee (Scheme 57).[70] However, substantial racemisation occurs in the ring expansion of monocyclic cyclopropanes.



Scheme 57

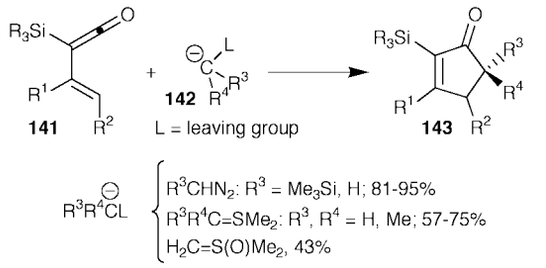
In the presence of a catalytic amount of tributylphosphine, substituted alk-2-ynoates and 2,3-allenoates react with electron-deficient olefins to give cyclopentenes in 38–81% yield.[71] The reaction is apparently non-synchronous as alkyne **139** gives cyclopentene **140** with both diethyl maleate and diethyl fumarate (Scheme 58).



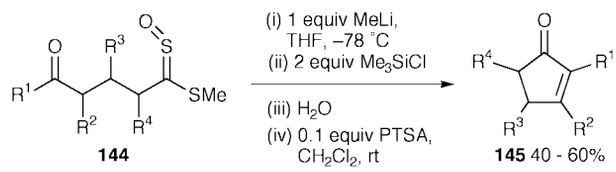
Scheme 58

4.3 [4 + 1] Annulations

A new [4 + 1] annulation strategy involves the reaction of (trialkylsilyl)vinylketenes **141** with carbenoid reagents **142** (sulfonium ylides, sulfoxonium ylides and diazo compounds) to give cyclopentenones **143** in 43–96% yield with total diastereoselectivity (Scheme 59).[72] An umpolung, four-step [4 + 1] annulation strategy has also been reported: 1,4-addition of dithioester enolates to conjugated ketones, followed by oxidation of the resulting δ-oxodithioesters to the corresponding sulfines **144** and reaction with methyllithium followed by acid gives cyclopentenes **145** (Scheme 60).[73]

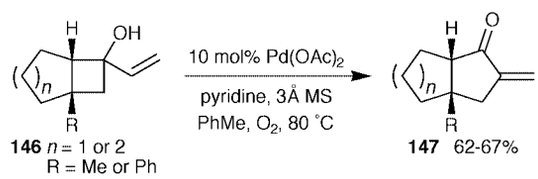


Scheme 59



Scheme 60

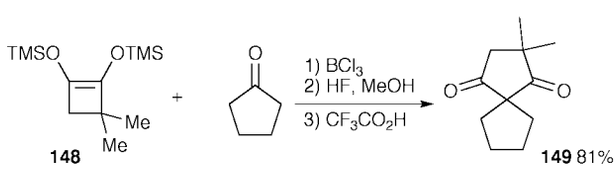
Tertiary cyclobutanols **146** undergo palladium(II)-catalysed ring expansion under an oxygen atmosphere to give α-methylenecyclopentanones **147** (Scheme 61).[74] The opposite



Scheme 61

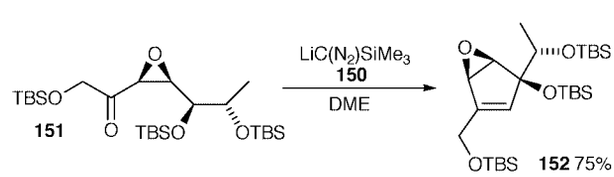
C–C bond migrates under other conditions for palladium-catalysed ring expansions. Since tertiary cyclobutanols are easily made from cyclobutanones, the ring expansion is the second step of a two step [4 + 1] annulation method.

An efficient one-pot procedure for the geminal acylation of ketones has been developed, *e.g.* boron trichloride-mediated aldol reaction between 1,2-bis[(trimethylsilyl)oxy]cyclobutene **148** and cyclopentanone, followed by desilylation and acid-induced acyl migration gave 4,4-dimethylcyclopentane-1,3-dione **149** in 81% yield (Scheme 62).[75]



Scheme 62

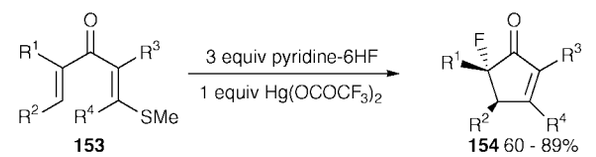
The key step in a synthesis of the antibiotic (−)-isonitrin B illustrates another important [4 + 1] annulation procedure (Scheme 63).[76] When lithiated trimethylsilyldiazomethane **150** reacts with ketone **151**, a carbene alkylidene is generated and undergoes intramolecular C–H insertion with retention of configuration to give cyclopentene **152** in 75% yield.



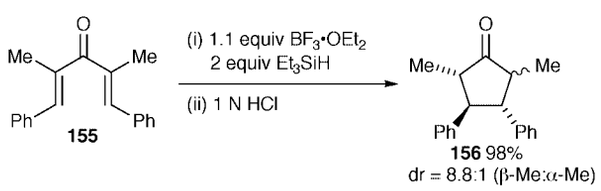
Scheme 63

4.4 Electrocyclisations

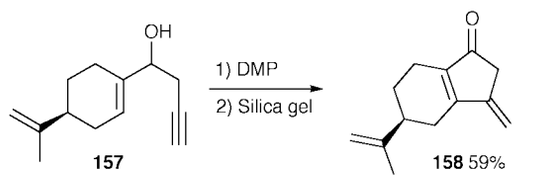
Nazarov cyclisation is a popular method of making cyclopentenones.[77] β-Methylthio divinyl ketones **153** undergo a fluorocyclisation variant of the Nazarov reaction to give fluorocyclopentenone derivatives **154** (Scheme 64). When R^2 = phenyl, the reaction is completely diastereoselective.[78] Tri- and tetra-substituted 1,4-dien-3-ones give cyclopentanones in 63–98% yield and with excellent stereocontrol by a novel reductive Nazarov cyclisation, *e.g.* dienone **155** gave an 8.8 : 1 mixture of cyclopentanones **156** in 98% yield (Scheme 65).[79] Allenyl vinyl ketones, generated by Dess–Martin periodinane (DMP) oxidation of homopropargylic alcohols‡ and isomerisation on silica gel, undergo spontaneous Nazarov cyclisation on silica gel. Thus, alcohol **157** is converted into ketone **158** in 59% yield (Scheme 66).[80] Tius and co-workers have developed ionic electrocyclisations of alkoxyallenes to give prostanoids, *e.g.* alkoxyallene **159** gives Δ7-unsaturated prostanoid **160** as a mixture of geometrical isomers (Scheme 67).[81]



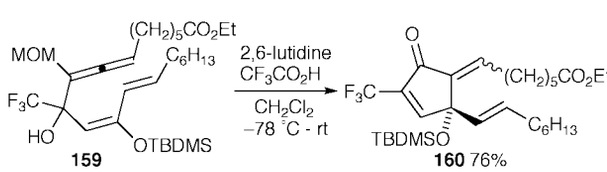
Scheme 64



Scheme 65



Scheme 66

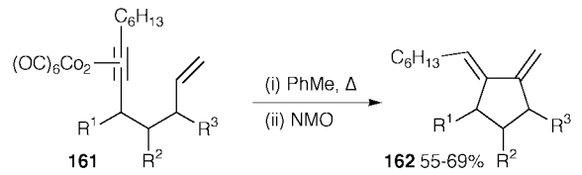


Scheme 67

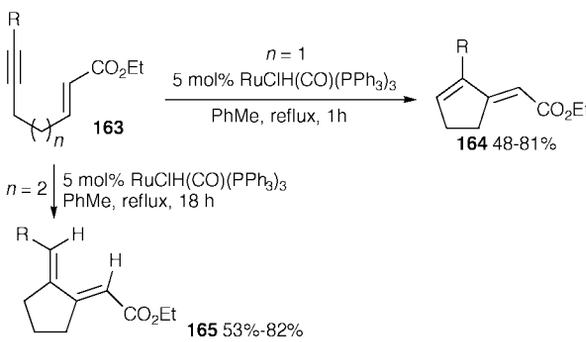
5 Five- or six-membered carbocycles by forming one endocyclic bond

5.1 Organometallic-mediated cyclisations forming carbon–carbon single bonds

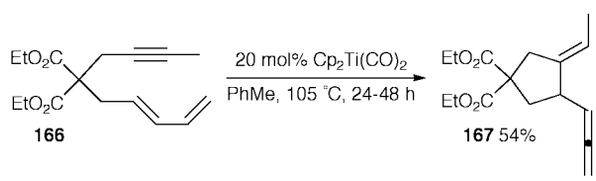
Cycloisomerisation of 1,6- and 1,7-enynes and diynes are well known to occur in the presence of a number of transition metal catalysts.[82] A new stoichiometric reaction is the thermolysis of the hexacarbonyldicobalt complex of 1,6-enynes **161** to give monocyclic dienes **162** (Scheme 68).[83] The reaction, which is also effective for 1,7-enynes, is particularly significant as it is closely related to the Pauson–Khand reaction already discussed, and deuterium labelling studies rule out an α-elimination mechanism and implicate an allylic C–H insertion pathway rather than a β-elimination route for diene formation. A new ruthenium-catalysed intramolecular cyclisation of enynes **163** uses $RuClH(CO)(PPh_3)_3$ to give five-membered carbocycles **164** and **165** (Scheme 69).[84] The best yields are obtained when R is an electron-rich aromatic ring. $Cp_2Ti(CO)_2$ is the first example of an early transition metal catalyst that cycloisomerise enynes to give 1,4-dienes (79–97% yield).[85] Cyclisation of dienyne **166** led to the unprecedented formation of an allene **167** by loss of a β-hydrogen from the intermediate allyl–metal complex (Scheme 70).



Scheme 68

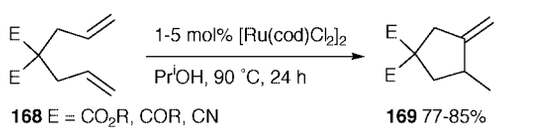


Scheme 69

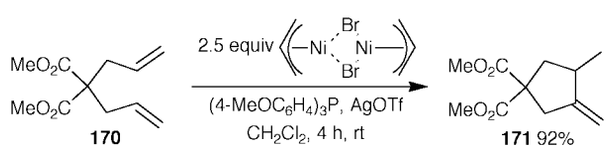


Scheme 70

Ruthenium-catalysed cycloisomerisation of dienes **168** using $[Ru(cod)Cl_2]_2$ gives *exo*-methylene cyclopentanes **169** in good yield (Scheme 71).[86] Even better yields can be obtained with the oligomeric and almost insoluble complex $[Ru(cod)Cl_2]_n$ under the same conditions under either air or nitrogen atmosphere. Palladium(II) and nickel(II) also catalyse cycloisomerisation of α,ω-dienes, *e.g.* diene **170** cyclises to give methylenecyclopentane **171** in excellent yield (Scheme 72).[87] $Cp^*_2YMe(THF)$ does not effect cyclisation of this substrate and "Cp_2Zr" and "Cp_2ScH" are incompatible with ester groups.



Scheme 71

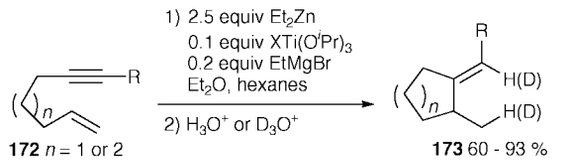


Scheme 72

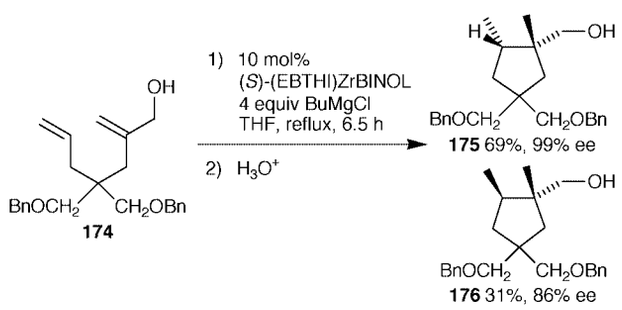
Titanacyclopentadienes can be generated from diynes **103** and reacted with iodine to give exocyclic 1,4-diiodobutadienes **104** in 40–89% yield (Scheme 42).[51] A novel trimetallic zinc–titanium–magnesium reagent system has been used to

‡ The IUPAC name for propargyl is prop-2-ynyl.

cyclise enynes **172** to give cyclopentanes and cyclohexanes **173** in high yield (Scheme 73).[88] Only catalytic quantities of the titanium(IV) alkoxide and the Grignard reagent are needed, and the research constitutes a breakthrough in developing catalytic versions of reactions currently carried out using stoichiometric quantities of titanium–magnesium reagents. Catalytic cyclisations involving related zirconacycles are now being made asymmetric. Cyclisation of diene **174** using (*S*)-(EBTHI)ZrBINOL (10 mol%) [EBTHI = ethylenebis(tetrahydroindenyl)] and butylmagnesium bromide gives cyclopentanes **175** and **176** in high ee (Scheme 74).[89]

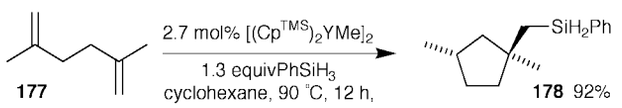


Scheme 73

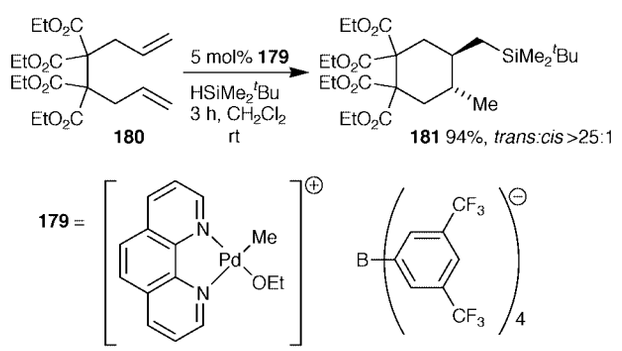


Scheme 74

$[(Cp^{TMS})_2YMe]_2$ catalyses the cyclisation–silylation reaction of hindered dienes **177** to give cyclopentanes **178** in high yield setting up new quaternary centres with excellent stereocontrol (Scheme 75).[90] In a similar reaction, cationic palladium complex **179** catalyses the cyclisation–hydrosilylation of functionalised 1,7-dienes (*e.g.* **180**) to form silylated cyclohexanes (*e.g.* **181**) in good yield and with moderate to good *trans*-selectivity (Scheme 76).[91] The rhodium-catalysed silyl carbocyclisation–hydrosilylation of diyne **121** gives cyclopentene **123** as the sole product (Scheme 51). Carbonylation occurs at higher pressures of carbon monoxide to give cyclopentenone **122**.[63]

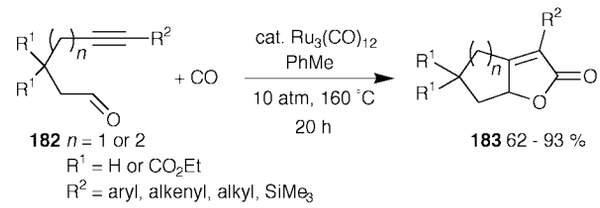


Scheme 75



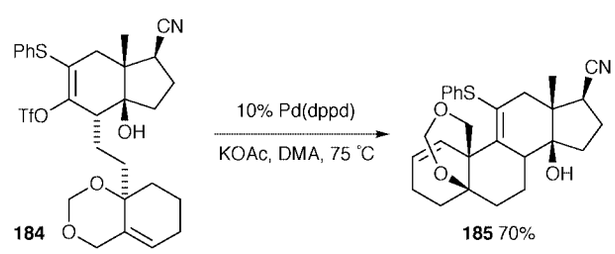
Scheme 76

Metallacyclopentenes are usually produced by the cycloaddition of a coordinated alkyne and an alkene. Heteroatom containing metallacyclopentenes are known for early transition metals but the metal–oxygen bond is strong for these metals and makes catalysis difficult. However, ruthenium carbonyl catalyses the cyclocarbonylation of yne-aldehydes **182** to give bicyclic γ-butenolides **183** in good yield (Scheme 77).[92]

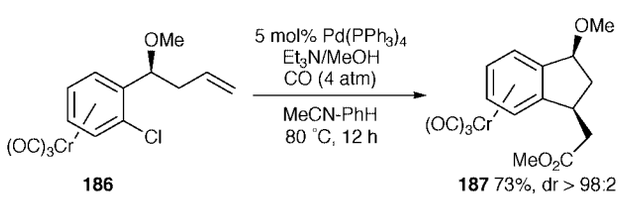


Scheme 77

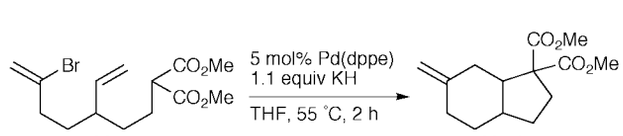
Palladium complexes catalyse a huge range of carbon–carbon bond forming reactions. One process that is widely applied to the synthesis of carbocycles is the Heck reaction. Even highly substituted alkenes can be coupled in the intramolecular Heck reaction, *e.g.* α-sulfenyl enol triflate **184** gave the pentacyclic cardenolide precursor **185** in 70% yield (Scheme 78).[93] Cyclisation can be combined with carbonylation, as in the conversion of *o*-butenylchlorobenzene tricarbonyl complexes **186** into esters **187** (Scheme 79).[94] Wacker-type cyclisations are also popular. When malonate derivative **188** is treated with potassium hydride and 5 mol% Pd(dppe), it cyclises exclusively to the *trans*-hydrindane **189** in 70% yield (Scheme 80).[95] Palladium(0)–acetic acid catalyses intramolecular allylation of malonitrile derivatives **190** with phenylalkynes to give five- and six-membered carbocycles **191** and **192** in 84–93% yield (Scheme 81).[96] The procedure is highly atom efficient and the substrates are easily made. Palladium-catalysed allylic alkylation has been used to prepare silyl substituted cyclopentene **194** in 74% yield from pentenol **193** *via* a 5-*endo*-*trig* process (Scheme 82).[97] 3-*exo* Cyclisations are preferred in the absence of the silicon atom.



Scheme 78

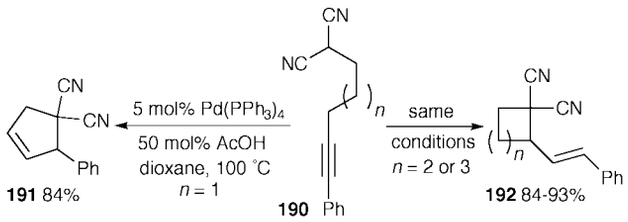


Scheme 79

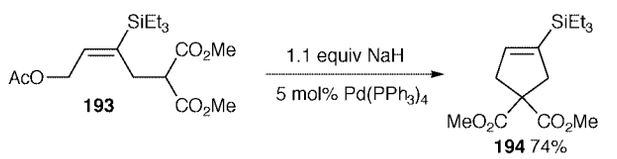


Scheme 80

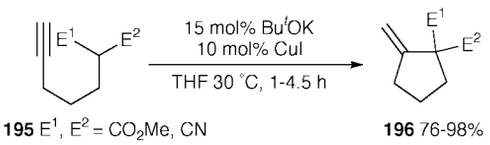
Intramolecular carbometallations are effective ring-forming processes. Carbocupration of terminal alkynes **195** using catalytic base and copper(I) give methylenecyclopentanes **196** (Scheme 83).[98] Disubstituted alkynes also cyclise in 65–88% yield but require stoichiometric quantities of the reagents.



Scheme 81

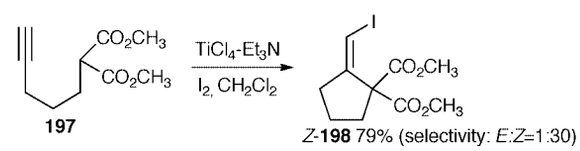


Scheme 82

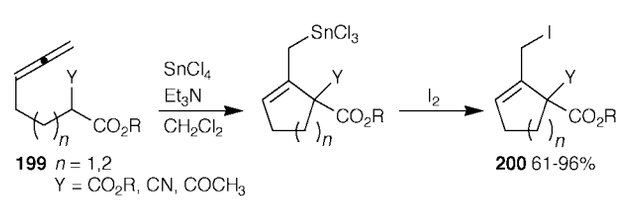


Scheme 83

Intramolecular carbotitanation of active methine compounds having an unactivated alk-4-ynyl group proceeds in a highly *cis*-selective manner in the presence of titanium tetrachloride and triethylamine *e.g.* alkyne **197** is stereoselectively converted into *Z*-vinyl iodide **198** (Scheme 84).[99] The method complements the high *trans*-selectivity observed when titanium(IV) alkoxides are used in iodocarbocyclisations.[100] Iodocarbocyclisation of various active methine groups with alkenes also proceed in good yield using the titanium(IV) chloride–triethylamine reagent system.[101] Intramolecular carbostannation of active methine compounds **199** that have an allenyl group gives five- and six-membered carbocycles **200** in good yield (Scheme 85).[102]



Scheme 84

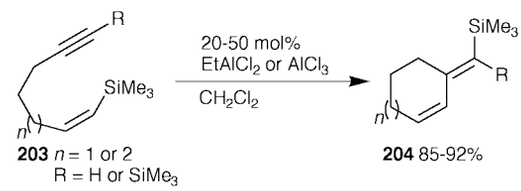


Scheme 85

Hafnium(IV) chloride catalyses intramolecular reaction between the alkyne and allylsilane groups of compounds **201** to give five-, six- and seven-membered carbocycles **202** in moderate to good yield (Scheme 86).[103,104] These are the first examples of carbocyclisations proceeding exclusively by the *endo-dig* mode. The Lewis acid-catalysed reaction of carbon-tethered alkynyl vinylsilanes **203** gives (*E*)-cyclic dienylsilanes **204** (Scheme 87). This is the first example of vinylsilylation of unactivated alkynes and is a new method for the preparation of six- and seven-membered cyclic dienylsilanes.[105]

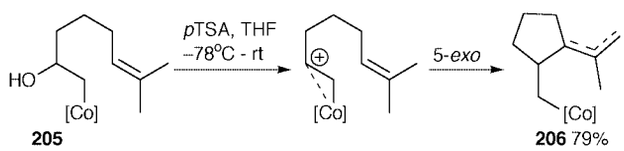
5-*exo*, 5-*endo* and 6-*endo* but not 6-*exo* orientated double bonds cyclise onto cobaloxime π-cations to give five- and six-membered ring cyclovinylcobaloximes in 40–79% yield,[106] *e.g.*

Scheme 86



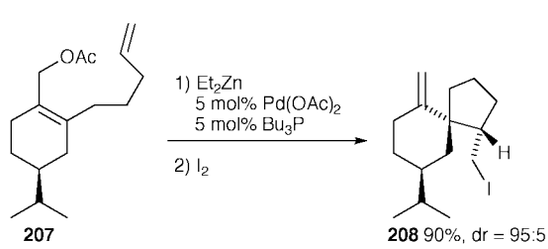
Scheme 87

when cobaloxime **205** is treated with acid, it gives five-membered carbocycle **206** in 79% yield as a mixture of double bond regioisomers (Scheme 88).

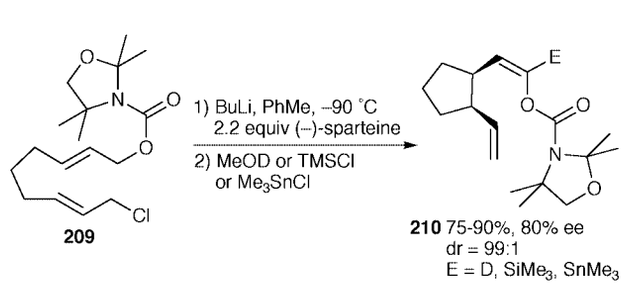


Scheme 88

Intramolecular metallo-ene reactions are efficient methods for the construction of substituted ring systems. A good example is the intramolecular palladium-catalysed zinc-ene reaction that was used to convert diene **207** into spirocycle **208** as the key step in an efficient synthesis of (−)-erythro-diene (Scheme 89).[107] Metallo-ene reactions often suffer from unfavourable equilibria and this problem has been overcome in the first asymmetric lithium-ene reaction. Enantioselective deprotonation of allylic carbamate **209** is followed by cyclisation with irreversible elimination of lithium chloride (Scheme 90).[108] A further deprotonation generates a vinyllithium that can be quenched with electrophiles to give cyclopentanes **210** in good yield and 80% ee.

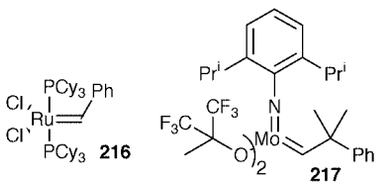


Scheme 89



Scheme 90

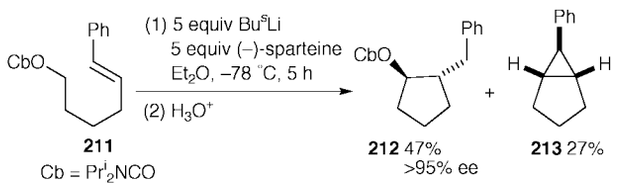
The related carbanion cyclisation of carbamate **211**, when induced with a *sec*-butyllithium–(−)-sparteine system, affords cyclopentanol **212** and bicyclohexane **213** in extremely high ee



216 **217**

Fig. 1

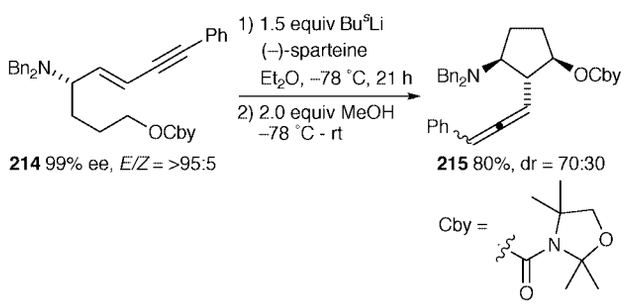
(Scheme 91).[109] Similarly, when chiral α-oxyalkyllithiums are generated from carbamates **214** that contain a diene or an enyne at C-5 and a sterically-demanding substituent at the allylic position (to prevent abstraction of the remaining allylic proton), intramolecular carbolithiation gives cyclopentanes **215** with total stereocontrol over the two new chiral centres (Scheme 92).[110]



211 Cb = Pr^i_2NCO

212 47% >95% ee **213** 27%

Scheme 91



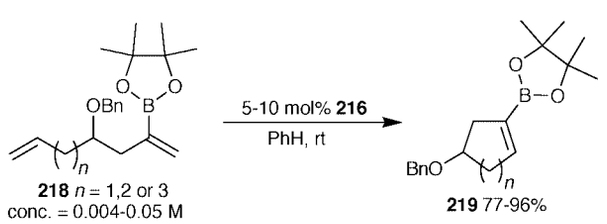
214 99% ee, *E/Z* = >95:5

215 80%, dr = 70:30

Scheme 92

5.2 Ring closing metathesis (RCM) and related reactions

The advent of the Grubbs and Schrock RCM catalysts, **216** and **217**, has revolutionised the synthesis of carbocyclic alkenes (Fig. 1).[111–113] RCM of vinylboronates **218** using the Grubbs catalyst **216** is a reliable and practical procedure for the synthesis of trisubstituted cyclic vinylboronates **219** (Scheme 93).[114] Both the Grubbs catalyst **216** and the Schrock catalyst **217** will selectively activate one terminal double bond of tetraenes **220** and induce diastereoselective ring closure. A second RCM reaction then gives a new class of bicyclic diallyl alcohol derivatives **221** with high *cis* selectivity (Scheme 94).[115] Similar selectivity can be obtained in the cyclisation of trienes to give five- and six-membered monocycles. Complex **216** also catalyses polycyclisation reactions *via* ring-opening–ring-closing metathesis reactions (Scheme 95).[116]

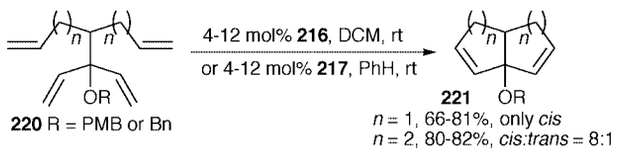


218 *n* = 1,2 or 3
conc. = 0.004-0.05 M

219 77-96%

Scheme 93

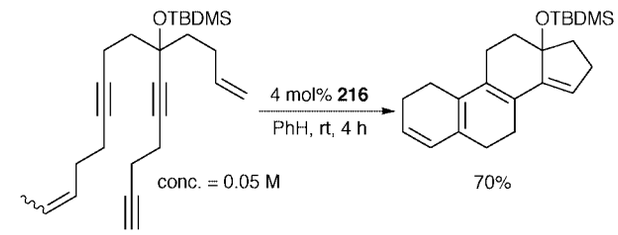
New reaction conditions for RCM have been developed. The intramolecular RCM of terminal alkynes **222** gives dienes **223** and the reaction is much more effective under an ethene atmosphere than under an argon atmosphere (Scheme 96).[117] Many interesting substrates for RCM are derived from biological systems and are insoluble in organic solvents. Ruthenium catalyst **224** is soluble in water and in methanol and will catalyse RCM reactions in these solvents to give either cyclopentenes or cyclohexenes.[118] Water-soluble substrate **225** was cyclised to cyclopentene **226** in 90% yield using 10 mol% of this catalyst in water (Scheme 97).



220 R = PMB or Bn

221 *n* = 1, 66-81%, only *cis*
n = 2, 80-82%, *cis*:*trans* = 8:1

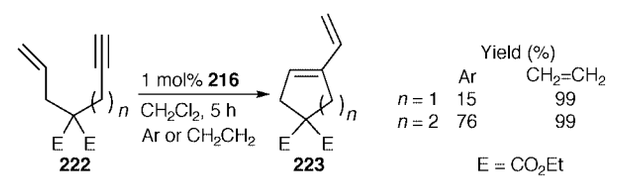
Scheme 94



conc. = 0.05 M

70%

Scheme 95

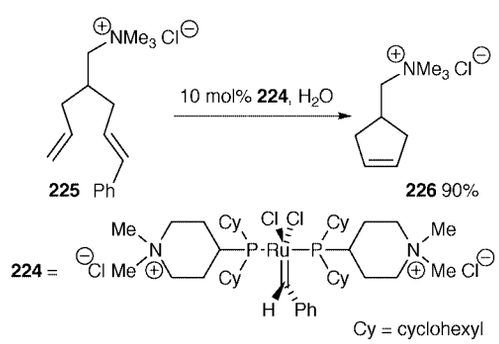


222 **223**

	Yield (%) Ar	$CH_2=CH_2$
n = 1	15	99
n = 2	76	99

E = CO_2Et

Scheme 96

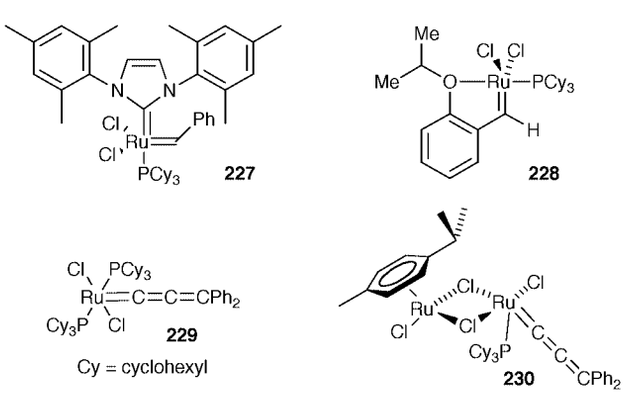


225 Ph **226** 90%

224 =

Cy = cyclohexyl

Scheme 97



227 **228**

229

Cy = cyclohexyl

230

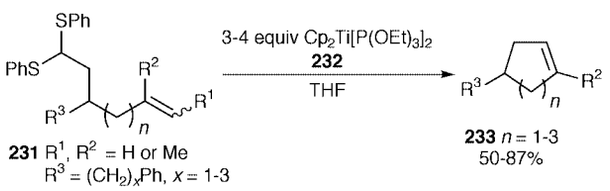
Fig. 2

A number of important new RCM catalysts have been reported during the review period (Fig. 2). The imidazolinylidene substituted ruthenium-based complex **227** is more air and

water tolerant and a more efficient RCM catalyst than Grubbs catalyst **216** at elevated temperatures. Di-, tri-, and even tetra-substituted cycloalkenes have been prepared in moderate to excellent yield from diene precursors using 5 mol% of catalyst **227**.[119] Ruthenium complex **228** is an extremely robust pre-catalyst for ring closing metathesis. It mediates the RCM of five-, six-, seven- and eight-membered carbocycles and heterocycles and can be recovered by chromatography on silica gel performed in air with undistilled, reagent-grade solvents.[120]

A new and very user-friendly protocol for RCM reactions involves heating a solution of the diene substrates with 2.5–5 mol% of commercially available $[(p\text{-cymene})RuCl_2]_2$ with PCy_3 under a neon light.[121] Well defined, coordinatively unsaturated allenylidene complexes **229** and **230** provide an alternative route into the catalytic RCM cycles that operate from benzylidene complex **216**. They are very easily prepared, highly tolerant of functional groups and can be used (1–5 mol%) to form five-, six-, seven-, eight-, fifteen-, sixteen- and eighteen-membered rings in 60–98% yield (15 examples for each catalyst).[122]

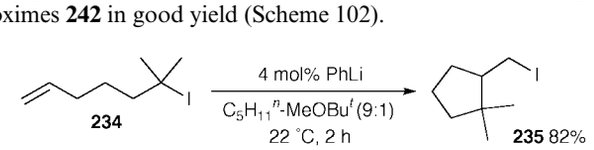
Titanium alkylidene complexes are an alternative to ruthenium-based chemistry. Titanium alkylidenes, generated by treating unsaturated thioacetals **231** with titanocene(II) complex **232**, cyclise to give five-, six- and seven-membered cycloalkenes **233** (Scheme 98).[123]



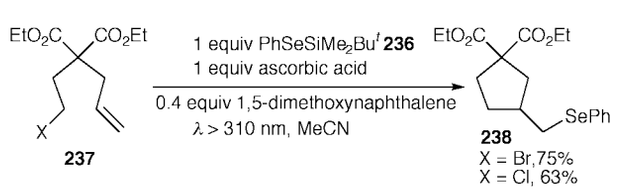
Scheme 98

5.3 Free radical cyclisations

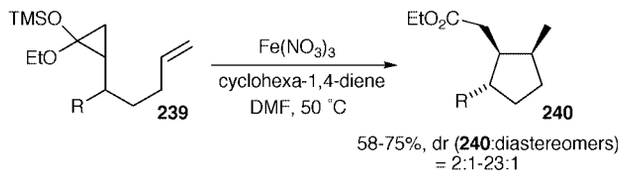
Cyclopentyl rings are almost always formed by 5-*exo* cyclisation of hex-5-enyl or hex-5-ynyl radicals.[124] A number of new methods of generating such radicals have been reported. Phenyllithium-initiated cycloisomerisation of alk-5-enyl and alk-5-ynyl iodides gives cyclopentanes in 43–91% yield and appears to be a radical process.[125] Thus, cyclisation of tertiary alkyl iodide **234** to give cyclopentane **235** is successful (Scheme 99). Photosensitised electron transfer (PET) reductive activation of selenosilane **236** generates silyl radicals that can generate carbon-centred free radicals from alkyl halides **237** and induce cyclisation to give cyclopentanes **238** (Scheme 100).[126] The incorporation of selenium functionality into the product is an advantage of this approach. Iron(III) nitrate reduction of the acetals of cyclopropanones **239** generates carbon-centred free radicals that cyclise to give cyclopentanes **240** with modest to excellent diastereoselectivity (Scheme 101).[127] Acylgermane benzyloxime ethers and dimethylhydrazones are excellent radical acceptors and undergo 5-*exo* cyclisations about three times faster than for the parent acylgermanes.[128] Thus, irradiation of acylgermane oxime **241** in the presence of an initiator gives oximes **242** in good yield (Scheme 102).



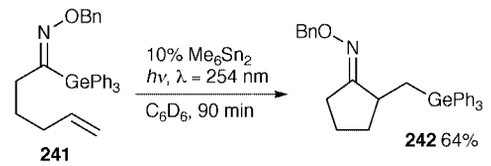
Scheme 99



Scheme 100

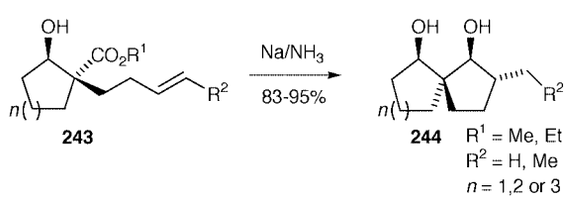


Scheme 101

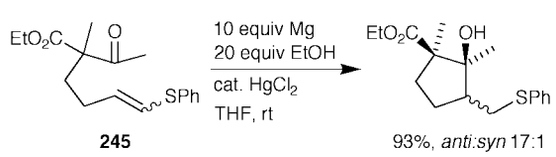


Scheme 102

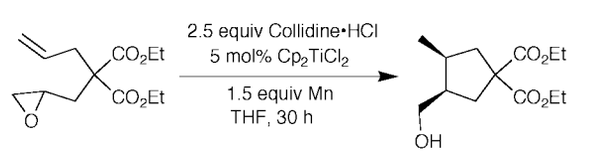
Ketyl anion radicals may be generated by sodium–ammonia reduction of esters **243** (Scheme 103). 5-*exo-trig* Cyclisation then gives cyclopentanols **244** in high yield and with excellent selectivity.[129] Similar cyclisations occur in up to 96% yield when ketones are reduced with magnesium in the presence of catalytic mercury(II) chloride.[130] Interestingly, vinyl sulfides **245** (1 : 1 ratio of diastereomers) cyclise smoothly under these conditions but fail to cyclise with samarium(II) iodide (Scheme 104). Titanium(III)-catalysed reductive cyclisation of epoxides onto alkenes or alkynes gives cyclopentanes in 55–78% yield (*e.g.* Scheme 105). The collidine hydrochloride protonates both titanium–oxygen and titanium–carbon bonds to release titanocene dichloride which is reduced by manganese to regenerate the catalyst.[131]



Scheme 103



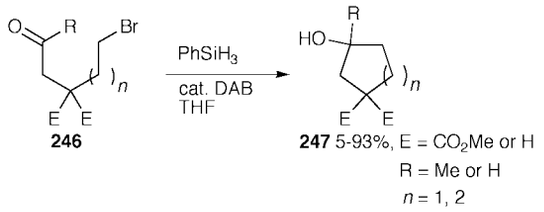
Scheme 104



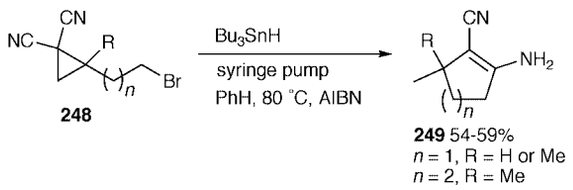
Scheme 105

Most free radical cyclisations use carbon–carbon multiple bonds as radical traps. However, phenylsilane has been used to accomplish intramolecular reaction between carbon-centred radicals generated from alkyl bromides **246** and aldehydes and ketones to give cyclopentanols and cyclohexanols **247** in 5–93% yield (Scheme 106).[132] The reaction is successful because organosilanes are relatively good H-atom donors to oxygen-centred radicals. Nitriles can also be used in radical cyclisations: dicyanocyclopropanes **248** give five- and six-membered ring enaminonitriles **249** by an *exo-dig* cyclisation–ring expansion process (Scheme 107).[133]

Enantioselective 5-*exo-trig* radical cyclisation has been achieved using a sulfoxide chiral auxiliary.[134] Enantiopure vinyl

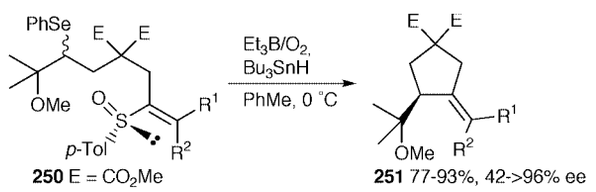


Scheme 106



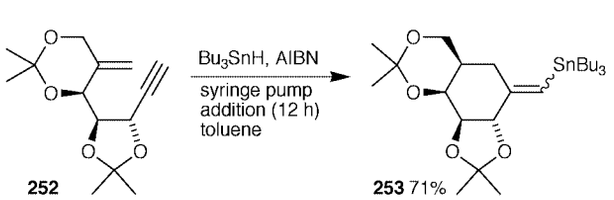
Scheme 107

sulfoxides **250** give (*S*)-cyclopentenyl derivatives **251** in good yield and moderate to excellent enantioselectivity (Scheme 108). No *endo* cyclisation is observed and when R^1 is cyclopropyl, no ring opening occurs.



Scheme 108

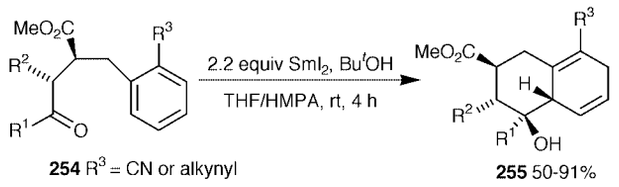
Cyclohexanes are generally made by 6-*exo* cyclisation of hept-6-enyl and hept-6-ynyl radicals *e.g.* functionalised cyclohexane derivatives and carbasugars can be made by 6-*exo-dig* cyclisation of alk-6-ynyl radicals derived from monosaccharides.[135] However, a number of useful 6-*endo* cyclisations of hex-5-enyl and hex-5-ynyl radicals have appeared during the review period. One such reaction that has been used to make carbasugars is the unusual radical cyclisation of alkyne **252** to give vinyltins **253** (Scheme 109).[136] The 6-(*π-exo*)*endo-trig* mode of cyclisation is favoured both by the substitution pattern of the alkene and by the strain associated with the presence of the *trans*-2,3-*O*-isopropylidene ring. Similarly, ketyl radical anions, generated by samarium diiodide reduction of ketones **254**, attack aryl substituents to give cyclohexa-1,4-dienes **255** in 50–91% yield as single diastereomers (Scheme 110).[137] The reaction is unsuccessful when R^1 is bulky (*e.g.* $R^1 = Pr^i$). Silyl enol ethers **256** react with arene radical cations, generated by photosensitised electron transfer, by the *endo* mode to give ketones **257** (Scheme 111, DCN = 1,4-dicyanonaphthalene).[138]



Scheme 109

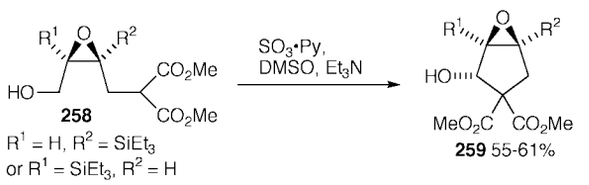
5.4 Intramolecular nucleophilic attack on carbonyl groups

Intramolecular aldol reactions and condensations are often used to make carbocycles. Enantiopure epoxy alcohols **258** cyclise to give cyclopentanols **259** under mild oxidation conditions (Scheme 112).[139] The reaction is totally diastereoselective. Enone **260** undergoes a novel tandem conjugate-reduction–



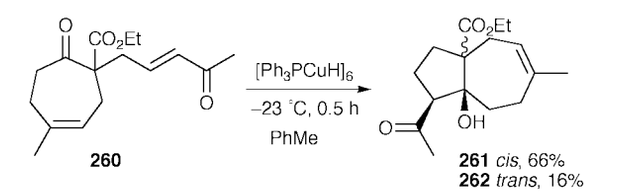
Scheme 110

Scheme 111

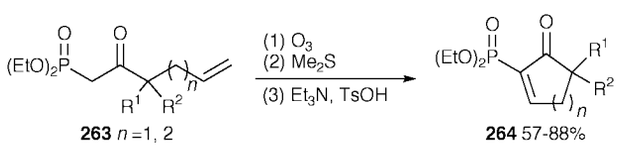


Scheme 112

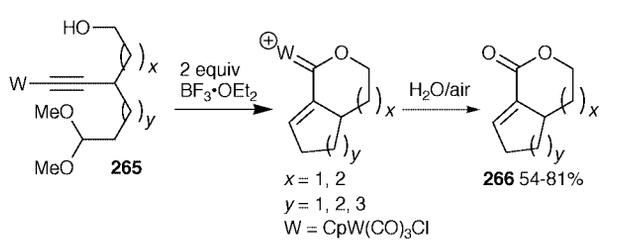
5-*exo-trig* intramolecular aldol reaction when treated with Stryker's reagent to give a mixture of ketones **261** and **262** in good yield (Scheme 113).[140] Phosphonates **263** are easily made from β-ketophosphonates and undergo a one-pot ozonolysis–acid-induced aldol condensation to give α-phosphonato-α,β-unsaturated ketones **264** in good yield (Scheme 114).[141] A related reaction is the cyclisation of tungsten-η^1-alkynols **265** to give δ- and ε-lactones fused with five-, six- and seven-membered carbocycles **266** (Scheme 115).[142]



Scheme 113



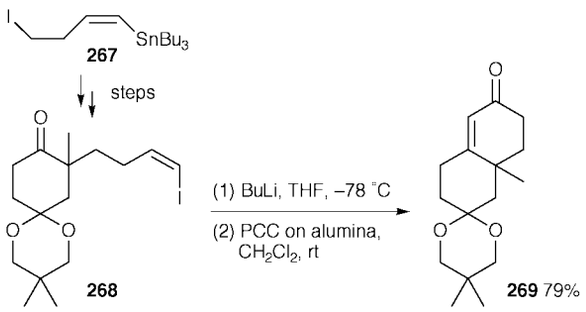
Scheme 114



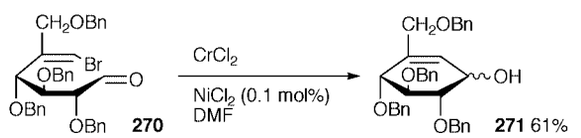
Scheme 115

Another approach to annulation is to generate an organometallic that will react nucleophilically with a carbonyl group in the same compound. A new annulation method for the synthesis of cyclohexenones uses bifunctional reagent **267**, *e.g.* lithium–iodine exchange between butyllithium and vinyl iodide **268**, derived from vinyltin **267**, leads to cyclisation and this is

followed by PCC oxidation to give cyclohexenone **269** (Scheme 116).[143] A Nozaki–Kishi reaction of vinyl bromide **270** gives cyclohexenols **271** (Scheme 117) and is the key step in a synthesis of the carbasugar gabosine I.[144] This approach provides efficient access to functionalised cyclohexenes.

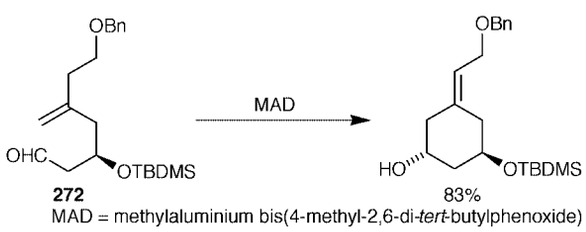


Scheme 116

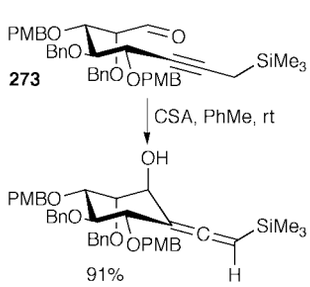


Scheme 117

Lewis-acid mediated cyclisations include the carbonyl ene reaction, which has been widely used during the review period; the diastereoselective cyclisation of aldehyde **272** is representative of this class of reaction (Scheme 118).[145] Propargylsilane **273** undergoes ring closure in the presence of camphorsulfonic acid in a similar process (Scheme 119).[146] The retention of the silyl group is unusual. A new Lewis acid-mediated cyclisation is the reaction of methylenecyclopropyl ketones, ketals and aldehydes to give six and seven-membered carbocycles in moderate yield (11–70%, 6 examples) *e.g.* aldehyde **274** is converted into cyclohexene **275** in the presence of titanium(IV) chloride (Scheme 120).[147]



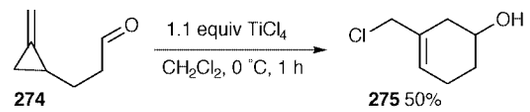
Scheme 118



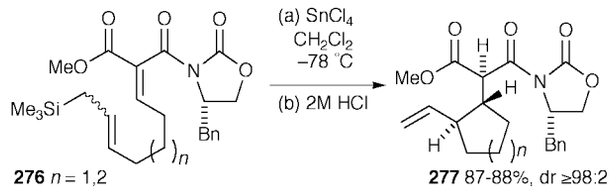
Scheme 119

5.5 Other methods

Enantiomerically pure *trans*-1,2-disubstituted cyclopentanes and cyclohexanes have been synthesised from allyl silanes **276** bearing an oxazolidinone chiral auxiliary (Scheme 121). Lewis acid-induced intramolecular addition of the allyl silane moiety onto the alkylidene-1,3-dicarbonyl group gives cycloadducts **277** with near total diastereoselectivity.[148]

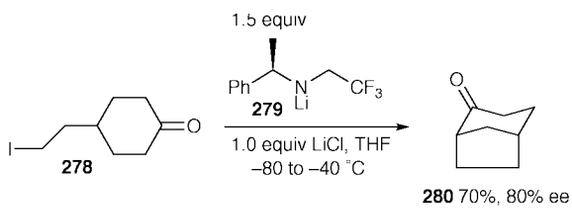


Scheme 120



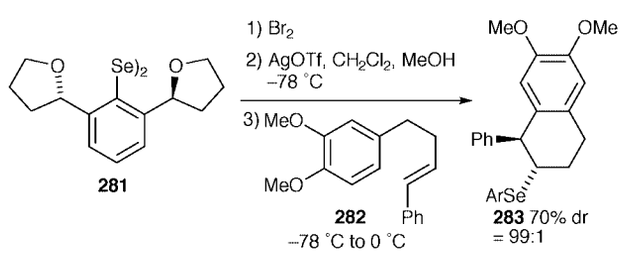
Scheme 121

Cyclisations of cyclohexanone **278** using an enantiopure lithium amide base **279** gives (*S*,*S*)-adduct **280** in 80% ee (Scheme 122). This is the first example of such enantioselective cyclisations and both the chemical yield and the enantioselectivity are highly dependent upon the reaction conditions.[149]



Scheme 122

The chiral trifluoromethanesulfonate salt derived from chiral organoselenium reagent **281** efficiently converts alkene **282** into a selenomethoxylated intermediate which cyclises upon treatment with acid to give selenide **283** with very high diastereoselectivity (Scheme 123).[150]

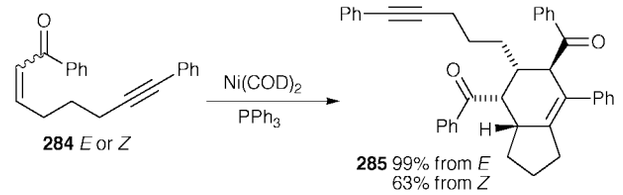


Scheme 123

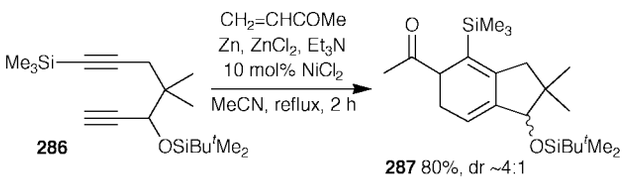
6 Six-membered carbocycles

6.1 [2 + 2 + 2] Annulations

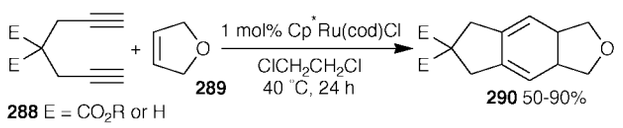
[2 + 2 + 2] Annulations can be achieved by transition metal-catalysed cycloisomerisations and by generation and reaction of metallacyclopentanes. A novel nickel-catalysed [2 + 2 + 2] cycloaddition between alkynyl enones and electron deficient alkenes has been reported. The reaction is unusual both in its chemoselectivity for an alkene over an alkyne in the intermolecular coupling and for its stereoconvergence, *i.e.* both *E* and *Z* enones **284** dimerise to give cyclohexene **285** (Scheme 124).[151] Nickel(0)-mediated [2 + 2 + 2] cycloaddition between trimethylsilyl-substituted diynes (*e.g.* **286**) and but-3-en-2-one gives total regioselectivity for cyclohexadienes with the trimethylsilyl and ketone groups adjacent in 63–80% yield (*e.g.* **287**, Scheme 125).[152] Cp*Ru(cod)Cl catalyses the cycloaddition of electronically-nonactivated hepta-1,6-diynes **288** with allylic ether **289** to give cyclohexadienes **290** in good yield (Scheme 126).[153] The oxygen atom of the allylic ether is essential to the transformation and is believed to coordinate to the ruthenium atom during the cycloaddition.



Scheme 124



Scheme 125



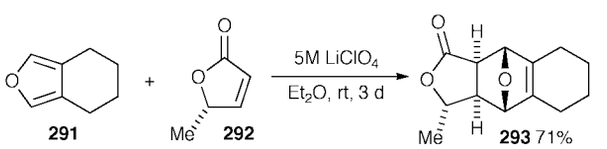
Scheme 126

In the presence of copper(I) chloride, zirconacyclopentanes **126**, synthesised from diynes, react with unactivated terminal alkynes to give cyclohexenes **128** in a two-step [2 + 2 + 2] annulation (Scheme 53).[65]

6.2 [4 + 2] Annulations

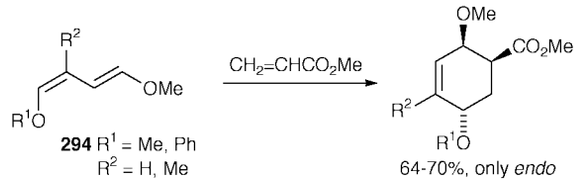
6.2.1 Intermolecular Diels–Alder reactions

The Diels–Alder reaction is probably the most powerful method of synthesising six-membered carbocycles, since it forms two carbon–carbon bonds, often regioselectively, and up to four chiral centres in a controlled way,[154] *e.g.* the key step in a synthesis of (+)-himbacine is the highly diastereoselective reaction between diene **291** and dienophile **292** to give adduct **293** (Scheme 127).[155] Research into the Diels–Alder reaction has concentrated on three areas: introducing new types of dienes and dienophiles; using new solvents that accelerate the reaction, allow easy purification of the products and are environmentally friendly; and developing new catalysts that may be used in low concentration, will induce asymmetry and can be recycled.

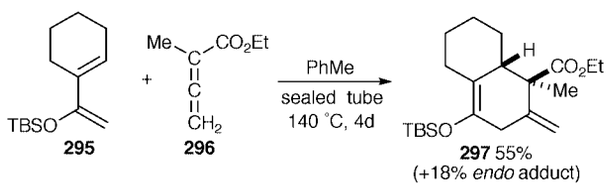


Scheme 127

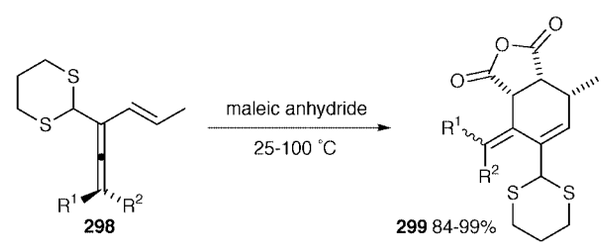
A number of novel dienes and dienophiles have been introduced. Dialkoxybutadienes **294** are easily made from allylic acetals and show total *endo* selectivity in Diels–Alder reactions with methyl acrylate (Scheme 128).[156] Interestingly, Diels–Alder reactions of the analogous 1*E*,3*E* dienes are completely unselective. As a model for the synthesis of dysidiolide, a natural phosphatase inhibitor, (silyloxyvinyl)cyclohexene **295** was reacted with allenecarboxylate **296** to give the formal *exo*-Diels–Alder adduct **297** as the major product in 55% yield (Scheme 129).[157] The product of a competing [2 + 2] cycloaddition rearranges selectively to give only the *exo* adduct **297** under the reaction conditions. Vinylallenes act as dienes in [4 + 2]-cycloadditions and can be used to construct tetrasubstituted exocyclic alkenes (28–96% yield), including very strained ones, that are difficult to access by other methods (Scheme 130).[158]



Scheme 128



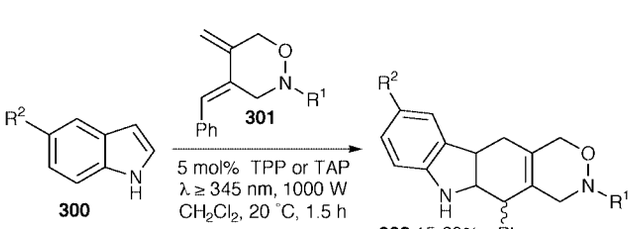
Scheme 129



Scheme 130

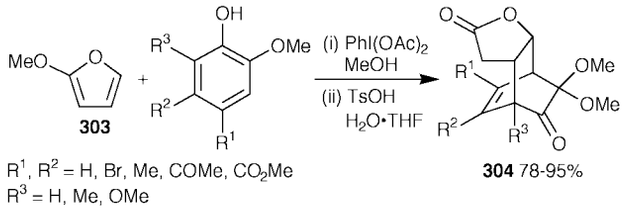
Reactions between allenes **298** and maleic acid give rise to 3:1 to >49:1 mixtures of geometrical isomers **299**. The geometry of the exocyclic double is controlled by the relative sizes of the R^1 and R^2 substituents.

Aromatic heterocycles may be used as dienophiles. Indoles **300** undergo radical cation Diels–Alder reactions with electron-rich dienes **301** using photoinduced electron transfer (PET) to give cycloadducts **302** as 1:1 mixtures of diastereomers (Scheme 131).[159] Dienes **301** have a rigid s-*cis*-conformation, which is required for reaction, and contain an N–O bond that can be cleaved by reduction with sodium amalgam to give highly functionalised tetrahydrocarbazole derivatives. Furans, including benzofurans, may be used as dienophiles in intermolecular Diels–Alder reactions with masked *ortho*-benzoquinones.[160] 2-Methoxyfuran **303** corresponds to a masked but-3-enolide and allows stereoselective synthesis of β,γ-fused γ-butyrolactones **304** (Scheme 132).[161]

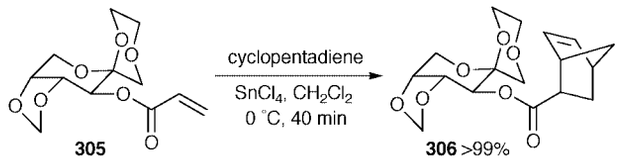


Scheme 131

New types of dienes and dienophiles have been developed for asymmetric Diels–Alder reactions. Fructose derivative **305** is an efficient chiral auxiliary for tin(IV) chloride-mediated asymmetric Diels–Alder reaction (Scheme 133).[162] The auxiliary is easily removed from cycloadduct **306** by reduction with lithium aluminium hydride. Similarly, dienophiles bearing auxiliaries **307** and **308** form Diels–Alder adducts with dr's of up to 99% (Fig. 3).[163] Diels–Alder reactions can also be used to induce C_2



Scheme 132



Scheme 133

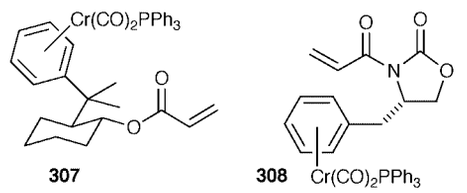
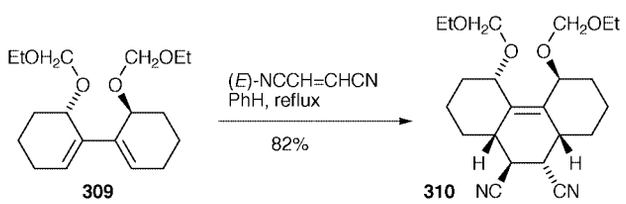


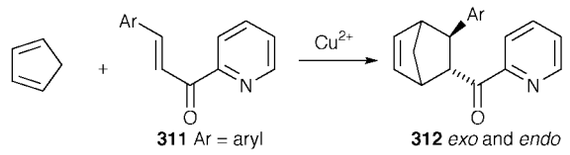
Fig. 3

symmetry-breaking by functionalisation at both homotopic sites of chiral diene **309** (Scheme 134).[164] A single stereoisomer **310** is formed in the reaction with fumaronitrile.

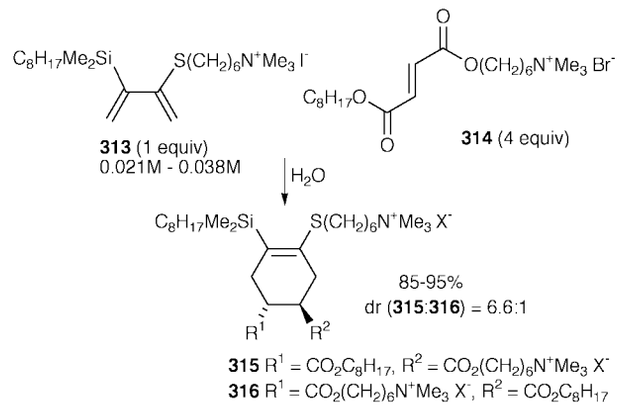


Scheme 134

Water as a solvent for Diels–Alder reactions has obvious environmental and economic benefits and allows the synthesis of polar compounds; it also enhances the rate of Diels–Alder reactions. The Diels–Alder reaction between bidentate dienophiles **311** and cyclopentadiene to give adducts **312** has been used to test the usefulness of copper(II) catalysis in aqueous systems (Scheme 135). A copper(II) complex of the amino acid (*S*)-abrine catalyses (10 mol%) the formation of Diels–Alder adducts **312** (Ar = Ph) in water in 94% yield: there is >90% selectivity for the *endo*-diastereomer, which is produced in 74% ee (configuration unknown).[165] The enantioselectivity in water is significantly superior to that obtained in organic solvents using the same catalyst. Micelles of sodium dodecyl sulfate (SDS), cetyltrimethylammonium bromide (CTAB) and dodecyl heptaoxyethylene ether ($C_{12}E_7$) retard Diels–Alder reaction between cyclopentadiene and dienophiles **311** relative to reaction in pure water.[166] However, copper(II) dodecyl sulfate micelles catalyse the reaction extremely efficiently with rate enhancements of up to 1.8 million-fold compared to reaction in acetonitrile in the absence of catalyst. The reaction benefits from combined Lewis acid and micellar catalysis in water. The Diels–Alder reaction of surfactant 1,3-diene **313** and surfactant dienophile **314** within aqueous mixed micelles at 25 °C gave a 6.6:1 ratio of cycloadducts **315** and **316** in excellent yield (Scheme 136).[167] Cycloadduct **315** arises from the quaternary head groups aligning at the aggregate–water interface with the remainder of each surfactant extended into the micelle interior. The Diels–Alder reaction of non-surfactant analogues in

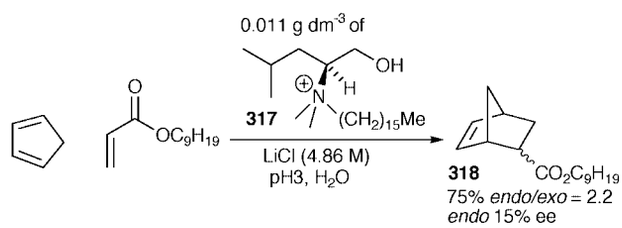


Scheme 135



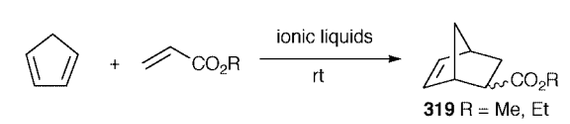
Scheme 136

toluene shows no regioselectivity. Ammonium salt **317** is the first example of a chiral surfactant used in aqueous micellar catalysis of a Diels–Alder reaction (Scheme 137). Nonyl acrylate reacted with cyclopentadiene to give cycloadducts **318** with low enantioselectivity.[168]



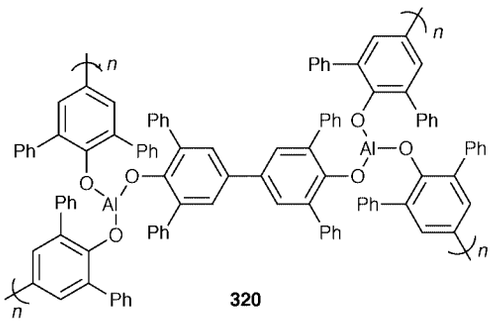
Scheme 137

Room temperature ionic liquids are a class of liquids constituted entirely of ions. The use of such liquids as solvents for Diels–Alder reactions has been tested using the reaction between cyclopentadiene and methyl or ethyl acrylate as a standard (Scheme 138). High levels of *endo* selectivity were observed relative to reaction in non-polar solvents. The cycloadducts **319** were obtained in 91% yield with 82:18 *endo*:*exo* selectivity when using 1-ethyl-3-methylimidazolium perchlorate. This solvent is appropriate for moisture-sensitive compounds and unlike $LiClO_4$ in ether, the reaction is biphasic and the products can be isolated by simply decanting the organic layer.[169] A 51:49 mixture of aluminium trichloride and 1-ethyl-3-methyl-1*H*-imidazolium chloride can act as both solvent and catalyst giving cycloadducts **319** in 79% yield with a 95:5 *endo*:*exo* selectivity after 72 h.[170] The acidity of chloroaluminate ionic liquids can easily be varied from acidic to basic by altering the ratio of the components and organic compounds dissolve well in the media.



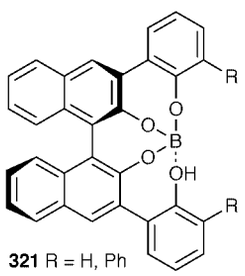
Scheme 138

New catalysts for the Diels–Alder reaction have been developed that aid both purification of products and catalyst recovery. 1 Mol% of solid polymer **320** is sufficient to efficiently



320

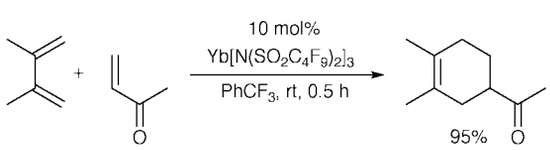
Fig. 4



321 R = H, Ph

Fig. 5

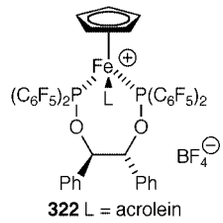
catalyse the Diels–Alder reaction between simple dienes and α,β-enals to give cycloadducts in 40% to >99% yield (Fig. 4).[171] The active catalyst is recovered quantitatively by simple filtration. Lanthanide perfluoroalkylsulfonylamide complexes catalyse Diels–Alder reactions in fluorous phase solvents such as benzotrifluoride and hexafluoro-*p*-xylene (*e.g.* Scheme 139).[172] Fluorous-phase synthesis combines the favourable purification features of solid-phase synthesis with the favourable reaction and analysis features of liquid-phase organic synthesis.



Scheme 139

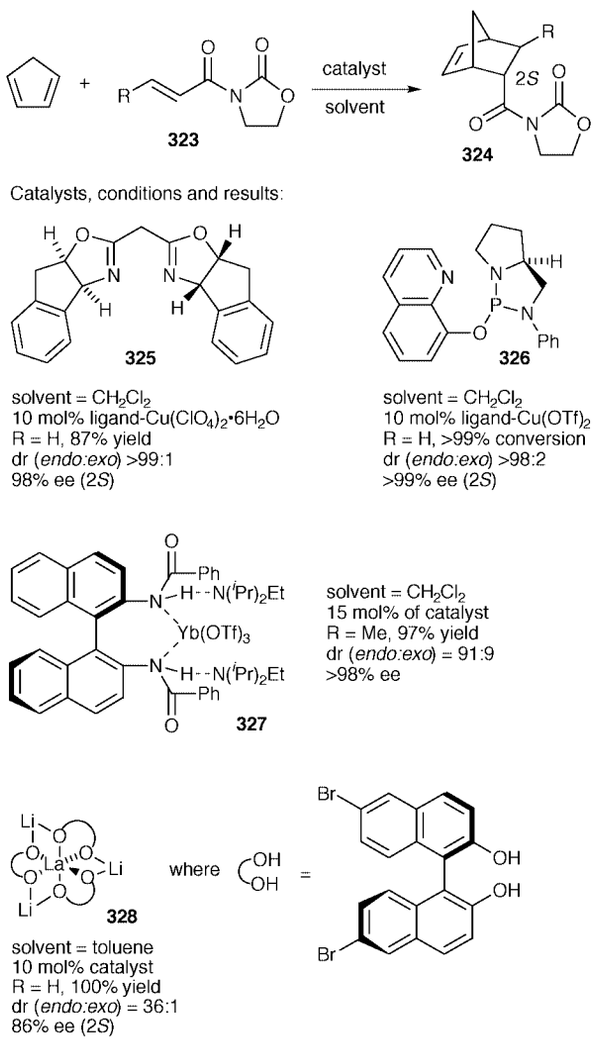
New chiral catalysts for the Diels–Alder reaction are constantly being reported.[173] Enals and acrylate esters are formal single point binding dienophiles, but Yamamoto's Brønsted acid-assisted, chiral Lewis acid catalysts **321** for enantioselective Diels–Alder reactions combine intramolecular hydrogen bonding interactions and attractive π–π donor–acceptor interactions (Fig. 5).[174] They catalyse the reaction of cyclopentadiene with a range of α,β-unsaturated aldehydes to give cycloadducts in very high yields and with outstanding diastereoselectivity and enantioselectivity (92 to >99% ee). Optically active 2-dichloroboryl-1,1′-binaphthyls reported by the same group give lower enantioselectivities (≤78% ee).[175] A new C_2-symmetric phosphorus ligand BIPHOP-F derived from (*R*, *R*)- or (*S*, *S*)-hydrobenzoin forms iron(II) complexes **322** that catalyse Diels–Alder reactions between α,β-unsaturated aldehydes and dienes in the presence of DMAP to give cycloadducts in good yield in 87 to 99% ee and with modest to good diastereoselectivity (Fig. 6).[176]

Many catalysts have been developed for asymmetric Diels–Alder reactions between cyclopentadiene and two-point-binding dienophiles **323** to give *endo* adducts **324** (Scheme 140). Copper complexes of ligands **325**[177] and **326**[178] and chiral lanthanide complexes **327**[179] and **328**[180] catalyse these Diels–Alder reactions under the conditions shown with high



322 L = acrolein

Fig. 6



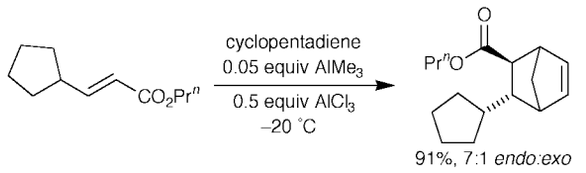
Scheme 140

diastereoselectivity and enantioselectivity. α-Thioacrylates are useful alternative two-point-binding dienophiles for copper(II)-catalysed asymmetric Diels–Alder reactions.[181]

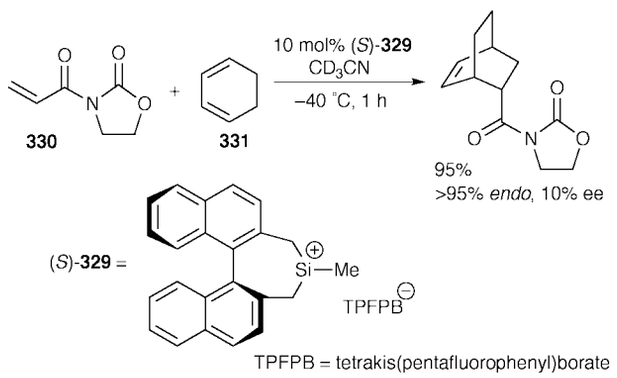
Other catalysts have been developed to improve reactivity or simply to demonstrate a concept. Improved conditions have been developed for Diels–Alder cycloadditions between cyclopentadiene and sterically hindered dienophiles (*e.g.* Scheme 141).[182] The first silylcationic species **329** has been prepared, characterised and shown to be an effective catalyst for Diels–Alder reactions (Scheme 142).[183] The enantioselectivity in the reaction between acryloyl oxazolidinone **330** and cyclohexadiene **331** is poor (10% ee), but the catalytic activity is higher than cationic copper(II) bisoxazoline catalysts. A self-assembled molecular capsule termed "hydroxy softball" shows modest catalysis of the Diels–Alder reaction between *p*-benzoquinone and a thiophene dioxide derivative.[184]

6.2.2 Intramolecular Diels–Alder reactions

Entropy is the main barrier to Diels–Alder reaction, but this

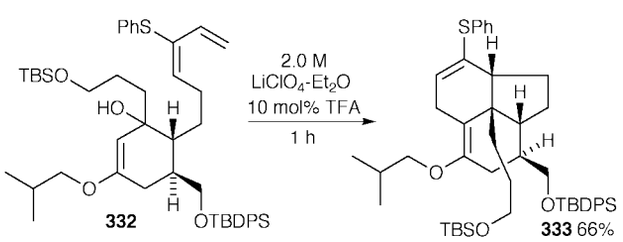


Scheme 141



Scheme 142

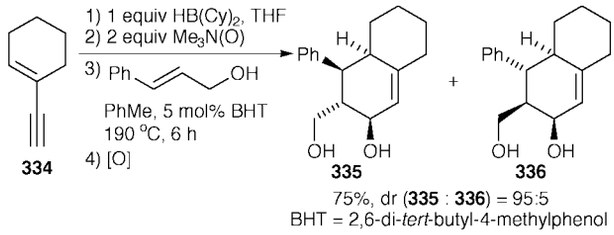
barrier is very substantially reduced when the reaction is intramolecular. Phenylthio-substituted dienes and γ-substituted, heteroatom-stabilised allyl cations (generated *in situ*) can be used to set up quaternary carbon chiral centres by intramolecular Diels–Alder reaction.[185] Thus, diene **332** cyclises to give tricyclic enol ether **333** with complete *exo* selectivity (Scheme 143).[186] This was the key step in a synthesis of (±)-lycopodine.



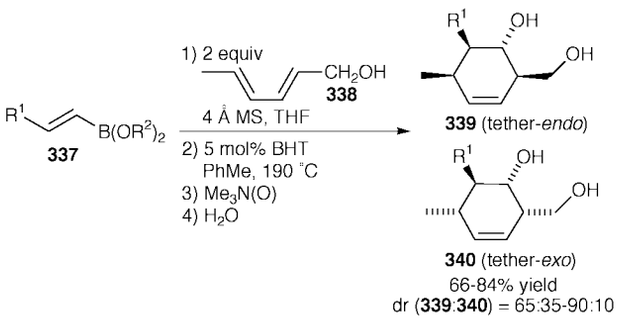
Scheme 143

Intermolecular reaction between 1,3-dienylboronic esters and methyl acrylate typically occurs in 40–50% yield.[187] The modest yields in such reactions can be improved by making the Diels–Alder reaction intramolecular.[188] 1,3-Dienylboronic esters, attached to allylic and homoallylic alcohols by a C–B–O tether, undergo efficient intramolecular Diels–Alder reaction to give cyclohexanols, after oxidation (40–82% yield, tether-*exo*:tether-*endo* 25:75–95:5), *e.g.* alkyne **334** was converted into 95:5 mixture of cyclohexanols **335** and **336** in 75% yield (Scheme 144). The boron-tethered intramolecular Diels–Alder reaction using vinylboronic esters as dienophile components also gives high yields (14 examples, 66–85%) and complete regioselectivity.[189] Treatment of boronic esters **337** with 1 equiv. of sorbyl alcohol **338** in a sealed tube at 190 °C and subsequent oxidation gives diols **339** and **340** with high *endo* selectivity (Scheme 145). The preference for *endo* or *exo* mode of cyclisation depends on the tether length.

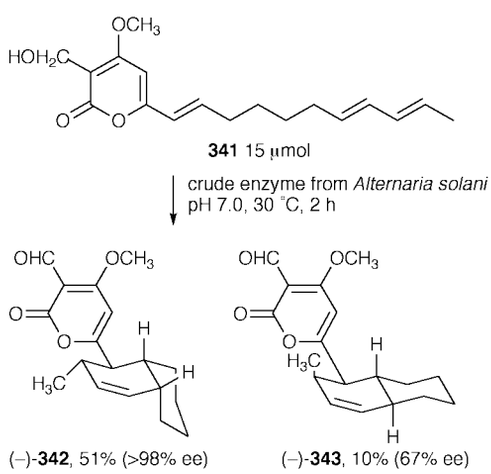
The enzymatic oxidation and intramolecular Diels–Alder reaction of prosolanapyrone II **341** affords (−)-solanapyrone A **342** in 51% yield and >98% ee, together with solanapyrone D **343** in lower enantiomeric purity (Scheme 146).[190] Although solanapyrone synthase has not yet been isolated as a single band on SDS-PAGE, a partial purification has been undertaken[191] and this represents the most significant progress towards the first isolation of a Diels–Alderase to date.[192]



Scheme 144

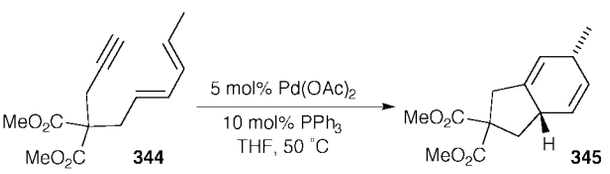


Scheme 145

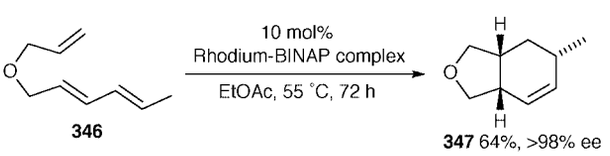


Scheme 146

Palladium(II) acetate and triphenylphosphine catalyses the formal intramolecular Diels–Alder reaction of dienyne **344** to give diene **345** in 89% yield (Scheme 147).[193] Cyclisation of the corresponding ethyl ester analogue of dienyne **344** catalysed by 6 mol% of a rhodium-methyl DUPHOS complex gave the corresponding diene in 78% yield and 91% ee.[194] The same paper describes the asymmetric cyclisation of triene **346** to give bicycle **347** in >98% ee (Scheme 148).



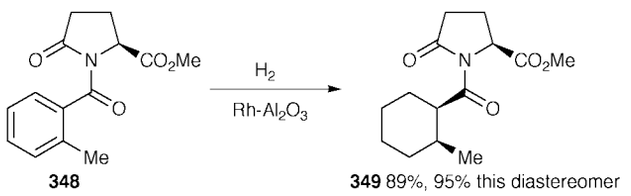
Scheme 147



Scheme 148

6.3 Other methods

Hydrogenation of enantiopure *o*-toluic acid derivative **348** using a Rh–Al_2O_3 catalyst gives *cis*-2-methylcyclohexanoic acid derivatives with 95% diastereoselectivity for the (1*R*, 2*S*, 2*S*′)-isomer **349** (Scheme 149).[195]

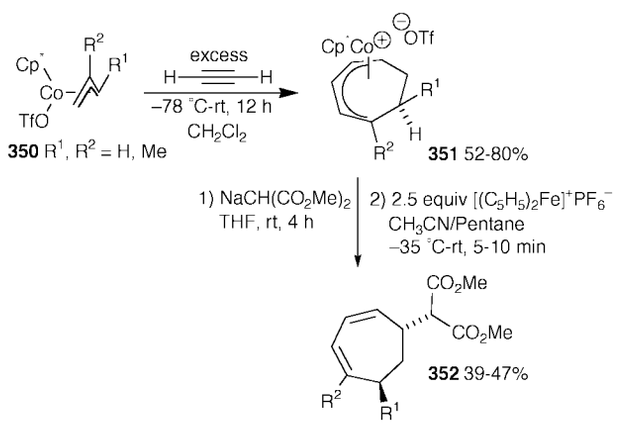


Scheme 149

7 Seven-membered carbocycles

7.1 [3 + 2 + 2] Annulations

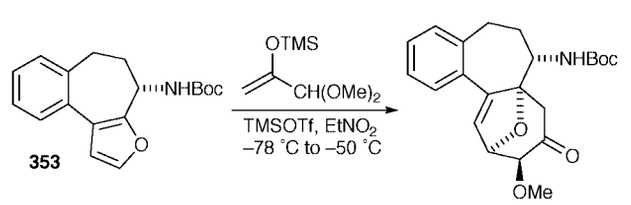
Unsaturated permethylcyclopentadienylcobalt(III) allyl complexes (*e.g.* **350**, Scheme 150) react with alkynes to give substituted η^3-cycloheptadienyl complexes (*e.g.* **351**) in 47–88% yield (7 examples) by metal-mediated [3 + 2 + 2] cycloaddition. Subsequent nucleophilic attack by an enolate followed by decomplexation gives functionalised cycloheptadienes (*e.g.* **352**) in a highly regioselective and stereoselective manner in 36–60% yield.[196]



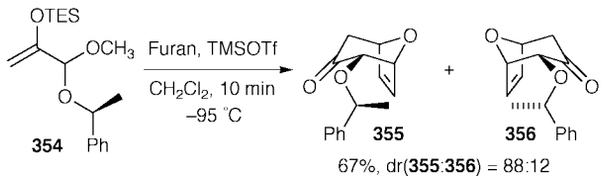
Scheme 150

7.2 [4 + 3] Annulations

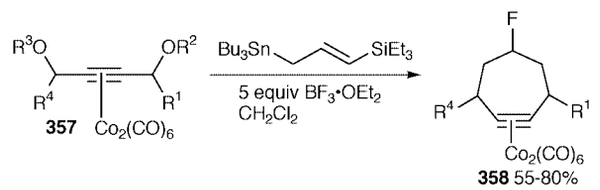
Colchicine has been synthesised using an α-methoxy-substituted oxyallyl [4 + 3] cycloaddition (Scheme 151).[197] The synthesis takes advantage of high face selectivity due to the chiral centre in the furan substrate **353**, but a more general approach to asymmetric [4 + 3] cycloadditions uses a chiral auxiliary, derived from (*S*)-1-phenylethanol: diastereoselective [4 + 3] cycloaddition between furan and enantiopure silyl enol ether **354** gives an 88 : 12 dr of cycloheptenone adducts **355** and **356** in 67% yield (Scheme 152).[198] Another novel, Lewis acid-mediated cycloaddition occurs between alkynyldiether hexacarbonyldicobalt complexes **357** and stannylsilanes to give cycloheptenyne complexes or fluorocycloheptyne complexes **358** (Scheme 153).[199]



Scheme 151

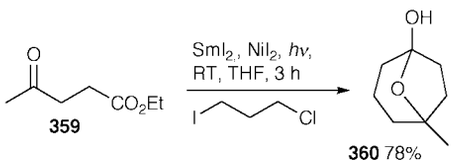


Scheme 152



Scheme 153

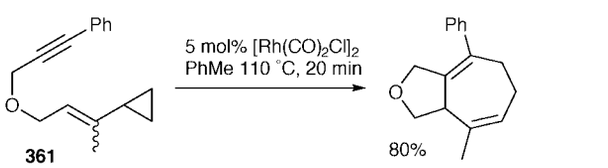
Samarium(II) iodide promoted carbonyl addition–nucleophilic acyl substitution provides an efficient method for synthesising seven-, eight- and nine-membered monocyclic, bicyclic and tricyclic hydroxyketones–hemiketals by intermolecular reaction between readily-available ketoesters and dihaloalkanes.[200] Thus, ketoester **359** is converted into hemiketal **360** in good yield (Scheme 154).



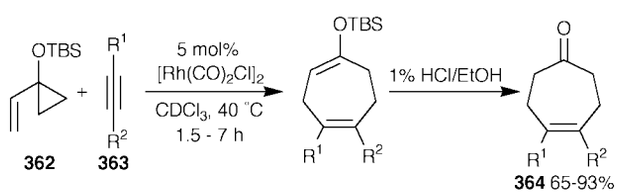
Scheme 154

7.3 [5 + 2] Annulations

Wender and co-workers have found that $[Rh(CO)_2Cl]_2$ is superior to the Wilkinson catalyst in inducing intramolecular [5 + 2] cycloadditions of substituted alkynyl vinylcyclopropanes (*e.g.* **361**, Scheme 155).[201] An important breakthrough is the discovery that the same complex catalyses intermolecular [5 + 2] cycloadditions between vinylsiloxycyclopropanes **362** and alkynes **363** to give cycloheptenones **364** in 65–93% yield (Scheme 156).[202] These are the first *intermolecular* metal-catalysed [5 + 2] cycloadditions and they tolerate ketones, esters, ethers and even unprotected alcohols. The alkynes may be electron-rich, electron-poor, conjugated, internal, or terminal and even acetylene itself undergoes the reaction.



Scheme 155

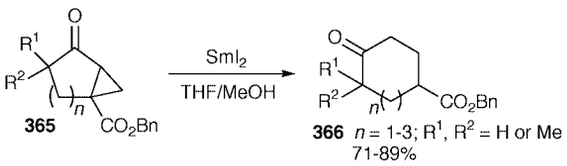


Scheme 156

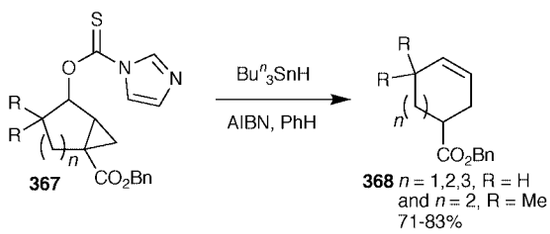
7.4 Ring expansions

Radical ring expansion of oxobicyclo[*n*.1.0]alkanes is a good way of making cycloheptanes and other carbocycles provided

that (normally disfavoured) endocyclic opening of the cyclopropane can be achieved. High selectivity for endocyclic opening can be induced by suitable positioning of an ester group. Cyclopropylcarbinyl radicals generated by samarium iodide reduction of ketones **365** undergo ring expansion to give 4-oxocycloalkanecarboxylates **366** in good yield (Scheme 157).[203] Similarly, radicals generated from thiocarbamates **367** rearrange to give six-, seven- and eight-membered carbocycles **368** in good yield (Scheme 158).[204]

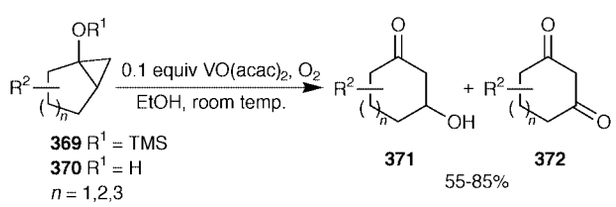


Scheme 157



Scheme 158

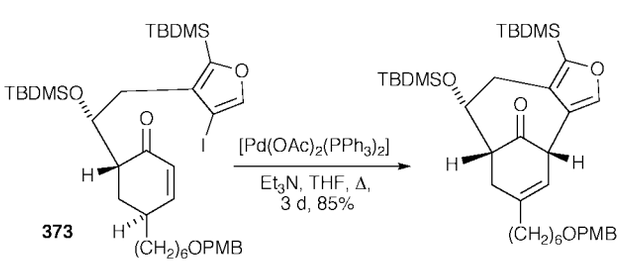
1-(Trimethylsilyloxy)bicyclo[*n*.1.0]alkanes **369** and bicyclo[*n*.1.0]alkanols **370** react with a catalytic amount of vanadyl acetylacetonate under an oxygen atmosphere to afford six-, seven- and eight-membered β-hydroxyketones **371** and β-diketones **372** in 55–85% yield (Scheme 159).[205]



Scheme 159

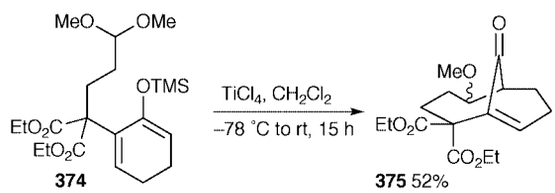
7.5 Cyclisations forming one endocyclic bond and rearrangements

Although seven-membered carbocycles are more difficult to synthesise than five- and six-membered carbocycles, many of the methods described in Section 5 are applicable to all three ring sizes. Among organometallic-mediated reactions, ring closing metathesis and related reactions are particularly useful (Schemes 93 and 98)[114,123] and the new metathesis catalysts **229**–**230** (Fig. 2)[120–122] are effective. The intramolecular Heck reaction is also an effective reaction for the construction of seven-membered carbocycles, *e.g.* cyclisation of furan **373** is a key step in Danishefsky's approach to the *ras*-farnesyl protein transferase inhibitors CP-225,917 and CP-263,114 (Scheme 160).[206]

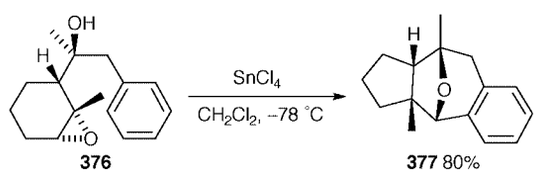


Scheme 160

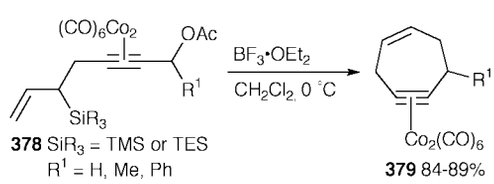
Lewis acid-mediated reactions have been applied to the synthesis of seven-membered carbocycles. Intramolecular Mukaiyama aldol reaction of acetal **374** to give ketones **375** is the key step in a synthesis of the core ring system of CP-225,917 and CP-263,114 (Scheme 161).[207] A related reaction involving the cyclisation of tungsten-η[1]-alkynols **265** that contain an acetal group has already been discussed (Scheme 115).[142] Another cyclisation onto an oxonium ion is the final step of the domino reaction that takes place when 3,4-epoxyalcohol **376** is treated with tin(IV) chloride. The epoxyalcohol **376** undergoes a stereospecific ring contraction, lactolisation, cyclisation sequence to give bridged ether **377** containing a new carbocyclic seven-membered ring (Scheme 162).[208] Boron trifluoride-induced cyclisation of allylsilanes **378** gives cycloheptenyne hexacarbonyldicobalt complexes **379** in 84–89% yield (Scheme 163).[209] Other cyclisations involving allylsilanes[103,104] (Scheme 86) and vinylsilanes[105] (Scheme 87) have already been discussed.



Scheme 161

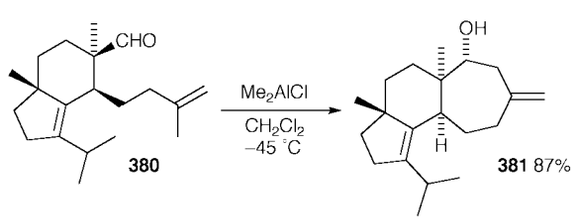


Scheme 162



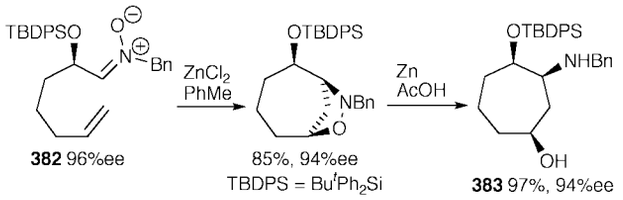
Scheme 163

Cycloadditions that have heterocyclic transition states are often used to make carbocycles. An example of a one-step process is the intramolecular carbonyl ene reaction of aldehyde **380** that gives a single alcohol **381** in 87% yield (Scheme 164).[210] Intramolecular cycloaddition of chiral nitrone **382** followed by reductive opening of the isoxazolidine ring, gives highly functionalised cycloheptanols **383** in high enantiomeric purity by a two-step process (Scheme 165).[211]

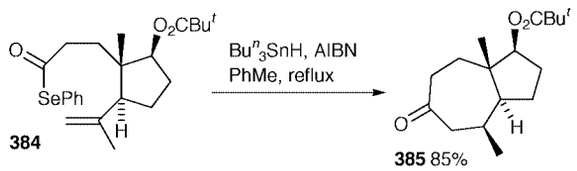


Scheme 164

A novel and general route to pseudoguaianolide sesquiterpenoids employs a diastereoselective 7-*endo-trig* acyl radical cyclisation of phenylselenyl ketone **384** to give bicycle **385** in 85% yield as the only product (Scheme 166).[212] 7-*endo-trig* Cyclisation by reaction of silyl enol ethers with arene radical



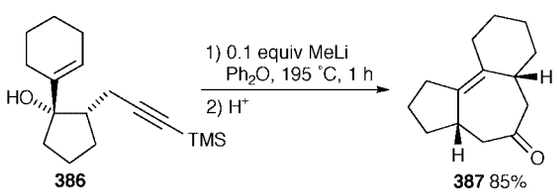
Scheme 165



Scheme 166

cations is also a high yielding process (Scheme 111, DCN = 1,4-dicyanonaphthalene).[138]

Finally, the cycloheptenone ring of tricyclic 5-7-6 ring systems has been constructed by a one-pot 5-*exo*-*dig* cyclisation–Claisen rearrangement sequence. Alcohol **386** is converted into a single ketone product **387** in 85% yield (Scheme 167, 3 other examples, 50–85% yield).[213]



Scheme 167

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