Cycloadditions in synthesis

COLIN P. DELL

Lilly Research Centre Ltd., Erl Wood Manor, Windlesham, Surrey, GU20 6PH, UK

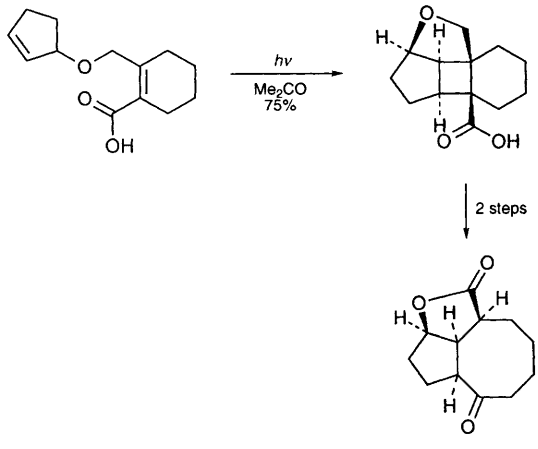
Reviewing the literature from January 1995 to June 1996

1 Introduction

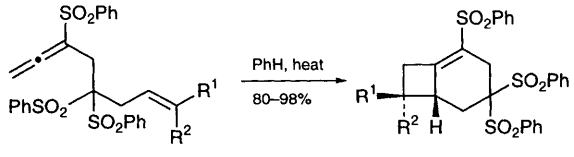
A number of authors have published review articles, either specifically on cycloadditions, or incorporating cycloadditions as a major theme in their articles.[1,2] Cycloadditions of vinylheterocycles have also been reviewed.[3] Preparation of indole alkaloids by Diels–Alder reactions of vinylindoles has been described by Blechert.[4] Several articles within one issue of *Chemical Reviews* cover aspects of cycloadditions: transition metal mediated (Lautens), domino reactions (Tietze), tandem [4+2]–[3+2]-reactions (Denmark) and tandem Diels–Alder reactions (Winkler).[5–8] The use of *N*-acylnitroso hetero Diels–Alder approaches to nitrogeneous natural products has been reviewed.[9] The [4+4]-cycloaddition area has been the subject of a recent review.[10]

2 [2+2]-Cycloadditions

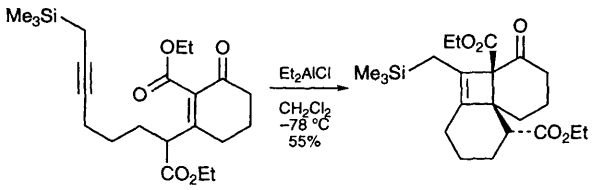
Photocycloaddition strategies have proved valuable in a brief approach to the asteriscanolide skeleton[11] (**Scheme 1**) and to (+)- and (−)-grandisol.[12] A new route to indolizidine and pyrrolizidine alkaloids involves a [2+2]-cycloaddition between ketenes and ene carbamates.[13] Thermal intramolecular cycloadditions of phenylsulfonylallenes lead to 4,6-fused systems (**Scheme 2**).[14] An attempted intramolecular Lewis acid promoted conjugate addition of a prop-2-ynylsilane to an enone results in a mixture of the desired spirocycle and the cyclobutene (**Scheme 3**).[15] The formation of this silicon retaining product is



Scheme 1

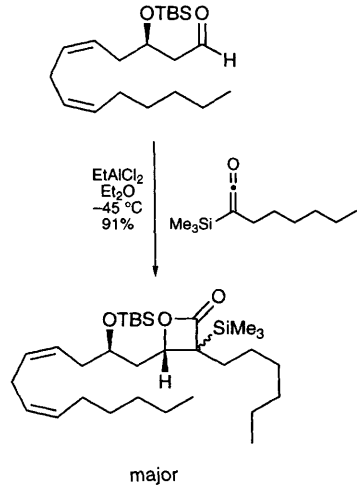


Scheme 2

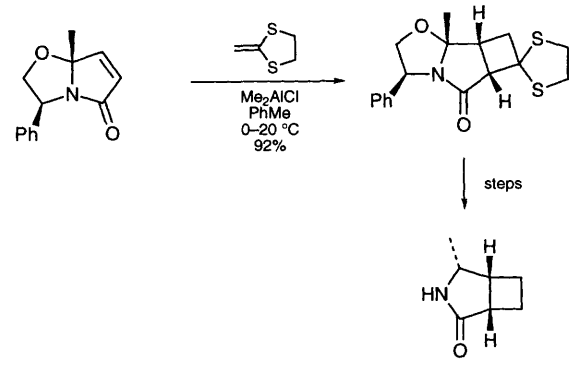


Scheme 3

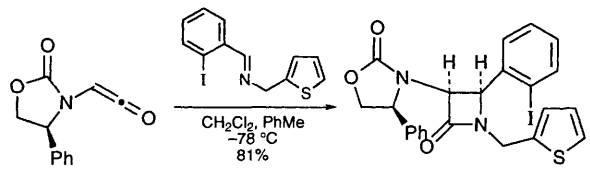
highly unusual. Silicon has been used as a temporary tether in cycloadditions of enynes to yield cyclobutenes.[16] The use of a carbohydrate template allows asymmetric induction in an intramolecular photoreaction of allenes.[17] Lewis acid catalysed reaction between a silylketene and a dienal is the key step in the first total synthesis of (−)-lipstatin (**Scheme 4**).[18] The use of methylaluminoimidazolines allows enantioselective approaches to oxetanones.[19] Chelation control by magnesium bromide etherate allows asymmetric synthesis of β-lactones.[20] Cyclobutanopyrrolidinones are available *via* Lewis acid catalysed addition of a ketene dithioacetal to a homochiral unsaturated lactam (**Scheme 5**).[21] Another asymmetric approach to four-membered rings involves irradiation of compounds in chiral



Scheme 4



Scheme 5



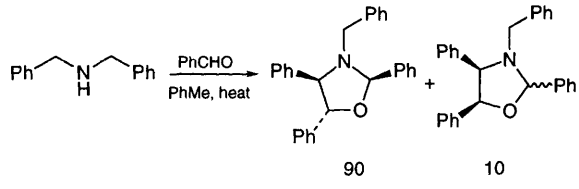
Scheme 6

hosts.[22] Homochiral ketenes add to imines in a diastereoselective fashion allowing access to nonracemic β-lactams (**Scheme 6**).[23]

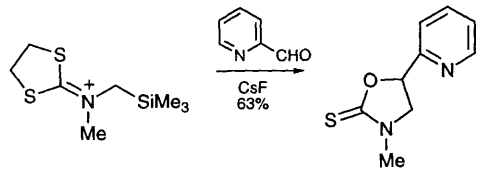
3 [3+2]-Cycloadditions

3.1 Azomethine ylides

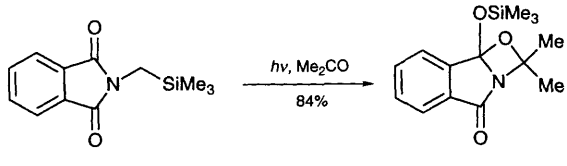
A simple one-pot reaction between benzaldehyde, benzylic amines and dipolarophiles proceeds *via* the intermediacy of the azomethine ylide yielding diarylpyrrolidines or triaryloxazolidines in a stereoselective manner (**Scheme 7**).[24] A new type of azomethine ylide allows access to thiolactams and cyclic thiocarbamates (**Scheme 8**).[25] New routes to azomethine ylides include photochemical reactions of *N*-(trimethylsilylmethyl)phthalimides (**Scheme 9**)[26,27] and NBS oxidation of allylic tertiary amines (**Scheme 10**).[28] The latter proceeds *via* an iminium ion that is used to generate the azomethine ylide *in situ*. This constitutes a key step in a synthesis of (±)-quinocarcinamide. Complexation of pyrroles with an osmium species generates an azomethine



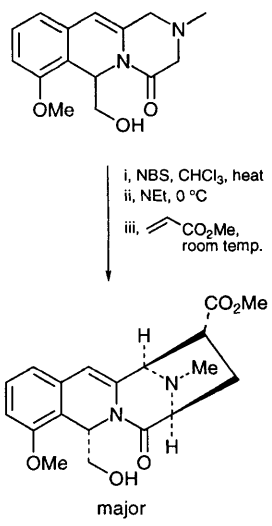
Scheme 7



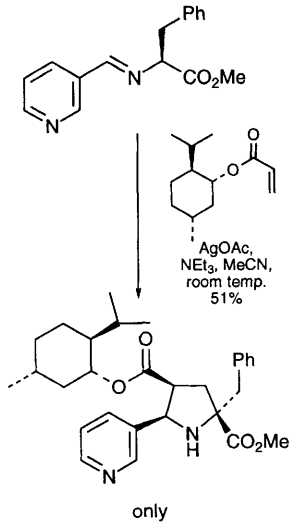
Scheme 8



Scheme 9

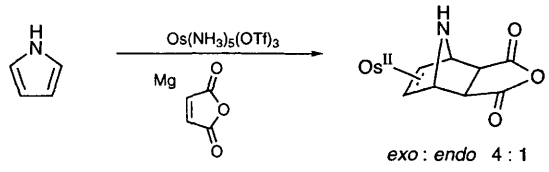


Scheme 10

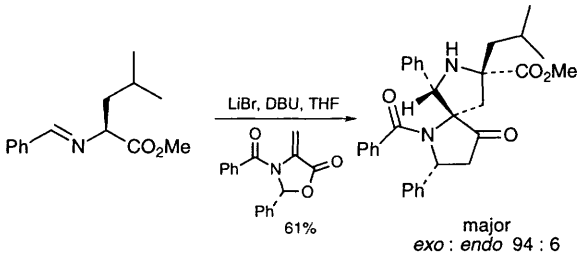


Scheme 14

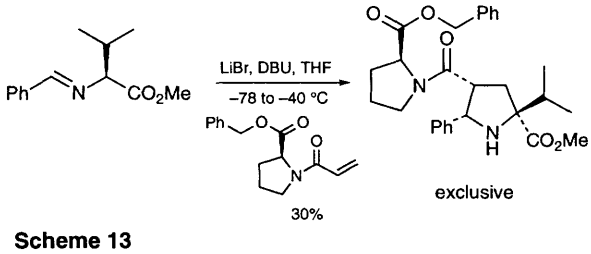
ylide that undergoes [3+2]-cycloadditions to furnish 7-azanorbornanes (**Scheme 11**).[29] Azomethine ylides derived from α-amino acid esters add in an *exo* selective fashion to homochiral methylene oxazolidinones providing a route to polyfunctionalised prolines (**Scheme 12**).[30] The addition of such dipoles to *N*-acryloyl (*S*)-proline esters and other homochiral acrylates has been investigated by a number of workers allowing access to a variety of homochiral pyrrolidines (**Schemes 13,14**).[31–35]



Scheme 11



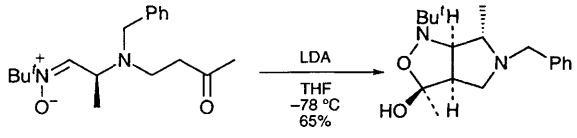
Scheme 12



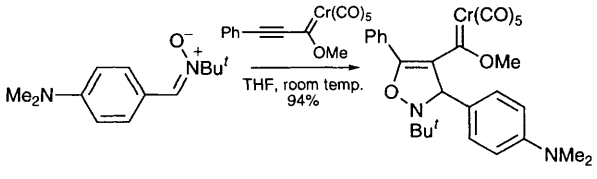
Scheme 13

3.2 Nitrones

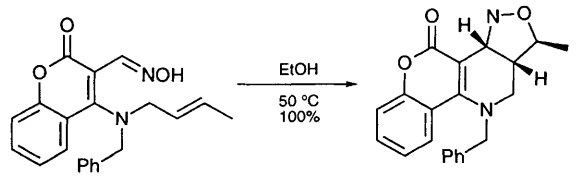
Ketone enolates can be used as dipolarophiles in an intramolecular [3+2]-cycloaddition with nitrones (**Scheme 15**).[36] Alkynyl Fischer carbene complexes undergo chemo- and regio-selective reaction with nitrones to provide 2,3-dihydroisoxazole carbene complexes (**Scheme 16**).[37] Facile oxime–nitrone isomerisations have been noted in a number of systems. In the presence of an intramolecular trap, complex polycyclic frameworks can be rapidly assembled (**Scheme 17**).[38,39] Intramolecular trapping by alkynes or allenes allows access to a variety of



Scheme 15

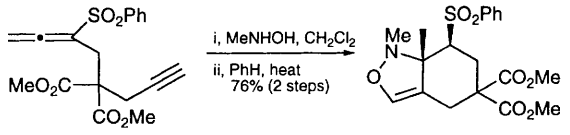


Scheme 16

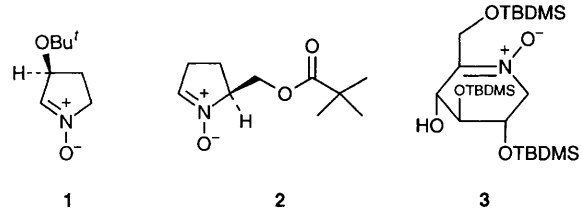


Scheme 17

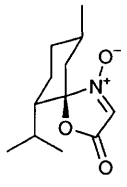
bicyclic heterocycles (**Scheme 18**).[40] Cyclic nitrones undergo regio- and stereo-selective addition to homochiral butenolides.[41] Interestingly, azomethine ylides give poor results with these dipolarophiles. Unsaturated lactams derived from (*S*)-pyroglutaminol also undergo regio- and stereo-selective cycloadditions with nitrones (**Scheme 19**).[42] Homochiral nitrones such as **1, 2, 3** and **4** have been examined by a number of groups.[43–46] An elegant tandem sequence involves reaction of aldoximes with divinyl sulfone (**Scheme 20**). This triggers



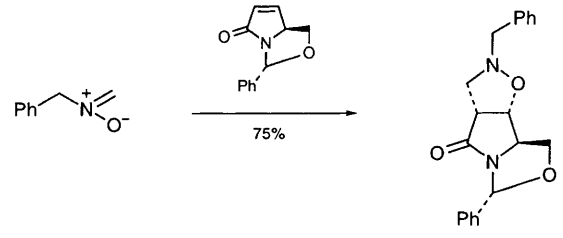
Scheme 18



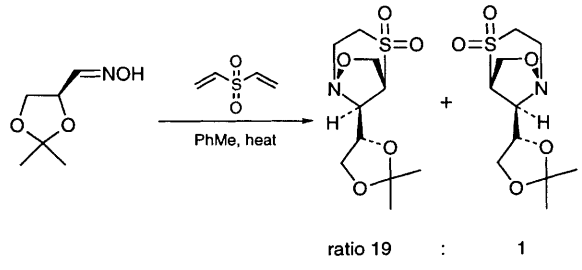
1 2 3



4



Scheme 19

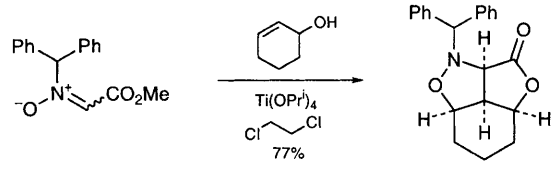


Scheme 20

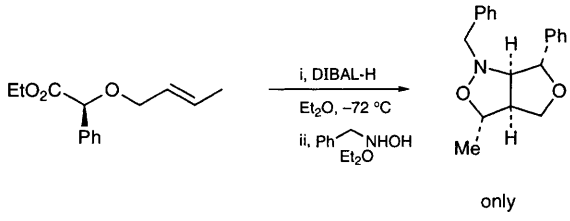
nitrone formation and subsequent intramolecular cycloaddition.[47] High diastereoselectivities are observed when the aldoxime has an α-chiral centre that is part of a ring. Another tandem process involves titanium(IV) isopropoxide mediated transesterification of α-methoxycarbonyl nitrones with allylic alcohols followed by cyclisation (**Scheme 21**).[48,49] Related species bearing an ether rather than ester linkage also cyclise in a highly stereoselective fashion (**Scheme 22**).[50]

3.3 Nitrile oxides

Nitrile oxides undergo [3+2]-cycloaddition to nitriles to furnish 1,2,4-oxadiazoles (**Scheme 23**).[51] Addition to polyfunctional enamines allows access to trisubstituted isoxazoles (**Scheme 24**).[52] The chemoselectivity issues with addition to enynes have been resolved by generating a dicobalt hexacarbonyl complex of the alkyne. Cycloaddition then occurs in a chemo, regio- and stereo-selective fashion (**Scheme 25**).[53] In natural product synthesis, a Taxol precursor has been prepared from the oxime **5** which on oxidation with NaOCl produces the nitrile oxide necessary for intramolecular cycloaddition (**Scheme 26**).[54] Polycyclic homochiral tetrahydrofurans can be obtained by spontaneous intramolecular cycloaddition of glucal derived nitrile oxides generated *in situ* from the oxime precursor (**Scheme 27**).[55]

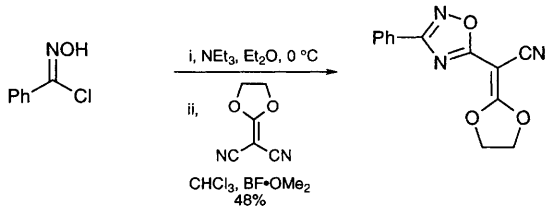


Scheme 21

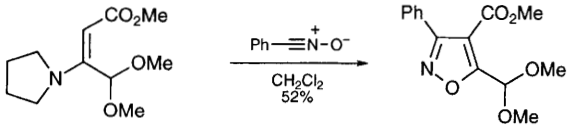


only

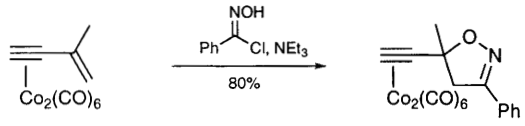
Scheme 22



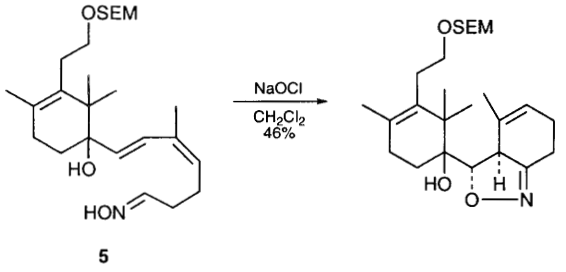
Scheme 23



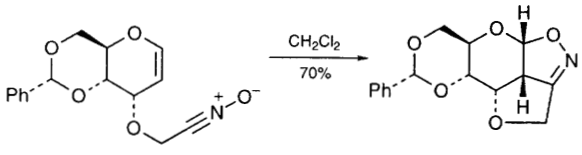
Scheme 24



Scheme 25



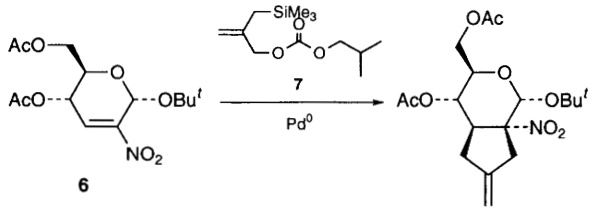
Scheme 26



Scheme 27

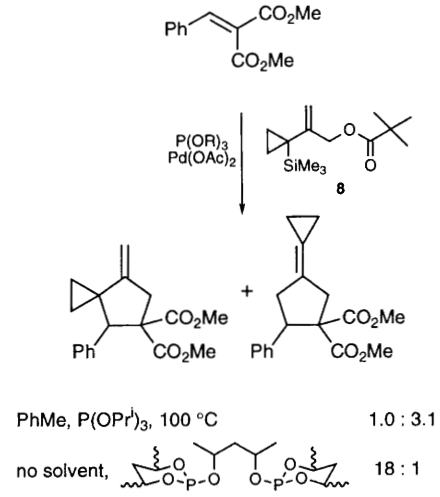
3.4 Palladium generated species

Palladium catalysed [3+2]-cycloadditions involving Trost's trimethylenemethane (TMM) precursor and related compounds are popular approaches to the preparation of methylene cyclopentanes. Unsaturated carbohydrates bearing sulfone or nitro groups to activate the double bond can be used as dipolarophiles (**Scheme 28**).[56,57] The nitroolefin **6** fails to react with the normal TMM precursor under palladium(0) catalysis; however, with the more reactive isobutyl carbonate **7** [3+2]-cycloaddition does occur in good yield. Trost observes that when

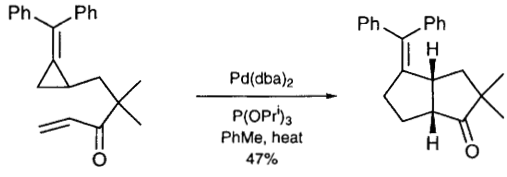


Scheme 28

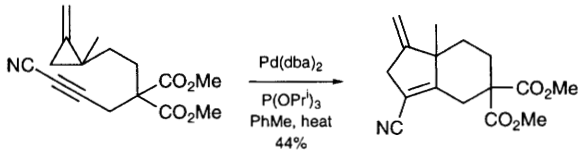
using the cyclopropyl TMM analogue **8**, changing from triisopropyl phosphite to a bidentate phosphorus ligand results in a reversal of regiochemistry in the addition to dimethyl benzylidenemalonate (**Scheme 29**).[58] Motherwell has explored the use of methylenecyclopropanes in intramolecular [3+2]-cycloadditions to alkenes and alkynes as a powerful route to polycylic frameworks (**Schemes 30, 31**).[59–61] An alternative to using palladium catalysed reactions is to generate a cation radical reactive intermediate from a cyclopropane. In the presence of an internal olefinic trap, [3+2]-cycloaddition occurs (**Scheme 32**).[62]



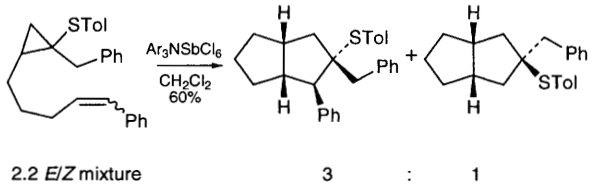
Scheme 29



Scheme 30



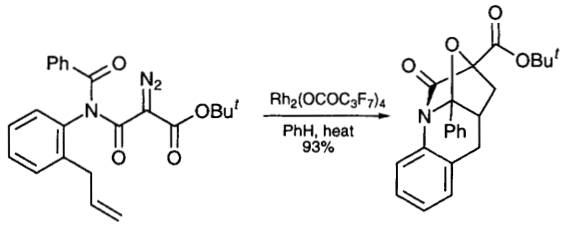
Scheme 31



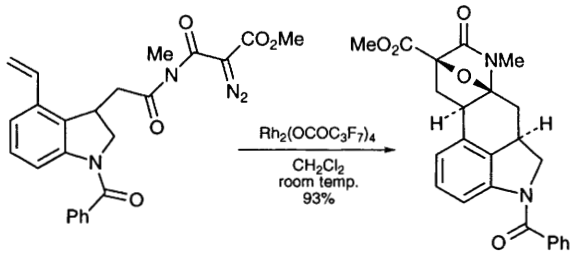
Scheme 32

3.5 Carbonyl ylides

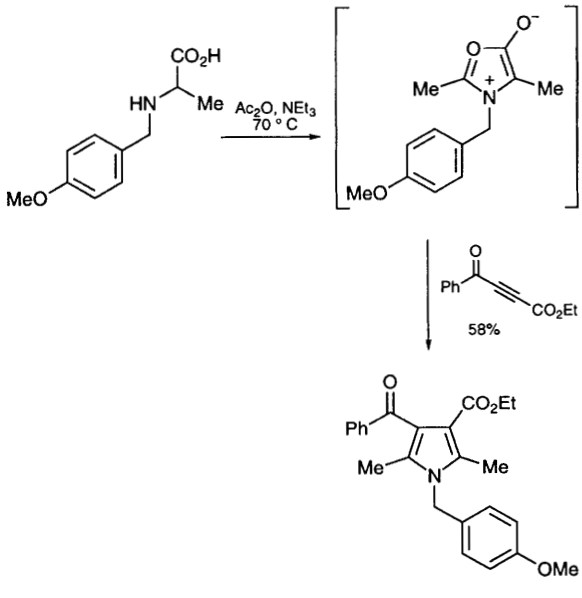
Isomünchnones generated from diazoimides by rhodium mediated decomposition and cyclisation onto the imide carbonyl undergo trapping by internal olefins in an *exo* selective fashion to form cyclic structures (**Scheme 33**).[63] This has been used as an approach to lysergic acid (**Scheme 34**).[64] Mesoionic oxazoles generated from amino acids have been used in an approach to the calcium channel activator FPL 64176. A model sequence is shown in **Scheme 35**.[65] The use of other carbonyl ylides generated from the cyclisation of rhodium carbenoids onto carbonyl groups has produced an approach to the pterosin sesquiterpenes (**Scheme 36**),[66,67] the *Aspidosperma* alkaloids (**Scheme 37**)[68] and other complex polycyclic structures.[69] In some instances, the carbonyl ylides do not undergo [3 + 2]-cycloaddition; rather rearrangement by proton transfer occurs, followed by other reaction pathways.[70] Thiocarbonyl ylides can be generated thermally from bis(trimethylsilylmethyl) sulfoxides and then trapped to form di- or tetra-hydrohydrothiophenes (**Scheme 38**).[71]



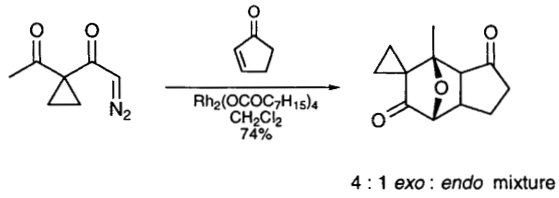
Scheme 33



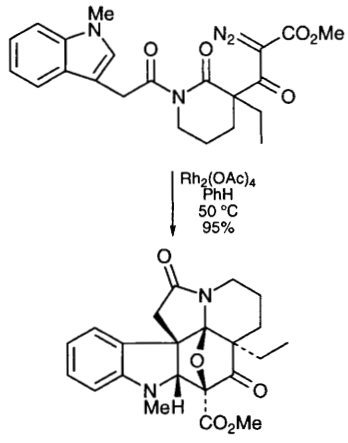
Scheme 34



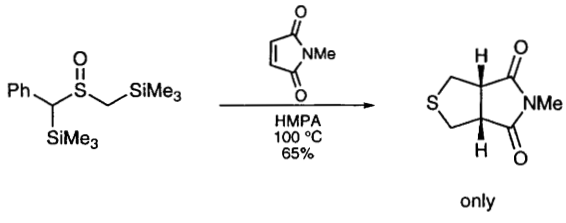
Scheme 35



Scheme 36



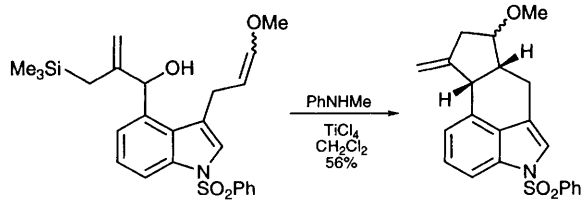
Scheme 37



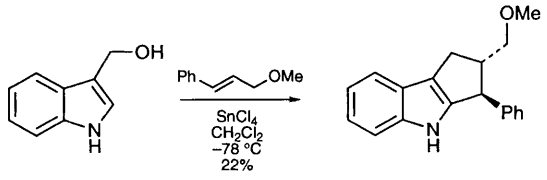
Scheme 38

3.6 Other [3 + 2]-cycloadditions

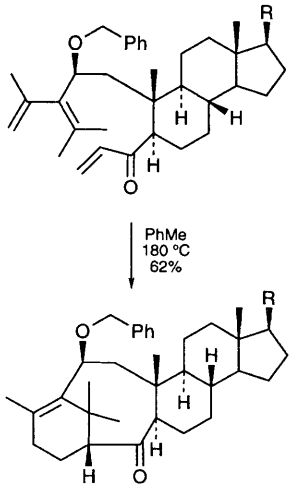
Cationic species can undergo formal [3 + 2]-cycloadditions as evidenced by the work of Mann on the ergot alkaloid skeleton (**Scheme 39**),[72] Moody on cyclopent[*b*]indoles (**Scheme 40**)[73] and Kuwajima on cyclopentanones.[74] A variety of alkynyl and alkenyl Fischer carbene complexes undergo formal [3 + 2]-cycloadditions to yield a variety of cyclopentadienes.[75–77]



Scheme 39



Scheme 40

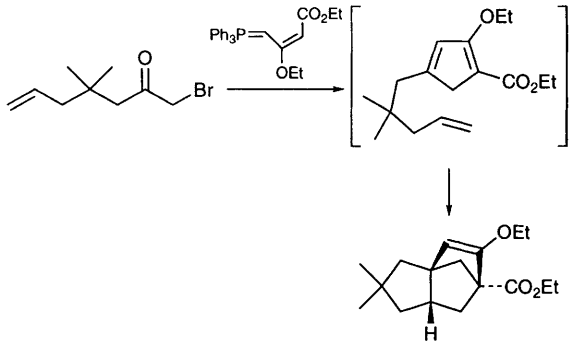


Scheme 42

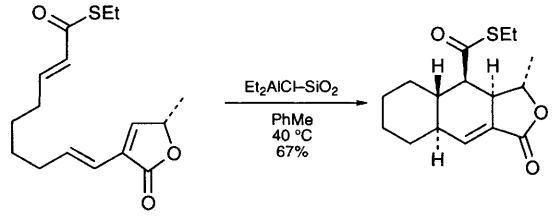
4 [4+2]-Cycloadditions

4.1 Natural products as targets

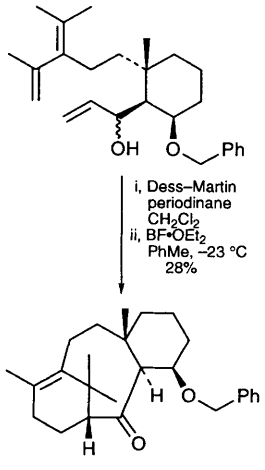
A number of major natural products have enjoyed approaches using a [4+2]-cycloaddition. These include an intramolecular Diels–Alder (IMDA) approach to taxanes (**Scheme 41**),[78] and to baccatin III models (**Scheme 42**).[79,80] In the latter, the stereochemistry of the benzyloxy substituent at C-10 is crucial to the success of the IMDA reaction. The epimeric species undergoes 1,4-elimination of benzyl alcohol to give a triene that cyclises to give a [6.6.6]-fused product, as well as retro-ene–hetero Diels–Alder products. The key step in a synthesis of the triquinane (±)-pentalenene involves an intramolecular [4+2]-cycloaddition of an *in situ* generated cyclopentadiene (**Scheme 43**).[81] The carbon skeleton of the piperidine alkaloid (+)-himbacine is assembled *via* a diethylaluminium chloride–silica gel promoted intramolecular cycloaddition, giving the desired *endo* adduct as the major product (*endo*:*exo* 20:1; thermally the ratio is



Scheme 43

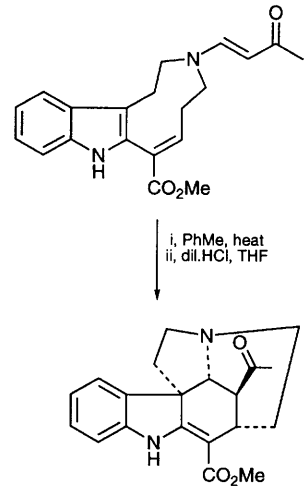


Scheme 44

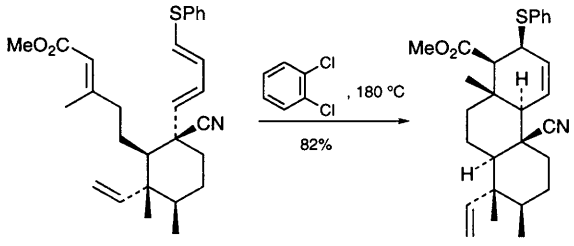


Scheme 41

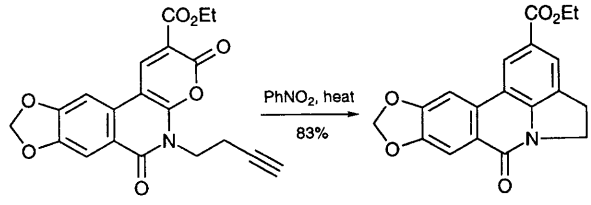
a poor 3:2) (**Scheme 44**).[82] The alkaloids lagunamine, isolagunamine, condylocarpine and isocondylocarpine are all available from a common precursor assembled by an intramolecular cycloaddition of a 2-vinylindole (**Scheme 45**).[83] The diterpene portion of the radarin indole alkaloids can be assembled by cycloaddition of a phenylthiobutadiene (**Scheme 46**).[84] The tricyclic *trans* decalin core of the azadirachtins can be generated from an intramolecular cycloaddition of a variety of trienes, but the reactions give a mixture of four diastereomers.[85] The lycorine alkaloids have been a popular target of IMDA approaches, with contributions from several groups,[86,87] Castedo utilising an α-pyrone as a key intermediate (**Scheme 47**). An



Scheme 45

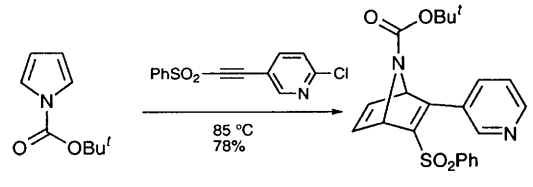


Scheme 46

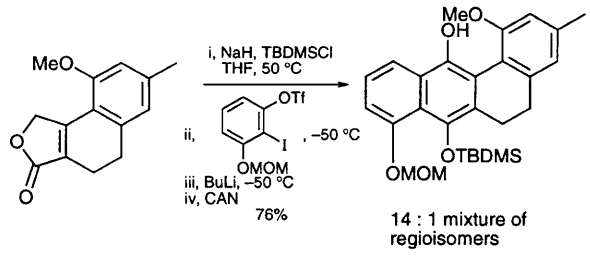


Scheme 47

intermolecular approach to epibatidine relies on a [4+2]-cycloaddition of a pyrrole to an alkynyl sulfone (**Scheme 48**).[88] An intermolecular benzyne–furan cycloaddition has been used to prepare the antibiotic C104 (**Scheme 49**).[89] An alternative approach to the angucycline antibiotics by Larsen uses more conventional Diels–Alder chemistry,[90]



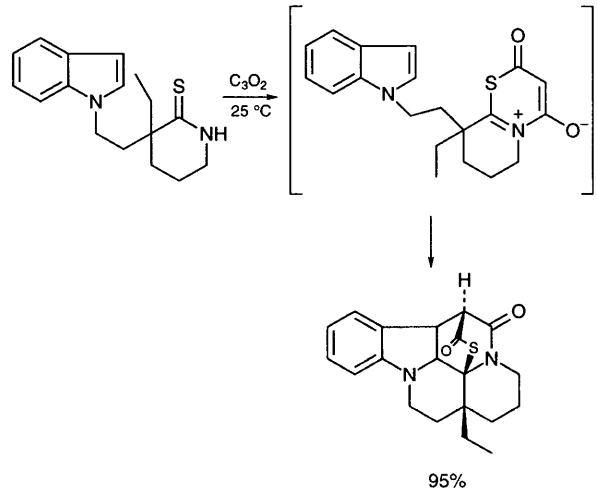
Scheme 48



Scheme 49

4.2 1,4-Dipoles

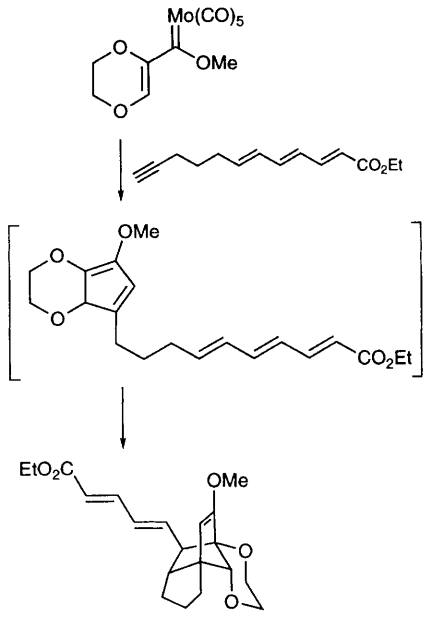
Padwa has exploited intramolecular [4+2]-cycloadditions of 1,4-dipolar heteroaromatic betaines in approaches to a variety of nitrogen containing polycyclic frameworks, in including *epi*-eburnamenine (**Scheme 50**)[91,92] Recent work in this area has been reviewed.[93]



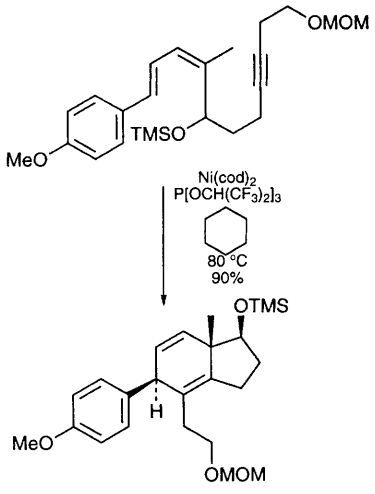
Scheme 50

4.3 Metal assisted reactions

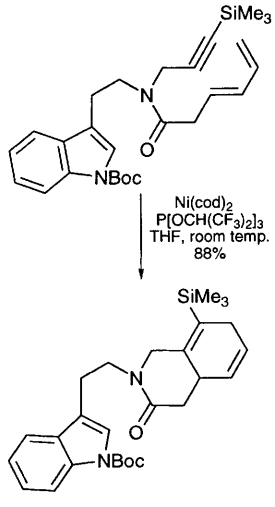
A dioxenylmolybdenum carbene complex, on reaction with enynes, is thought to provide a cyclopentadienyl intermediate which subsequently undergoes intramolecular [4+2]-cycloaddition (**Scheme 51**).[94] It is presently unclear whether that is a simple thermal reaction or is metal templated. Wender has used nickel(0) catalysed intramolecular cycloadditions as a powerful route to vitamin D analogues (**Scheme 52**)[95] and to the yohimban alkaloid skeleton (**Scheme 53**).[96] He has also applied rhodium catalysed intramolecular cycloadditions to a variety of [6.5]-, [6.6]- and [5.7]-fused ring systems (**Scheme 54**).[97] Zirconacyclopentadienes undergo cycloaddition with alkynes in the presence of copper chloride (**Scheme 55**).[98] Cobalt substituted dienes react with dienophiles, in the case of maleic anhydride, in an *exo* selective manner (up to 20:1) (**Scheme 56**).[99,100] With other dienophiles, selectivity



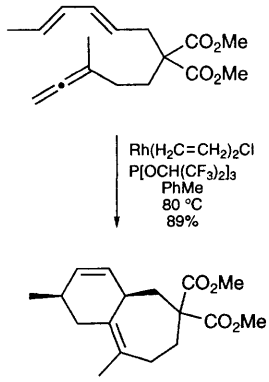
Scheme 51



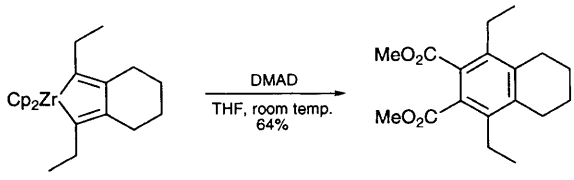
Scheme 52



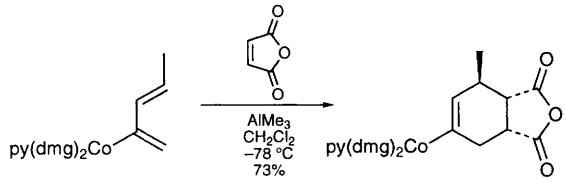
Scheme 53



Scheme 54

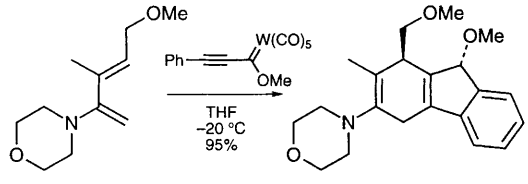


Scheme 55



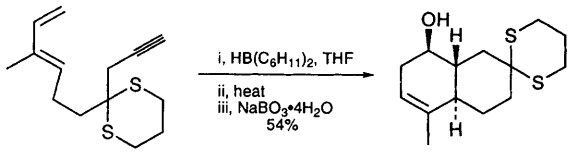
dmg = dimethylglyoxime

Scheme 56



Scheme 57

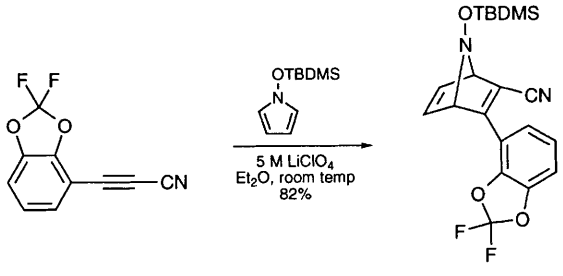
is poor. The cobalt can be readily removed without compromising the integrity of the cycloadduct. Phenylalkynyl tungsten carbene complexes react with amino-substituted butadienes yielding [6.5.6]-systems (**Scheme 57**).[101] Furans substituted with the electron donating cyclopentadienyl tungsten-(tricarbonyl) group undergo Diels–Alder reactions with electron deficient dienophiles.[102] Vinylboranes undergo IMDA reactions, giving a two step approach to *trans* decalins (**Scheme 58**).[103]



Scheme 58

4.4 New catalysts

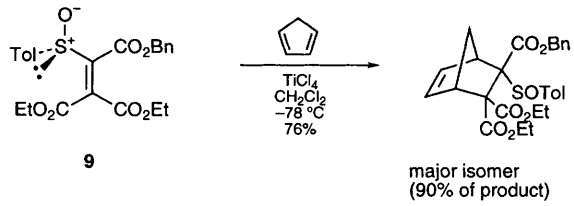
Lewis acid catalysis of a Diels–Alder reaction in water has been reported. In the presence of 10 mM copper(II) nitrate in water, there is a 250 000-fold rate enhancement over that in acetonitrile for the reaction between cyclopentadiene and 3-(4-nitrophenyl)-1-(2-pyridyl)propen-1-one.[104] A new combination for the Diels–Alder reaction of nitroalkenes has been reported. This involves the use of 4 M lithium perchlorate in nitromethane at room temperature, an improvement over both thermal and 5 M lithium perchlorate in ether conditions that were also examined.[105] Lithium perchlorate in ether was used as a catalyst for the [4+2]-cycloaddition of an *N*-hydroxypyrrole (**Scheme 59**).[106] The reaction failed under conventional thermal conditions in a number of solvents and also failed in the presence of aluminium chloride, titanium tetrachloride and boron trifluoride–diethyl ether. Silver perchlorate in combination with either diphenyltin sulfide or Lawesson's reagent have been reported as effective catalytic promoters for the Diels–Alder reaction.[107]



Scheme 59

4.5 Asymmetric reactions

Favourite chiral auxiliaries in asymmetric Diels–Alder methodology include the sulfinyl and sulfoximine moieties. Carretero and Ruano have shown that the cycloaddition of the enantiopure sulfoxide-bearing trialkoxycarbonyl alkene **9** with cyclopentadiene under Lewis acid catalysis can proceed with good selectivity (ratio of the four diastereomers up to 90:4:6:0) (**Scheme 60**).[108] The use of acyclic dienes gives product dienes (after elimination of toluenesulfinic acid) with low enantiomeric excess, indicating lower π-facial selectivity in these cases. Cyclopentadiene similarly produces good results with the homochiral

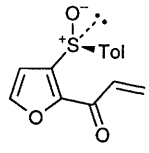


9

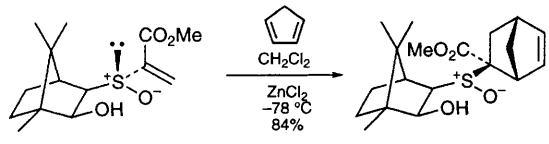
major isomer
(90% of product)

Scheme 60

tolylsulfinylfuran **10** under Lewis acid catalysis (the best was 96:4 *endo*:*exo*, 97% diastereomeric excess within the *endo* pair).[109] A new α-sulfinylacrylate **11** derived from (1*R*, 2*S*, 3*R*)-3-mercaptocamphan-2-ol reacts with cyclopentadiene under zinc chloride catalysis at −78 °C to give in 84% yield essentially a single cycloadduct (99.7% *endo* adduct, attack from the *si*-face; 0.3% *exo* adduct, *si*-face attack) (**Scheme 61**).[110]



10

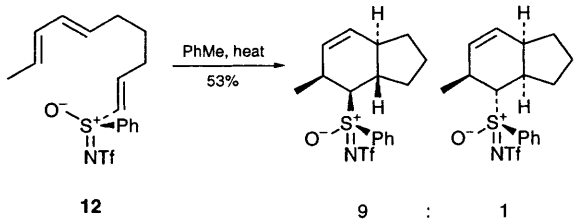


11

99.7%
endo, *si* adduct

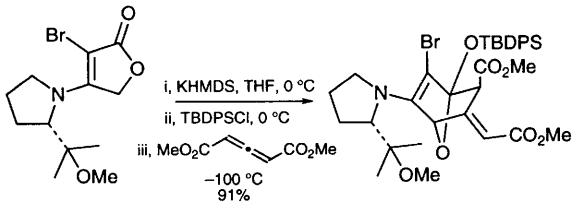
Scheme 61

In an intramolecular sense, Craig has used a variety of sulfoximine-substituted trienes to study diastereocontrol, with the best results being obtained from the 1,6,8-decatriene **12**, yielding only one *trans* and one *cis* product, in the ratio of 9:1 (**Scheme 62**).[111] A proline derived auxiliary has been used by Schlessinger in an enantioselective synthesis of (+)-cyclophellitol (**Scheme 63**), utilising a doubly diastereofacially selective Diels–Alder reaction with an allenyl diester,[112] and in an approach to the highly oxygenated core of the zaragozic acids.[113] *N*-Acryloyl derivatives of a new oxazolidinone derived from D-diphenylalaninol react in a highly



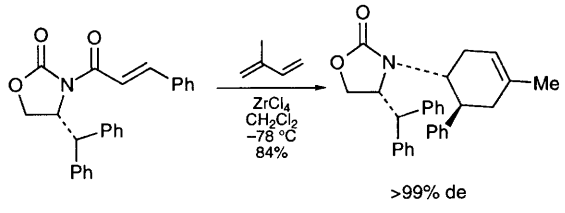
12 9 : 1

Scheme 62

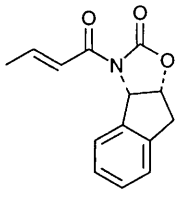


Scheme 63

diastereoselective manner (>99% de) with isoprene, the high control being assumed to result from π-stacking interactions with one of the phenyl groups (**Scheme 64**).[114] A range of constrained phenylglycinols have been used to prepare related *N*-butenoyloxazolidinones, such as **13**, and the use of these has been investigated in reactions with isoprene and piperylene. The reactions occur with high *endo* selectivity and high diastereocontrol.[115] Optically active 2-alkoxybutadienes prepared from chiral alcohols, undergo [4+2]-cycloadditions with, for example phenytriazolinedione (PTAD), providing adducts with good diasteromeric excesses (87–91%).[116]

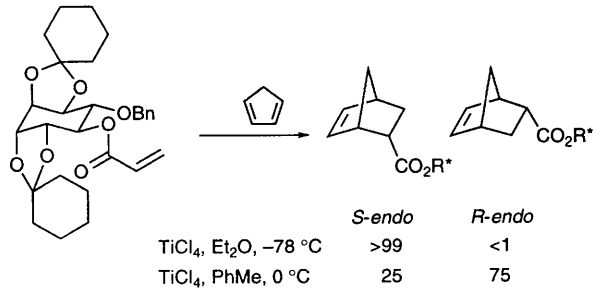


Scheme 64

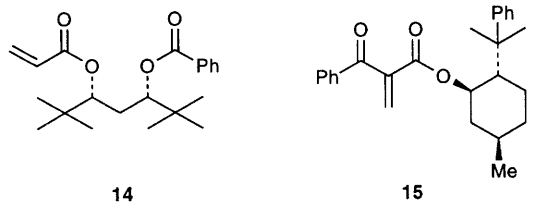


13

The use of homochiral cyclitols as chiral auxiliaries in the reaction between an acrylate ester and cyclopentadiene is reported to have a striking solvent dependence.[117] With titanium(IV) chloride in ether, the ratio of (*S*)-*endo* to (*R*)-*endo* is >99:1. This is *reversed* to 25:75 by simply using toluene as the solvent, although the yield is poor in this case (**Scheme 65**). Reaction of (3*R*, 5*S*)-5-benzoyloxy-2,2,6,6-tetramethylhept-3-yl acrylate **14** with cyclopentadiene in the presence of a combined *o*-phenylene mercury–titanium(IV) chloride catalyst gives mainly (71% *endo*, 29% *exo*) the *endo* pair of norbornene cycloadducts, with the (*R*):(*S*) ratio within the *endo* pair being 71:29.[118] This ratio is reversed to 19:81 if titanium(IV) chloride is used alone. These results are interpreted by suggesting



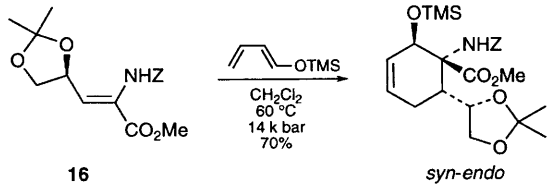
Scheme 65



14 **15**

that titanium(IV) chloride stabilises the s-*trans* conformation of the unsaturated ester, whereas the combined mercury–titanium catalyst stabilises the s-*cis*. The (−)-8-phenylmenthyl ester **15** reacts with cyclopentadiene in the presence of $FeCl_2I$ giving only the (*R*)-*exo* adduct.[119] An (*S*)-allene-1,3-dimenthyl ester reacts with cyclopentadiene under aluminium chloride catalysis furnishing a high yield of a single homochiral *endo* adduct.[120]

High pressure reaction between the homochiral α,β-didehydroamino acid **16** and 1-trimethylsilyloxybutadiene gives a 6:3:1 ratio of the *syn endo*:*syn exo*: mixture of *anti* products, providing a route to optically pure cyclohexane amino acids (**Scheme 66**).[121] The effect of heterogeneous catalysis (silica gel, alumina) in the absence of solvent on the reaction between (−)-menthyl *N*-acetyl α,β-didehydroalaninate and cyclopentadiene has been investigated.[122] The *exo*:*endo* ratio is poor (*ca.* 2:1) but one of the *exo* pair is formed almost exclusively (>97:3). A constrained homochiral α,β-didehydroamino acid **17** reacts with simple butadienes to give adducts with good diastereofacial selectivity.[123] All four 1-amino-2-phenylcyclohexane-1-carboxylic acids have been prepared in enantiomerically pure form by Cativiela and then used as chiral auxiliaries in the reaction between the appropriate *N*-acryloyl derivative and cyclopentadiene.[124] In the best case, the *endo*:*exo* ratio was



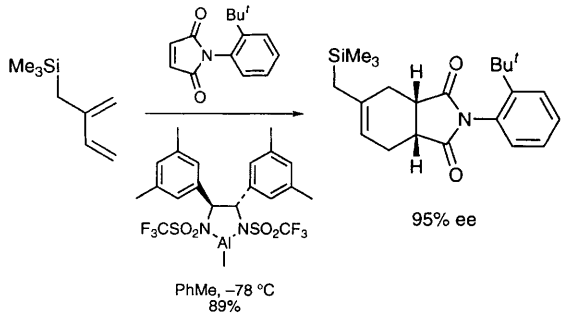
16 *syn-endo*

Scheme 66

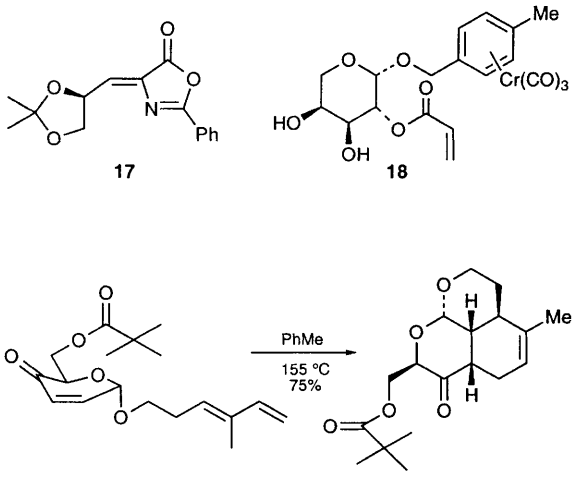
99:1, with the (*R*)-*endo* predominating over the (*S*)-*endo* by 9:1. L-Arabinose tricarbonylchromium(0) acrylates, for example **18**, undergo Lewis acid catalysed asymmetric Diels–Alder reactions with dienes.[125] Nitroalkenes appended to D-galactose or D-mannose skeletons undergo regioselective, and in the case of the D-galactose derivative, *si*-face specific, additions to 1-*O*-substituted 1,3-butadienes.[126]

An intramolecular Diels–Alder approach to homochiral *cis* decalins is based on a carbohydrate template (**Scheme 67**).[127] The enantioselective addition of 3-butenoyl-1,3-oxazolidin-2-one to cyclopentadiene catalysed by dichlorotitanium complexes of homochiral α,α,α′,α′-tetraaryl-1,3-dioxolane-4,5-dimethanols (TADDOLs, **19**) has been systematically investigated by Seebach.[128] Best results (*endo*:*exo* 90:10, 94:6 ratio within the *endo* pair) were obtained at −78 °C in the presence of 4 Å molecular sieves using 15 mol% catalyst generated *in situ* in toluene. Reactions of 3-methylthiofuran with 3-acryloyl-1,3-oxazolidin-2-ones using these chiral catalysts have also been examined.[129] The mechanism of titanium TADDOLate catalysed asymmetric Diels–Alder reactions has been investigated by Jørgensen.[130] A model to explain the stereocontrol observed is invoked that bears the four oxygens of the TADDOL and the *N*-acyloxazolidine bound to the titanium in an equatorial plane with the two chloride ions in axial positions (**20**).[131] An X-ray crystal structure of such a chiral titanium olefin complex assisted the generation of this model.

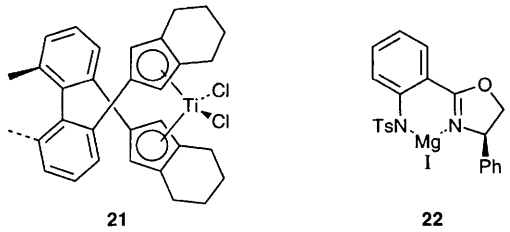
Coreyhasrecentlyusedahomochiraldiazaaluminolidine in a catalytic asymmetric Diels–Alder approach to the preparation of gracilins B and C (**Scheme 68**).[132] The key Diels–Alder step occurred to give a product with 95% enantiomeric excess. Other examples of homochiral catalysts used include titanocene complexes **21**,[133] a magnesium complex of the D-phenylglycine derived oxazoline **22**,[134] a variety of oxo(salen)manganese(v) complexes **23**,[135] copper(II) bisoxazolines[136] and a polymer-supported oxazaborolidinone derived from *N*-sulfonyl amino acids.[137] Differentiation of enantiotopic double bonds in a Diels–Alder process using a homochiral cyclopentadiene provides a novel approach to enantiopure fluorocyclohexenones (**Scheme 69**).[138] Winterfeldt has published a feature article on this work.[139]

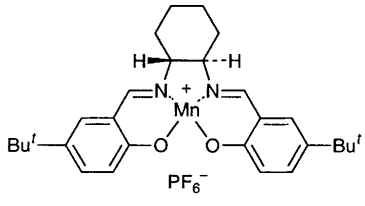


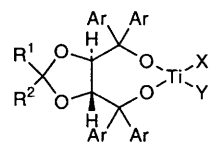
Scheme 68

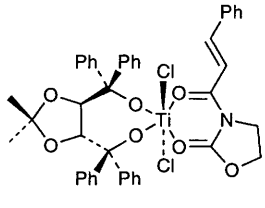


Scheme 67



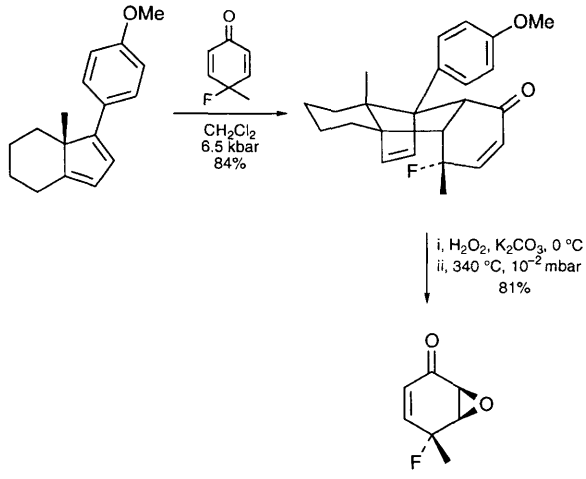




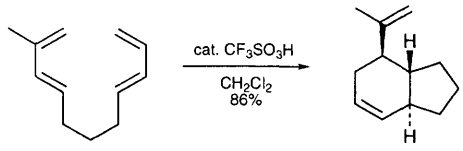


4.6 Ionic reactions

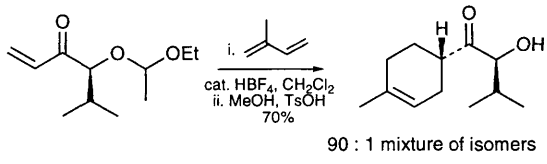
Tetraenes can undergo intramolecular ionic Diels–Alder reactions on treatment with trifluoromethanesulfonic acid (**Scheme 70**).[140] A variant on Gassman's ionic Diels–Alder reaction of α,β-unsaturated acetals involving cyclic vinyloxocarbenium ions has been described. By using chiral α,β-unsaturated ketones bearing an α′-hydroxy group (protected as an acetal), the authors were able to



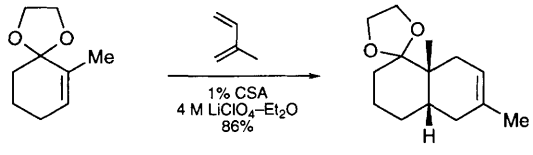
Scheme 69



Scheme 70



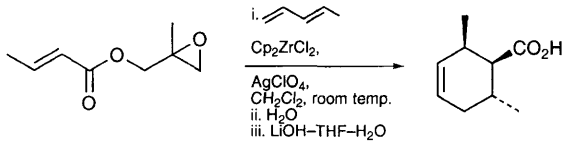
Scheme 71



Scheme 72

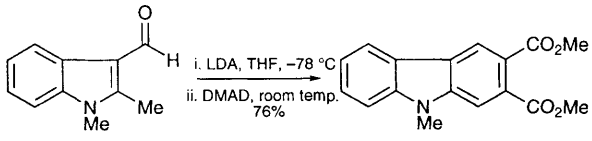
generate a diastereoselective procedure which on acetal hydrolysis lead to optically enriched products (**Scheme 71**).[141] Grieco has described the use of acid catalysed (1 mol% CSA) Diels–Alder reactions of ketals and orthoesters of enones in 4 or 5 M lithium perchlorate–ether (**Scheme 72**).[142] A cationic zirconocene species, generated from zirconocene dichloride by treatment with silver(I) perchlorate, allows formation of vinyloxocarbenium ions from α,β-unsaturated esters of glycidols (**Scheme 73**).[143] These intermediates cyclise to yield cyclohexene carboxylic acids in a stereoselective fashion. Addition of a one electron oxidant, such as Ar_3NSbF_6, to an electron rich arylallene and a substituted cyclopentadiene results in rapid, highly chemo-, regio- and facially selective Diels–Alder cycloadditions.[144]

Anionic reactions have also been described, including cycloadditions of indole-2,3-dienolates

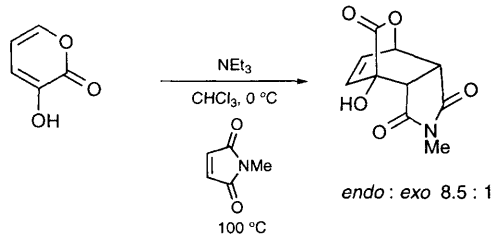


Scheme 73

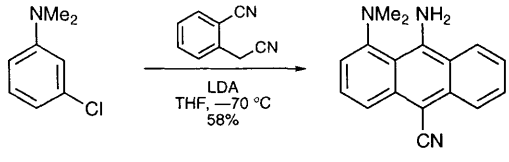
leading to a regiospecific carbazole synthesis (**Scheme 74**)[145] and of the triethylammonium salt of a 3-hydroxy-2-pyrone (**Scheme 75**).[146] Lithiated phenylacetonitriles can react with arynes to produce anthracenes (**Scheme 76**),[147] although a tandem addition–rearrangement reaction pathway can occur instead. Perhaps the most exciting use of an anionic reaction is the cycloaddition of a pyrone to the sensitive quinone imine as a successful approach to the synthesis of (±)-dynemycin A (**Scheme 77**).[148]



Scheme 74



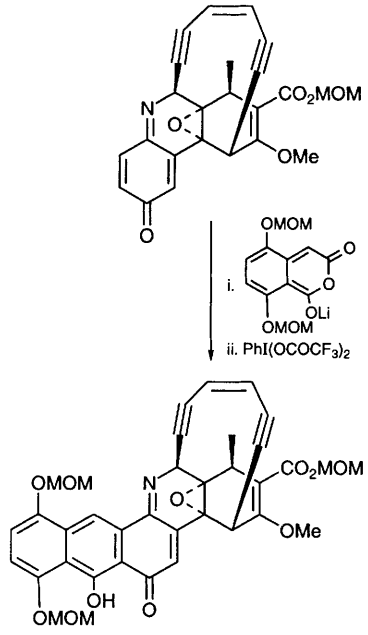
Scheme 75



Scheme 76

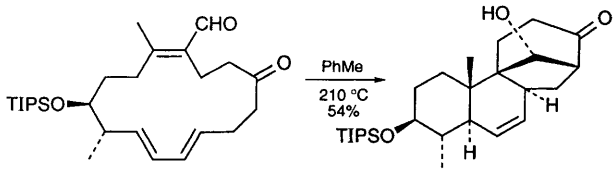
4.7 Transannular reactions

Deslongchamps' group has again provided the premier published material in the transannular Diels–Alder area, focusing on reactions of cyclopentadecatrienes.[149–153] The energy of activation for [4+2]-cycloaddition of macrocyclic trienes is lower than for the acyclic case and allows rapid entry into tricyclic structures bearing four new stereogenic centres. The use of an internal diene of *trans*, *trans* configuration allowed synthetic access to the *trans*,

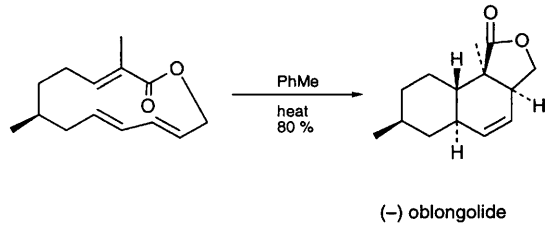


Scheme 77

syn, *trans* ABC [6.6.7] ring system of 8-*epi*-aphidicolin, using an unprecedented stereospecific tandem transannular Diels–Alder aldol reaction sequence (**Scheme 78**).[151] Some macrocyclic trienes have been observed to interconvert thermally *via* [1,5]-hydrogen shifts, thus complicating the transannular Diels–Alder picture.[153] Semi-empirical calculations have been used successfully to answer questions posed by this competition between pericyclic processes. Lewis acids have been used for the first time in a transannular process and do indeed accelerate the reaction.[150] Shing reported a synthesis of (−)-oblongolide in which he was able directly to compare intramolecular and transannular [4+2]-reactions (**Scheme 79**).[154] He found that the latter process was superior, delivering the product in higher yield in a shorter time at a lower temperature than the intramolecular variant.



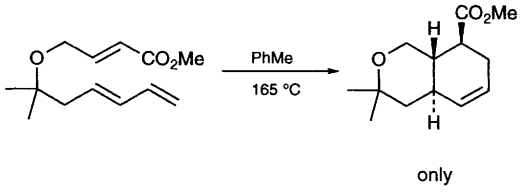
Scheme 78



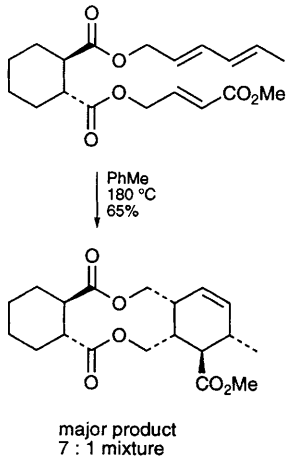
Scheme 79

4.8 Tethered reactions

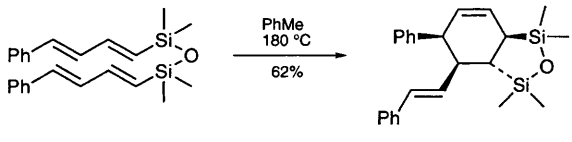
Intramolecular Diels–Alder reactions of trienes containing either ether or ester tethers have been described by Craig (**Schemes 80, 81**).[155,156] The removable tether allows higher levels of regio- and stereo-control than would be accessible *via* an intermolecular approach. Siloxane tethered bis-dienes undergo stereoselective intramolecular Diels–Alder reactions (**Scheme 82**), the products of which can be transformed to cyclohexenediols by Tamao oxidation.[157] A temporary silicon tether has been used in a key step in the preparation of (+)-adrenosterone,[158] and in the preparation of vitamin D3 analogues by Posner (**Scheme 83**).[159] The use of temporary magnesium and aluminium tethers has been reported by Stork.[160] Addition of vinylmagnesium or aluminium species to a lithium alkoxide followed by heating allows access to the cyclohexenemethanol (**Scheme 84**). The reaction is remarkably tolerant of steric bulk, allowing disubstitution at the β-position of the vinyl organometallic or at the diene terminus. Addition of phenylboronic acid is thought to provide a tempo-



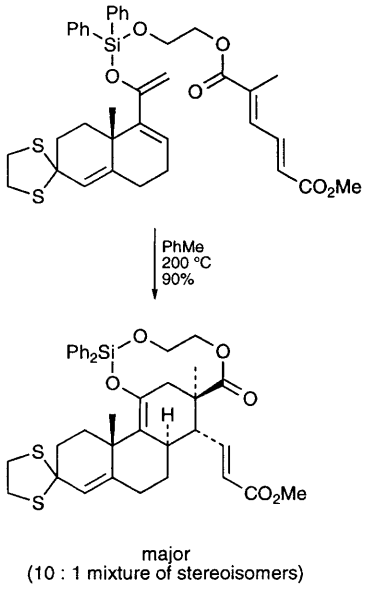
Scheme 80



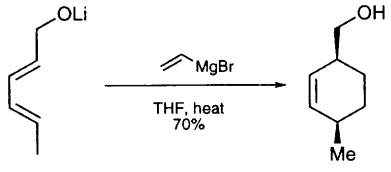
Scheme 81



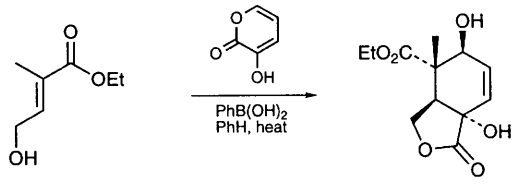
Scheme 82



Scheme 83



Scheme 84

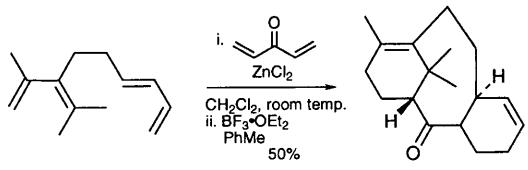


Scheme 85

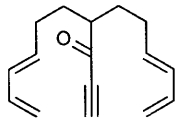
rary boron tether which reverses the normal regioselectivity of a cycloaddition, allowing access to a key Taxol intermediate (**Scheme 85**).[161]

4.9 Tandem reactions

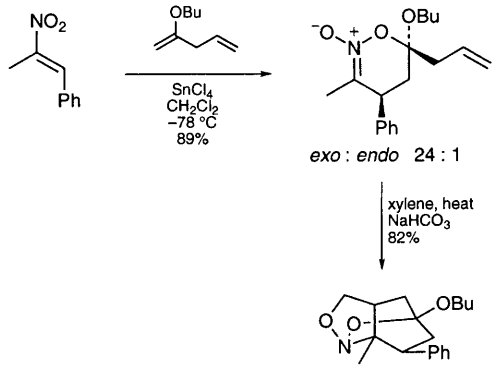
Tandem Diels–Alder sequences have been described, including an approach to Taxol by Winkler (**Scheme 86**).[162] Giguere reports on the first example of a branched tandem intramolecular process, involving sequential reactions of the alkyne **24**.[163] A powerful stereoselective approach to a variety of ring systems, including pyrrolidines and cyclohexanes, is the tandem [4+2]–[3+2]-cycloaddition of nitroalkenes pioneered by Denmark (**Scheme 87**).[164] The reactions can be carried out in an asymmetric fashion with high enantiomeric excesses by utilising chiral enol ethers[165] or chiral



Scheme 86



24

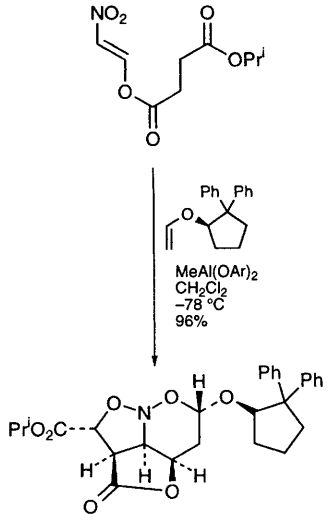


Scheme 87

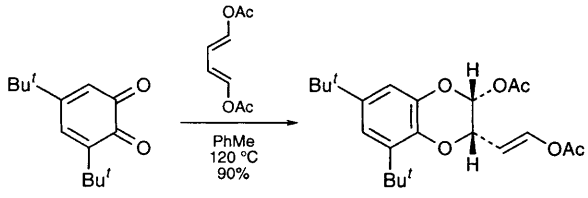
heterodienes.[166] Denmark has used this as a route to (−)-rosmarinecine (**Scheme 88**).[167]

4.10 *o*-Benzoquinones, *o*-quinodimethanes and related species

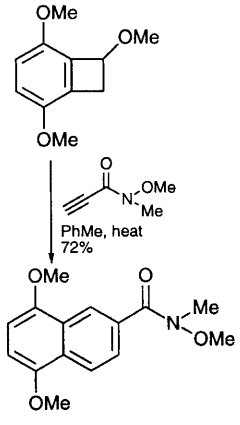
o-Benzoquinones have been reported to react with a variety of acyclic dienes, producing benzodioxine adducts (**Scheme 89**).[168] The use of 1-methoxybenzocyclobutenes substituted with alkoxy groups in the benzene nucleus as *o*-quinodimethane precursors has been reported by Keay (**Scheme 90**).[169] The use of methoxy- rather than hydroxy-cyclobutenes allows access to the desired naphthalene substitution pattern (the hydroxybenzocyclobutene produces none of the desired cycloadduct, rather producing a product thought to arise from a [1,5]-hydrogen shift in the *o*-quinodimethane). Useful functionality, such as a Weinreb amide, can be introduced into the naphthalene nucleus in this manner. An intramolecular approach to the polycyclic framework of the kaurane diterpenes involving a benzocyclobutene as an *o*-quinodimethane precursor has been described.[170] Cathodic reduction of α,α'-dibromo-1,2-dialkylbenzenes in the presence of dienophiles such as maleic anhydride yields cycloadducts *via* the intermediacy of the *o*-quinodimethane.[171] Dieno-



Scheme 88

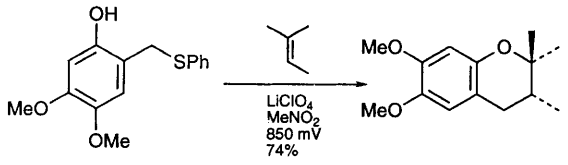


Scheme 89



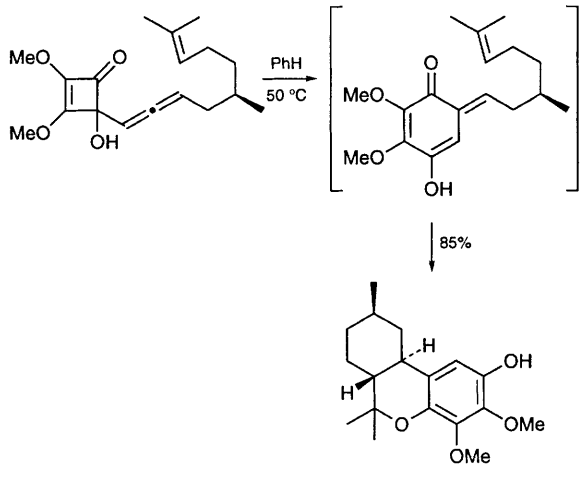
Scheme 90

philes bearing only a single activating group produce lower yields owing to competing dimerisation–polymerisation of the *o*-quinodimethane. In related chemistry, electrochemical oxidation of *o*-[1-(phenylthio)alkyl]phenols in lithium perchlorate–nitromethane is presumed to produce an *o*-quinomethane *in situ* and this can be trapped by dienophiles (**Scheme 91**).[172] The chemistry allows access to chromanes containing the euglobal skeleton. The reaction is suggested to occur by single electron oxidation of the sulfide followed by

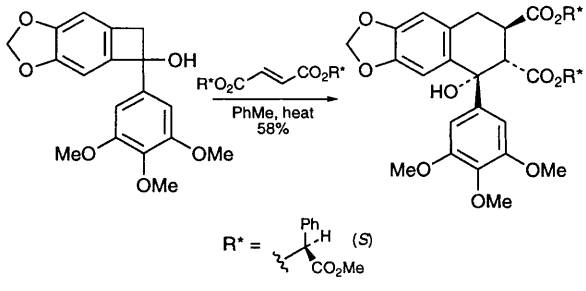


Scheme 91

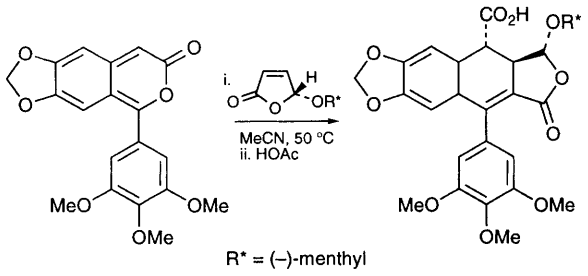
loss of phenylthio radical to generate the reactive intermediate. In the absence of electric current, the cycloadditions do not occur. Ring expansion of allenyl cyclobutenones generates quinomethanes *in situ*. Intramolecular trapping can lead to the preparation of enantiomerically pure hexahydrocannabinols (**Scheme 92**).[173] Two related approaches to an asymmetric synthesis of the podophyllotoxin skeleton have been reported, each involving an *o*-quinonoid intermediate (**Schemes 93, 94**).[171,175] Chiral tricarbonyl (η^6-cyclobutabenzene)chromium complexes have been prepared in a diastereoselective fashion and then used as precursors for *o*-quinodimethanes in asymmetric cycloaddition reactions (**Scheme 95**).[176] Vinyl sulfones react with good to excellent *exo* selectivity whereas methyl acrylate prefers an *endo* mode of addition. Other workers have used racemic tricarbonyl (η^6-cyclobutabenzene)chromium complexes.[177] Benzo- and naphtho-thietes, and new equivalents for them, have



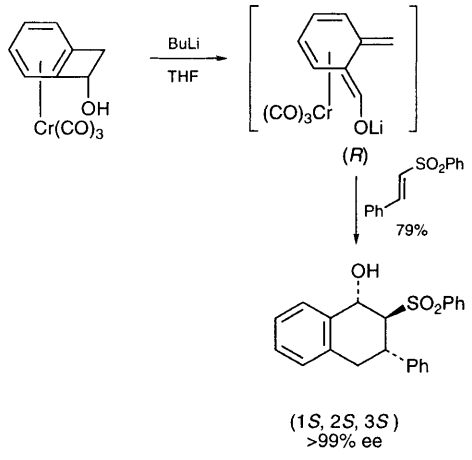
Scheme 92



Scheme 93

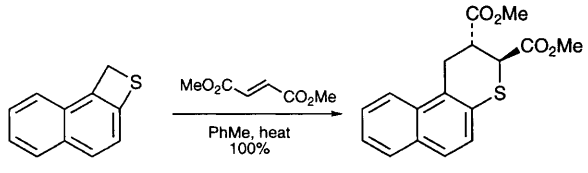


Scheme 94

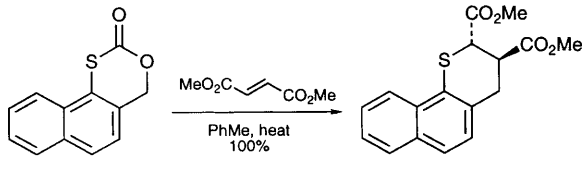


Scheme 95

recently been described by Meier (**Schemes 96, 97**).[178,179] These benzo-fused 1,3-oxathiin-2-ones on thermolysis in the presence of dienophiles extrude carbon dioxide, generate the *o*-thiobenzoquinomethane which is trapped in a [4 + 2]-process to yield thiopyrans. Flash vacuum pyrolysis in the absence of a trap produces the benzo- and naphtho-thietes. The generation of heterocyclic *o*-quinodimethanes continues to be a topic of great research interest.

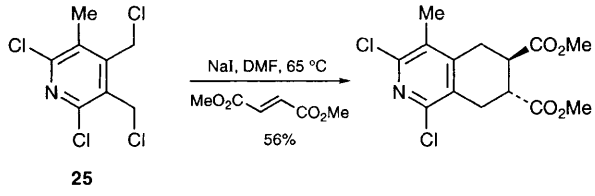


Scheme 96

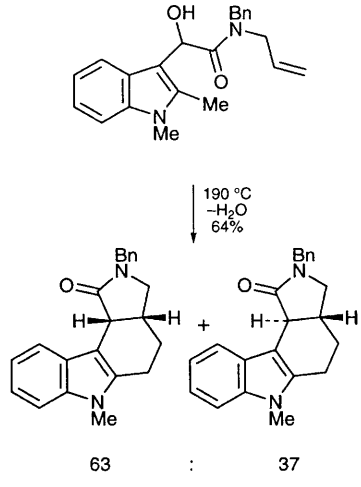


Scheme 97

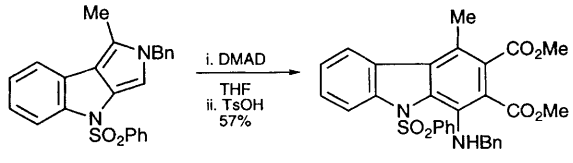
Conversion of the dichloro compound **25** to the diiodide followed by a 1,4-elimination of iodine allows generation of a pyridine *o*-quinodimethane. This can be trapped with *N*-phenylmaleimide, dimethyl fumarate, methyl acrylate and dihydrofuran (**Scheme 98**). In the case of methyl acrylate, a 1:1 mixture of regioisomeric adducts is formed.[180] Indolo-2,3-quinodimethanes generated by two different means have been used in an IMDA approachtopyrrolo[3,4-*c*]carbazolesandpyrido[4,3-*c*] carbazoles (**Scheme 99**).[181] The use of 2,4-dihydropyrrolo[3,4-*b*]indoles as indole 2,3-quinodimethane equivalents and their trapping with dienophiles to produce carbazoles has been described (**Scheme 100**).[182] A quinoxaline 2,3-quinodimethane can be similarly prepared from the dibromo compound **26** and then trapped with diethyl azodicarboxylate or dimethyl acetylenedicarboxylate (**Scheme 101**).[183] A quinoline 3,4-quinodimethane can be generated from the fused 3-sulfolene and trapped by diethyl fumarate (**Scheme 102**).[184] The isomeric quinoline 2,3-quinodimethane cannot be generated in this



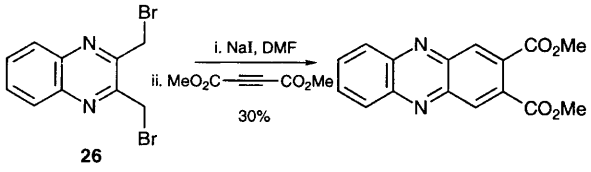
Scheme 98



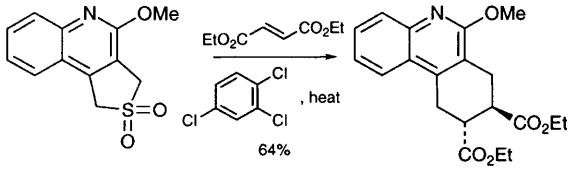
Scheme 99



Scheme 100

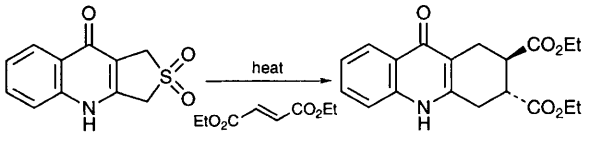


Scheme 101

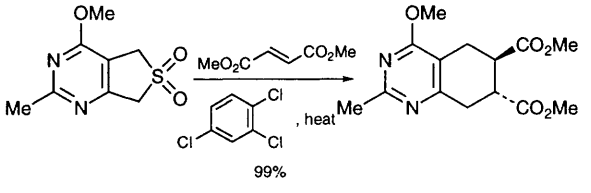


Scheme 102

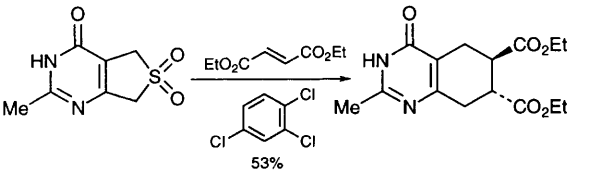
manner, presumably due to the low bond order of the sulfolene 3,4-bond. This can be tackled by utilising a quinolene instead of a quinolone, thus providing a quinolone 2,3-quinodimethane (**Scheme 103**).[184,185] Pyrimidine and pyrimidone fused 3-sulfolenes on heating extrude sulfur dioxide to yield pyrimidine[186] and pyrimidone[187] derived *o*-quinodimethanes which can be trapped with dienophiles to furnish Diels–Alder adducts (**Schemes 104,105**). In a similar manner, thieno-,[188,189] pyrazolo-,[189,190] isoxazolo-[189] and isothiazolo-3-sulfolenes[191] can behave as precursors to *o*-quinodimethanes derived from thiophene, pyrazole, isoxazole and isothiazole respectively (**Schemes 106–109**).



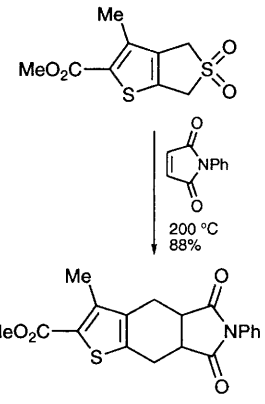
Scheme 103



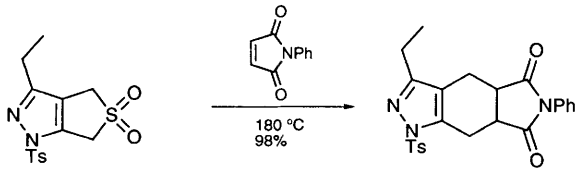
Scheme 104



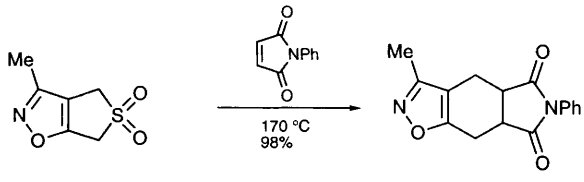
Scheme 105



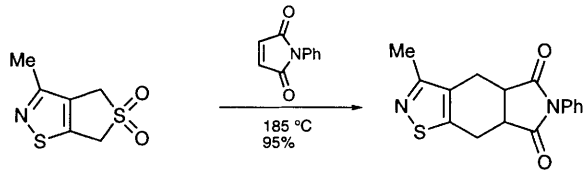
Scheme 106



Scheme 107



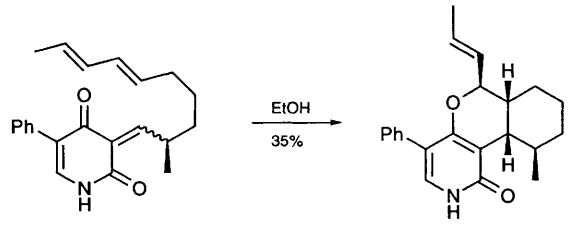
Scheme 108



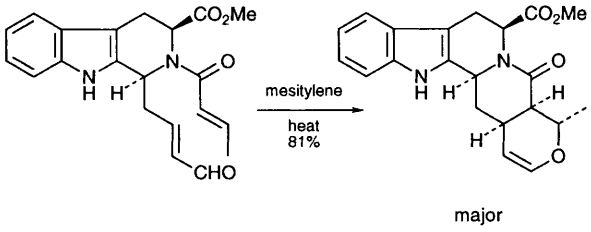
Scheme 109

4.11 Hetero Diels–Alder reactions

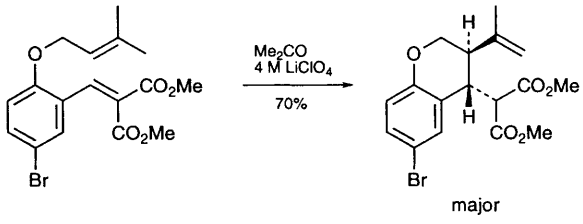
Intramolecular hetero Diels–Alder approaches have been used by a number of workers as approaches to complex natural products, including Snider's synthesis of (±)-leporin A (**Scheme 110**)[192] and Martin's approach to (−)-ajmalacine and related heteroyohimboid alkaloids (**Scheme 111**).[193] Inorganic perchlorates can have a marked effect on the course of an attempted hetero Diels–Alder approch tricyclic systems (**Scheme 112**).[194] Lithium and barium perchlorates provide the desired adducts, whereas magnesium perchlorate gives the ene product instead. Enol ethers react with α-diketones to provide 1,4-dioxines.[195] Lactams have



Scheme 110

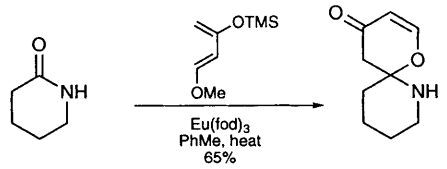


Scheme 111

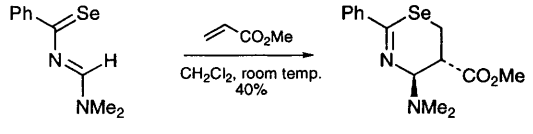


Scheme 112

recently been shown to react, generally with the assistance of a Lewis acid, in a hetero Diels–Alder fashion with Danishefsky's diene (**Scheme 113**).[196] *N*-Acylthioformamides will similarly function as dienes under titanium(IV) chloride catalysis.[197] *N*-Selenoacylamidines allows access to selenopyrans and selenoazines (**Scheme 114**).[198] Aza Diels–Alder reactions represent a powerful route of assembly for

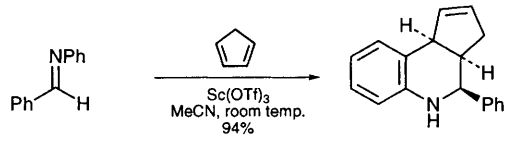


Scheme 113

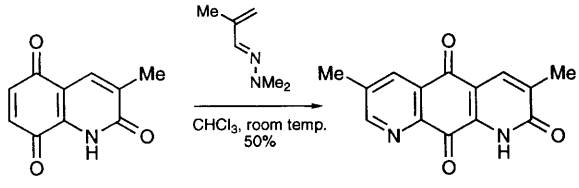


Scheme 114

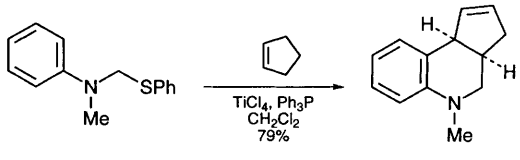
nitrogen heterocycles. Recent examples include preparation of piperidines from *N*-phenyl-1-aza-2-cyano-buta-1,3-dienes[199] and from alkenes plus enamines,[200] pyridines and quinolines from *N*-arylaldimines under lanthanide trifluoromethanesulfonate catalysis[201,202] (**Scheme 115**) and pyrimidines from 1,3-diazabuta-1,3-dienes.[203] Quinolinetriones react with aldehyde *N*,*N*-dimethylhydrazones to give 1,8-diazaanthracenetriones related to diazaquinomycin A (**Scheme 116**).[204] Ghosez has described striking rate enhancements of the reaction between unsaturated *N*,*N*-dimethylhydrazones and electron poor dienophiles in concentrated solutions of lithium trifluorosulfonimide in acetonitrile.[205] Aqueous aza Diels–Alder reactions between an iminium salt and a diene can be catalysed by lanthanide(III) trifluoromethanesulfonates.[206] Treatment of arylthiomethylamines[207] or arylsulfonylmethylamines[208] with a Lewis acid yields cationic azabutadienes which react with dienophiles to give tetrahydroquinolines (**Scheme 117**). Two intramolecular aza Diels–Alder reactions involving arynes have been used as an approach to the lycorines (**Schemes 118,119**),[209,210] one involving an



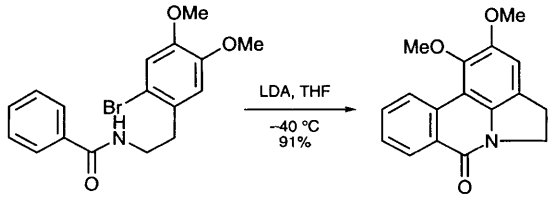
Scheme 115



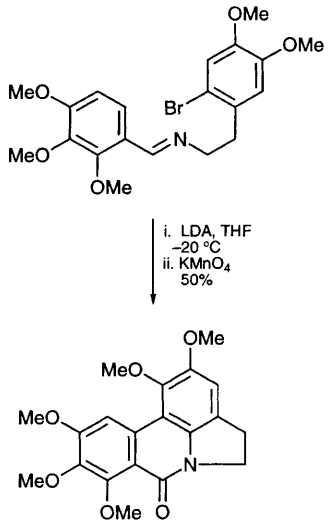
Scheme 116



Scheme 117

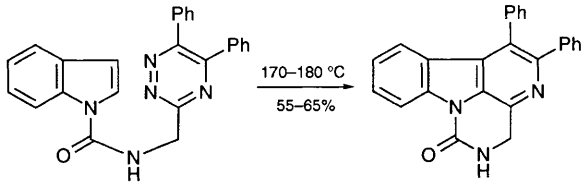


Scheme 118

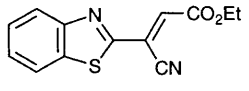


Scheme 119

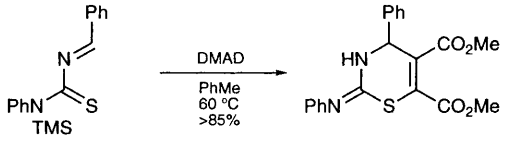
anionic amide cyclisation.[209] Indole can undergo intramolecular reactions with 1,2,4-triazines, leading to β-carbolines after extrusion of nitrogen (**Scheme 120**).[211] The benzothiazole **27** has been shown to be a very reactive heterodienophile in both inter- and intra-molecular reactions with electron rich dienophiles.[212] Barluenga has shown that 2-amino-1-thia-3-azabutadienes, generated *in situ* from *N*-(trimethylsilyl)imines and aryl isothiocyanates, react with electron deficient dienophiles to yield 1,3-thiazines (**Scheme 121**).[213] The use of dialkyl azodicarboxylates or PTAD allows access to 1,2,3,5-thiatriazines. Schaumann has used the heterocumulenic *N*-sulfonylimines, generated *in situ*, in a [4+2]-approach to sultams.[214] Thiocarbonyl



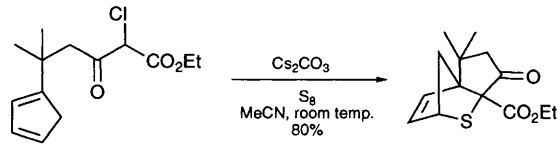
Scheme 120



27

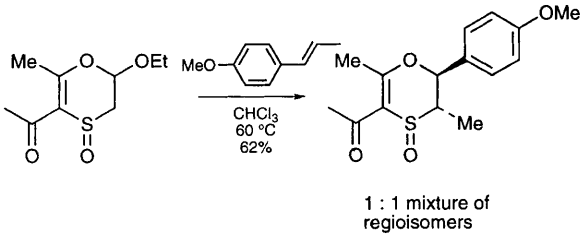


Scheme 121



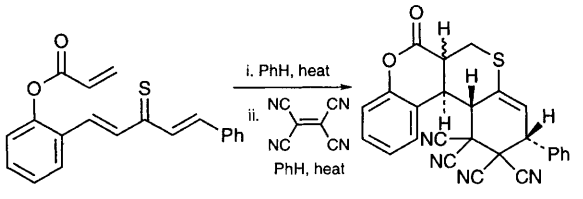
Scheme 122

compounds, generated *in situ*, can be trapped intramolecularly by a cyclopentadiene moiety, yielding unusual tricyclic structures (**Scheme 122**).[215] Oxathiine *S*-oxides undergo thermal retro Diels–Alder reactions generating α,α′-dioxo thioketone *S*-oxides that subsequently can be reacted with dienes or electron rich dienophiles (**Scheme 123**).[216] The 'diene-transmissive' (tandem) hetero Diels–Alder reaction, whereby a cross conjugated divinyl ketone[217] or thioketone[218] reacts in two sequential [4+2]-reactions, has been exploited by two Japanese groups as a powerful route to polycyclic frameworks (**Scheme 124**). Transannular hetero Diels–Alder processes have also been examined (**Scheme 125**).[219]

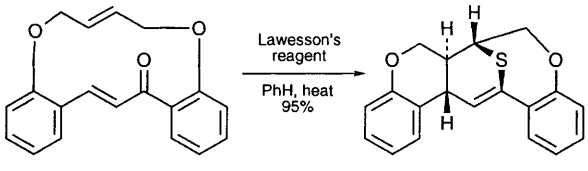


1 : 1 mixture of regioisomers

Scheme 123



Scheme 124

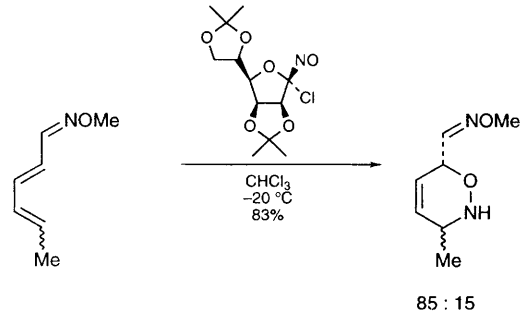


Scheme 125

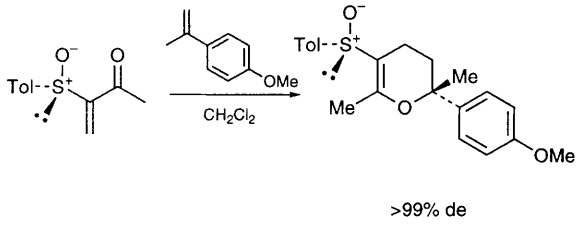
4.12 Asymmetric hetero Diels–Alder reactions

Asymmetric hetero Diels–Alder reactions involving nitroso compounds have been extensively investigated by Defoin's group.[220,221] Reported examples involve for example, the reaction of a *C*-nitroso derivative of D-mannose in a Diels–Alder reaction

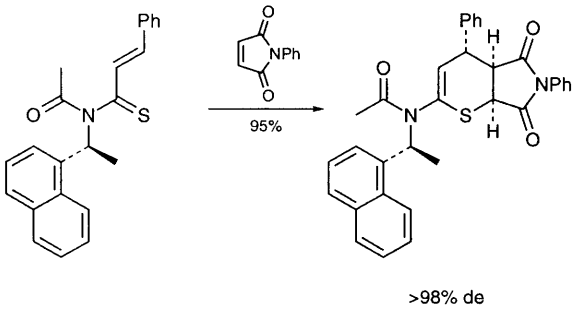
with sorbaldehyde *O*-methyloxime (providing a route to optically pure dideoxynojirimycin analogues) (**Scheme 126**) and the reaction of *N*-dienyl-L-pyroglutamate esters with acylnitroso species (providing dihydrooxazines with moderate diastereoselection).[220] A review of the group's work on azasugar synthesis *via* this methodology has been published.[222] A homochiral tolylsulfinyl moiety attached to an unsaturated ketone allows asymmetric hetero Diels–Alder reactions to occur with enol ethers and styrenes (**Scheme 127**). Diastereomeric excesses are excellent with the styrenes and poor with enol ethers.[223] Glucose derived aromatic aldehydes undergo diastereoselective reactions with Danishefsky's diene yielding a 9:1 mixture of isomers.[224] Fishwick has published on the highly *exo* selective hetero Diels–Alder reactions of homochiral 2-(*N*-acylamino)-1-thia-1,3-dienes, allowing access to optically pure thiopyrans (**Scheme 128**).[225] An enantioselective approach to pyrrolidines relies on Lewis acid catalysed reaction between a homochiral vinyl ether derived from (*R*)-2,2-di-



Scheme 126

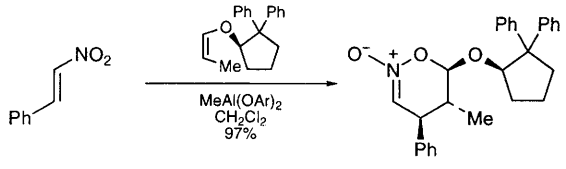


Scheme 127

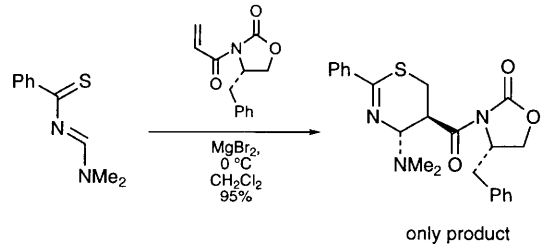


Scheme 128

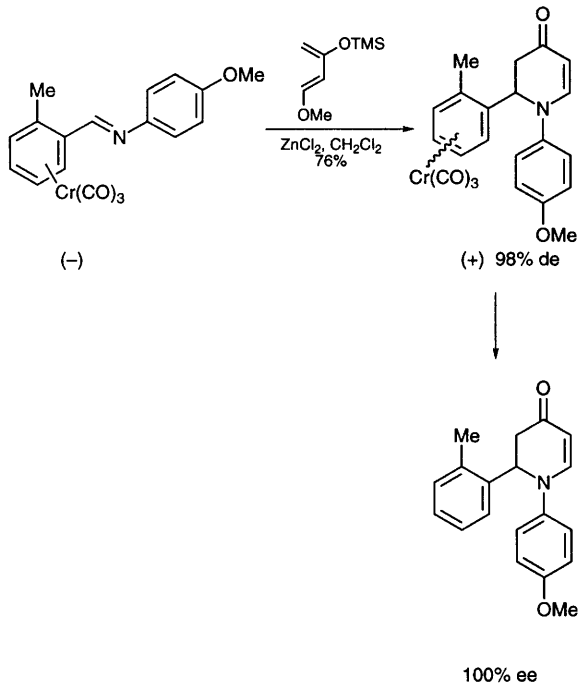
phenylcyclopentanol and nitroalkenes (**Scheme 129**). The resulting cyclic nitronates are transformed readily to the pyrrolidines.[226] A synthetic route to homochiral pipecolic acid derivatives involving an asymmetric aza Diels–Alder reaction between a camphorsulfonyl derived imine and Danishefsky's diene unfortunately only proceeds with low diastereoselection.[227] A D-glucose derived imine undergoes diastereoselective reaction with Danishefsky's diene to yield a 9:1 mixture of piperidones, the major isomer being taken through to a quinolizidine analogue of castanospermine.[228] An approach to homochiral 5,6-dihydro-1,3-thiazines involving a thioacyl amidine and a homochiral olefin under magnesium bromide catalysis proceeded with complete diastereocontrol (**Scheme 130**). After removal of the chiral auxiliary using LiOBn, the optically pure benzyl ester was isolated.[229] The use of chiral copper(II) complexes and a striking effect of polar solvents such as nitromethane in the asymmetric hetero Diels–Alder reaction between glyoxylic esters and dienes has been investigated.[230,231] Enantiomeric excessess are high but there is a major problem with a competing ene reaction pathway. A modified binaphthol titanium complex also catalyses these reactions in an asymmetric fashion.[232] Homochiral yttrium bis(trifluoromethanesulfonamide)s have been used as catalysts in reactions between glyoxylic esters and Danishefsky's diene. Enantiomeric excesses are only moderate.[233] A catalyst prepared from (*R*)-BINOL [(*R*)-1,1′-bi(2-naphthol)] and titanium(IV) isopropoxide allows enantioselective preparation of pyranones from aldehydes and Danishefsky's diene (ees up to 97%).[234] Several groups have successfully used chiral chromium tricarbonyl complexes of subsituted benzaldehyde imines in Lewis acid catalysed aza Diels–Alder reactions with Danishefsky's diene.[235,236] These reactions occur with excellent diastereomeric excess (**Scheme 131**).



Scheme 129



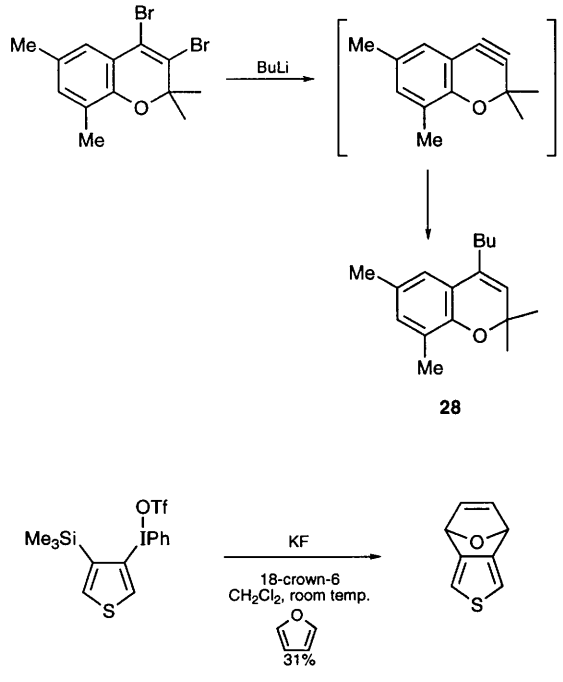
Scheme 130



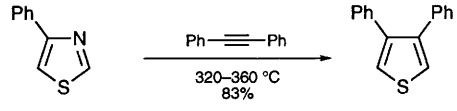
Scheme 131

4.13 Miscellaneous

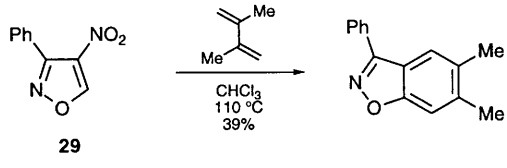
Treatment of a dibromobenzopyran with butyllithium leads to **28**, presumably *via* the 3,4-didehydro-2*H*-1-benzopyran.[237] This can actually be trapped by furans in a [4+2]-sense. The hetaryne 3,4-didehydrothiophene has also been generated and characterised by identification of [4+2]-adducts with a variety of dienes (**Scheme 132**).[238] The same workers have prepared 3,4-disubstituted thiophenes by a cycloaddition–reversion sequence involving thiazoles and alkynes at very high temperature (**Scheme 133**).[239] The nitroisoxazole **29** acts as an equivalent of the hetaryne in Diels–Alder reactions as the nitro group can either be eliminated thermally or by base (**Scheme 134**).[240] New methods for the generation of 2,3-pyridyne have recently been disclosed.[241] The first intramolecular cycloaddition of a benzyne with an acyclic diene has been reported[242] and then extended to a synthesis of pseudopterosin A and E aglycone (**Scheme 135**).[243] A novel alkyne, 1-(phenylseleno)-2-(4-tolylsulfonyl)-ethyne, has been used as a ketene equivalent in cycloadditions with dienes.[244] Aggarwal has introduced a chiral ketene equivalent **30**.[245] Intramolecular activation of the sulfone **31** by boron trifluoride transforms an unreactive dienophile into a reactive one, giving a mixture of two adducts with cyclopentadiene.[246] This is thought to occur *via* the oxosulfonium ion **32**. *N*-Allyl lactams and enamides undergo Diels–Alder reactions with cyclopentadiene, but only after iodine mediated activation.[247] The reaction pathway is thought to involve a reactive iminium species, generated by iodolactonisation (**Scheme 136**). Similarly, the acrylate ester **33**, unreactive itself, is activated by replacement of ethyl by pentafluorophenyl as in **34**, allowing Diels–Alder reactions to occur.[248] Ultrasonic irradiation has been shown to enhance yield and stereoselectivity, but apparently only in halogenated solvents.[249] Micro-



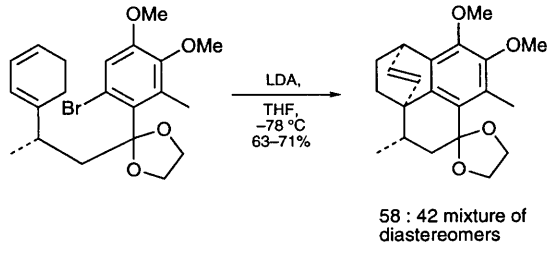
Scheme 132



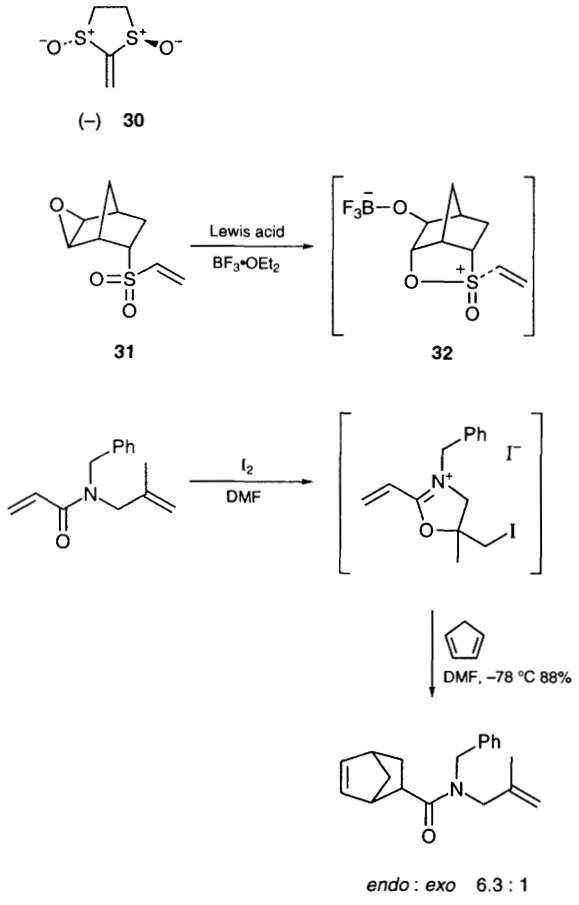
Scheme 133



Scheme 134



Scheme 135

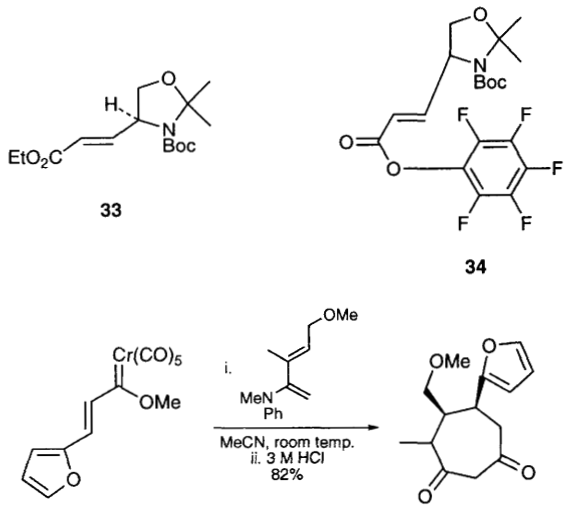


Scheme 136

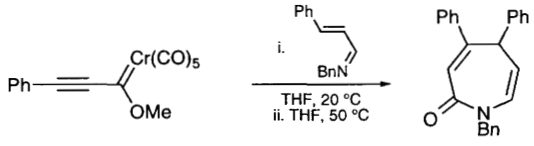
wave irradiation enhances the rate of an intramolecular Diels–Alder appraoch to compactin.[250] Enzymatic catalysis can also assist, with a crude preparation from *Alternaria solani* allowing conversion of prosolonapyrone III to the *exo* [4+2]-adduct solanapyrone A.[251] This product was assessed as having 92% optical purity by HPLC. Enantioselective catalysis is also provided by anti-metallocene antibodies.[252] Haptens produced from a ferrocene dicarboxylic acid were conjugated to keyhole limpet haemocyanin and bovine serum albumin. Monoclonal antibodies were obtained from mice under standard procedures. In a reaction between 4-carboxybenzyl *trans*-1,3-butadiene-1-carbamate and *N*,*N*-dimethylacrylamide, antibody 4D5 allowed access to a single enantiomer of the *ortho endo* adduct (95% ee), whilst antibody 13D5 allowed access to a single enantiomer of the *ortho exo* adduct (95% ee). Antibodies can also catalyse the hetero Diels–Alder reaction, in this instance a reaction between piperylene and a nitroso dienophile.[253]

5 [4+3]-Cycloadditions

Barluenga's group have used [4+3]-cycloadditions between vinyl Fischer carbene complexes and aminobutadienes and azadienes as a synthetic route to cycloheptanediones[254] and azepines[255] respectively

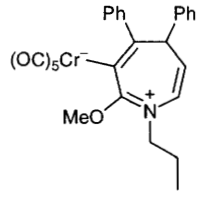


Scheme 137

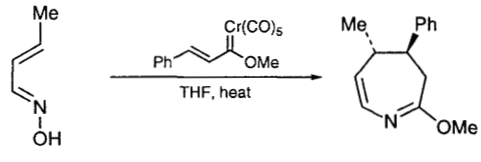


Scheme 138

(**Schemes 137**, **138**). The methodology can also utilise α,β-unsaturated oximes as the diene component and alkynyl Fischer carbene complexes as the three atom moiety (**Scheme 139**).[256] NMR Studies suggest an ionic mechanism is in operation, proceeding *via* nucleophilic addition of the imine nitrogen to the carbene. Additional evidence for this pathway is provided by an X-ray crystal structure elucidation of a chromium bearing zwitterionic intermediate **35**.[255] The reaction can also be conducted using chiral, non-racemic carbene complexes. Although the diastereomeric excesses were only moderate (*ca.* 40%), the major diaster-

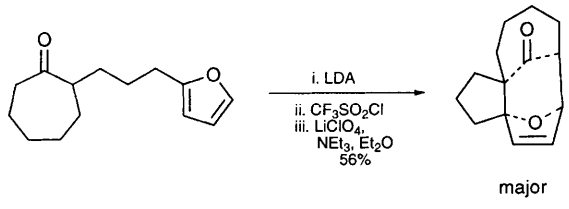


35

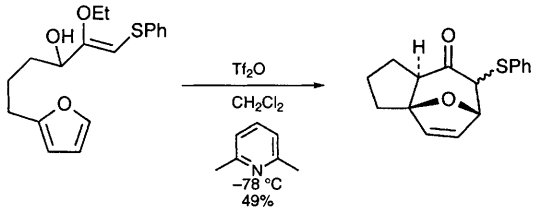


Scheme 139

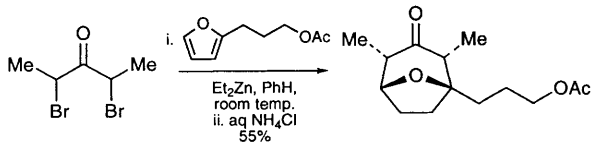
eomer crystallised out in each case, allowing isolation of enantiomerically pure azepines. In the carbocyclic series, the use of a prolinol derived aminobutadiene allowed access to trisubstituted cycloheptane-1,3-diones in moderate to high enantiomeric excess.[254] The research of Harmata's group in this area has focused on intramolecular [4+3]-cycloadditions involving trapping of furan by oxyallyl cations.[257] One example involved a brief route to the ABC ring framework of the ingenane diterpene family, utilising an α-chloro ketone as the oxyallyl cation precursor (**Scheme 140**).[258] Vinylthionium ions generated from alkoxy substituted allylic sulfones or sulfoxides and from phenylthio substituted allylic alcohols also serve as useful precursors (**Scheme 141**).[259] Hardinger has reported on the use of bis(sulfonyl) ketones as a new source for oxyallyl cations, with a number of iron and cobalt carbonyl complexes proving suitable for the conversion of the precursor to the reactive intermediate.[260] Dibromo ketones can be reacted with diethylzinc, the oxyallyl cation thus generated being trapped by various substituted furans (**Scheme 142**).[261] In an approach to [5.7]-fused bicyclic structures, Lautens has utilised intermolecular reactions of furans with oxyallyl cations generated from polybromo ketones and a zinc–silver couple.[262] The presence of additional functionality in the oxyallyl cation has been of interest to Walters who reports on the first nitrogen substituted oxyallyl cation [4+3]-cycloadditions (**Scheme 143**).[263] Cha has had



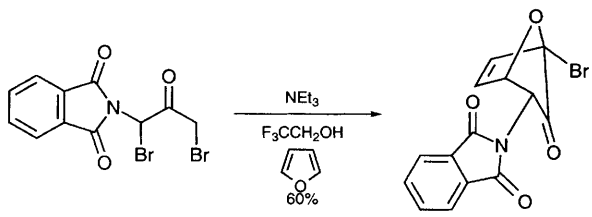
Scheme 140



Scheme 141



Scheme 142



Scheme 143

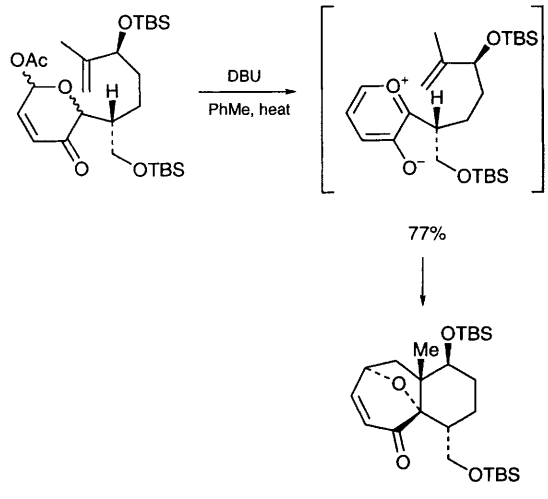
an interest in a number of aspects of the [4+3]-cycloaddition, describing work directed towards *cis*-2,8-disubstituted oxocanes and in reactions of cyclic oxyallyl cations with cyclic 1,3-dienes.[264,265] Cha generates his oxyallyl cations either using the Fohlisch protocol from the α-chloro ketone or by the Schmid procedure from the α′-chloroenamine.

6 [4+4]-Cycloadditions

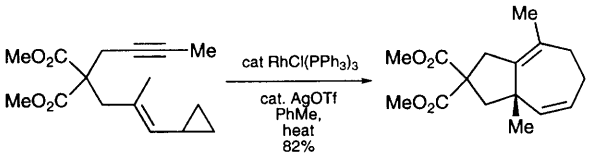
Sieburth reports that *N*-butyl-2-pyridone reacts under photochemical irradiation with 4-methoxy-2-pyridone to yield a variety of [4+4]-products, including the *trans* cross product and photodimer.[266] The *cis* isomers of each of these are formed as minor components. The formation of the dimer of the *N*-butyl-2-pyridone can be minimised by increasing the concentration of the other component. The [4+4]-cycloaddition area has been the subject of a recent review.[10]

7 [5+2]-Cycloadditions

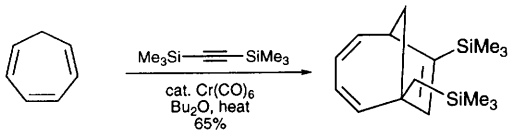
Magnus and co-workers have recently described a novel approach to a BC-ring fragment of Taxol using an intramolecular [5+2]-cycloaddition of a pyrylium ylide (**Scheme 144**).[267] The use of transition metal catalysis in the intramolecular cycloaddition of vinyl cyclopropanes with alkynes has provided a homologue of the Diels–Alder reaction, allowing access to seven membered rings (**Scheme 145**).[268]



Scheme 144



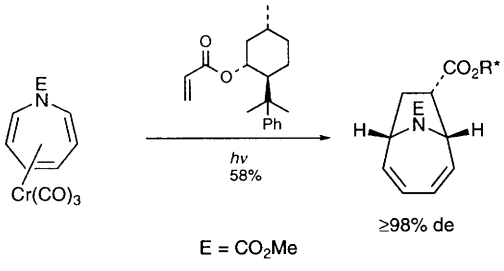
Scheme 145



Scheme 146

8 [6+2]-Cycloadditions

Rigby's group have been particularly active in this area, using both thermally and photochemically activated cycloadditions of chromium(0) complexes of trienes or azepines with alkenes.[269–271] Alkynes can also be used as the 2π partner (**Scheme 146**).[272] Asymmetric induction is possible with a successful route to the tropane alkaloid (+)-ferruginine having been achieved.[273] The key step involved reaction between tricarbonyl [*N*-(methoxycarbonyl)-azepine]chromium(0) and (−)-8-phenylmenthyl acrylate to provide the desired diastereomerically homogeneous homotropane *endo* adduct as the major product (**Scheme 147**). Regioselective thallium (III) mediated ring contraction then furnished an optically pure tropane suitable for further elaboration.



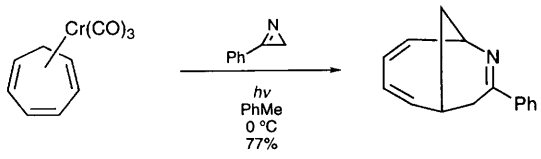
Scheme 147

9 [6+3]-Cycloadditions

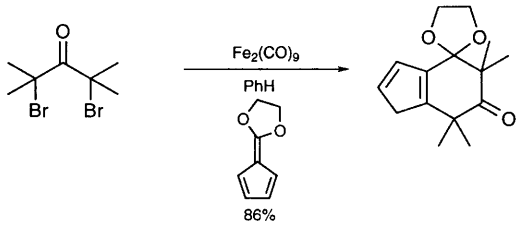
Irradiation of the tricarbonyl chromium(0) complex of cyclohepatriene in the presence of an azirine yields bicyclic imine [6+3]-cycloadducts (**Scheme 148**).[274] Reaction of a fulvene ketene acetal with oxyallyl cations, generated from α,α'-dibromo ketones using diiron nonacarbonyl, provides highly substituted indan ring systems (**Scheme 149**).[275]

10 [6+4]-Cycloadditions

Intermolecular photochemically activated cycloadditions of cycloheptatriene tricarbonyl chromium(0)

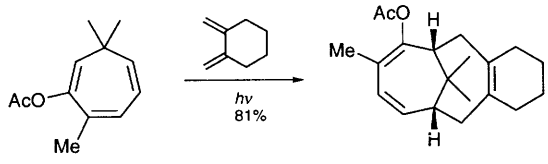


Scheme 148

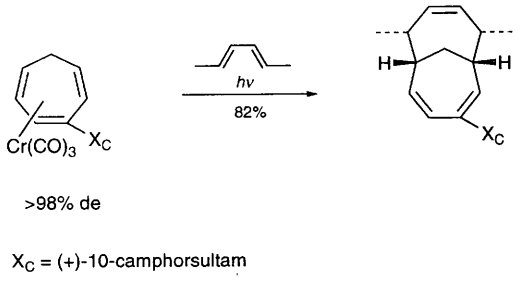


Scheme 149

complexes with 1,3-dienes yields products suitable for synthetic approaches to the diterpenes ingenol, phorbol and Taxol (**Scheme 150**).[276] It has proved possible to form a single diastereomer of the tricarbonylchromium(0) complex of a (+)-camphorsultam derived cycloheptatriene (**Scheme 151**).[270] Photocyclisation of this with hexa-2,4-diene followed by removal of the auxiliary gave an enantiomerically pure enone. Interestingly, both (+)-isopinocampheol and (−)-8-phenylmenthol derived cycloheptatrienes yielded mixtures of diastereomeric tricarbonyl chromium(0) complexes. Both metal assisted and metal free intramolecular [6+4]-cycloadditions have been reported, allowing rapid access to complex polycyclic frameworks.[277] The thermal reactions proceed to yield *exo* adducts, whereas the reactions of the trienylchromium(0) complexes



Scheme 150

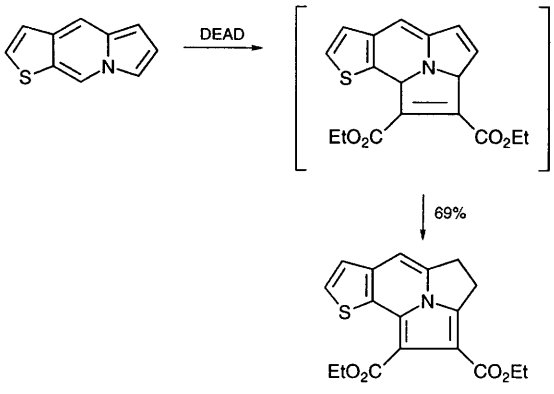


Scheme 151

provide *endo* adducts. The effect of high pressure on the palladium catalysed cycloadditions of unsymmetrical trimethylenemethanes to tropones has been investigated by Trost, finding that the regioselectivity of addition could be reversed at 15 kbar.[278] Fulvene ketene acetals react with α-pyrones to give [6+4]-adducts which undergo cheletropic extrusion of carbon dioxide to provide azulenols.[279] Fulvenes are also reported to react with mesoionic compounds.[280]

11 [8+2]-Cycloadditions

Reaction of thieno[2,3-*f*]indolizine and thieno[3,2-*f*]indolizine with diethyl acetylenedicarboxylate has been reported to provide the respective [8+2]-adducts (**Scheme 152**).[281]



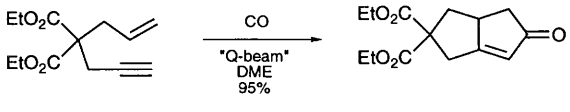
Scheme 152

12 [10+2]-Cycloadditions

Tropothione *S*-sulfide reportedly undergoes a [10+2]-cycloaddition with dimethyl acetylenedicarboxylate (DMAD).[282]

13 [2+2+1]-Cycloadditions

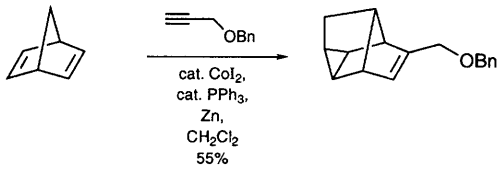
Light initiated Pauson–Khand reactions have been described by Livinghouse.[283] The important advantage in this chemistry is that the reaction is one of the first successful Pauson–Khand reactions using catalytic quantities of cobalt octacarbonyl. The method apparently has advantages over existing procedures in that only one atmosphere of carbon monoxide is required and the reaction can be conducted at room temperature (**Scheme 153**).



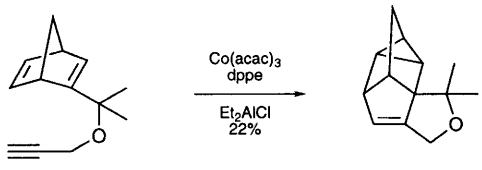
Scheme 153

14 [2+2+2]-Cycloadditions

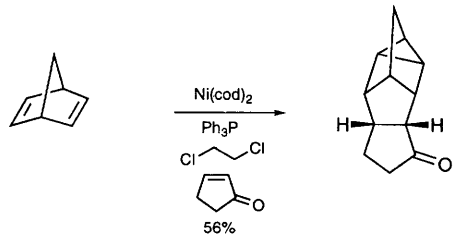
A route to deltacyclenes using a catalytic cobalt(II) iodide–zinc [2+2+2]-cycloaddition strategy has been described by Buono (**Scheme 154**).[284] This can be conducted in an enantioselective fashion using a phosphorus ligand derived from (*S*)-valinol. Lautens has also investigated the asymmetric approach, as well as an intramolecular [2+2+2]-reaction in a racemic sense (**Scheme 155**).[285] The use of nickel(0) catalysts for the reaction has also been demonstrated to be successful (**Scheme 156**).[286]



Scheme 154



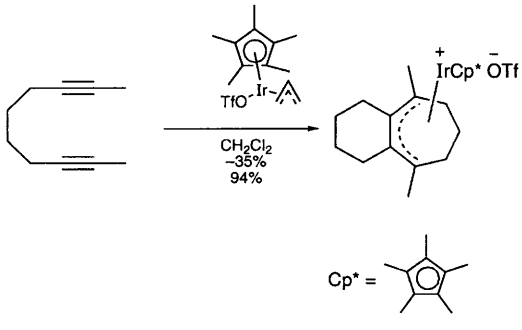
Scheme 155



Scheme 156

15 [3+2+2]-Cycloadditions

Transition metal mediated cycloaddition between a η^3-allyl species and two alkynes provides η^5-cycloheptadienyl complexes, thus providing a new seven membered ring synthesis (**Scheme 157**).[287] The



Scheme 157

reaction is thought to proceed *via* an initial coupling of the alkyne and allyl ligands to yield an unsaturated σ, π-vinyl olefin complex. This then undergoes coordination and insertion of the second alkyne followed by a series of rearrangements that eventually yield the observed product.

References

1 P. G. Sammes and D. J. Weller, *Synthesis*, 1995, 1205.
2 B. M. Trost, *Angew. Chem., Int. Ed. Engl.*, 1995, **34**, 259.
3 J. Sepúlveda-Arques, B. Abarca-González and M. Medio-Simón, *Adv. Heterocycl. Chem.*, 1995, **63**, 339.
4 S. Blechert, R. Knier, H. Schroers and T. Wirth, *Synthesis*, 1995, 592.
5 M. Lautens, W. Klute and W. Tam, *Chem. Rev.*, 1996, **96**, 49.
6 L. F. Tietze, *Chem. Rev.*, 1996, **96**, 115.
7 S. E. Denmark and A. Thorarensen, *Chem. Rev.*, 1996, **96**, 137.
8 J. D. Winkler, *Chem. Rev.*, 1996, **96**, 167.
9 C. Kibayashi and S. Aoyagi, *Synlett*, 1995, 873.
10 S. M. Sieburth and N. T. Cunard, *Tetrahedron*, 1996, **52**, 6251.
11 K. I. Booker-Milburn and J. K. Cowell, *Tetrahedron Lett.*, 1996, **37**, 2177.
12 K. Langer and J. Mattay, *J. Org. Chem.*, 1995, **60**, 7256.
13 C. R. D. Correia, A. R. de Faria and E. S. Carvalho, *Tetrahedron Lett.*, 1995, **36**, 5109.
14 A. Padwa, M. Meske, S. S. Murphree, S. H. Watterson and Z. Ni, *J. Am. Chem. Soc.*, 1995, **117**, 7071.
15 J. D. Spence, L. E. Lowrie and M. H. Nantz, *Tetrahedron Lett.*, 1995, **36**, 5499.
16 C. L. Bradford, S. A. Fleming and S. C. Ward, *Tetrahedron Lett.*, 1995, **36**, 4189.
17 A. Tenaglia and D. Barillé, *Synlett*, 1995, 776.
18 A. Pommier, J.-M. Pons and P. J. Kocienski, *J. Org. Chem.*, 1995, **60**, 7334.
19 B. W. Dymock, P. J. Kocienski and J.-M. Pons, *Chem. Commun.*, 1996. 1053.
20 R. Zemribo and D. Romo, *Tetrahedron Lett.*, 1995, **36**, 4159.
21 A. I. Meyers, M. A. Tschantz and G. P. Brengel, *J. Org. Chem.*, 1995, **60**, 4359.
22 F. Toda, H. Miyamoto and S. Kikuchi, *J. Chem. Soc., Chem. Commun.*, 1995, 621.
23 M. Burwood, B. Davies, I. Diaz, R. Grigg, P. Molina, V. Sridharan and M. Hughes, *Tetrahedron Lett.*, 1995, **36**, 9053.
24 C. Wittland, M. Arend and N. Risch, *Synthesis*, 1996, 367.
25 C. W. G. Fishwick, R. J. Foster and R. E. Carr, *Tetrahedron Lett.*, 1996, **37**, 711.
26 U. C. Yoon, D. U. Kim, C. W. Lee, Y. S. Choi, Y.-J. Lee, H. L. Ammon and P. S. Mariano, *J. Am. Chem. Soc.*, 1995, **117**, 2698.
27 U. C. Yoon, S. J. Cho, Y.-J. Lee, M. L. Mancheno and P. S. Mariano, *J. Org. Chem.*, 1995, **60**, 2353.
28 M. E. Flanagan and R. M. Williams, *J. Org. Chem.*, 1995, **60**, 6791.
29 J. Gonzalez, J. I. Koontz, L. M. Hodges, K. R. Nilsson, L. K. Neely, W. H. Myers, M. Sabat and W. D. Harman, *J. Am. Chem. Soc.*, 1995, **117**, 3405.
30 S. G. Pyne, J. Safaei-G. and F. Koller, *Tetrahedron Lett.*, 1995, **36**, 2511.
31 H. Waldemann, E. Bläser, M. Jansen and H.-P. Letschert, *Chem. Eur. J.*, 1995, **1**, 150.
32 G. Galley, J. Liebscher and M. Pätzel, *J. Org. Chem.*, 1995, **60**, 5005.
33 D. A. Barr, M. J. Dorrity, R. Grigg, S. Hargreaves, J. F. Malone, J. Montgomery, J. Redpath, P. Stevenson and M. Thornton-Pett, *Tetrahedron*, 1995, **51**, 273.
34 R. Grigg, V. Sridharan, S. Suganthan and A. W. Bridge, *Tetrahedron*, 1995, **51**, 295.
35 D. M. Cooper, R. Grigg, S. Hargreaves, P. Kennewell and J. Redpath, *Tetrahedron*, 1995, **51**, 7791.
36 H. G. Aurich and H. Köster, *Tetrahedron*, 1995, **51**, 6285.
37 K. S. Chan, M. L. Yeung, W. Chan, R.-J. Wang and T. C. W. Mak, *J. Org. Chem.*, 1995, **60**, 1741.
38 M. Gotoh, T. Mizui, B. Sun, K. Hirayama and M. Noguchi, *J. Chem. Soc., Perkin. Trans. 1*, 1995, 1857.
39 M. Gotoh, B. Sun, K. Hirayama and M. Noguchi, *Tetrahedron*, 1996, **52**, 887.
40 A. Padwa, M. Meske and Z. Ni, *Tetrahedron*, 1995, **51**, 89.
41 A. D. Reed and L. S. Hegedus, *J. Org. Chem.*, 1995, **60**, 3787.
42 N. Langlois, N. V. Bac, N. Dahuron, J.-M. Delcroix, A. Deyine, D. Griffart-Brunet, A. Chiaroni and C. Riche, *Tetrahedron*, 1995, **51**, 3571.
43 S. Cicchi, A. Goti and A. Brandi, *J. Org. Chem.*, 1995, **60**, 4743.
44 P. de March, M. Figueredo, J. Font, T. Gallagher and S. Milán, *J. Chem. Soc., Chem. Commun.*, 1995, 2097.
45 L. A. G. M. van den Broek, *Tetrahedron*, 1996, **52**, 4467.
46 N. Katagiri, M. Okada, C. Kaneko and T. Furuya, *Tetrahedron Lett.*, 1996, **37**, 1801.
47 M. Frederickson, R. Grigg, Z. Rankovic, M. Thornton-Pett, J. Redpath and R. Crossley, *Tetrahedron*, 1995, **51**,, 6835.
48 O. Tamura, T. Okabe, T. Yamaguchi, K. Gotanda, K. Noe and M. Sakamoto, *Tetrahedron*, 1995, **51**, 107.
49 O. Tamura, T. Okabe, T. Yamaguchi, J. Kotani, K. Gotanda and M. Sakamoto, *Tetrahedron*, 1995, **51**, 119.
50 H. G. Aurich and F. Biesemeier, *Synthesis*, 1995, 1171.
51 R. Neidlein and S. Li, *Synth. Commun.*, 1995, **25**, 2379.
52 F. Fariña, M. T. Fraile, M. R. Martín, M. V. Martín and A. M. de Guereñu, *Heterocycles*, 1995, **40**, 285.
53 S. Dare, B. Ducroix, S. Bernard and K. M. Nicholas, *Tetrahedron Lett.*, 1996, **37**, 4341.
54 L. Alcaraz, J. J. Harnett, C. Mioskowski, T. Le Gall, D.-S. Shin and J. R. Falck, *J. Org. Chem.*, 1995, **60**, 7209.
55 A. T. Hewson, J. Jeffery and N. Szczur, *Tetrahedron Lett.*, 1995, **36**, 7731.
56 C. W. Holzapfel and T. L. van der Merwe, *Tetrahedron Lett.*, 1996, **37**, 2303.
57 C. W. Holzapfel and T. L. van der Merwe, *Tetrahedron Lett.*, 1996, **37**, 2307.
58 B. M. Trost, J. R. Parquette and C. Nübling, *Tetrahedron Lett.*, 1995, **36**, 2917.
59 R. T. Lewis, W. B. Motherwell, M. Shipman, A. M. Z. Slawin and D. J. Williams, *Tetrahedron*, 1995, **51**, 3289.
60 H. Corlay, R. T. Lewis, W. B. Motherwell and M. Shipman, *Tetrahedron*, 1995, **51**, 3303.
61 H. Corlay, W. B. Motherwell, A. M. K. Pennell, M. Shipman, A. M. Z. Slawin, D. J. Williams, P. Binger and M. Stepp, *Tetrahedron*, 1996, **52**, 4883.

62 Y. Takemoto, S. Furuse, H. Koike, T. Ohra, C. Iwata and H. Ohishi, *Tetrahedron Lett.*, 1995, **36**, 4085.
63 A. Padwa, D. J. Austin, A. T. Price and M. D. Weingarten, *Tetrahedron*, 1996, **52**, 3247.
64 J. P. Marino, M. H. Osterhout and A. Padwa, *J. Org. Chem.*, 1995, **60**, 2704.
65 B. Santiago, C. R. Dalton, E. W. Huber and J. M. Kane, *J. Org. Chem.*, 1995, **60**, 4947.
66 E. A. Curtis, V. P. Sandanayaka and A. Padwa, *Tetrahedron Lett.*, 1995, **36**, 1989.
67 A. Padwa, E. A. Curtis and V. P. Sandanayaka, *J. Org. Chem.*, 1996, **61**, 73.
68 A. Padwa and A. T. Price, *J. Org. Chem.*, 1995, **60**, 6258.
69 A. Padwa, J. M. Kassir, M. A. Semones and M. D. Weingarten, *J. Org. Chem.*, 1995, **60**, 53.
70 A. Padwa, A. T. Price and L. Zhi, *J. Org. Chem.*, 1996, **61**, 2283.
71 M. Aono, Y. Terao and K. Achiwa, *Heterocycles*, 1995, **40**, 249.
72 S. Barbey and J. Mann, *Synlett*, 1995, 27.
73 C.-A. Harrison, R. Leineweber, C. J. Moody and J. M. J. Williams, *J. Chem. Soc., Perkin. Trans. 1*, 1995, 1127.
74 K. M. K. Domon, K. Tanino and I. Kuwajima, *Synlett*, 1996, 157.
75 B. L. Flynn, F. J. Funke, C. C. Silveira and A. de Meijere, *Synlett*, 1995, 1007.
76 A. G. Meyer and R. Aumann, *Synlett*, 1995, 1011.
77 R. Neidlein, S. Gürtler and C. Krieger, *Synthesis*, 1995, 1389.
78 S. M. Rubenstein and R. M. Williams, *J. Org. Chem.*, 1995, **60**, 7215.
79 I. J. Kim, T. K. Park and S. J. Danishefsky, *Tetrahedron Lett.*, 1995, **36**, 1015.
80 T. K. Park, I. J. Kim, S. J. Danishefsky and S. de Gala, *Tetrahedron Lett.*, 1995, **36**, 1019.
81 M. Hatanaka, F. Ueno and I. Ueda, *Tetrahedron Lett.*, 1996, **37**, 89.
82 D. J. Hart and W.-L. Wu, *J. Am. Chem. Soc.*, 1995, **117**, 9369.
83 M. E. Kuehne, C. S. Brook, D. A. Frasier and F. Xu, *J. Org. Chem.*, 1995, **60**, 1864.
84 M. Ihara, A. Katsumata, M. Egashira, S. Suzuki, Y. Tokunaga and K. Fukumoto, *J. Org. Chem.*, 1995, **60**, 5560.
85 N. Kanoh, J. Ishihara and A. Murai, *Synlett*, 1995, 895.
86 D. Pérez, G. Burés, E. Guitián and L. Castedo, *J. Org. Chem.*, 1996, **61**, 1650.
87 O. Hoshino, M. Ishizaki, K. Kamei, M. Taguchi, T. Nagao, K. Iwaoka, S. Sawaki, B. Umezawa and Y, Iitaka, *J. Chem. Soc., Perkin. Trans. 1*, 1996, 571.
88 P. L. Kotian and F. I. Carroll, *Synth. Commun.*, 1995, **25**, 63.
89 T. Matsumoto, T. Sohma, H. Yamaguchi, S. Kurata and K. Suzuki, *Tetrahedron*, 1995, **51**, 7347.
90 D. S. Larsen and M. D. O'Shea, *J. Chem. Soc., Perkin. Trans. 1*, 1995, 1019.
91 K. T. Potts, T. Rochanapruk, A. Padwa, S. J. Coats and L. Hadjiarapoglou, *J. Org. Chem.*, 1995, **60**, 3795.
92 A. Padwa and M. A. Semones, *Tetrahedron Lett.*, 1996, **37**, 335.
93 A. Padwa, S. J. Coats, S. R. Harring, L. Hadjiarapoglou and M. A. Semones, *Synthesis*, 1995, 973.
94 D. F. Harvey and E. M. Grenzer, *J. Org. Chem.*, 1996, **61**, 159.
95 P. A. Wender and T. E. Smith, *J. Org. Chem.*, 1995, **60**, 2962.
96 P. A. Wender and T. E. Smith, *J. Org. Chem.*, 1996, **61**, 824.
97 P. A. Wender, T. E. Jenkins and S. Suzuki, *J. Am. Chem. Soc.*, 1995, **117**, 1843.
98 T. Takahashi, M. Kotora and Z. Xi, *J. Chem. Soc., Chem. Commun.*, 1995, 361.
99 M. W. Wright and M. E. Welker, *J. Org. Chem.*, 1996, **61**, 133.
100 M. Tada, N. Mutoh and T. Shimizu, *J. Org. Chem.*, 1995, **60**, 550.
101 J. Barluenga, F. Aznar and S. Barluenga, *J. Chem. Soc., Chem. Commun.*, 1995, 1973.
102 L.-H. Shiu, H.-K. Shu, D.-H. Cheng, S.-L. Wang and R.-S. Liu, *Chem. Commun.*, 1996, 1041.
103 D. A. Singelton and Y.-K. Lee, *Tetrahedron Lett.*, 1995, **36**, 3473.
104 S. Otto and J. B. F. N. Engberts, *Tetrahedron Lett.*, 1995, **36**, 2645.
105 M. Ayerbe and F. P. Cossío, *Tetrahedron Lett.*, 1995, **36**, 4447.
106 N. E. Heard and J. Turner, *J. Org. Chem.*, 1995, **60**, 4302.
107 T. Mukaiyama, K. Watanabe and I. Shiina, *Chem. Lett.*, 1995, 1.
108 J. C. Carretero, J. L. G. Ruano and L. M. M. Cabrejas, *Tetrahedron*, 1995, **51**, 8323.
109 Y. Arai, T. Masuda, Y. Masaki and M. Shiro, *J. Chem. Soc., Perkin. Trans. 1*, 1996, 759.
110 T.-K. Yang, C.-J. Chen, D.-S. Lee, T.-T. Jong, Y.-Z. Jiang and A.-Q. Mi, *Tetrahedron: Asymmetry*, 1996, **7**, 57.
111 D. Craig, N. J. Geach, C. J. Pearson, A. M. Z. Slawin, A. J. P. White and D. J. Williams, *Tetrahedron*, 1995, **51**, 6071.
112 R. H. Schlessinger and C. P. Bergstrom, *J. Org. Chem.*, 1995, **60**, 16.
113 R. H. Schlessinger, X.-H. Wu and T. R. R. Pettus, *Synlett*, 1995, 536.
114 M. P. Sibi, P. K. Deshpande and J. Ji, *Tetrahedron Lett.*, 1995, *36*, 8965.
115 I. W. Davies, C. H. Senanayake, L. Castonguay, R. D. Larsen, T. R. Verhoeven and P. J. Reider, *Tetrahedron Lett.*, 1995, **36**, 7619.
116 J. Barluenga, M. Tomás, A. Suárez-Sobrino and L. A. López, *J. Chem. Soc., Chem. Commun.*, 1995, 1785.
117 T. Akiyama, N. Horiguchi, T. Ida and S. Ozaki, *Chem. Lett.*, 1995, 975.
118 I. Kadota, T. Kobayashi, N. Asao and Y. Yamamoto, *J. Chem. Soc., Chem. Commun.*, 1995, 1271.
119 M. Yamauchi, Y. Honda, N. Matsuki, T. Watanabe, K. Date and H. Hiramatsu, *J. Org. Chem.*, 1996, **61**, 2719.
120 I. Ikeda, K. Honda, E. Osawa, M. Shiro, M. Aso and K. Kanematsu, *J. Org. Chem.*, 1996, **61**, 2031.
121 R. M. Ortuño, J. Ibarzo, J. d'Angelo, F. Dumas, A. Alvarez-Larena and J. F. Piniella, *Tetrahedron: Asymmetry*, 1996, **7**, 127.
122 C. Cativiela, J. I. Garcia, J. A. Mayoral, E. Pires, A. J. Roya and F. Figueras, *Tetrahedron*, 1995, **51**, 1295.
123 E. Buñuel, C. Cativiela and M. D. Diaz-de-Villegas, *Tetrahedron*, 1995, **51**, 8923.
124 A. Avenoza, C. Cativiela, M. Paris and J. M. Peregrina, *Tetrahedron*, 1996, **52**, 4839.
125 T. K. M. Shing, H.-F. Chow and I. H. F. Chung, *Tetrahedron Lett.*, 1996, **37**, 3713.
126 J. A. Serrano, L. E. Cáceres and E. Román, *J. Chem. Soc., Perkin. Trans. 1*, 1995, 1863.
127 C. Taillefumier, Y. Chapleur, D. Bayeul and A. Aubry, *J. Chem. Soc., Chem. Commun.*, 1995, 937.
128 D. Seebach, R. Dahinden, R. E. Marti, A.K. Beck, D. A. Plattner and F. N. M. Kühnle, *J. Org. Chem.*, 1995, **60**, 1788.

129 I. Yamamoto and K. Narasaka, *Chem. Lett.*, 1995, 1129.
130 K. V. Gothelf and K. A. Jørgensen, *J. Org. Chem.*, 1995, **60**, 6847.
131 K. V. Gothelf, R. G. Hazell and K. A. Jørgensen, *J. Am. Chem. Soc.*, 1995, **117**, 4435.
132 E. J. Corey and M. A. Letavic, *J. Am. Chem. Soc.*, 1995, **117**, 9616.
133 W. Odenkirk and B. Bosnich, *J. Chem. Soc., Chem. Commun.*, 1995, 1181.
134 T. Fujisawa, T. Ichiyanagi and M. Shimizu, *Tetrahedron Lett.*, 1995, **36**, 5031.
135 Y. Yamashita and T. Katsuki, *Synlett*, 1995, 829.
136 I. W. Davies, C. H. Senanayake, R. D. Larsen, T. R. Verhoeven and P. J. Reider, *Tetrahedron Lett.*, 1996, **37**, 1725.
137 K. Kamahori, S. Tada, K. Ito and S. Itsuno, *Tetrahedron: Asymmetry*, 1995, **6**, 2547.
138 H. Weinmann and E. Winterfeldt, *Synthesis*, 1996, 357.
139 C. Born, D. Meibom and E. Winterfeldt, *Chem. Commun.*, 1996, 887.
140 D. B. Gorman and P. G. Gassman, *J. Org. Chem.*, 1995, **60**, 977.
141 T. Sammakia and M. A. Berliner, *J. Org. Chem.*, 1995, **60**, 6652.
142 P. A. Grieco, J. L. Collins and S. T. Handy, *Synlett*, 1995, 1155.
143 P. Wipf and W. Xu, *Tetrahedron*, 1995, **51**, 4551.
144 M. Schmittel and C. Wöhrle, *J. Org. Chem.*, 1995, **60**, 8223.
145 M. V. B. Rao, J. Satyanarayana, H. Ila and H. Junjappa, *Tetrahedron Lett*, 1995, **36**, 3385.
146 H. Okamura, T. Iwagawa and M. Nakatani, *Tetrahedron Lett.*, 1995, **36**, 5939.
147 W. Han, Y. Lu, H. Zhao, M. Dutt and E. R. Biehl, *Synthesis*, 1996, 59.
148 M. D. Shair, T. Yoon and S. J. Danishefsky, *Angew. Chem., Int. Ed. Engl.*, 1995, **34**, 1721.
149 D. G. Hall, R. Müller and P. Deslongchamps, *Can. J. Chem.*, 1995, **73**, 1675.
150 D. G. Hall, R. Müller and P. Deslongchamps, *Can. J. Chem.*, 1995, **73**, 1695.
151 D. G. Hall and P. Deslongchamps, *J. Org. Chem.*, 1995, **60**, 7796.
152 D. G. Hall,, A.-S. Caillé, M. Drouin, S. Lamothe, R. Müller and P. Deslongchamps, *Synthesis*, 1995, 1081.
153 Y. L. Dory, P. Soucy, M. Drouin and P. Deslongchamps, *J. Am. Chem. Soc.*, 1995, **117**, 518.
154 T. K. M. Shing and J. Yang, *J. Org. Chem.*, 1995, **60**, 5785.
155 P. J. Ainsworth, D. Craig, J. C. Reader, A. M. Z. Slawin, A. J. P. White and D. J. Williams, *Tetrahedron*, 1996, **52**, 695.
156 D. Craig, M. J. Ford and J. A. Stones, *Tetrahedron Lett.*, 1996, **37**, 535.
157 R.-M. Chen, W.-W. Weng and T.-Y. Luh, *J. Org. Chem.*, 1995, **60**, 3272.
158 C. D. Dzierba, K. S. Zandi, T. Möllers and K. J. Shea, *J. Am. Chem. Soc.*, 1996, **118**, 4711.
159 G. H. Posner, C.-G. Cho, T. E. N. Anjeh, N. Johnson, R. L. Horst, T. Kobayashi, T. Okano and N. Tsugawa, *J. Org. Chem.*, 1995, **60**, 4617.
160 G. Stork and T. Y. Chan, *J. Am. Chem. Soc.*, 1995, **117**, 6595.
161 K. C. Nicolaou, J.-J. Liu, Z. Yang, H. Ueno, E. J. Sorensen, C. F. Claiborne, R. K. Guy, C.-K. Hwang, M. Nakada and P. G. Nantermet, *J. Am. Chem. Soc.*, 1995, **117**, 634.
162 J. D. Winkler, H. S. Kim and S. Kim, *Tetrahedron Lett.*, 1995, **36**, 687.
163 M. A. Brodney, J. P. O'Leary, J. A. Hansen and R. J. Giguere, *Synth. Commun.*, 1995, **25**, 521.
164 S. E. Denmark, A. Stolle, J. A. Dixon and V. Guagnano, *J. Am. Chem. Soc.*, 1995, **117**, 2100.
165 S. E. Denmark, M. E. Schnute, L. R. Marcin and A. Thorarensen, *J. Org. Chem.*, 1995, **60**, 3205.
166 M. Avalos, R. Babiano, P. Cintas, F. J. Higes, J. L. Jiménez, J. C. Palacios and M. A. Silva, *J. Org. Chem.*, 1996, **61**, 1880.
167 S. E. Denmark, A. Thorarensen and D. S. Middleton, *J. Org. Chem.*, 1995, **60**, 3574.
168 V. Nair and S. Kumar, *J. Chem. Soc., Perkin Trans. 1*, 1996, 443.
169 N. G. Andersen, S. P. Maddaford and B. A. Keay, *J. Org. Chem.*, 1996, **61**, 2885.
170 P. Cruciani, C. Aubert and M. Malacria, *Synlett*, 1996, 105.
171 E. Eru, G. E. Hawkes, J. H. P. Utley and P. B. Wyatt, *Tetrahedron*, 1995, **51**, 3033.
172 K. Chiba, J. Sonoyama and M. Tada, *J. Chem. Soc., Chem Commun.*, 1995, 1381.
173 M. Taing and H. W. Moore, *J. Org. Chem.*, 1996, **61**, 329.
174 D. E. Bogucki and J. L. Charlton, *J. Org. Chem.*, 1995, **60**, 588.
175 E. J. Bush and D. W. Jones, *J. Chem. Soc., Perkin Trans. 1*, 1996, 151.
176 E. P. Kündig, J. Leresche, L. Sauden and G. Bernardinelli, *Tetrahedron*, 1996, **52**, 7363.
177 M. Brands, H. G. Wey, R. Krömer, C. Krüger and H. Butenschön, *Liebigs Ann.*, 1995, 253.
178 A. Mayer, N. Rumpf and H. Meier, *Liebigs Ann.*, 1995, 2221.
179 H. Meier and A. Mayer, *Synthesis*, 1996, 327.
180 P. R. Carly, F. Compernolle and G. J. Hoornaert, *Tetrahedron Lett.*, 1995, **36**, 2113.
181 E. Ciganek and E. M. Schubert, *J. Org. Chem.*, 1995, **60**, 4629.
182 A. Jeevanandam and P. C. Srinivasan, *J. Chem. Soc., Perkin Trans. 1*, 1995, 663.
183 N. E. Alexandrou, G. E. Mertzanos, J. Stephanidou-Stephanatou, C. A. Tsoleridis and P. Zachariou, *Tetrahedron Lett.*, 1995, **36**, 6777.
184 L. A. White, P. M. O'Neill, B. K. Park and R. C. Storr, *Tetrahedron Lett.*, 1995, **36**, 5983.
185 L. A. White and R. C. Storr, *Tetrahedron*, 1996, **52**, 3117.
186 A. C. Tomé, J. A. S. Cavaleiro and R. C. Storr, *Tetrahedron*, 1996, **52**, 1735.
187 A. C. Tomé, J. A. S. Cavaleiro and R. C. Storr, *Tetrahedron*, 1996, **52**, 1723.
188 H.-H. Tso, H. Tsay and J.-H. Li, *Synth. Commun.*, 1995, **25**, 3435.
189 H.-H. Tso, N.-C. Yang and Y.-M. Chang, *J. Chem. Soc., Chem. Commun.*, 1995, 1349.
190 H.-H. Tso, Y.-M. Chang and H. Tsay, *Synth. Commun.*, 1996, **26**, 569.
191 H.-H. Tso and M. Chandrasekharam, *Tetrahedron Lett.*, 1996, **37**, 4189.
192 B. B. Snider and Q. Lu, *J. Org. Chem.*, 1996, **61**, 2839.
193 S. F. Martin, C. W. Clark and J. W. Corbett, *J. Org. Chem.*, 1995, **60**, 3236.
194 G. Desimoni, G. Faita and P. P. Righetti, *Tetrahedron Lett.*, 1995, **36**, 2855.
195 R. Sustmann and M. Felderhoff, *Heterocycles*, 1995, **40**, 1027.
196 A. P. Degnan, C. S. Kim, C. W. Stout and A. G. Kalivretenos, *J. Org. Chem.*, 1995, **60**, 7724.
197 R. Arnaud, P. Y. Chavant, K. Molvinger and Y. Vallée, *J. Chem. Soc., Chem. Commun.*, 1995, 1897.

198 D. Dubreuil, J. P. Pradère, N. Giraudeau, M. Goli and F. Tonnard, *Tetrahedron Lett.*, 1995, **36**, 237.
199 N. J. Sisti, I. A. Motorina, M.-E. Tran Huu Dau, C. Riche, F. W. Fowler and D. S. Grierson, *J. Org. Chem.*, 1996, **61**, 3715.
200 F. Palacios, I. Perez de Heredia and G. Rubiales, *J. Org. Chem.*, 1995, **60**, 2384.
201 S. Kobayashi, H. Ishitani and S. Nagayama, *Synthesis*, 1995, 1195.
202 Y. Makioka, T. Shindo, Y. Taniguchi, K. Takaki and Y. Fujiwara, *Synthesis*, 1995, 801.
203 A. Guzmán, M. Romero, F. X. Talamás, R. Villena, R. Greenhouse and J. M. Muchowski, *J. Org. Chem.*, 1996, **61**, 2470.
204 M. M. Blanco, M. A. Alonso, C. Avendaño and J. C. Menéndez, *Tetrahedron*, 1996, **52**, 5933.
205 R. Tamion, C. Mineur and L. Ghosez, *Tetrahedron Lett.*, 1995, **36**, 8977.
206 L. Yu, D. Chen and P. G. Wang, *Tetrahedron Lett.*, 1996, **37**, 2169.
207 U. Beifuss and S. Ledderhose, *J. Chem. Soc., Chem. Commun.*, 1995, 2137.
208 U. Beifuss, O. Kunz, S. Ledderhose, M. Taraschewski and C. Tonko, *Synlett*, 1996, 34.
209 C. González, D. Pérez, E. Guitián and L. Castedo, *J. Org. Chem.*, 1995, **60**, 6318.
210 C. González, E. Guitián and L, Castedo, *Tetrahedron Lett.*, 1996, **37**, 405.
211 W.-H. Fan, M. Parikh and J. K. Snyder, *Tetrahedron Lett.*, 1995, **36**, 6591.
212 M. Sakamoto, M. Nagano, Y. Suzuki, K. Satoh and O. Tamura, *Tetrahedron*, 1996, **52**, 733.
213 J. Barluenga, M. Tomás, A. Ballesteros and L. A. López, *Synthesis*, 1995, 985.
214 I. Tornus and E. Schaumann, *Tetrahedron*, 1996, **52**, 725.
215 D. A. Nugiel and M. M. Abelman, *J. Org. Chem.*, 1995, **60**, 3554.
216 G. Capozzi, P. Fratini, S. Menichetti and C. Nativi, *Tetrahedron Lett.*, 1995, **36**, 5089.
217 O. Tsuge, T. Hatta, H. Yoshitomi, K. Kurosaka, T. Fujiwara, H. Maeda and A Kakehi, *Heterocycles*, 1995, **41**, 225.
218 T. Saito, H. Kimura, K. Sakamaki, T. Karakasa and S. Moriyama, *Chem. Commun.*, 1996, 811.
219 S. Moriyama, T. Karakasa, T. Inoue, K. Kurashima, S. Satsumabayashi and T. Saito, *Synlett*, 1996, 72.
220 A. Defoin, H. Sarazin and J. Streith, *Helv. Chim. Acta*, 1996, **79**, 560.
221 J.-B. Behr, A. Defoin, J. Pires, J. Streith, L. Macko and M. Zehnder, *Tetrahedron*, 1996, **52**, 3283.
222 J. Streith and A. Defoin, *Synlett*, 1996, 189.
223 P. Hayes, G. Dujardin and C. Maignan, *Tetrahedron Lett.*, 1996, **37**, 3689.
224 R. P. C. Cousins, A. D. M. Curtis, W. C. Ding and R. J. Stoodley, *Tetrahedron Lett.*, 1995, **36**, 8689.
225 A. S. Bell, C. W. G. Fishwick and J. E. Reed, *Tetrahedron Lett.*, 1996, **37**, 123.
226 S. E. Denmark and L. R. Marcin, *J. Org. Chem.*, 1995, **60**, 3221.
227 A. K. McFarlane, G. Thomas and A. Whiting, *J. Chem. Soc., Perkin Trans. 1*, 1995, 2803.
228 P. Herczegh, I. Kovács, L. Szilágyi, F. Sztaricskai, A. Berecibar, C. Riche, A. Chiaroni, A. Olesker and G. Lukacs, *Tetrahedron*, 1995, **51**, 2969.
229 A. Marchand, D. Mauger, A. Guingant and J.-P. Pradère, *Tetrahedron: Asymmetry*, 1995, **6**, 853.
230 M. Johannsen and K. A. Jørgensen, *J. Org. Chem.*, 1995, **60**, 5757.
231 M. Johannsen and K. A. Jørgensen, *Tetrahedron*, 1996, **52**, 7321.
232 Y. Motoyama, M. Terada and K. Mikami, *Synlett*, 1995, 967.
233 K. Mikami, O. Kotera, Y. Motoyama and H. Sakaguchi, *Synlett*, 1995, 275.
234 G. E. Keck, X.-Y. Li and D. Krishnamurthy, *J. Org Chem.*, 1995, **60**, 5998.
235 C. Baldoli, P. Del Buttero, M. di Ciolo, S. Maiorana and A. Papagni, *Synlett*, 1996, 258.
236 E. P. Kündig, L. H. Xu, P. Romanens and G. Bernardinelli, *Synlett*, 1996, 270.
237 C. D. Gabbutt, B. M. Heron, J. D. Hepworth and M. M. Rahman, *Tetrahederon Lett.*, 1996, **37**, 1313.
238 X.-S. Ye, W.-K. Li and H. N. C. Wong, *J. Am. Chem. Soc.*, 1996, **118**, 2511.
239 X.-S. Ye and H. N. C. Wong, *Chem. Commun.*, 1996, 339.
240 S. Turchi, D. Giomi, R. Nesi and P. Paoli, *Tetrahedron*, 1995, **51**, 7085.
241 M. A. Walters and J. J. Shay, *Tetrahedron Lett.*, 1995, **36**, 7575.
242 K. R. Buszek, *Tetrahedron Lett.*, 1995, **36**, 9125.
243 K. R. Buszek and D. L. Bixby, *Tetrahedron Lett.*, 1995, **36**, 9129.
244 T. G. Back and D. Wehrli, *Synlett*, 1995, 1123.
245 V. K. Aggarwal, J. Drabowicz, R. S. Grainger, Z. Gültekin, M. Lightowler and P. L. Spargo, *J. Org. Chem.*, 1995, **60**, 4962.
246 J. Zanon, V. Lucchini, L. Pasquato and O. De Lucchi, *Chem. Commun.*, 1996, 709.
247 O. Kitagawa, K. Aoki, T. Inoue and T, Taguchi, *Tetrahedron Lett.*, 1995, **36**, 593.
248 T. Kan and Y. Ohfune, *Tetrahedron Lett.*, 1995, **36**, 943.
249 T. P. Caulier and J. Reisse, *J. Org. Chem.*, 1996, **61**, 2547.
250 K. Takatori, K. Hasegawa, S. Narai and M. Kajiwara, *Heterocycles*, 1996, **42**, 525.
251 H. Oikawa, K. Katayama, Y. Suzuki and A. Ichihara, *J. Chem. Soc., Chem. Commun.*, 1995, 1321.
252 J. T. Yli-Kauhaluoma, J. A. Ashley, C.-H. Lo, L. Tucker, M. M. Wolfe and K. D. Janda, *J. Am. Chem. Soc.*, 1995, **117**, 7041.
253 A. A. P. Meekel, M. Resmini and U. K. Pandit, *J. Chem. Soc., Chem Commun.*, 1995, 571.
254 J. Barluenga, F. Aznar, A. Martin and J. T. Vázquez, *J. Am. Chem. Soc.*, 1995, **117**, 9419.
255 J. Barluenga, M. Tomás, E. Rubio, J. A. López-Pelegrin, S. García-Granda and P. Pertierra, *J. Am. Chem. Soc.*, 1996, **118**, 695.
256 J. Barluenga, M. Tomás, A. Ballesteros, J. Santamaria, R. J. Carbajo, F. López-Ortiz, S. García-Granda and P. Pertierra, *Chem. Eur. J.*, 1996, **2**, 88.
257 M. Harmata, C. B. Gamlath, C. L. Barnes and D. E. Jones, *J. Org. Chem.*, 1995, **60**, 5077.
258 M. Harmata, S. Elahmad and C. L. Barnes, *Tetrahedron Lett.*, 1995, **36**, 1397.
259 M. Harmata and D. E. Jones, *Tetrahedron Lett.*, 1996, **37**, 783.
260 S. A. Hardinger, C. Bayne, E. Kantorowski, R. McClellan, L. Larres and M.-A. Nuesse, *J. Org. Chem.*, 1995, **60**, 1104.
261 L. C. de A. Barbosa and J. Mann, *Synthesis*, 1996, 31.
262 M. Lautens and S. Kumanovic, *J. Am. Chem. Soc.*, 1995, **117**, 1954.
263 M. A. Walters, H. R. Arcand and D. J. Lawrie, *Tetrahedron Lett.*, 1995, **36**, 23.
264 H. Kim, C. Ziani-Cherif, J. Oh and J. K. Cha, *J. Org. Chem.*, 1995, **60**, 792.

265 S. Jin, J.-R. Choi, J. Oh, D. Lee and J. K. Cha, *J. Am. Chem. Soc.*, 1995, **117**, 10914.
266 S. M. Sieburth and C. Lin, *Tetrahedron Lett.*, 1996, **37**, 1141.
267 W. Bauta, J. Booth, M. E. Bos, M. DeLuca, L. Diorazio, T. Donohoe, N. Magnus, P. Magnus, J. Mendoza, P. Pye, J. Tarrant, S. Thom and F. Ujjainwalla, *Tetrahedron Lett.*, 1995, **36**, 5327.
268 P. A. Wender, H. Takahashi and B. Witulski, *J. Am. Chem. Soc.*, 1995, **117**, 4720.
269 J. H. Rigby, S. Scribner and M. J. Heeg, *Tetrahedron Lett.*, 1995, **36**, 8569.
270 J. H. Rigby, P. Sugathapala and M. J. Heeg, *J. Am. Chem. Soc.*, 1995, **117**, 8851.
271 J. H. Rigby and F. C. Pigge, *Tetrahedron Lett.*, 1996, **37**, 2201.
272 K. Chaffee, P. Huo, J. B. Sheridan, A. Barbieri, A. Aistars, R. A. Lalancette, R. L. Ostrander and A. L. Rheingold, *J. Am. Che, Soc.*, 1995, **117**, 1900.
273 J. H. Rigby and F. C. Pigge, *J. Org. Chem.*, 1995, **60**, 7392.
274 K. Chaffee, H. Morcos and J. B. Sheridan, *Tetrahedron Lett.*, 1995, **36**, 1577.
275 B. Hong and S. Sun, *Tetrahedron Lett.*, 1996, **37**, 659.
276 J. H. Rigby, N. M. Niyaz, K. Short and M. J. Heeg, *J. Org. Chem.*, 1995, **60**, 7720.
277 J. H. Rigby, S. D. Rege, V. P. Sandanayaka and M. Kirova, *J. Org. Chem.*, 1996, **61**, 842.
278 B. M. Trost, J. R. Parquette and A. L. Marquart, *J. Am. Chem. Soc.*, 1995, **117**, 3284.
279 B. Hong and S. Sun, *Chem. Commun.*, 1996, 937.
280 H. Kato, T. Kobayashi, M. Ciobani, H. Iga, A. Akutsu and A. Kakehi, *Chem. Commun.*, 1996, 1011.
281 A. Daich, P. Ohier and B. Decroix, *Tetrahedron Lett.*, 1995, **36**, 83.
282 T. Machguchi, M. Minoura, S. Yamabe and T. Minato, *Chem. Lett.*, 1995, 103.
283 B. L. Pagenkopf and T. Livinghouse, *J. Am. Chem. Soc.*, 1996, **118**, 2285.
284 O. Pardigon, A. Tenaglia and G. Buono, *J. Org. Chem.*, 1995, **60**, 1868.
285 M. Lautens, W. Tam, J. C. Lautens, L. G. Edwards, C. M. Crudden and A. C. Smith, *J. Am. Chem. Soc.*, 1995, **117**, 6863.
286 M. Lautens, L. G. Edwards, W. Tam and A. J. Lough, *J. Am. Chem. Soc.*, 1995, **117**, 10276.
287 K. E. Schwiebert and J. M. Stryker, *J. Am. Chem. Soc.*, 1995, **117**, 8275.