CHAPTER **5**

Intermolecular cyclization reactions to form carbocycles

PATRICK H. BEUSKER and HANS W. SCHEEREN

Department of Organic Chemistry, NSR Center for Molecular Structure, Design and Synthesis, University of Nijmegen, Toernooiveld, 6525 ED Nijmegen, The Netherlands
*Fax: +31 24 652929,   e-mail: jsch@sci.kun.nl*

I. GENERAL INTRODUCTION

Dienes and polyenes can undergo a variety of intermolecular cyclization reactions, the exact nature of which is dependent on the number of double bonds, the relative positions of these bonds with respect to each other, the preferred conformation of the diene or polyene system and the reaction partner.

This chapter deals with [2 + 2], [4 + 2], [6 + 4], [8 + 2] and [2 + 2 + 2] cycloaddition reactions of dienes and polyenes. Most attention is devoted to the [4 + 2] cycloaddition reaction (Diels–Alder reaction) which is likely to be the most studied reaction in the chemical literature.

II. [2 + 2] CYCLOADDITION REACTIONS

A. Conjugated Dienes

Conjugated dienes may undergo [2 + 2] cycloadditions, if they have a fixed or strongly biased *transoid* conformation or if they are reacted with specific dienophiles. Classic examples of the latter are cycloadditions of dienes with ketenes leading to [2 + 2] cycloadducts, even when the dienes have a *cisoid* conformation. [2 + 2] Cycloadditions of cyclopentadiene (**1**) to ketenes **2** (equation 1) have been studied extensively[1], as the cycloadducts **3** are suitable precursors of prostaglandines. The corresponding Diels–Alder adducts can be prepared using ketene equivalents with masked carbonyl groups[2].

$$(1)$$

(1)   **(2)**   **(3)**
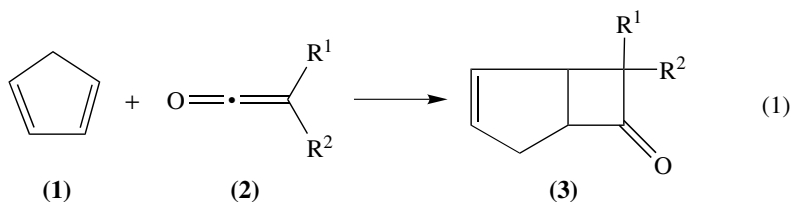
Strongly polarized 1,1-difluoro-2-triphenylsilyloxy-1,3-butadiene (**4**) reacted with *captodative* olefins **5a** and **5b** to give [2 + 2] cycloadducts **6a** and **6b**, respectively (equation 2)[3].

Symmetrically substituted dienophiles such as *p*-benzoquinone and *N*-phenylmaleimide reacted with **4** to give the expected [4 + 2] cycloadducts. No cycloaddition took place, however, in the reaction of 1,1-difluoro-2-triphenylsilyloxy-1-propene with 2-chloroacrylonitrile, which showed the importance of an additional vinyl group for the reactivity of **4** in the [2 + 2] cycloaddition.

$$(2)$$

(**4**) (**5a**; R^1 = CN, R^2 = OMe) (**6a**; R^1 = CN, R^2 = OMe)
   (**5b**; R^1 = CO$_2$Et, R^2 = Br) (**6b**; R^1 = CO$_2$Et, R^2 = Br)
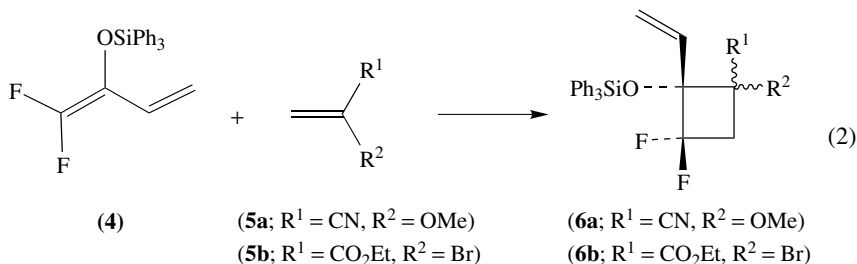
Another example of a diene undergoing a [2 + 2] cycloaddition reaction with an alkene has been reported recently[4]. 2-Dimethylaluminumoxy-1,3-cyclohexadiene (**7**) reacted with phenyl vinyl sulfoxide (**8**) to afford a diastereomeric mixture of *cis* substituted cyclobutanols **9** (equation 3). The occurrence of a [2 + 2] cycloaddition as well as the high *cis* stereoselectivity observed were explained by a pre-organization of the reactants by complexation of the diene bound aluminum with the sulfoxide oxygen on the olefin.


$$(3)$$

(**7**) (**8**) (**9**)
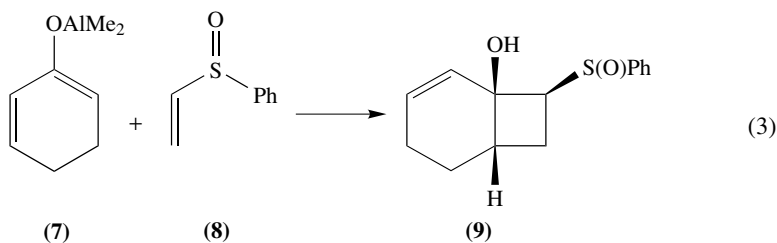
B. Cumulated Dienes (Allenes)

Like ketenes, allenes generally undergo [2 + 2] cycloadditions with alkenes affording methylene cyclobutanes[5]. In reactions with 1,3-butadienes, both Diels–Alder adducts and [2 + 2] cycloadducts are formed. Cyclopentadiene, however, has been reported to react with several allenes to give exclusively Diels–Alder adducts[6]. From the several possible mechanisms by which [2 + 2] cycloaddition reactions of allenes could occur, i.e. [$\pi 2_s + \pi 2_a$], [$\pi 2_s + (\pi 2_s + \pi 2_s)$] or diradical, the diradical mechanism is generally considered to be the most probable one[6−10].

The most recent review[5d] about [2 + 2] cycloadditions of allenes covers the literature up to 1992. This section deals with recent results combined with some representative results from the past decade.

Pasto and colleagues studied the stereochemical features of the [2 + 2] cycloadditions of chiral allenes. The formation of a diradical intermediate in the cycloadditions of enantiomerically enriched 1,3-dimethylallene (**10**) with acrylonitrile (**11a**) and methyl acrylate (**11b**) (equation 4) was shown to be irreversible. 1,3-Dimethylallene recovered from the reaction mixture was shown to have the same ee as the starting material. Interestingly,

a surprisingly large amount of the ee of **10** was transferred to cycloadducts **12** and **13**. The exact amount proved dependent on the size of the alkene substituent, being larger for methyl acrylate than for acrylonitrile. These results were discussed in terms of preferred conformations of approach adopted by both reactants to form the activated complex leading to the diradical intermediate[7].

(10)	(11a; R = CN)	(12a; R = CN)	(13a; R = CN)	(4)
	(11b; R = CO$_2$Me)	(12b; R = CO$_2$Me)	(13b; R = CO$_2$Me)	
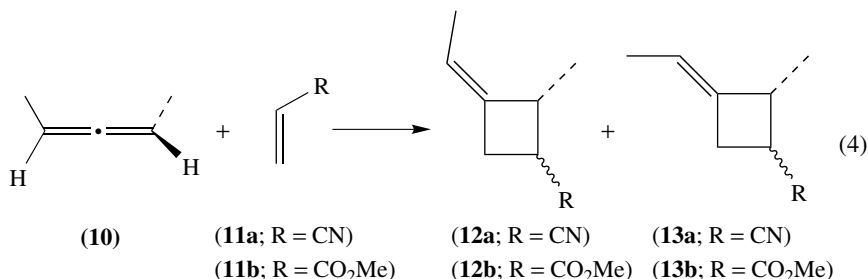
In the $[2+2]$ cycloadditions of **10** with N-phenylmaleimide and dimethyl fumarate, the major cycloadducts were formed with a very high degree of ee transfer from 1,3-dimethylallene[8]. Similar results were obtained in the reaction of **10** with 1,1-dichloro-2,2-difluoroethene. The reaction with less reactive 1,1-diphenylethene did not lead to cycloadduct formation, but resulted in racemization of the chiral 1,3-dimethylallene instead[9], which implies reversible formation of the diradical intermediate in this case. Finally, the cycloaddition of 1,3-dimethylallene to methyl propiolate **(14)** afforded two cycloadducts, **15** and **16**, to which >40% of the initial ee had been transferred (equation 5)[11].

(10)	(14)	(15)	

$$(5)$$

(16)
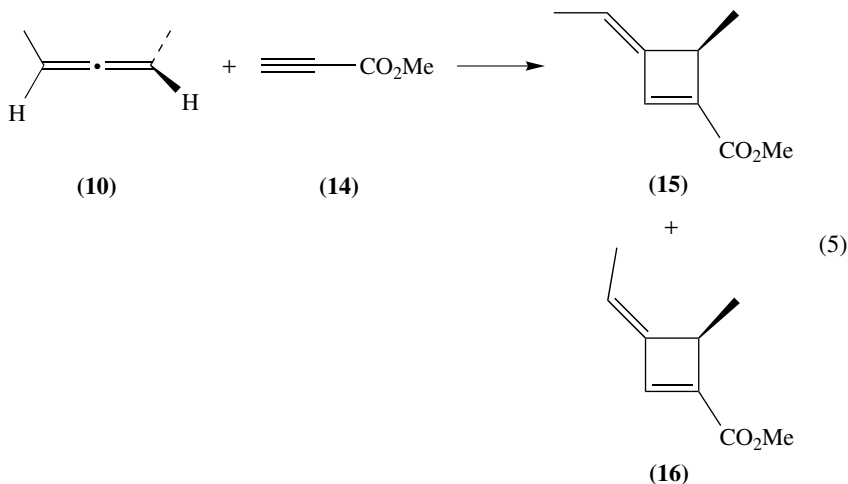
The reactions of 1-t-butyl-3-methylallene with several alkenes, e.g. N-phenylmaleimide, acrylonitrile and methyl acrylate, afforded exclusively $[4+2]$ cycloadducts of 1-t-butyl-1,3-butadiene, which had been formed from 1-t-butyl-3-methylallene by a [1,3] sigmatropic rearrangement[12]. The reaction of 1-t-butyl-3-methylallene with 1,1-dichloro-2,2-difluoroethene occurred more rapidly than the hydrogen shift, which allowed the

isolation of a mixture of four [2 + 2] cycloadducts, including one to which 91% of the initial ee had been transferred[10].

Introduction of an alkylthio group on the allene system increased the reactivity of the allene moiety in [2 + 2] cycloaddition reactions. It proved possible to conduct reactions of this allene at much lower temperatures. By adding Lewis acids, the reaction temperature could be decreased even more, as was illustrated by the Lewis acid catalyzed [2 + 2] cycloadditions of 1-trimethylsilyl-1-methylthio-1,2-propadiene with a variety of electron-poor alkenes, including cyclic and non-cyclic enones, acrylates, methyl fumarate and acrylonitrile[13]. When a chiral diol **21** based titanium catalyst was employed, the [2 + 2] cycloaddition reactions of *N*-acryloyl-1,3-oxazolidin-2-ones **17a** and **17b** with allenyl sulfides **18** yielded methylenecyclobutanes **19** and **20** with high optical purities (equation 6)[13,14]. The highest yields were obtained with electron-poor allenophile **17b**. The substituent R^2 proved to have a strong effect on the yield, as the yield was quantitative for **18a**, whereas no reaction was observed for **18c**.

Reactions of 3-methylthio-4-trimethylsilyl-1,2-butadiene with electron-poor monosubstituted and disubstituted alkenes were promoted by a catalytic amount of ethylaluminum dichloride, affording the corresponding methylenecyclobutanes with high selectivities and with yields ranging from 37% for methyl crotonate to 97% for methacrylonitrile[15].

Electron-rich 3-methoxy-4-trimethylsilyl-1,2-butadiene **(22)** reacted with several electron-poor alkenes in the presence of diethylaluminum chloride to afford methylene cyclobutanes **23**. Reactions with alkynes were performed in the presence of methylaluminum bis(2,4,6-tri-*t*-butylphenoxide) (equation 7)[16].
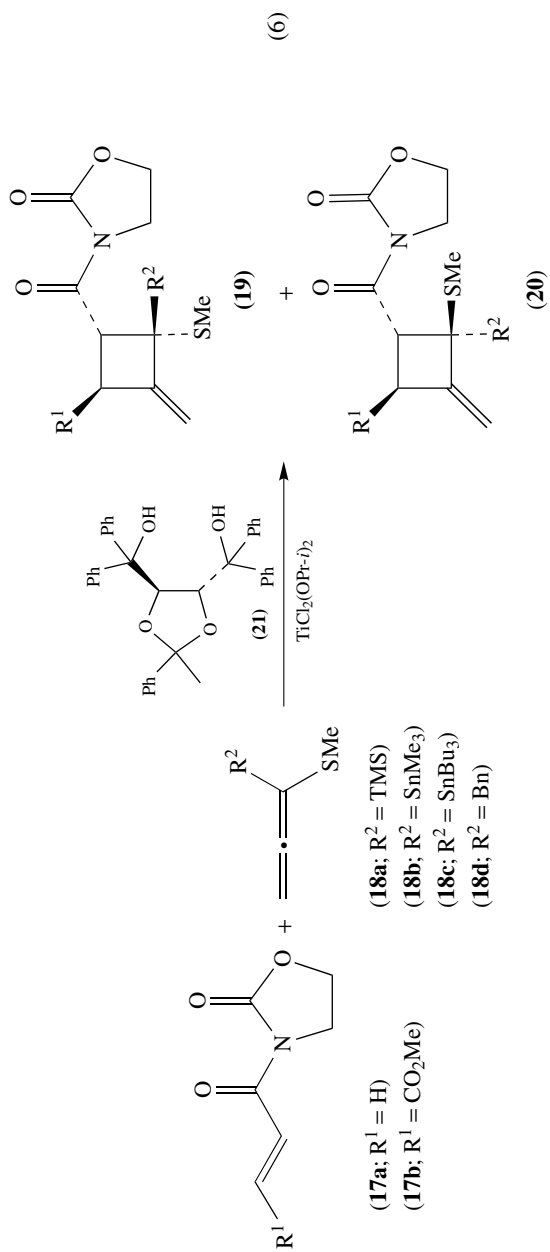
The nature of the substituents on the allene can have an impact on the outcome of a [2 + 2] cycloaddition reaction, as was illustrated by the Lewis acid catalyzed cycloadditions of 1-thioaryl-3,3-dimethylallene **(24)** and 1-methyl-1-trimethylsilylallene to various 2-alkoxy-*p*-benzoquinones **25** (e.g. equation 8)[17]. The reactions were considered to proceed via carbocation intermediates formed by nucleophilic attack of the thioallene on the Lewis acid activated quinone. At lower temperatures, these carbocations closed to cyclobutanes **26**, whereas at higher temperatures, the thermodynamically more stable benzofurans **27** were formed.

Titanium tetrachloride promoted reactions of 1-methyl-1-trimethylsilylallene with quinones **25** afforded products derived from a reaction with one of the carbonyl groups on the quinones. Besides the substitution pattern on the allene, the higher activity of titanium tetrachloride has to be considered to play a role in this abnormal product formation.

Cyclic allenes have improved reactivity due to ring strain. The cycloaddition of 1,2,4-cyclohexatriene **(28)** with styrene **(29)**, for example, afforded exclusively cyclobutane **31** (equation 9)[18]. Semi-empirical calculations (AM1) determined the diradical intermediate **30** to be at an energy minimum[19].

5,6-Didehydro-3,4-dihydro-2*H*-pyran, easily generated from 5-bromo-3,4-dihydro-2*H*-pyran, was trapped with enolates to give mixtures of cyclobutanes[20].

Elliot and coworkers[21] found that cephalosporin triflates **32** reacted with various alkenes and acetylenes via a strained six-membered cyclic allene intermediate to give cyclobutanes **33** and **34** (equation 10). The cycloaddition reaction had a broad scope with **32** reacting with electron-rich as well as electron-poor highly substituted olefins. The most facile cycloadditions (in terms of the highest yield and the lowest required excess of olefin) were found for electron-rich olefins. Close inspection of the products that were obtained indicated a concerted process. For example, vinylcyclopropane reacted to give a mixture of cyclobutane isomers in which the cyclopropyl group was still present. This ruled out a stepwise diradical mechanism, as the intermediate cyclopropylcarbinyl radical, having a very short lifetime, would undergo ring opening rather than bond rotation followed by ring

(6)

(17a; R^1 = H)
(17b; R^1 = CO$_2$Me)

(18a; R^2 = TMS)
(18b; R^2 = SnMe$_3$)
(18c; R^2 = SnBu$_3$)
(18d; R^2 = Bn)

(21)

TiCl$_2$(OPr-i)$_2$

(19) + (20)

closure. Olefins with electron-donating as well as electron-withdrawing substituents such as ethyl vinyl ether and methyl acrylate all afforded products with the same regiochemistry, which suggested that no zwitterionic intermediates were involved.

$$(7)$$

$$(8)$$

Ar = Ph, p-MeOC$_6$H$_4$

$$(9)$$
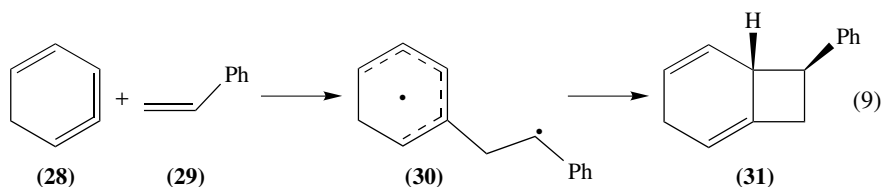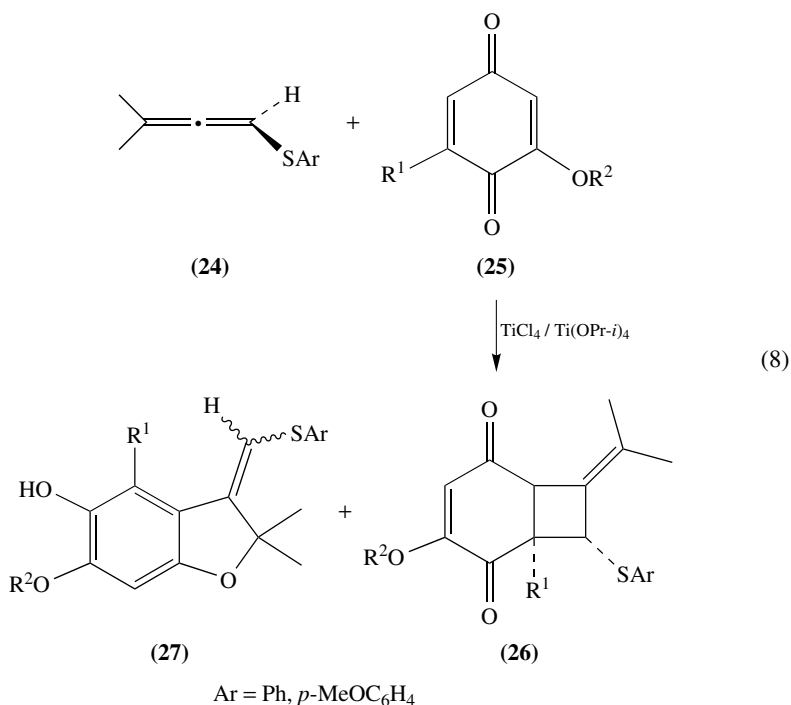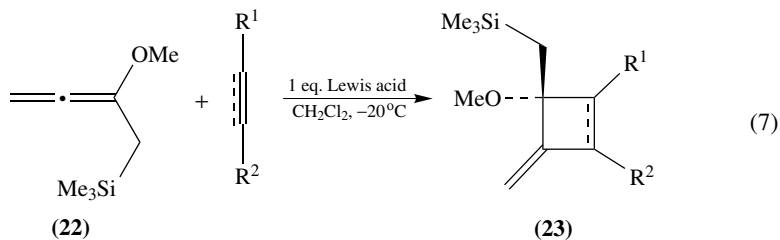
In addition to the concerted [2 + 2] cycloadditions of cyclic allenes reported by Elliot and colleagues, Kimura and coworkers[22] reported [2 + 2] cycloadditions of several 4-ethenylidene-1,3-oxazolidin-2-ones **35** with alkenes and alkynes (equation 11). The

$$(10)$$

$$(11)$$

(**35a**; R^1 = SO$_2$Ph)   (**36a**; R^1 = SO$_2$Ph)
(**35b**; R^1 = COPh)   (**36b**; R^1 = COPh)
(**35c**; R^1 = Tos)   (**36c**; R^1 = Tos)
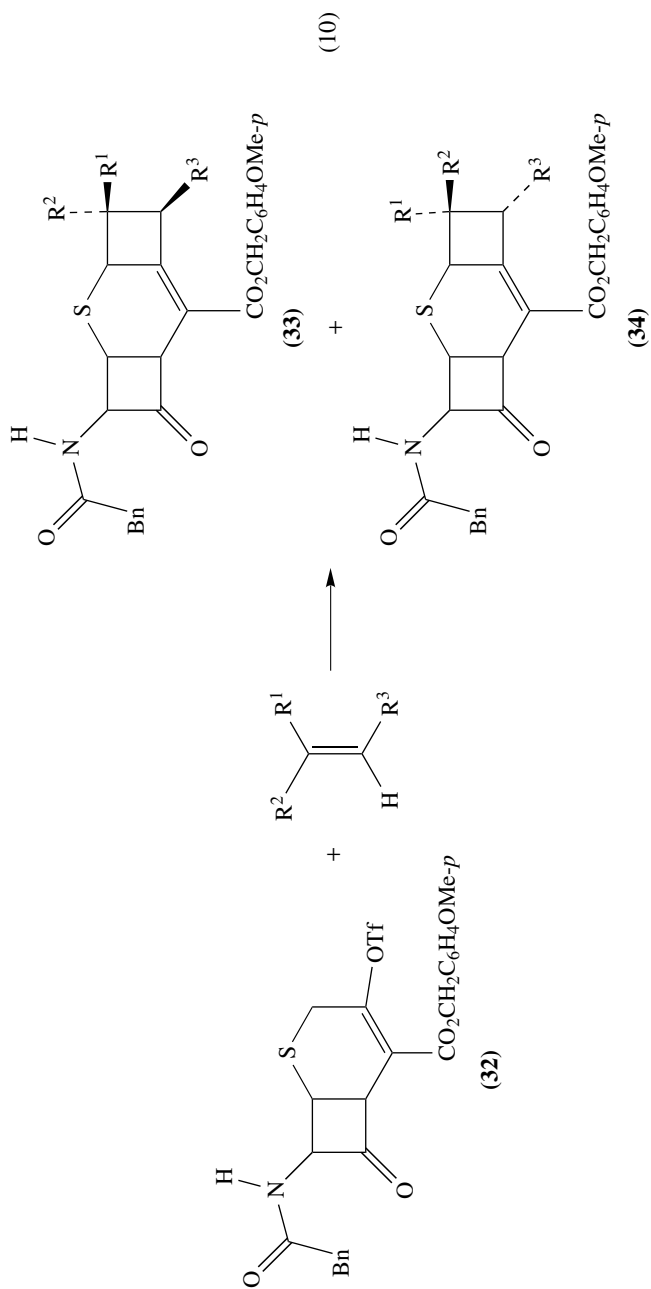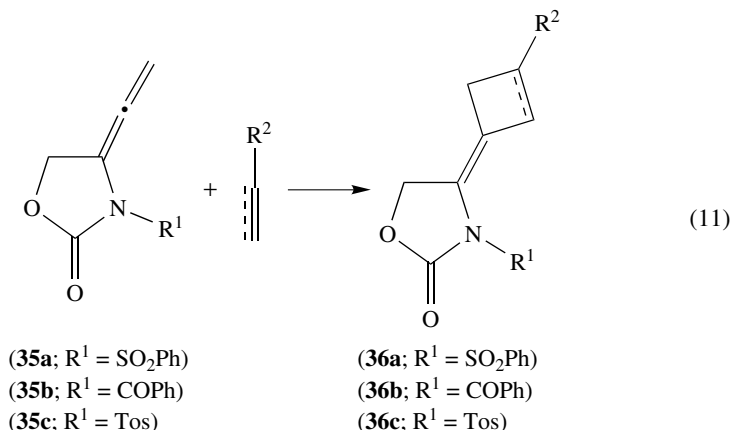
reactions were considered to proceed via a [$\pi2_s + (\pi2_s + \pi2_s)$] mechanism. The cyclo-additions provided **36** as single diastereomers, showing that the alkene or alkyne moieties were introduced *syn* to the *N*-phenylsulfonyl, *N*-tosyl or *N*-benzoyl group. The alkenes employed encompassed electron-attracting, electron-donating and conjugating groups. Even 1,3-dienes exclusively yielded [2 + 2] cycloaddition products.

III. DIELS–ALDER REACTIONS

The formation of compounds with an unsaturated six-membered ring through the addition of a conjugated diene to a double or triple bond is known as the Diels–Alder reaction (equation 12). Such a cycloaddition was already described by Zincke and Günther in 1893[23]. The names of Diels and Alder have, however, been connected to this type of reactions due to the systematic and extensive work which they have performed on these reactions since the 1920s,[24] and for which a Nobel prize was awarded in 1950. Since these early investigations, the Diels–Alder reaction has grown to become probably the most valuable and most applied reaction in synthetic organic chemistry. It has a very broad scope and it allows the stereochemically controlled introduction of up to four chiral centers in the adduct in one synthetic step. Besides all-carbon systems, dienes and dienophiles containing heteroatoms have been widely employed.

$$(12)$$
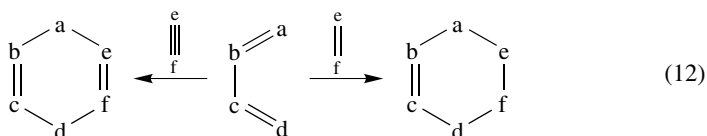
Although this chapter is limited to intermolecular all-carbon reactions, the literature connected to this type of Diels–Alder reactions is still immense. The last general reviews about intermolecular Diels–Alder reactions date from nearly ten years ago[25–27]. During the past decade, several reviews were published dealing with specialized topics such as mechanistic aspects[28–31], specific dienes[32–35] and dienophiles[2,36,37], applications in synthesis[38–40] and introduction of chirality by using chiral auxiliaries[41,42] or chiral Lewis acids[41,43,44].

In this section, the literature about Diels−Alder reactions will be presented in a conceptual and illustrative way. After a profound introduction dealing with the development of mechanistic understanding of the Diels−Alder reaction, some interesting recent synthetic developments and applications will be presented. The reaction types and fields of interest are structured in such a way that they can be easily linked to ongoing research from the past ten years. Special attention will be paid to the application of chiral auxiliaries and chiral Lewis acids in asymmetric Diels−Alder reactions.

A. The Diels−Alder Reaction. A Theoretical Description

1. Development of mechanistic understanding. Mechanistic facts and concepts

Mechanistic and theoretical studies of the Diels−Alder reaction have resulted in the characterization of this reaction as a concerted, although not necessarily synchronous, single-step process[28−31,45]. The parent reaction, the addition of 1,3-butadiene to ethylene yielding cyclohexene, has been the subject of an ongoing mechanistic debate. Experimental results supported a concerted mechanism, whereas results from calculations seemed to be dependent on the method used. Semi-empirical calculations predicted a stepwise mechanism, whereas *ab initio* calculations were in favor of a concerted pathway. At the end of the '80s experimental and theoretical evidence converged on the synchronous mechanism[29−31].

Zwitterionic intermediates have been reported for reactions of strongly electron-rich 1,3-butadienes, e.g. 1,1-dimethoxy-1,3-butadiene, with strongly electron-poor dienophiles[46]. In the reactions of 1,4-bis(dimethylamino)-1,3-butadiene with strongly electron-poor dienophiles, electron transfer from the diene to the dienophile was reported to occur[47].

The following mechanistic aspects have been found to be characteristic of the Diels−Alder reaction[28,45].

(i) *The 'cis principle'*: The steric arrangement of substituents in both addends is preserved in the adduct, i.e. groups which are *cis* or *trans* in the olefin remain *cis* and *trans*, respectively, in the adduct.

(ii) *Diene conformation*: Open-chain 1,3-dienes undergo [4 + 2] cycloadditions only in their *cisoid* conformation.

(iii) *Solvent effects*: Diels−Alder reactions are only slightly affected by a change of solvent.

(iv) *Activation parameters*: Diels−Alder reactions are accompanied by strong negative entropies of activation, $\Delta S^{\neq}$ (*ca* −35 eu), and large negative volumes of activation, $\Delta V^{\neq}$ (*ca* 30 cm^{3}mol^{-1}), but only small enthalpies of activation, $\Delta H^{\neq}$.

(v) *Isotope effects*: Small inverse secondary isotope effects at both termini undergoing sp^2−sp^3 changes during the cycloaddition are found.

(vi) *Regioselectivity*: Unsymmetrically substituted dienes and dienophiles afford mixtures of both regioisomers, one of which usually predominates. 1-Substituted dienes yield mostly *ortho* substituted adducts with monosubstituted dienophiles (equation 13), while

$$\text{(13)}$$

ortho   *meta*
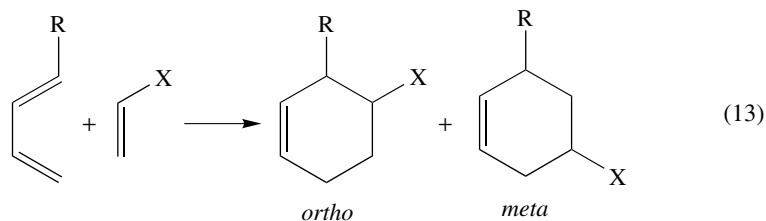
2-substituted dienes give predominantly *para* adducts (equation 14). The yield of the predominant isomer is increased by Lewis acid catalysis. The regioselectivity in the reactions of disubstituted and higher substituted dienes depends on the electronic properties and the relative positions of the substituents.

$$(14)$$

para   *meta*
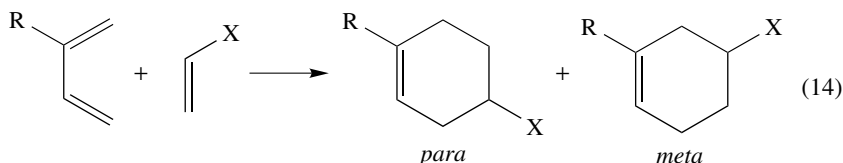
(vii) *The 'Alder rule', Reactivity*: Three different types of Diels–Alder reactions have been defined with respect to the electronic properties of the diene and dienophile substituents. [4 + 2] Cycloadditions between electron-rich dienes and electron-poor dienophiles are defined as *normal* Diels–Alder reactions. Their reaction rates increase with increasing electron-donating properties of the substituents on the dienes and increasing electron-withdrawing properties of the substituents on the dienophiles.

[4 + 2] Cycloadditions of reactants with opposite electronic properties are defined as Diels–Alder reactions with *inverse electron demand* or *inverse* Diels–Alder reactions.

Neutral Diels–Alder reactions encompass cycloadditions of dienes and dienophiles with intermediate electronic characters.

The *normal* [4 + 2] cycloadditions are most frequently observed and generally proceed more easily than the other reaction types. Recently, Sauer and colleagues[48] demonstrated that each of these three types of Diels–Alder reactions can be observed in the cycloadditions of a series of polyhalogenated cyclopentadienes with aryl substituted dienophiles, the actual reaction type observed depending on the substitution pattern of the reactants.

(viii) *The 'Alder endo rule', Stereochemistry*: Cycloadditions of monosubstituted or disubstituted dienophiles generally lead to the formation of the *endo* isomer as the main product. Assuming a 'sandwich'-like pre-organization of the reactants, the *endo* product arises from that orientation in which the larger substituent is directed towards the double bond to be formed at C(2) of the diene (Figure 1). Formation of the *endo* isomer is promoted by Lewis acid catalysis.
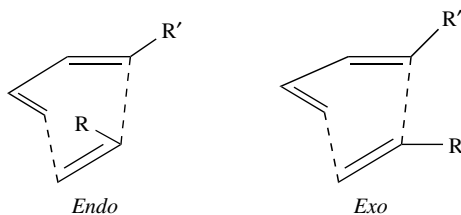

Endo   *Exo*

FIGURE 1. *Endo* and *exo* transition states of the Diels–Alder reaction

2. Frontier molecular orbital theory

A fundamental understanding of the mechanistic and stereochemical aspects of the Diels–Alder reaction was unfolded during the 1970s. Several theoretical approaches are available nowadays from which Fukui's Frontier Molecular Orbital theory (FMO theory) is most frequently used because of its simplicity[49–53].

This theory proves to be remarkably useful in rationalizing the whole set of general rules and mechanistic aspects described in the previous section as characteristic features of the Diels–Alder reaction. The application of perturbation molecular orbital theory as an approximate quantum mechanical method forms the theoretical basis of Fukui's FMO theory. Perturbation theory predicts a net stabilization for the intermolecular interaction between a diene and a dienophile as a consequence of the interaction of an occupied molecular orbital of one reaction partner with an unoccupied molecular orbital of the other reaction partner.

In order to simplify mathematical treatment, less important contributions from inter-actions between orbitals with large energy differences are neglected. The procedure is limited to the interaction of the frontier orbitals, viz. the highest occupied molecular orbitals (HOMOs) and the lowest unoccupied molecular orbitals (LUMOs), as illustrated in Figure 2.

With this simplification in mind, the stabilization energy ΔE can be given by equation 15, E_{HOMO} and E_{LUMO} being orbital energies, $C_{A'}^i$, C_A^i and $C_{D'}^i$, C_D^i being the relevant orbital coefficients at the carbon centers to which the new bonds are being formed; β_{AD}^i and $\beta_{A'D'}^i$ are the resonance integrals for the overlap at the sites of interaction.

$$\Delta E = 2\frac{\left[\sum_i C_A^i C_D^i \beta_{AD}^i\right]^2}{E_{HOMO}^{diene} - E_{LUMO}^{dienophile}} + 2\frac{\left[\sum_i C_{A'}^i C_{D'}^i \beta_{A'D'}^i\right]^2}{E_{HOMO}^{dienophile} - E_{LUMO}^{diene}} \tag{15}$$

The main stabilization in reactions with activated reaction partners, viz. when one partner is electron-rich and the other electron-poor, arises through interaction between the donor HOMO and the acceptor LUMO which are much closer in energy than the acceptor HOMO and the donor LUMO. Figure 2 illustrates which interactions between the frontier orbitals cause the main stabilization in *normal, neutral* and *inverse* Diels–Alder reactions. For example, the main stabilization in the reaction between an electron-rich diene and an electron-poor dienophile stems from the interaction of the diene HOMO with the dienophile LUMO.

Several quantitative descriptions of [4 + 2] cycloadditions have been reported applying equation 15 or derived equations. HOMO and LUMO energies can be calculated from ionization potentials or electron affinities. Orbital coefficients have been calculated for simple ethenes and dienes using various quantum mechanical methods, e.g. INDO, CNDO/2, AM1 and STO-3G. These different methods may, however, lead to substantially different results[54−56].
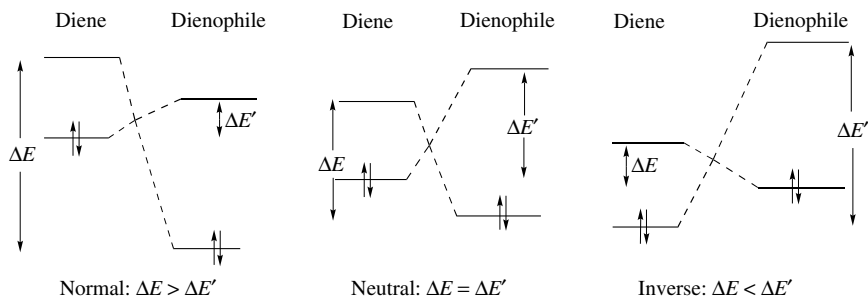

FIGURE 2. Energies of HOMOs and LUMOs as a function of the Diels–Alder reaction type

Discussions about reactivity, regioselectivity and stereoselectivity are mostly based on a more qualitative application of equation 15. To that aim, the following general considerations given by Fleming[51] and Houk[52] can be used to evaluate the influence of substituents on the reacting π systems:

(i) Conjugating substituents compress the frontier orbital separation of both diene and dienophile and lower the coefficients at the site of attachment in both frontier orbitals.

(ii) Electron-donating substituents, e.g. OAlk and N(Alk)$_2$, raise the energy levels of both frontier orbitals of each reactant. The HOMO level is generally raised more than the LUMO level. Electron-donating substituents enlarge the relative magnitude of the coefficients at the remote site in the HOMO [C(2) of the dienophile, C(2) and C(4) of the diene] and at the site of attachment in the LUMO [C(1) of the dienophile, C(1) and C(3) of the diene].

(iii) Electron-withdrawing groups lower both frontier orbital energies of each reactant. Since most electron-withdrawing groups are at the same time conjugating (e.g. CN, NO$_2$, and CO$_2$Me), the LUMO energy level is lowered more than the HOMO energy level. Electron-attracting groups reduce the relative magnitudes of the HOMO coefficients at C(2) and C(4). The LUMO coefficients at C(2) and C(4) of the diene and at C(2) of the dienophile are always relatively large in comparison with the coefficients at C(1).

(iv) Substituents at C(2) of the diene have a similar effect on the coefficients in comparison with the same substituents at C(1). They affect the π bond to which they are attached more than the other π bond. Electron-donating substituents cause the highest HOMO coefficient to be at C(1). Electron-withdrawing substituents cause the highest LUMO coefficient to be at C(1).

Application of these qualitative rules allows a simple prediction of the reactivity, regioselectivity and *endo/exo* selectivity. According to equation 15, the net stabilization energy ΔE depends on the frontier orbital energies. The highest stabilization is predicted for transition states derived from reactants of which one has a HOMO energy similar to the LUMO energy of the other. This means that electronically opposite substituents on the diene and the dienophile will increase the Diels–Alder reactivity. The largest increase of cycloaddition rate will be observed, if the electron-releasing substituent is present on the reactant with the higher HOMO energy. This usually is the diene partner because of its higher degree of conjugation.

The differences in stabilization energies for the formation of the various regioisomers are mainly determined by the differences in the largest term of equation 15. Formation of that regioisomer is favored for which the largest term consists of the largest frontier orbital coefficients from both diene and dienophile.

This means, for example, that in *normal* Diels–Alder reactions of 1-substituted dienes with 1-substituted ethenes, bond formation between C(4) of the diene and C(2) of the alkene, which leads to the *ortho* adduct, is favored over the other bond formation leading to the *meta* adduct. Formation of *para* products from 2-substituted dienes can be explained by a similar reasoning.

The *endo* selectivity in many Diels–Alder reactions has been attributed to attractive secondary orbital interactions. In addition to the primary stabilizing HOMO–LUMO interactions, additional stabilizing interactions between the remaining parts of the diene and the dienophile are possible in the *endo* transition state (Figure 3). This secondary orbital interaction was originally proposed for substituents having π orbitals, e.g. CN and CHO, but was later extended to substituents with π(CH$_2$) type of orbitals, as encountered in cyclopropene[57].

There has been, however, an ongoing debate about other factors which may control *endo* selectivity. *Endo* selectivity has been observed when no secondary orbital interactions are possible and have been ascribed to steric effects in these cases[58,59]. Recently, the
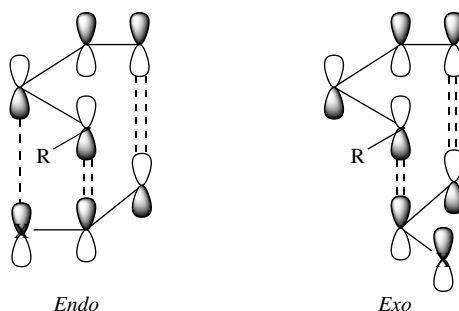
FIGURE 3. Primary and secondary orbital interactions between diene and dienophile

effect of pre-reactive van der Waals intermediates on the *endo/exo* selectivity has been investigated[60].

Secondary orbital interactions may also be involved in controlling the regioselectivity, if the differences between the terminal coefficients of diene and dienophile are small[61].

3. Effect of diene structure on reactivity. The resonance integral β

The reactivity of dienes in Diels–Alder reactions is also controlled by the diene conformation. The two planar conformations of 1,3-butadiene are referred to as *s-trans* and *s-cis* (equation 16). Calculations have shown the *s-trans* conformation to be $2-5$ kcal mol^{-1} more stable than the *s-cis* conformation. Open-chain dienes can only react in their *cisoid* conformation. Thus, 2-substituted dienes are generally more reactive than 1,3-butadiene due to their stronger preference for the *s-cis* conformation. 1-*Cis* substituted 1,3-butadienes are almost exclusively in the *s-trans* conformation and are not reactive in Diels–Alder reactions. Highly substituted dienes may, however, be present in the *s-cis* conformation during a sufficient amount of time to participate in Diels–Alder reactions, even if a 1-*cis* substituent is present[62].

$$(16)$$
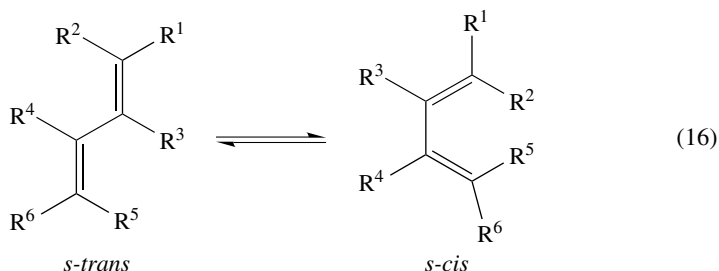
Reactivity may also depend on the C(1)–C(4) distance of the diene[63]. In a concerted [2 + 4] cycloaddition reaction, overlap has to be achieved between the lobes of the π orbital at C(1) and C(2) of the dienophile, lying about 1.3 Å apart, and the lobes of the π-orbital at C(1) and C(4) of the diene, lying about 3 Å apart. This means that the shorter the C(1)–C(4) distance is, the more efficient the overlap will be in the transition state. This is translated into a higher resonance integral β. It was shown for a series of equally substituted rigid 1,3-dienes that their reactivity in the cycloaddition reactions

with dienophiles depended strongly on the C(1)−C(4) distance. The decrease in reactivity toward cycloadditions going from cyclopentadiene to cyclohexadiene to cycloheptadiene can be attributed to increasing C(1)−C(4) distances of the dienes, the distances being 2.35, 2.85 and 3.15 Å, respectively.
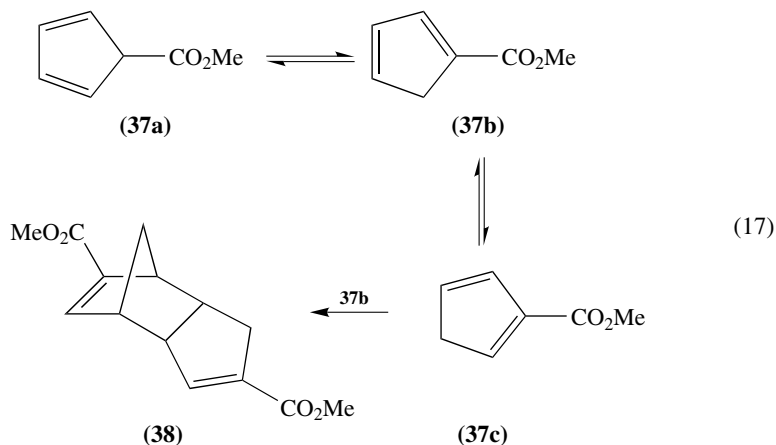
4. Limitations of the FMO theory

The FMO theory predicts the reactivity and selectivity in Diels−Alder reactions based on one dominant MO interaction. Especially in the last decade, many reactions have been found which disobey the FMO rules concerning reactivity and regiochemistry. For example, dienes having conjugating electron-withdrawing substituents at C(2) or C(3), e.g. CN, SO_2R and COR, are often more reactive toward electron-poor dienophiles than isoprene, 2,3-dimethyl-1,3-butadiene and 1,3-pentadiene[64−66]. This has been explained by taking into account the paralocalization energy of the diene in the transition state. This energy represents more or less the energy needed to reorganize the π-bonds in the cycloaddition reaction. Dienes with a conjugating substituent at C(2) or C(3) change from a cross-conjugated 6π electron system to a 4π electron system, whereas 1,3-butadiene changes from a 4π electron system to a 2π electron system, causing the paralocalization energy for these 2- and 3-substituted dienes to be lower than for 1,3-butadiene. In addition, calculations and experiments support an early reorganization of π electrons which entails an important contribution of this paralocalization energy to the transition state energy[64,65].
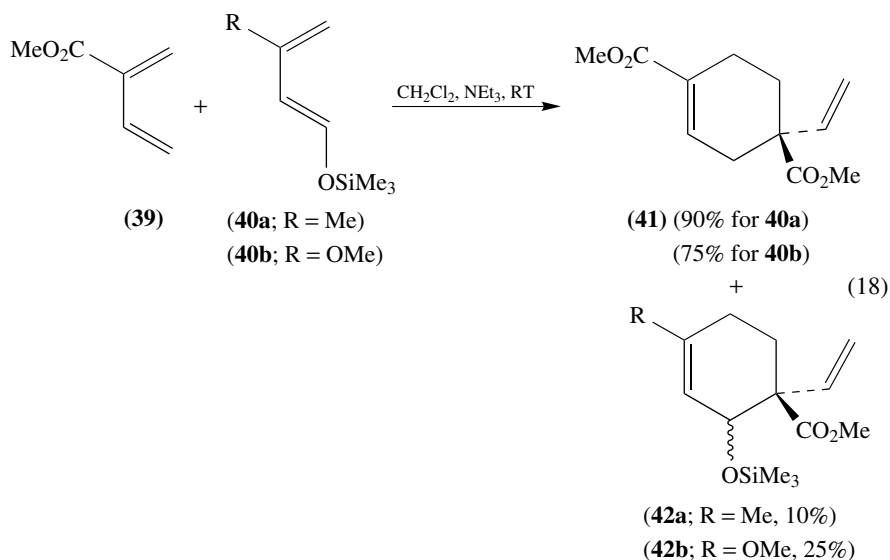
A classic example is the dimerization of methyl cyclopentadienylcarboxylate (**37**) to Thiele's ester (**38**)[67]. Although diene **37b** should be more reactive than **37c** according to the FMO theory, it was diene **37c** that reacted with diene **37b** (equation 17).

In a similar way, 2-(methoxycarbonyl)-1,3-butadiene (**39**) dimerizes rapidly, even in the presence of electron-rich dienes such as **40a** or **40b**, as illustrated in equation 18[65]. The dimeric adduct **41** and the mixed adduct **42** were obtained in ratios of 90 : 10 and 75 : 25 in the reactions of **39** with **40a** and **40b**, respectively.

The reactivity of **45** towards various dienophiles was similar to that of dienes **43** and **44**, whereas diene **46** was much less reactive[64]. According to the FMO theory, dienes **45** and **46** should have a similar reactivity.

The FMO model is sometimes unable to correctly predict the regioisomer to be obtained from cycloadditions of dienes having either two different substituents or two identical substituents at two different positions. For example, substituents at C(1) have proven to

(17)

(37a)   **(37b)**

(38)   **(37c)**

(39)   **(40a**; R = Me)   **(41)** (90% for **40a**)
                (40b; R = OMe)   (75% for **40b**)

                                                                                +   (18)

(42a; R = Me, 10%)
(42b; R = OMe, 25%)

exert greater control over regiochemistry than the same substituents at C(2), which is
not predicted by the FMO theory. An alternative model has been proposed by Hehre
and coworkers[68]. This model is based on matching complementary reactivity surfaces
for both diene and dienophile. This approach proved more successful in predicting the
regioselectivity in the cases mentioned above.

(43)   **(44)**   **(45)**   **(46)**
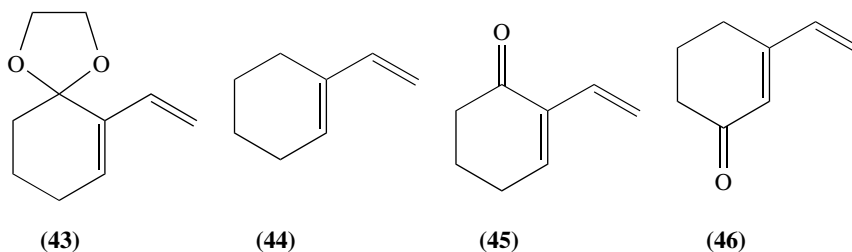
B. The Diels–Alder Reaction. Recent Developments

1. Diels–Alder reactions in targeted synthesis

Because the Diels–Alder reaction allows the construction of six-membered rings with
the introduction of up to four new stereocenters in a stereocontrolled fashion in one
single step, it is a very important tool for the synthesis of six-membered rings containing
natural compounds and derivatives. In many synthetic strategies toward these types of
compounds, the Diels–Alder reaction is a crucial step, as illustrated by the following
examples.

Many groups have employed a Diels–Alder strategy toward the synthesis of the well-
known antitumor compound paclitaxel, which has a tetracyclic core containing two

six-membered rings[69]. Nicolaou and colleagues[70] prepared both of these rings by a Diels−Alder approach. Coupling of these ring fragments ultimately led to the second total synthesis of paclitaxel in 1994[71].

The wide range of biological properties associated with the angucycline class of antibiotics has stimulated great interest in these compounds. Several groups reported a Diels−Alder approach toward angucyclinones **(47)**, a simpler subclass devoid of carbohydrate functionalities. The general strategy was to react a naphthoquinone derivative with an *inner−outer* diene which afforded the basic angucyclinone skeleton[72].
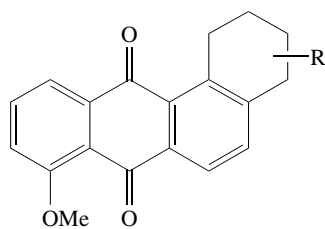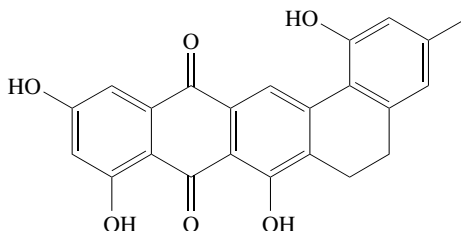
(47)   (48)
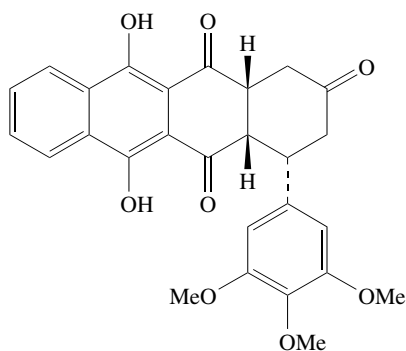
(49)

Kraus and Zhao[73] described the total synthesis of G-2N **(48)**, an angularly fused quinone natural product, using a Diels−Alder reaction between an *outerring* bicyclic diene and a *p*-benzoquinone derivative. Sahagún and colleagues[74] reported the synthesis of tetracyclic ketone **49** using a Diels−Alder approach. Ketone **49** was intended to be used in the synthesis of new anthracycline analogs.
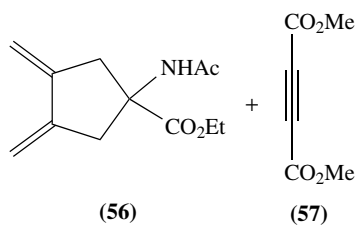
In the course of their research about drugs with oncologic activity, Martinez and Iglesias[75] examined the Diels−Alder reaction between 1-trimethylsilyloxy-1,3-butadiene **(50)** and nitroalkene **51** which afforded, after hydrolytic work-up, a mixture of two regioisomeric pairs of *endo/exo* isomers **52/53** and **54/55** in a ratio of **52/53/54/55** = 78 : 17 : 3 : 2 (equation 19).

Constrained α-amino acids, which have gained widespread use in peptide design and are important for controlling secondary structures, were prepared by Kotha and colleagues[76] via Diels−Alder reactions of *outerring* diene **56** with several dienophiles, followed by
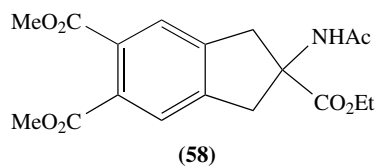
aromatization of the primary cycloadduct using DDQ. The reaction between **56** and dimethyl acetylenedicarboxylate **(57)**, which gives **58**, has been depicted in equation 20.
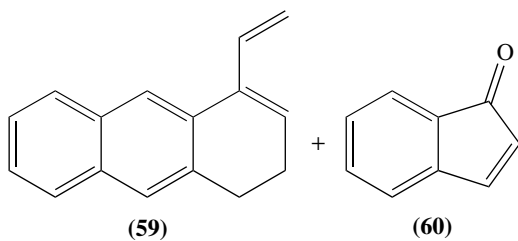

(50)   **(51)**

2. HCl (5%) − THF | 1. PhMe, Δ

(19)

(52; 78)   **(53**; 17)

+

(54; 3)   **(55**; 2)
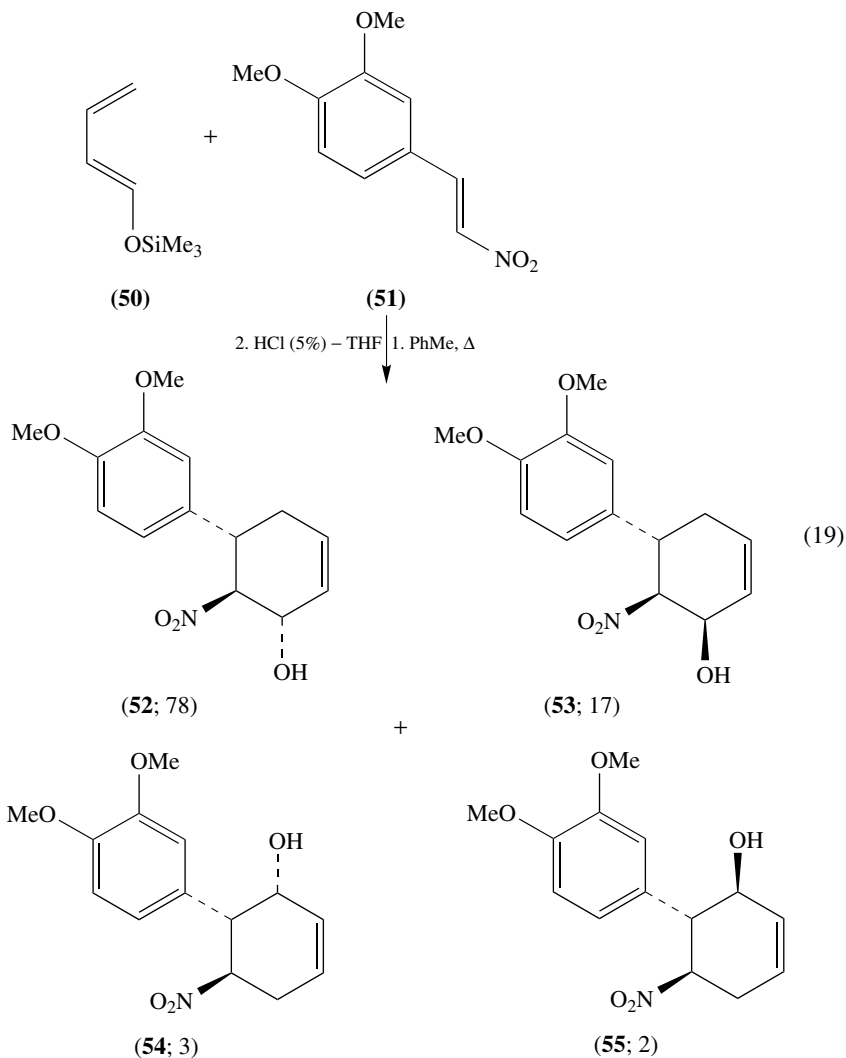
As a part of a broad study dealing with the development of synthetic methods for polycyclic aromatic compounds, Minuti and colleagues[77] prepared some [5]phenacenes and fluorenoanthracenes via Diels–Alder reactions between dienes such as **59** and several activated dienophiles. Oxidation of the primary adducts with DDQ afforded the desired polycyclic aromatic compounds. Equation 21 shows the reaction between 3,4-dihydro-1-vinylanthracene **(59)** and *in situ* generated 2-inden-1-one **(60)** which afforded a 3 : 1 mixture of regioisomers **61** and **62** with 51% overall yield.
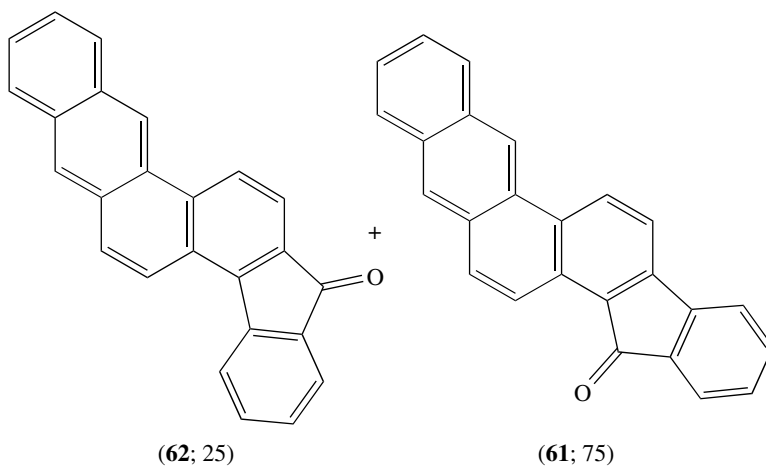
(20)

(**56**)   (**57**)

2. DDQ, benzene, Δ | 1. benzene, RT

(**58**)

(**59**)   (**60**)

2. DDQ | 1. CCl₄, Δ

(21)

(**62**; 25)   (**61**; 75)

Ohfune and coworkers[78] used Diels–Alder reactions between 2-trimethylsilyloxy-1,3-butadiene (63) and acrylate esters 64 to synthesize constrained L-glutamates which they intended to use for the determination of the conformational requirements of glutamate receptors. The reactions between 63 and acrylate esters 64a and 64b did not proceed. Changing the ethyl and methyl ester moieties into more electron-deficient ester moieties, however, led to formation of Diels–Alder adducts, the yields being moderate to good. In nearly all cases, the cycloadducts were obtained as single diastereomers, which is indicative of a complete facial selectivity (equation 22, Table 1). Other dienes, e.g. cyclopentadiene and isoprene, also showed a markedly enhanced reactivity toward acrylate 64g in comparison with acrylate 64a.

(22)
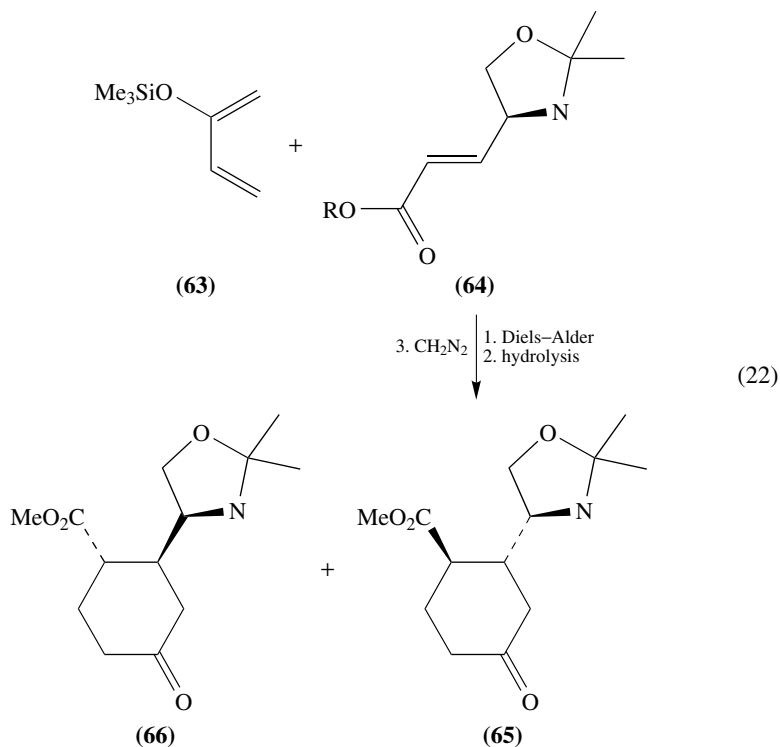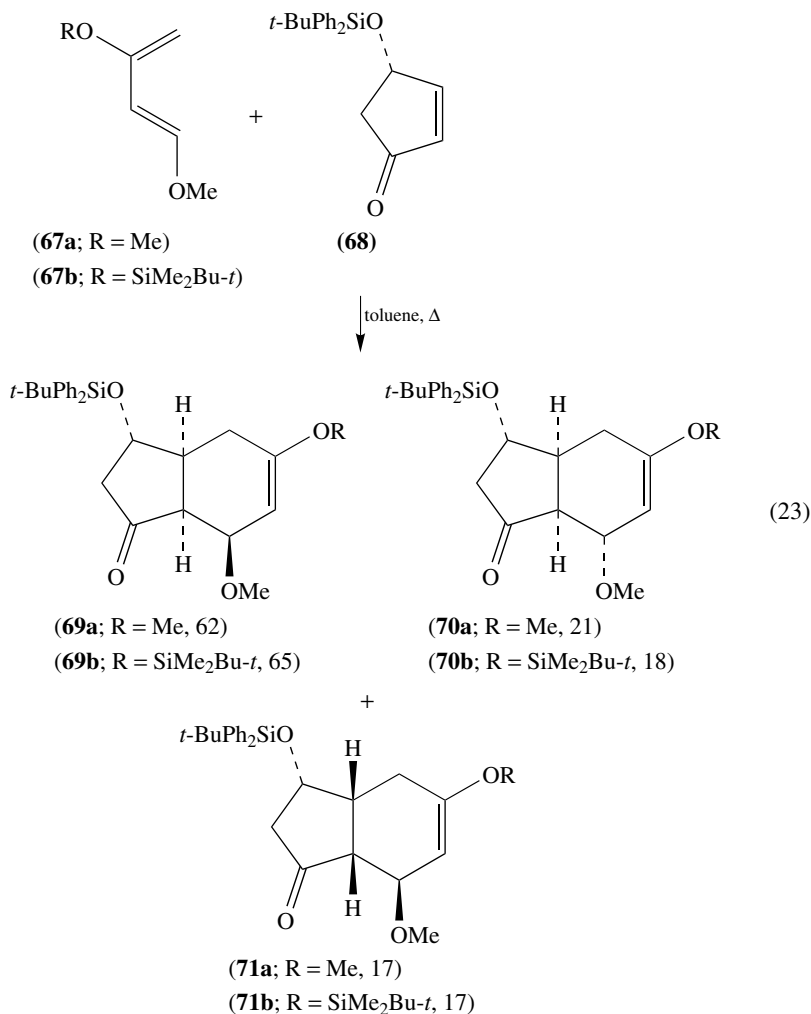
TABLE 1. Data for reaction 22

Entry	R	Dienophile	T (°C)	Yield (%)	65/66
1	Me	64a	160	—	
2	Et	64b	160	—	
3	CH_2CF_3	64c	130	47	80/20
4	$CH(CF_3)_2$	64d	130	71	100/0
5	Ph	64e	130	—	
6	p-$NO_2C_6H_4$	64f	130	52	100/0
7	C_6F_5	64g	130	84	100/0

Rokach and colleagues[79] made use of a Diels–Alder approach to synthesize iso-prostanes. Starting with dienes **67a/67b** and enantiomerically pure (>99% ee) dienophile **68**, they were able to obtain the desired adducts with high diastereofacial and regioselectivities (equation 23). *Endo* **69** and *exo* **70** were formed by attack of the diene at the less shielded upper face of the dienophile, whereas *exo* **71** resulted from attack at the more shielded lower face of **68**.

RO

t-BuPh$_2$SiO

+

OMe

O

(**67a**; R = Me)

(**67b**; R = SiMe$_2$Bu-*t*)

(**68**)

toluene, Δ

t-BuPh$_2$SiO   H

OR

O   H

OMe

(**69a**; R = Me, 62)

(**69b**; R = SiMe$_2$Bu-*t*, 65)

t-BuPh$_2$SiO   H

OR

O   H

OMe

(**70a**; R = Me, 21)

(**70b**; R = SiMe$_2$Bu-*t*, 18)

(23)

+

t-BuPh$_2$SiO   H

OR

O   H

OMe

(**71a**; R = Me, 17)

(**71b**; R = SiMe$_2$Bu-*t*, 17)

The Diels–Alder reaction has also been used to prepare special reagents. Thomas and coworkers[80], for instance, studied the Diels–Alder reactions of methyl (*E*)- and (*Z*)-3-(triphenylstannyl)acrylates **72a** and **72b** with cyclopentadiene and converted the organostannanes obtained to tin hydrides. (*E*)-**72a** afforded *endo* **73** exclusively with 99% yield, whereas (*Z*)-**72b** afforded a 2 : 1 mixture of *endo* **74** and *exo* **75** with 77% overall yield (equation 24). Cycloadduct **73** was easily converted to tin hydride **76**. By

extending this strategy to the use of chiral 3-(triphenylstannyl)acrylates, chiral tin hydrides were produced with high enantiomeric excesses[81].

(24)
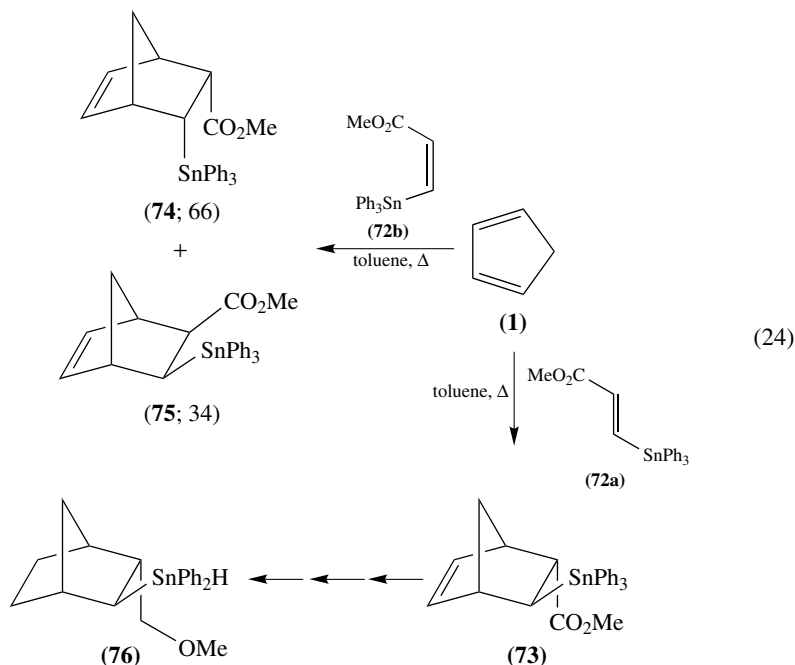
2. Lewis acid catalyzed Diels–Alder reactions

Lewis acid catalysts are often applied in Diels–Alder chemistry to enhance the reaction rate by co-ordinating to the dienophile, thereby lowering its LUMO energy. The catalyzed Diels–Alder reactions can, and usually *must*, be performed at lower temperatures and generally show an improved regioselectivity in comparison with the corresponding thermal reactions. New types of Lewis acids and Lewis acid mediated Diels–Alder reactions are published regularly, the following reactions being representative recent examples.

Baldwin and coworkers[82] studied the Diels–Alder reactions between dihydropyridinium ions and diene **77** with the aim to synthesize functionalized hydroisoquinolines. The reaction of diene **77** with dihydropyridinium ion **79**, which was prepared *in situ* by treating **78** with zinc bromide, afforded **80**. After acidic work-up, a mixture of methoxyketone **81** and enone **82** was obtained (equation 25). The reaction proceeded with complete *exo* selectivity. Without the addition of zinc bromide, no Diels–Alder reaction was observed.

Danishefsky and coworkers[83] used a dioxolenium mediated Diels–Alder reaction between **83** and **85**, generated from **84**, in their total synthesis of dysidiolide **(87)** (equation 26). The Diels–Alder reaction, using trimethylsilyl triflate as the dioxolenium generating species, proceeded with high facial, *endo* and regioselectivity affording **86** as the main product, together with 5% of a yet unidentified stereoisomer.

Desimoni and coworkers[84] probed the catalytic effect of metal perchlorate salts on the rate of the Diels–Alder reactions between malonates **88** and cyclopentadiene (equation 27). They found that especially magnesium perchlorate was able to catalyze the reaction by binding two malonates in a bidentate fashion. Reaction times were shortened up to 1000 times. The *endo/exo* selectivity was inverted from **89/90** = 40/60 ($n = 4$) and 17/83 ($n = 5$) for the thermal uncatalyzed reactions to **89/90** = 60/40 ($n = 4$) and 80/20 ($n = 5$) for the magnesium perchlorate catalyzed reactions.

Because of their previous findings that α,β-unsaturated thioesters were more reactive than their ester counterparts in Diels–Alder reactions[85], Hart and coworkers[86] performed a systematic study of the cycloaddition reactions of α,β-unsaturated thioesters and α,β-unsaturated selenoesters with several dienes. Thermal reactions were compared with Lewis acid catalyzed reactions at room temperature (equation 28 and Table 2). The results clearly demonstrated that use of a Lewis acid enhanced the regioselectivity (entries 1 *vs* 2, 3 *vs* 4, 5 *vs* 6 and 7 *vs* 8) as well as the *endo* (with respect to the thioester or selenoester group) selectivity (entries 5 *vs* 6 and 7 *vs* 8).

Hubbard and Miller[87] used a Lewis acid catalyzed Diels–Alder reaction between γ,γ-disubstituted α,β-unsaturated esters and cyclopentadiene in their approach toward oligomeric cyclopentanoids. In order for the reaction to proceed, they needed to add trimethylaluminum as a desiccant prior to addition of the Lewis acid catalyst aluminum trichloride. The *endo/exo* selectivity of the reaction with **97**, depicted in equation 29, increased from **98/99** = 75/25 to 88/12 when the reaction temperature was dropped from room temperature to $-20\,^{\circ}$C.
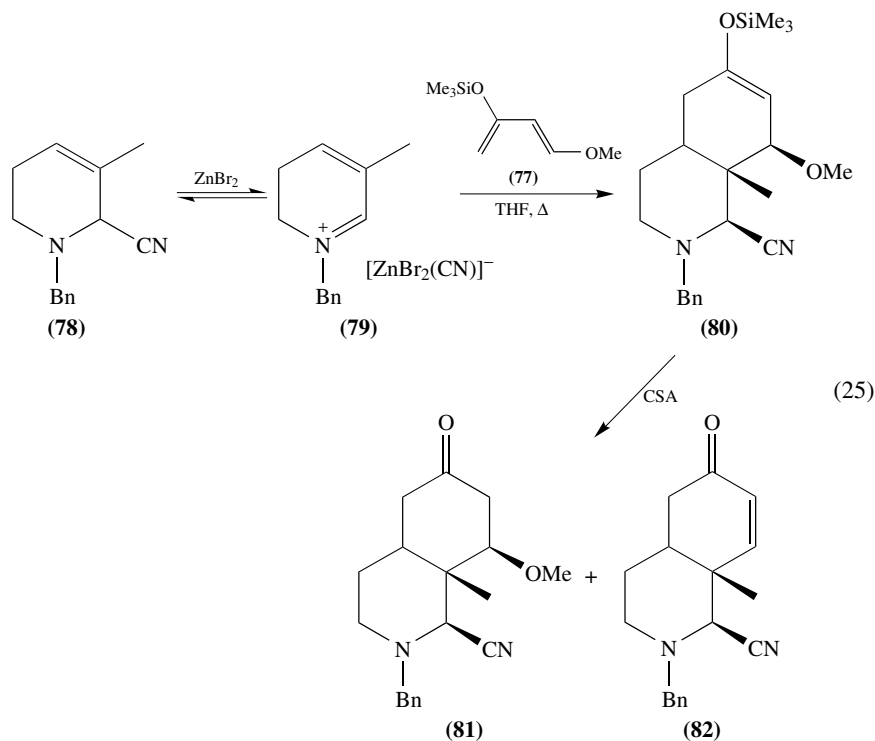
CSA = 10-Camphorsulfonic acid

(26)

(27)

(28)
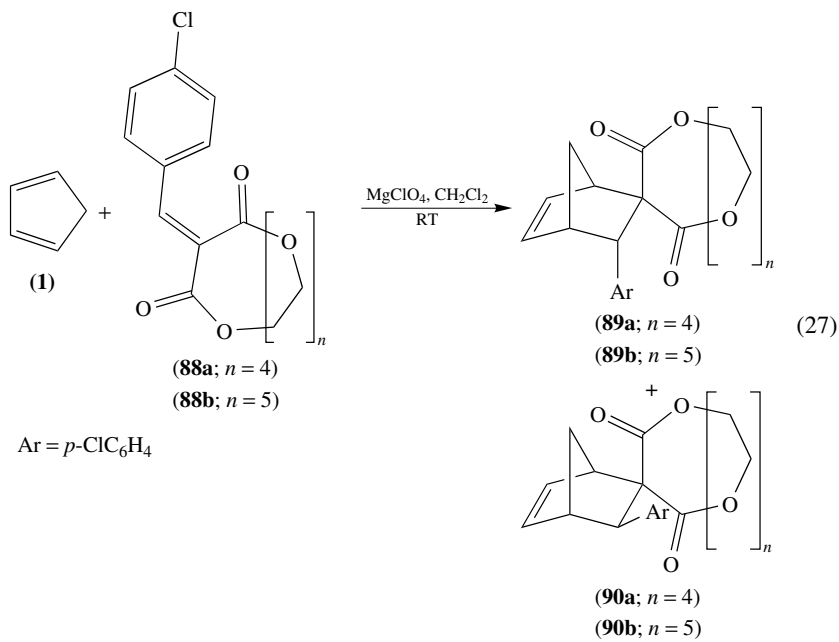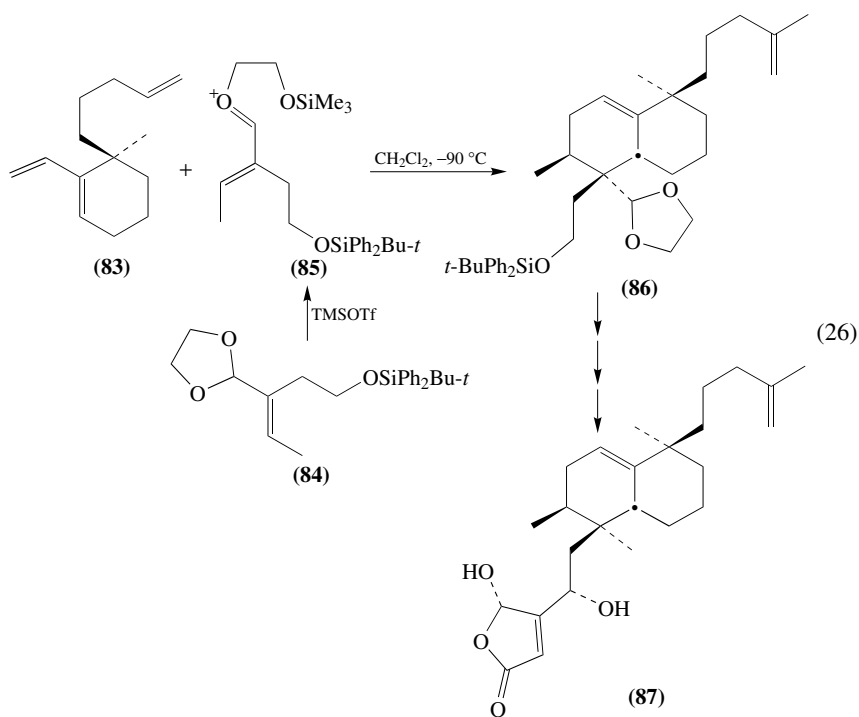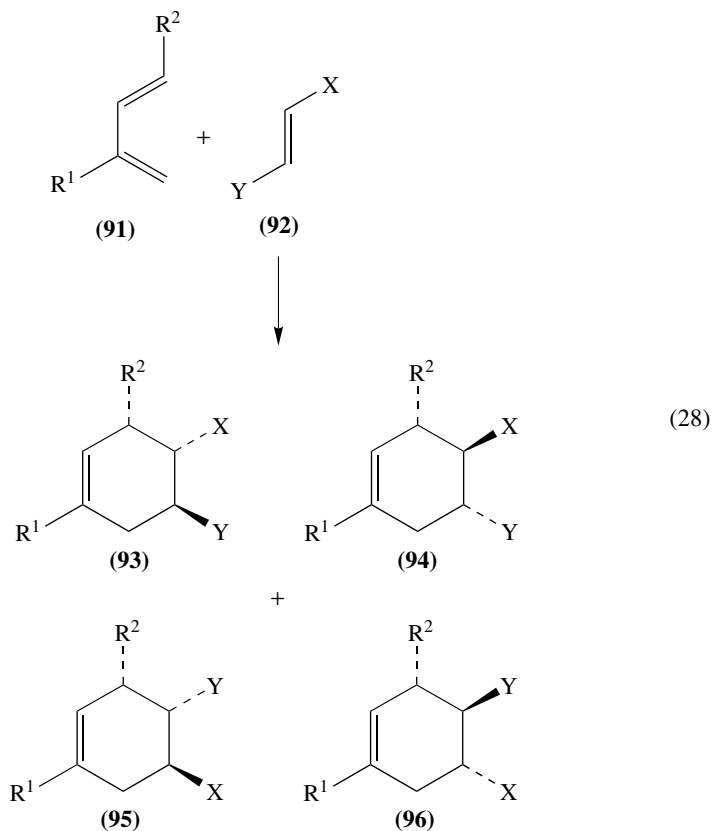
Oi and coworkers[88] employed a cationic palladium(II) complex to catalyze Diels–Alder reactions. The benefits of such a catalyst compared to traditional catalysts such as boron and aluminum halides were reported to possess better stability to air and moisture,

TABLE 2. Reaction conditions and product distribution for equation 28

Entry	R^1	R^2	Diene	X	Y	Dienophile	Conditions	**93/94/95/96**
1	Me	H	**91a**	COSPh	Me	**92a**	190–195 °C	63/37
2	Me	H	**91a**	COSPh	Me	**92a**	EtAlCl$_2$, RT	88/12
3	Me	H	**91a**	COSePh	CO$_2$Me	**92b**	190–195 °C	55/45
4	Me	H	**91a**	COSePh	CO$_2$Me	**92b**	TiCl$_4$, RT	100/0
5	H	Me	**91b**	COSPh	CO$_2$Me	**92c**	185–195 °C	29/27/24/20
6	H	Me	**91b**	COSPh	CO$_2$Me	**92c**	EtAlCl$_2$, RT	67/14/16/3
7	H	Me	**91b**	COSePh	Me	**92d**	185–195 °C	34/56/10/0
8	H	Me	**91b**	COSePh	Me	**92d**	EtAlCl$_2$, RT	80/20/0/0
9	OSiMe$_3$	H	**63**	COSPh	Me	**92e**	185–195 °C	>95/<5
10	OSiMe$_3$	H	**63**	COSePh	Me	**92f**	185–195 °C	>95/<5
11	OSiMe$_3$	H	**63**	COSPh	CO$_2$Me	**92g**	TiCl$_4$, RT	95/5
12	OSiMe$_3$	H	**63**	COSePh	CO$_2$Me	**92h**	TiCl$_4$, RT	100/0

higher turnover numbers and better-defined structures. A typical example of a reaction catalyzed by Oi's palladium complex is the reaction between methyl vinyl ketone **(100)** and cyclopentadiene (equation 30), which afforded a mixture of *endo/exo* isomers


(29)

(30)
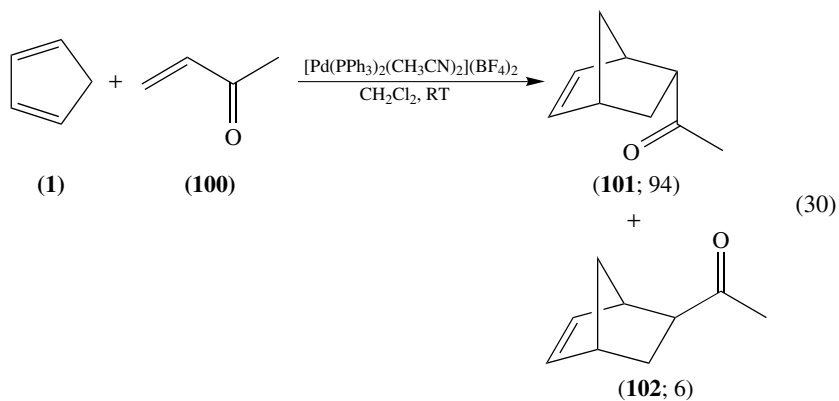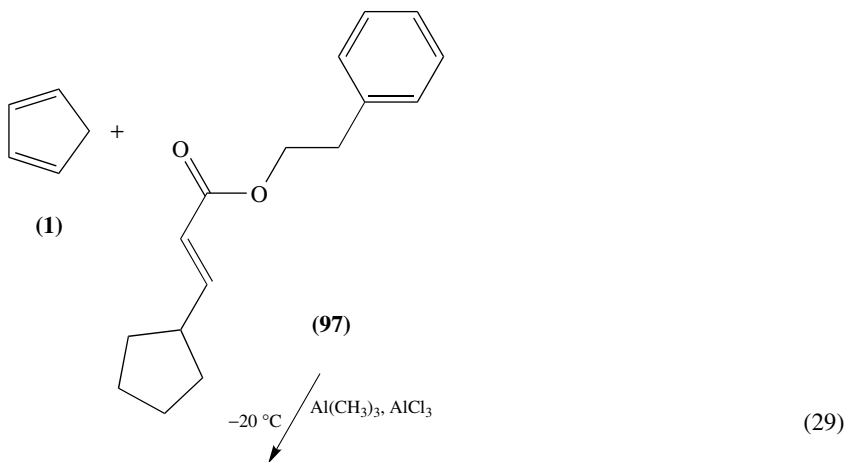
($\mathbf{101}/\mathbf{102} = 94/6$) in 94% overall yield. By replacing the two triphenylphosphine ligands by a chiral bidentate ligand, Oi and colleagues were able to conduct enantioselective Diels–Alder reactions.

3. Non-Lewis acid catalyzed Diels–Alder reactions

In recent years, supramolecular chemistry has produced a number of systems which have been shown to be able to effectively catalyze a Diels–Alder reaction. Most systems selectively afforded only one diastereomer because of a pre-organized orientation of the reactants. These systems include cyclodextrines, of which applications in Diels–Alder chemistry have recently been reviewed[89]. Some other kinds of non-Lewis acid catalyzed Diels–Alder reactions, including catalysis by proteins and ultrasound, have been discussed by Pindur and colleagues[90].

Kelly and colleagues[91] explored the use of bisphenylenediol **103** as a catalyst in Diels–Alder reactions of α,β-unsaturated carbonyl compounds. Activation of the dienophile occurred through double hydrogen bonding of the two hydroxyl functions on **103** to the carbonyl group on the dienophile. The reaction of cyclopentadiene with methyl vinyl ketone (equation 31) at ambient temperature showed, after a reaction time of 10 minutes, 3% of product formation in the absence of **103** against 90% of product formation in the presence of 0.4 equivalents of **103**.
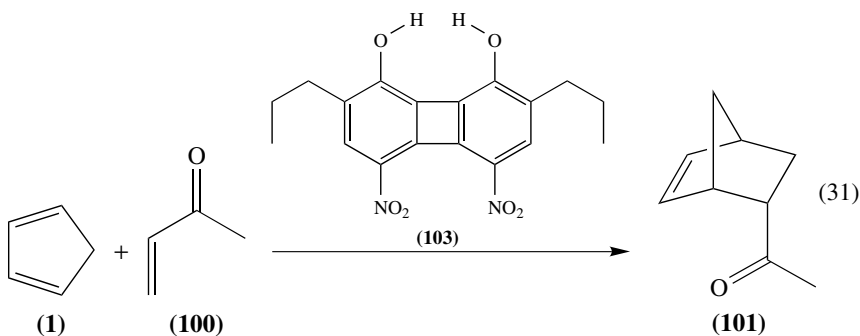

Rebek and colleagues[92] were able to accelerate the reaction of p-benzoquinone with several dienes, e.g. 1,3-cyclohexadiene and cyclopentadiene, by encapsulating the reaction partners into a pseudospherical capsule **105** built up of two self-assembling multiring compounds **104**. The effective molarities of the reaction partners in the reaction of 1,3-cyclohexadiene with p-benzoquinone, which afforded exclusively the *endo* cycloadduct, were more than 100 times higher than the corresponding concentrations in the bulk solution. Product inhibition prevented the system from turning over and offering true catalysis. That is why first-order kinetics were only observed till approximately 10% conversion was reached.

When thiophene dioxide (**106**) was used as the diene component, true catalysis was observed with **107**, affording the capsule bound adduct **108** (equation 32)[93]. The displacement of a single molecule of adduct by two molecules of starting material is, in principle, disfavored on entropic grounds, but turnover took place in this case due to the poorer affinity of the Diels–Alder adduct for the capsule. The rate enhancement of this reaction, based on the ratio of the half-life for the reaction outside *vs* inside the capsule, was 10-fold.
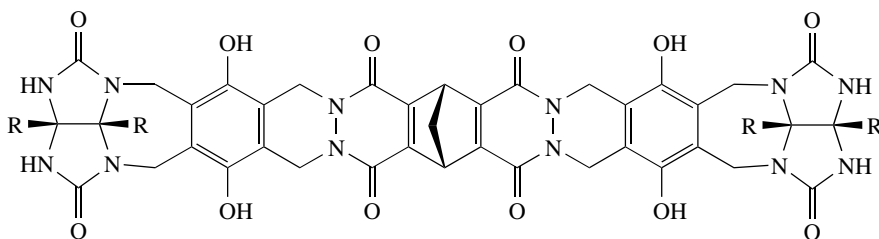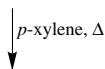
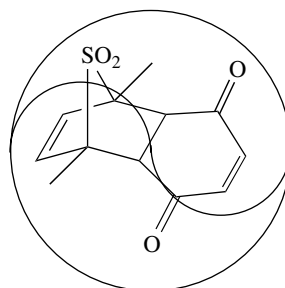(**104**; R = 4-*n*-heptylphenyl)

(**105**)   (**106**)   (**107**)

| *p*-xylene, Δ
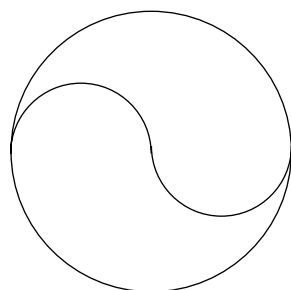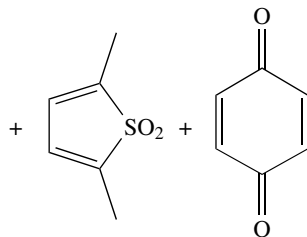
(32)

(**108**)

Philp and Robertson[94] developed a system which is capable of controlling the stere-ochemical outcome of the Diels–Alder reaction between a maleimide and a furan. By attaching functional groups which can recognize each other to both maleimide and furan, they were able to get a rate acceleration and a much higher *endo* selectivity compared to the control reaction of benzyl maleimide with furan **109**. Whereas the bulk concentrations were 5 mM in both reactants **109** and **110**, effective molarities of 64 mM and 6 mM were achieved within the *endo* and *exo* [**109** : **110**] complexes, respectively (equation 33). This difference, together with the fact that the *endo* adduct **111** is stabilized by an intramolec-ular hydrogen bond which makes the retro Diels–Alder reaction more difficult, caused the *exo* adduct **112** to be the minor adduct.

(33)
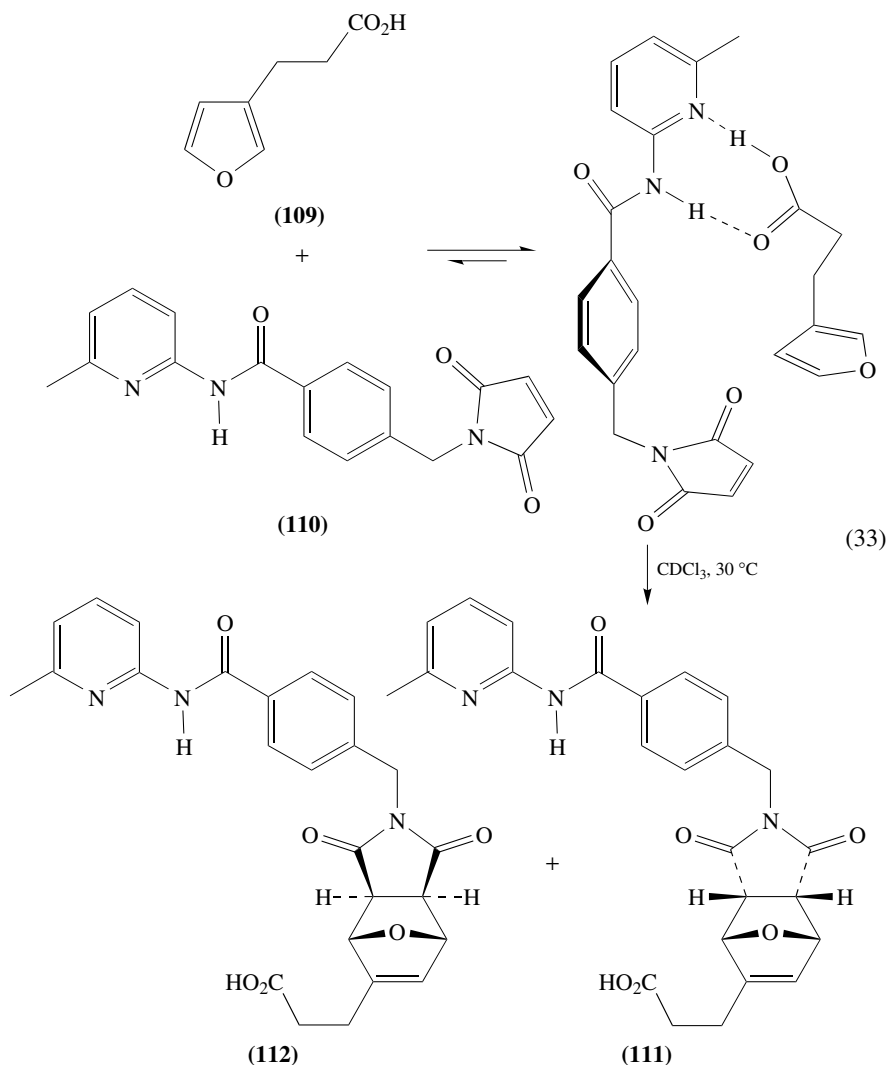
Wang and Sutherland[95] communicated an autocatalytic Diels–Alder reaction in which the adduct of diene **113** and olefin **114** catalyzed its own formation. This was accomplished through binding of both reactants in a pre-organized fashion by means of multiple hydrogen bonding (see complex below structures **113** and **114** overleaf).

Sanders and coworkers[96,97] catalyzed and directed the Diels–Alder reaction between 4-(maleimidomethyl)pyridine and 4-(3-furyl)pyridine using metalloporphyrin oligomers. When trimer **115a** having three butadiyne linkers was used as the catalyst, the *exo* adduct was the exclusive product isolated at both 30 °C and 60 °C, whereas the uncatalyzed reaction provided an *endo/exo* ratio of 2/1 at 30 °C and a transient trace of *endo* adduct

**(113)**   **(114)**
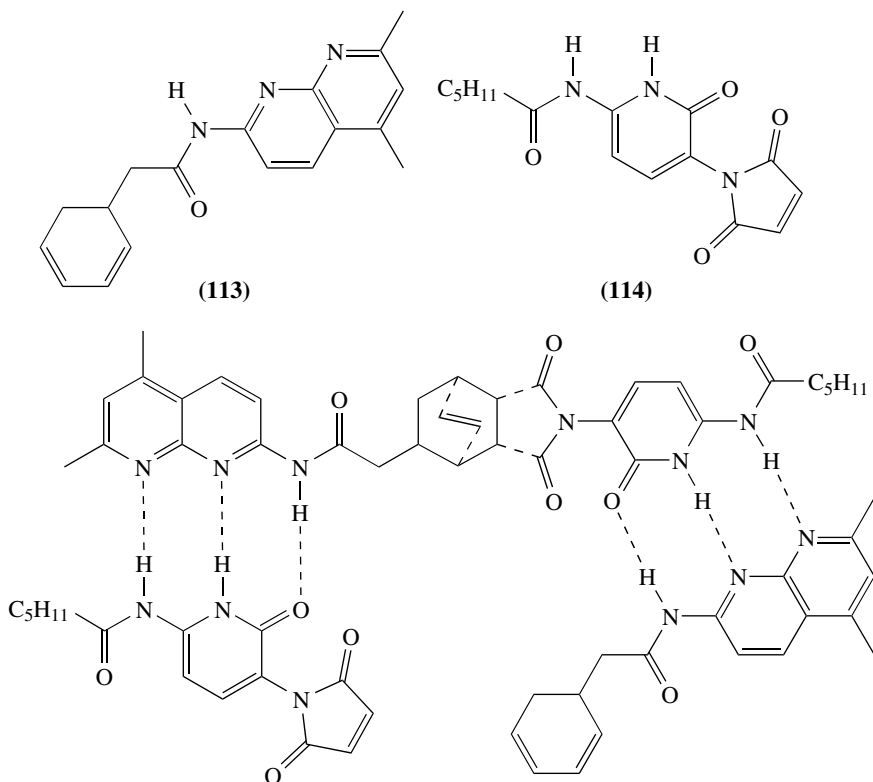
at 60 °C due to cycloreversion. When trimer **115b** was employed, the *endo* adduct was formed exclusively at 30 °C, whereas a mixture of *endo* and *exo* adducts was obtained at 60 °C. These results were considered to result from stabilization of the *exo* transition state by co-ordination of the pyridine nitrogens to two zinc ions in the case of trimer **115a** and stabilization of the *endo* transition state, in which the pyridine nitrogens are closer together, in the case of the smaller trimer **115b**.

Endo and coworkers[98] were able to catalyze the Diels–Alder reaction between acrolein and 1,3-cyclohexadiene by using a novel organic network material built up of anthracene-bisresorcinol derivatives which were held together by intermolecular hydrogen bonds. The suggested catalytic cycle was composed of sorption of the reactants in the cavities of the material, a pre-organized intracavity reaction, and desorption of the adduct.

Harman and colleagues[99] studied the activation of styrenes toward Diels–Alder reactions by application of a pentaammineosmium(II) complex. Cycloaddition reactions between styrenes and dienophiles generally require harsh reaction conditions, low yields and side products being the logical result. By complexing the phenyl ring with a pen-taammineosmium(II) complex, thereby partly localizing the π system, it proved possible to perform Diels–Alder reactions with a wide variety of dienophiles under mild con-ditions. The reactions proceeded with almost complete site selectivity, the *inner–outer* diene system of **116** being the preferred site of attack, as illustrated by the reaction with

N-methylmaleimide **(117)** depicted in equation 34. Cycloadduct **118** can be decomplexed by a variety of reagents, e.g. silver triflate, affording the free adduct **119**.

(**115a**; *n* = *m* = 2, R = CH₂CH₂CO₂Me)
(**115b**; *m* = 2, *n* = 1, R = CH₂CH₂CO₂Me)
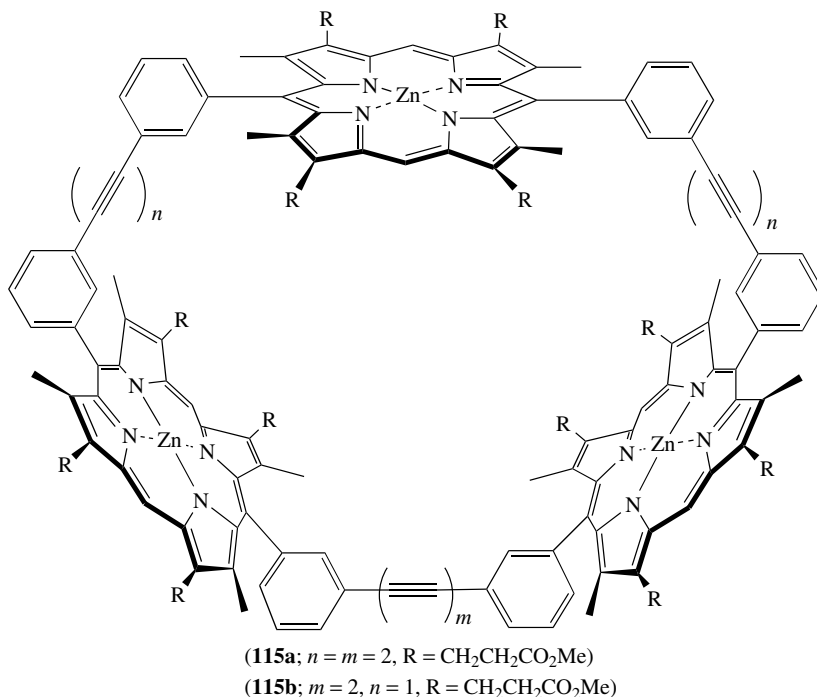
Kita and coworkers[100] reported the strong base catalyzed cycloaddition reactions between 4-phenylthio-substituted homophthalic anhydrides and various sulfinyl substituted dienophiles. The cycloaddition of **120** to **121a** afforded, after elimination of the sulfinyl group and extrusion of carbon dioxide under the reaction conditions employed, **122** as the ultimate reaction product (equation 35). The presence of the sulfinyl group proved essential for a sufficient activity of the 1,2-dicarbonyl substituted double bond of **121**, because substitution of the sulfinyl group by other leaving groups, e.g. Cl or Br (cf **121b** and **121c**), greatly diminished the reaction rate.

A modern method of catalysis is the application of microwave irradiation, which has, however, been used only sparingly to accelerate Diels–Alder reactions. Rao and colleagues[101] studied the differences in reaction rates between thermally and microwave activated Diels–Alder reactions of 1,2-difluoro-1-chlorovinyl phenyl sulfone **(123)** with several cyclic dienes. For example, the thermal reaction between **123** and cyclopentadiene took 10 hours in refluxing toluene for completion, whereas the microwave assisted reaction took only 3 minutes, affording *exo* adducts **124** and **125** in 95% yield and a **124/125** = 40/60 ratio (equation 36). Likewise, the reaction of **123** with furan did not take place under thermal conditions, whereas it proceeded within 7 minutes in the microwave, yielding the *endo* cycloadduct with 40% yield. The *endo* selectivity was considered to originate from secondary orbital interactions between the fluorine atoms and the bridged oxygen atom.

(34)

(35)

(**1**)   (**123**; *E/Z* = 40/60)   (**124**; 40)   (**125**; 60)

$$(36)$$
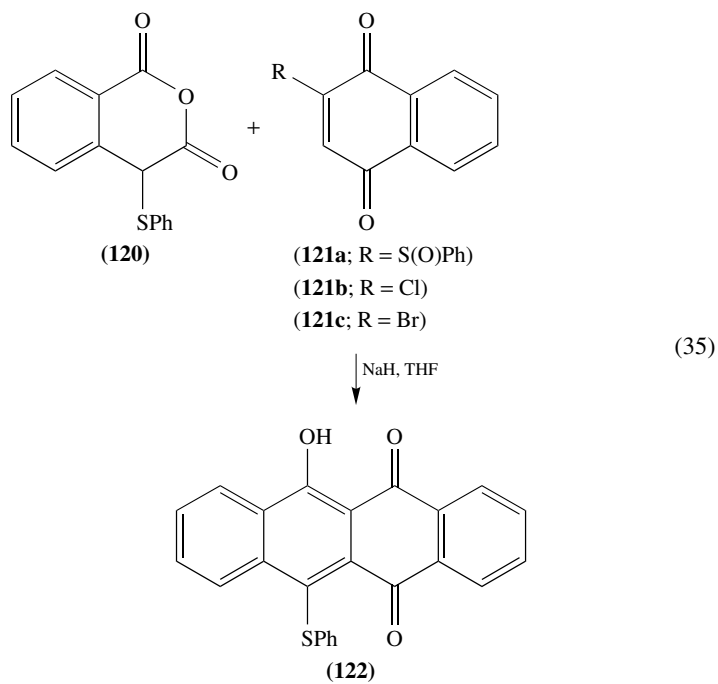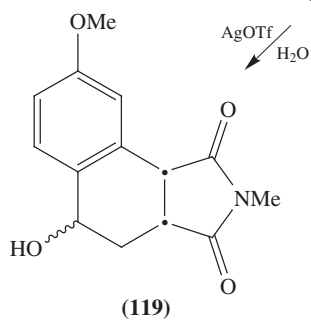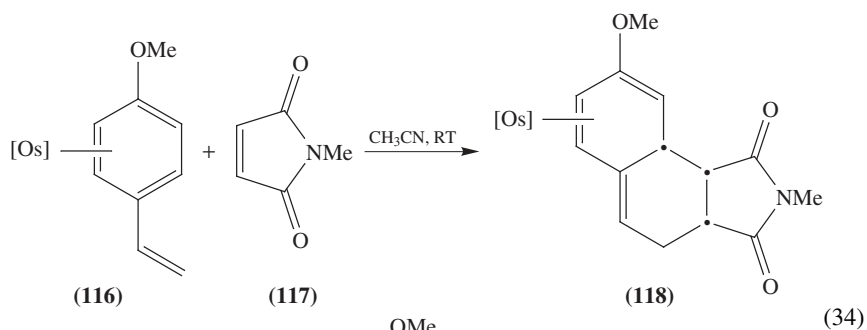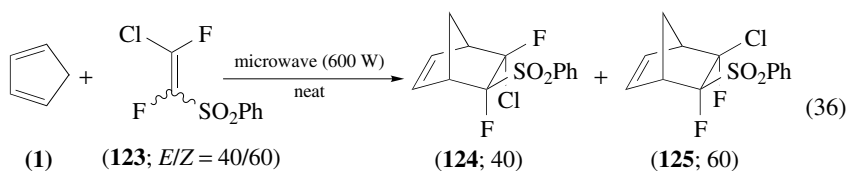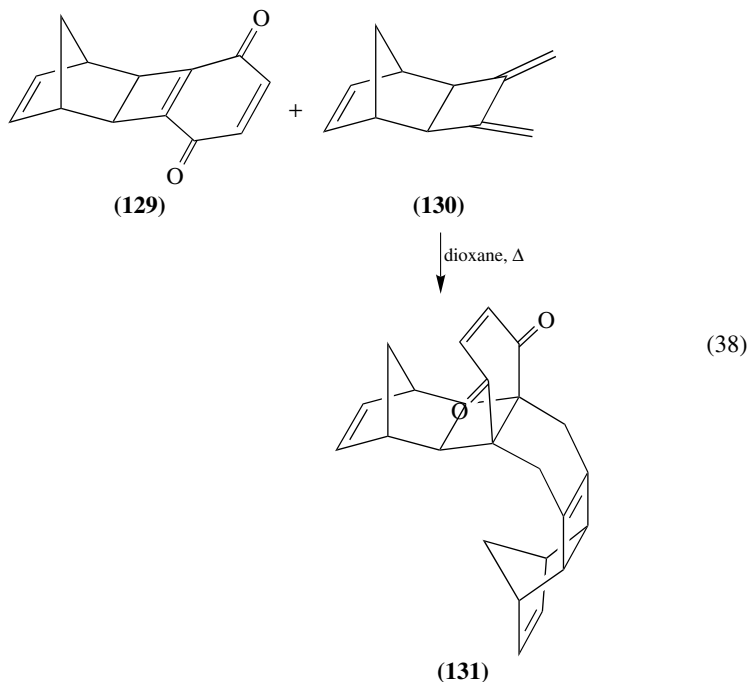
4. Site selective reactions

Dienophiles may contain more than one double or triple bond. This might result in multiple product formation, but in most instances the diene will attack one bond with high site specificity. This site selectivity is often controlled by substitution patterns and electronic or steric parameters.

Marchand and coworkers[102] reported a difference in site selectivity between the thermodynamically and kinetically controlled Diels–Alder reactions of cyclopentadiene with 2,3-dicyano-*p*-benzoquinone (**126**) (equation 37). Under kinetic conditions, the more reactive double bond of **126** reacted with cyclopentadiene affording **127**, whereas the less substituted double bond reacted under thermodynamic conditions affording **128**. Both reactions proceeded with complete *endo* selectivity. These findings were in agreement with *ab initio* HF/3–21G* calculations.

(**127**)   (**126**)
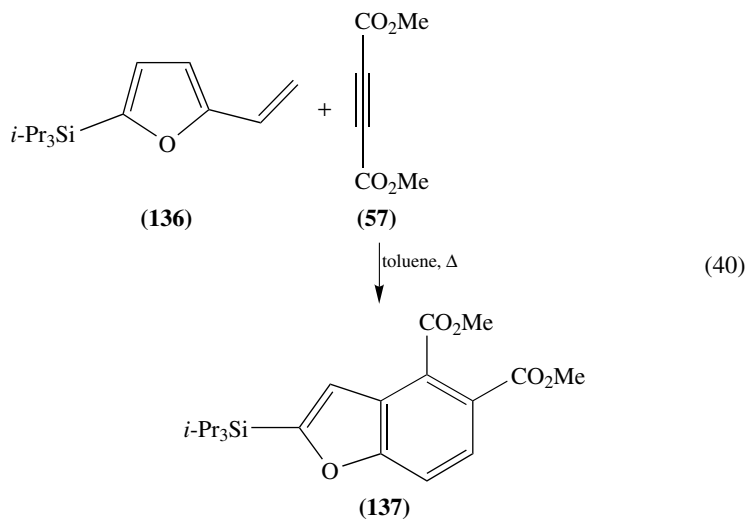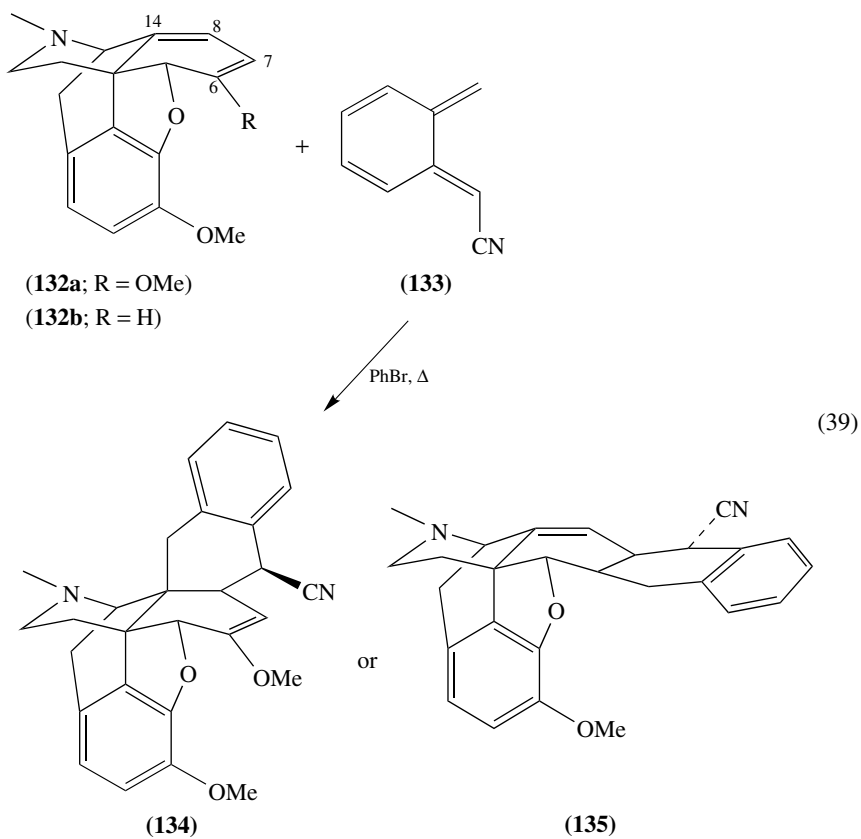
$$(37)$$

(**128**)
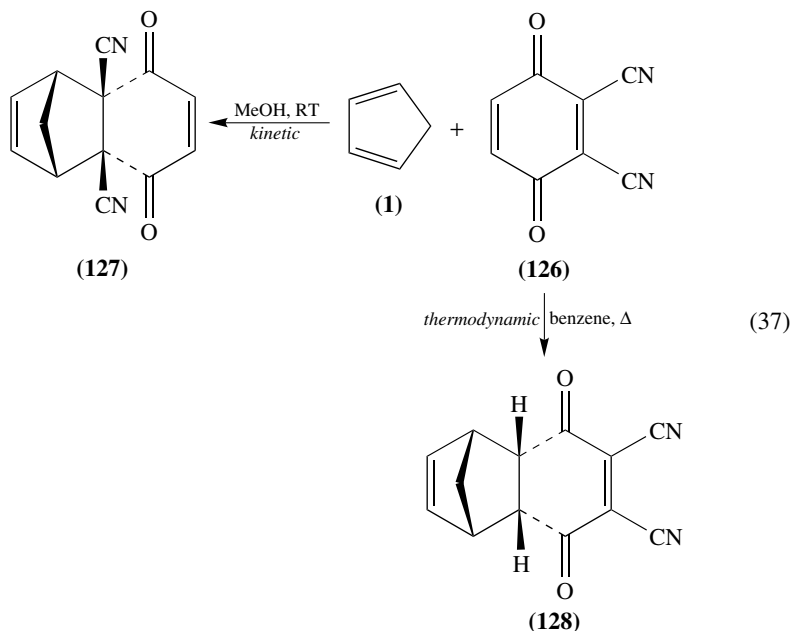
In general, 2,3-dialkyl-*p*-benzoquinones exhibit site selectivity in that they tend to give predominantly Diels–Alder adducts resulting from diene attack on the external rather than the internal double bond. This external site selectivity is, however, dramatically reversed when a (substituted) cyclobutane ring is fused to *p*-benzoquinone. Paddon-Row and coworkers[103] studied the reactions of *p*-benzoquinones such as **129** with several

dienes. The reaction with diene **130**, for example, afforded **131** as the exclusive adduct (equation 38). The complete site selectivity was explained by the great relief of strain upon cycloaddition to the internal double bond. This was confirmed by *ab initio* calculations which showed the transition states of the *endo* and *exo* internal cycloadditions to be 3.0 and 4.3 kcal mol^{-1} more stable, respectively, than those of the corresponding external cycloadditions.

(129)   +   **(130)**

dioxane, Δ

(38)

(131)

Portoghese and colleagues[104] employed opiate dienes **132** as dienophiles in the reactions with *in situ* generated **133** and studied the site selectivity in these reactions. When thebaine **(132a)** was reacted with **133**, the Diels–Alder reaction took place at the 8(14) double bond affording **134**, the diene approaching from the less hindered β face of **132a** (equation 39). According to the authors, the methoxy substituted double bond is too electron-rich to react with **133**. This was confirmed by the non-reactivity of the thebaine derivative obtained by hydrogenation of the 8(14) double bond. When **132b** was employed as the dienophile, the reaction took place at the less substituted double bond at C(6) affording **135**.

The Diels–Alder reactions of 'dienes' that have two or more pairs of conjugated double bonds may also exhibit site selectivity, as has been demonstrated by several groups[105]. Talamás and coworkers[106] found complete site selectivity when 5-triisopropylsilyl-2-vinylfuran **(136)** was reacted with dimethyl acetylenedicarboxylate, affording **137** (equation 40), and several other dienophiles. The same extra-annular site selectivity was found for 2-triethylsilyl-4-vinylfuran. The large silyl groups apparently block the intra-annular cycloaddition. When the triisopropylsilyl group on **136** was replaced by a tri(*n*-butyl)stannyl group, site selectivity diminished, probably because of a decreased bulkiness and a longer carbon–metal bond.

(**132a**; R = OMe)
(**132b**; R = H)

(**133**)

PhBr, Δ

(39)

(**134**)   or   (**135**)

(**136**)   (**57**)

toluene, Δ   (40)

(**137**)

5. Tandem reactions

Tandem pericyclic processes offer the opportunity to synthesize complex highly sub-stituted cyclic molecules in a completely stereocontrolled fashion in a few consecutive steps. As a consequence, tandem processes have been studied extensively. Some tandem processes involving Diels−Alder reactions have recently been reviewed[38,40,107].

Seitz and colleagues[108] made 10-ethylcolchicide (**138**), a colchicine derivative, react with several dienophiles. The reaction of **138** with dimethyl acetylenedicarboxylate (**57**) afforded a single Diels−Alder adduct (**139**) which underwent a consecutive [3 + 2] cyclo-addition with another equivalent of dimethyl acetylenedicarboxylate to give **140**. The formal elimination of C_2H_6 afforded **141**, whereas fragmentation led to **142** (equation 41).

Dailey and colleagues[109] employed a 'domino' Diels−Alder reaction to synthesize the complex hexacycle **146**. The intermolecular reaction of tetracycle **143** with maleic anhy-dride **144** afforded a single adduct (**145**) which immediately underwent an intramolecular Diels−Alder reaction to give **146** (equation 42). This reaction is similar to a reaction per-formed previously by Prinzbach and colleagues[110]. Prinzbach observed that when alkynes were used as dienophiles, either 'domino' or 'pincer' Diels−Alder reactions occurred. In the latter type, the triple bond reacts with both diene units.

Itoh and coworkers[111] carried out tandem [2 + 2 + 2]/[4 + 2] cycloadditions catalyzed by a ruthenium catalyst. The reaction of diyne **147** with excess norbornene **148** in the presence of ruthenium catalyst **153**, for example, afforded **149**. Adduct **150** either disso-ciated from the catalyst or reacted with another equivalent of norbornene. In the latter case, a ruthenium catalyzed Diels−Alder reaction occurred, affording hexacyclic adduct **152** via **151** (equation 43). Compounds **150** and **152** were obtained in yields of 78% and 10%, respectively. Both cycloaddition reactions proceeded with complete stereoselectiv-ity. When 1,6-heptadiyne was used instead of **147**, only trace amounts of a cycloadduct were obtained. Replacing norbornene by norbornadiene, which was expected to result in polymer formation, did not afford any adduct at all.
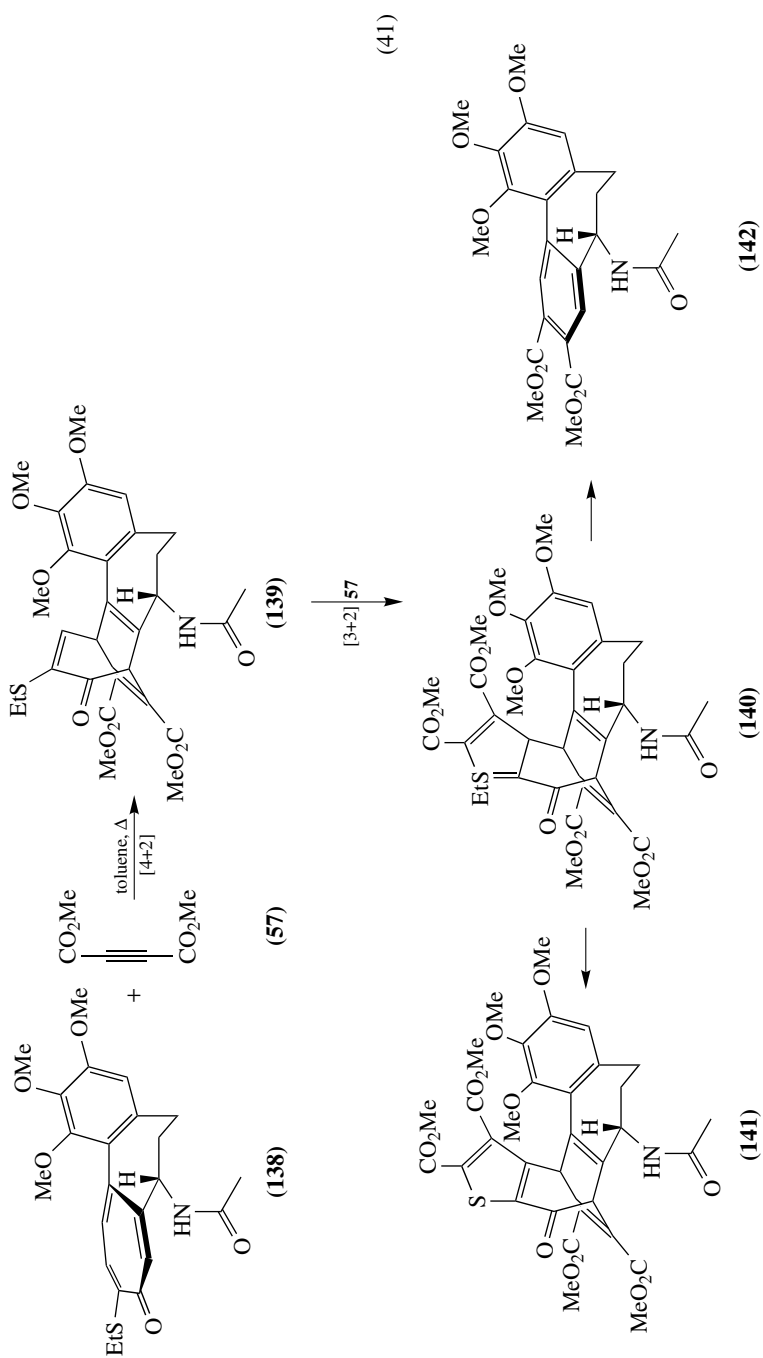
6. Diels−Alder polymerizations

Diels−Alder reactions have been used to synthesize and functionalize polymers, as reported by several groups. Rotello and coworkers[112], for example, covalently attached [60]fullerene to furan and cyclopentadiene substituted resins. The reaction with the furan substituted resin proved reversible. The resin was recovered by heating the fullerene functionalized resin.

Stranix and Darling[113] functionalized divinylbenzene-rich copolymers **154** by Diels−Alder reactions with both dienophiles and dienes. Treating polymer **154** with maleic anhydride (**144**) afforded polymer **155**. Re-aromatization to give **156** occurred by means of an ene reaction with another equivalent of **144** (equation 44).

Copolymers of [60]fullerene and *in situ* generated bis-*o*-quinodimethanes were prepared by Gügel and colleagues[114]. In order to get soluble polymers, it proved necessary to introduce flexible groups on the bis-*o*-quinodimethanes. A maximum of 10 [60]fullerene units were incorporated into oligomers when [60]fullerene was reacted with a 7 : 3 mixture of **157** and **158** (i.e. with *o*-quinodimethanes **159** and **160**). Monosulfone **158** was added to induce the formation of triple cycloadducts of [60]fullerene. This prevented polymerization of the oligomer (quadruple cycloadditions to [60]fullerene are hard to accomplish) and enhanced its solubility.

Kottner and Klemm[115] studied the Diels−Alder polymerization of bismaleimides with 4,4′-dimethyl-6,6′-(octamethylene)di-2-pyrone. When the maleimide units were connected

(41)

(138) + (57) $\xrightarrow[\text{[4+2]}]{\text{toluene, }\Delta}$ (139) $\xrightarrow[\text{57}]{\text{[3+2]}}$ (140)

(140) → (141)

(140) → (142)

via a flexible spacer group, polymers with a coronand structure were formed, together
with some cyclic oligomers.

(42)
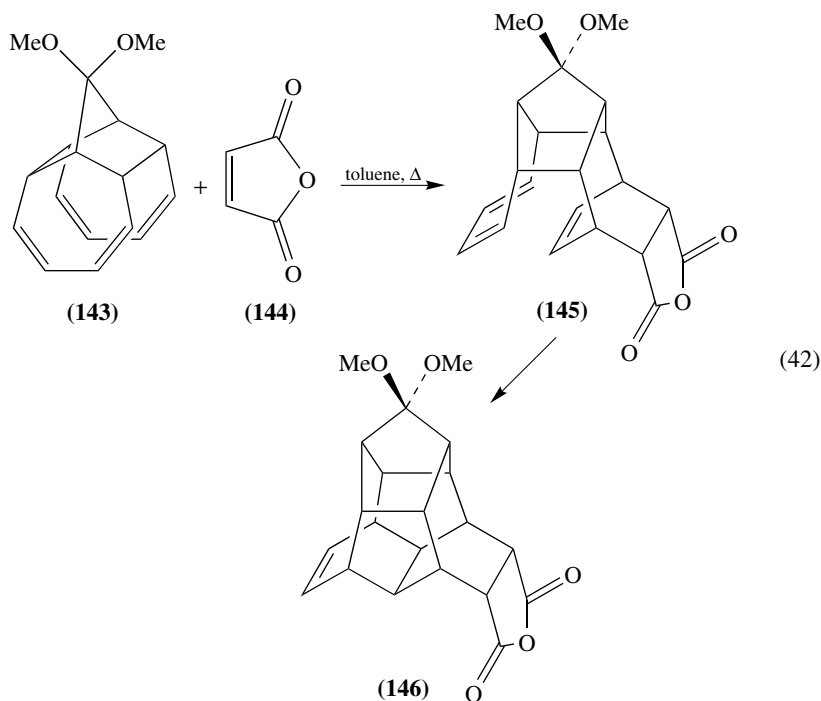
A rather novel application of the Diels−Alder reaction is the synthesis of dendrimers.
Müllen and coworkers[116] made cyclopentadienone **161** react with 3,3′,5,5′-tetraethynylbi-
phenyl **162**. This afforded, after extrusion of carbon monoxide, a first generation dendrimer
163 containing 22 phenyl rings (equation 45). Cyclopentadienone **161** reacted only as a
diene, since the bulky triisopropyl groups prevented the ethynyl functions from reacting.

7. Diels−Alder reactions of furans

Despite their aromatic character, furans have found widespread use as dienes in Diels−
Alder reactions[33]. The following examples have been intended to demonstrate the wide
applicability of and the ongoing interest in Diels−Alder reactions of this diene.

Copolymers with pendant furan moieties have been used to synthesize new polymer
structures by exploiting the reactivity of this heterocycle toward various dienophiles[117],
e.g. [60]fullerene[112b].

Gandini and coworkers[118] investigated the Diels−Alder reactions of furan rings attached
to a polymer with a polystyrene backbone. When copolymers **164a** and **164b** were
treated with excess N-phenylmaleimide (**165**), about 70% of the furan rings underwent a
Diels−Alder reaction to give **166a** and **166b**, respectively. When bismaleimide **167** was
used, cross-linking occurred to a high extent (equation 46). On heating polymer **168a** in the
presence of 2-methylfuran, **164a** was fully recovered by a sequence of retro Diels−Alder/
Diels−Alder reactions. Polymer **164b** was only partly regenerated using this same method.

(43)

(44)

(157)

(158)

(159)

(160)
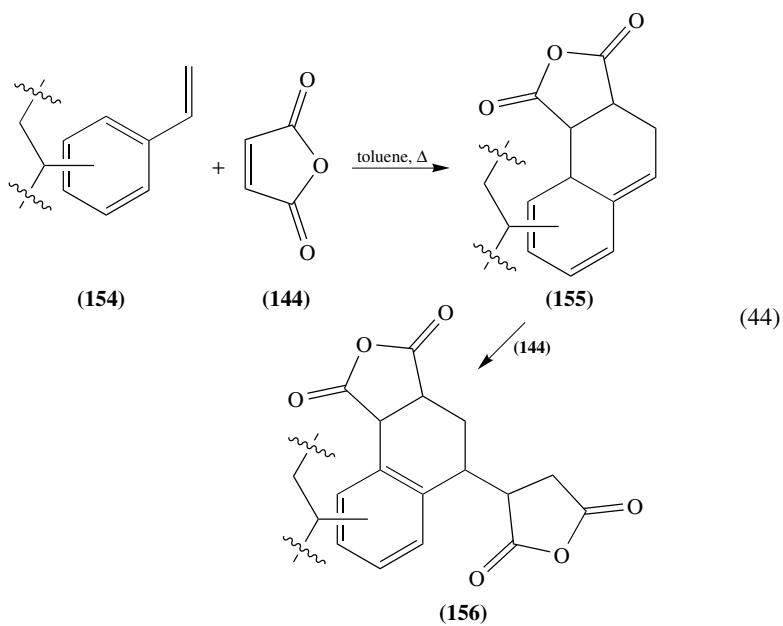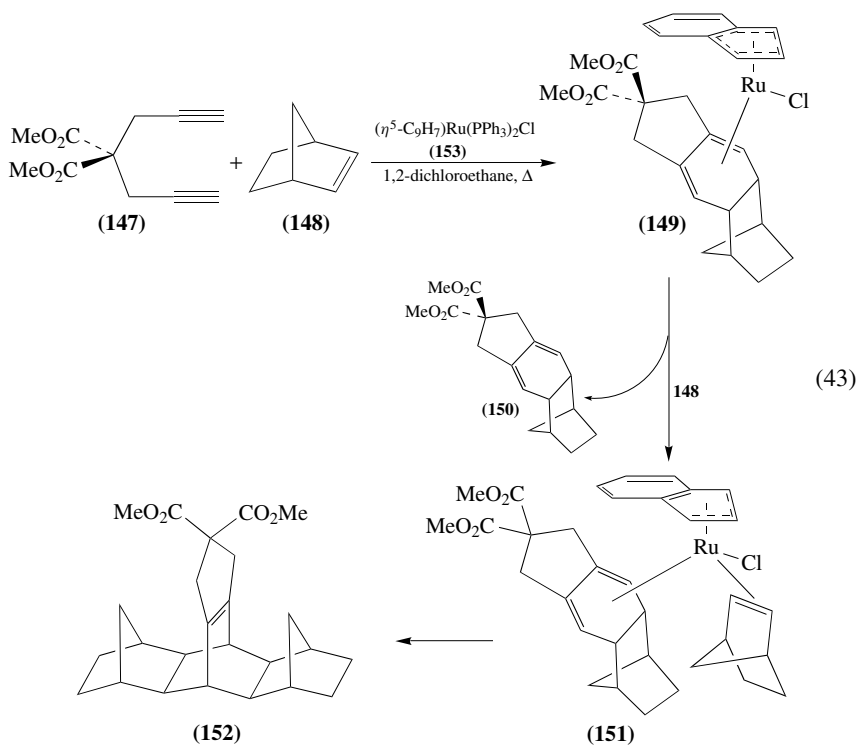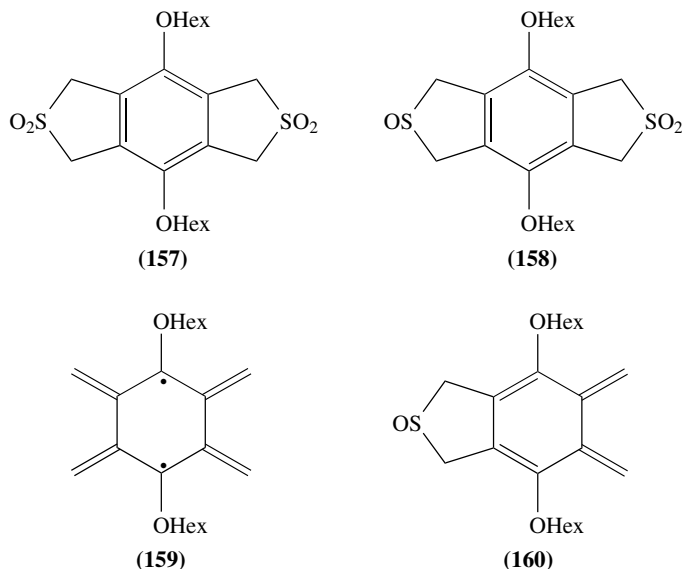
Berson and colleagues[119] re-examined the Diels–Alder reaction between 1,3-diphenyli-sobenzofuran and cyclopropenone. They selectively obtained the *exo* adduct, as was confirmed by X-ray analysis. *Ab initio* calculations indicated a kinetic preference for the *exo* isomer due to stabilizing interactions between the ether oxygen and the carbonyl carbon in the *exo* transition state[120].

The Lewis acid catalyzed reaction of furan **(169)** with ketovinylphosphonate **170** pro-duced a mixture of adducts, both of which slowly underwent retro Diels–Alder reactions at room temperature[121]. When diethylaluminum chloride was used as the catalyst, the *endo* selectivity (with respect to the keto functionality) was enhanced from $171/172 = 58/42$ to 78/22 by raising the reaction temperature from $-25\,^\circ$C to $0\,^\circ$C (equation 47). This is in agreement with the FMO theory, since initial Lewis acid complexation is with the phosphonate group.

Arjona and coworkers[122] studied the Diels–Alder reactions between some substi-tuted furans **173** and (*E*)-1,2-bis(phenylsulfonyl)ethylene **(174)** (equation 48). The results depicted in Table 3 show that all reactions of 2-substituted furans afforded **175** as the exclusive adduct, the reaction of furan **173c** being an exception. These findings were explained by unfavorable interactions of the 2-substituent with the *cis* sulfonyl group (steric repulsions) and by long-range favorable interactions with the *trans* sulfonyl group (electrostatic, dipolar, van der Waals). The reactions of **174** with 3-substituted furans **173f** and **173g** did not show any stereoselectivity.

Padwa and colleagues[123] reported Diels–Alder reactions of several 2-amino substituted furans. These dienes reacted smoothly with monoactivated olefins in the absence of Lewis acids to give the corresponding adducts with complete regioselectivity. In most cases, the 7-oxabicyclo[2.2.1]hept-5-enes ring-opened under the reaction conditions. In the case of 2-morpholino-5-nitrofuran **(177)**, consecutive ring-opening and elimination of HNO$_2$ afforded *p*-aminophenol **178** (equation 49). Phenol **179** was considered to be formed by ring-opening of the primary adduct followed by migration of the nitro group and consecutive aromatization. An additional [1,5] hydrogen shift was proposed to explain the formation of **180**.

(161)

(162)

Δ / Ph$_2$O : α-MeNaph (1 : 1)

(45)

(**163**; R = ——≡——Si(Pr-i)$_3$)
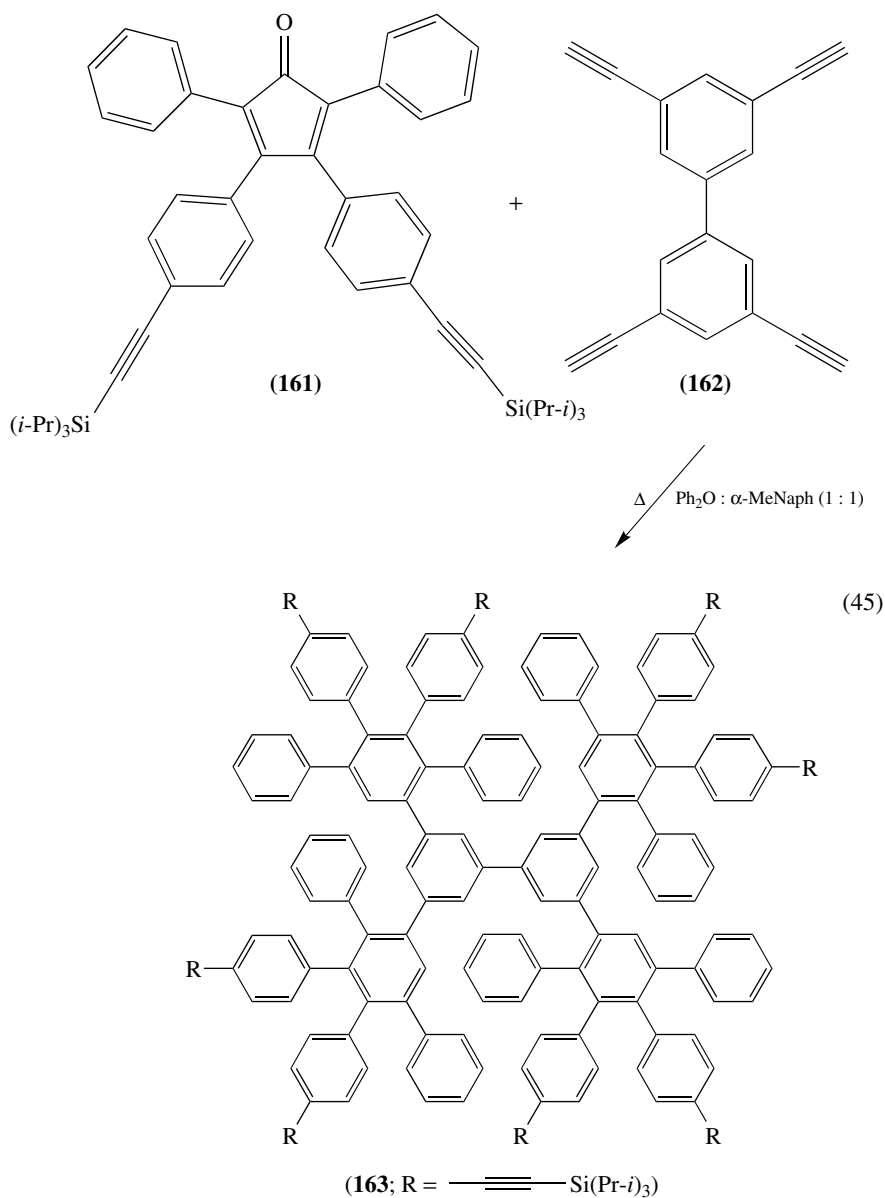
Liao and coworkers[124] studied the Diels–Alder reactions of substituted furans, now acting as dienophiles, with masked o-benzoquinones. A representative reaction has been depicted in equation 50. The masked o-benzoquinones such as **181** reacted with unacti- vated, electron-rich as well as electron-poor furans such as **182**. The substitution pattern of the masked o-benzoquinones proved, however, more important. An electron-withdrawing

(46)

(168a; $m = 94$, $n = 6$)
(168b; $m = 51$, $n = 49$)

(167)
CH$_2$Cl$_2$, Δ

(164a; $m = 94$, $n = 6$)
(164b; $m = 51$, $n = 49$)

NPh
CH$_2$Cl$_2$, Δ
(165)

(166a; $m = 94$, $n = 6$)
(166b; $m = 51$, $n = 49$)

$$(47)$$

$$(48)$$
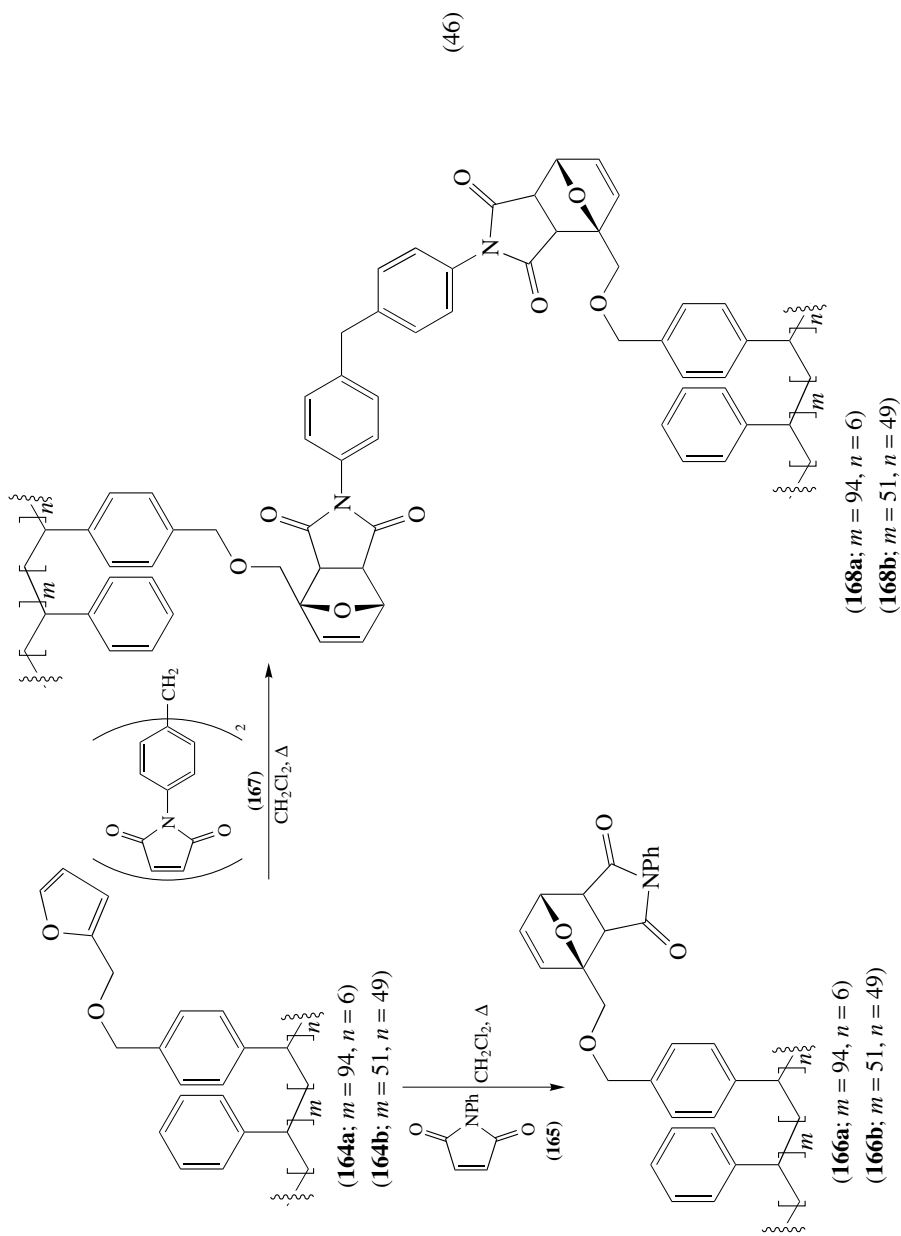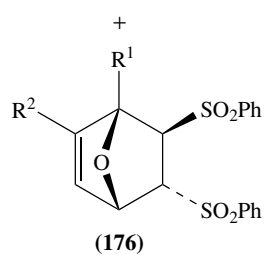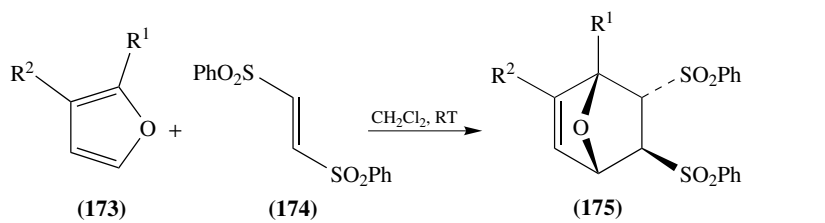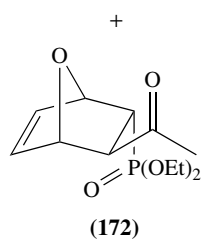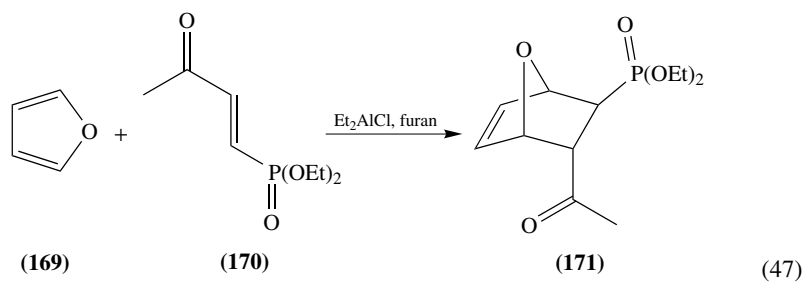
TABLE 3. Product distributions for equation 48

Entry	R^1	R^2	Furan	175/176
1	Me	H	**173a**	100/0
2	OMe	H	**173b**	100/0
3	CH_2OH	H	**173c**	70/30
4	CH_2OBn	H	**173d**	100/0
5	CH_2SH	H	**173e**	100/0
6	H	CH_2OH	**173f**	50/50
7	H	CH_2OBn	**173g**	50/50

group at C(3) or an electron-releasing group at C(2) greatly diminished reactivity. The reactions were completely site selective, i.e. the unsubstituted double bond of the substituted furans reacted in every instance to give adducts like **183**.

(**177**)   (**100**)   (**178**; 42)

(49)

(**180**; 19)   (**179**; 39)

(**181**)   (**182**)

(50)

(**183**)
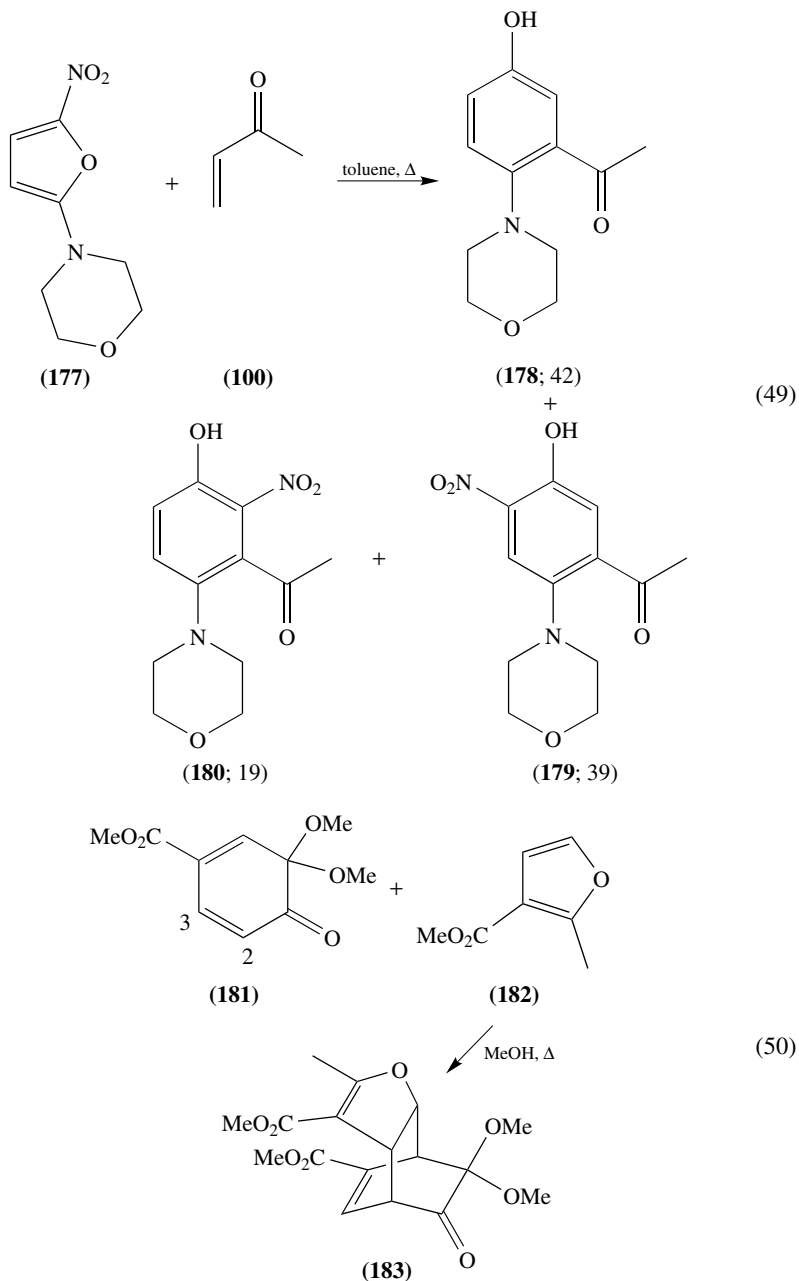
8. Diels–Alder reactions of pyrones and pyridones

Because α-pyrones and α-pyridones have some aromatic character, like furans, they undergo Diels–Alder reactions less easily than most cyclic dienes do. Nevertheless, suitable reaction conditions have been developed and their Diels–Alder reactions have been used intensively to generate useful synthetic intermediates[35]. Unsubstituted α-pyrones and α-pyridones generally react with electron-poor dienophiles in *normal electron demand* Diels–Alder reactions. The regioselectivity, determined by the weakly directing endocyclic heteroatom, is often poor. To improve regioselectivity, either electron-releasing or electron-withdrawing substituents must be present. The reaction becomes an *inverse electron demand* Diels–Alder reaction in the latter case.

By using electron-withdrawing N-substituents, the aromatic character of α-pyridones can be reduced and the efficiency as well as the stereoselectivity of the Diels–Alder reaction increased. The efficiency of the reactions of α-pyridones can be further improved by using bulky electron-withdrawing N-sulfonyl substituents, as was shown by Afarinkia and Mahmood[125]. N-Sulfonyl 2-pyridones generally rearrange easily to the thermodynamically more stable 2-(sulfonyloxy)pyridines. The authors found that use of the large 2,4,6-triisopropylbenzenesulfonyl group and solvents of low polarity suppressed this rearrangement, thereby improving the yields of the cycloaddition.

Guitián and colleagues[126] performed some Diels–Alder reactions between *in situ* generated cyclohexyne and several α-pyrones. The reactions were performed at 100 °C which resulted in immediate loss of carbon dioxide from the primary cycloadducts. Reaction yields were generally above 80%. The reaction between **184** and cyclohexyne, derived from **185**, to give **186** has been depicted in equation 51.

$$(51)$$
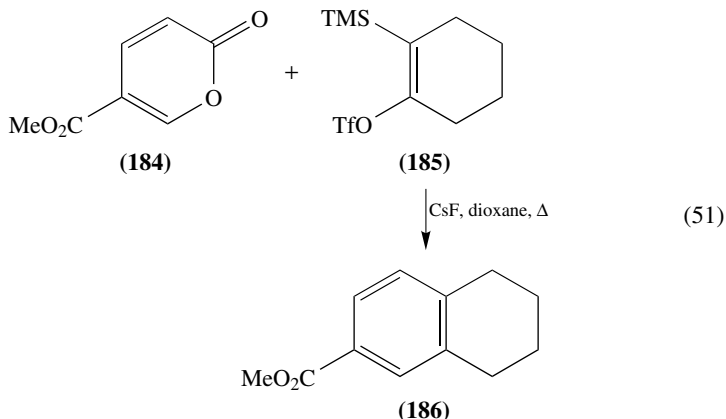
Hsung[127] used a [4 + 2] cycloaddition reaction of a γ-pyrone to synthesize the tetracyclic core of arisugacin, a novel inhibitor of acetylcholinesterase. He noticed an unexpected concentration effect on the stereoselectivity in the reactions of 3-cyano-γ-benzopyrone derivatives with electron-rich dienes[128]. When 1-methoxybutadiene **(187)** reacted with γ-benzopyrone **188**, for example, the ratio between *endo* adduct **189** and *exo* adduct **190** depended on the concentration of **188**, as demonstrated by the data given in Table 4 (equation 52). Raising the concentration of **188**, while keeping the diene concentration twice as high, caused the reaction to become less *endo* selective. Variation of the diene concentration, while keeping the γ-benzopyrone concentration constant, did not demonstrate a clear trend.

TABLE 4.   Reaction data for equation 52

Entry	[188] (M)	Equiv. 187	Time (h)	Yield (%)	*endo/exo*
1	0.10	2	30	74	90/10
2	0.45	2	48	79	50/50
3	0.10	17	24	71	96/4
4	0.10	29	26	67	95/5

(187)   (188)   (189)   (52)

+

(190)
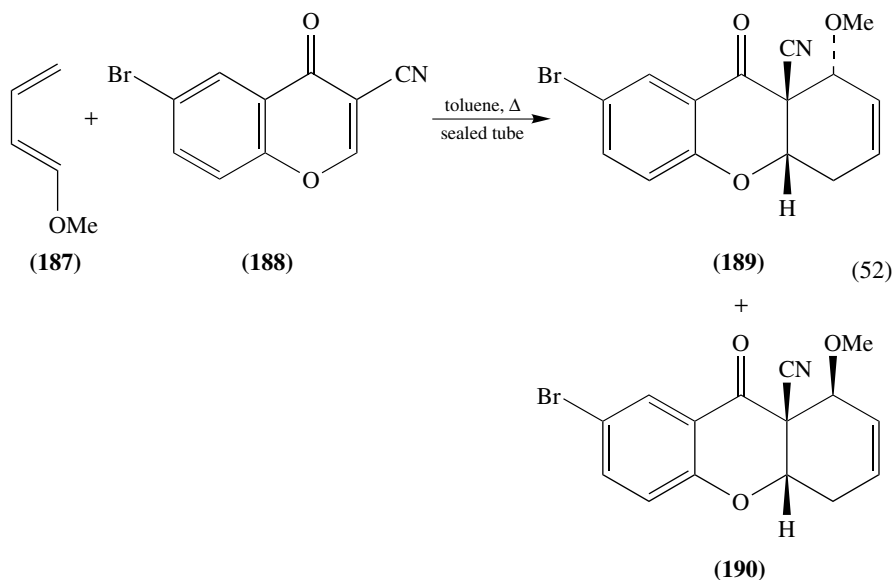
9. Diels–Alder reactions of dienes/dienophiles with cumulated double bonds

Ketenes generally dimerize easily to afford cyclobutanediones, but when silyl substituents are present, [2 + 2] cycloadditions are remarkably suppressed. This allows the application of silyl substituted vinylketenes as electron-rich dienes in Diels–Alder reactions. Danheiser and colleagues[129] showed that reactions of silyl substituted vinylketenes with reactive olefinic and acetylenic dienophiles proceed with high regioselectivity. For example, the reaction between vinylketene **191** and dienophile **192** afforded diastereomeric regioisomers **193** and **194** (equation 53). The carbonyl oxygen, acting as an electron-donor substituent, was considered to be the directing group.

Compared to the application of ordinary conjugated dienes, the use of vinylallenes as diene components is advantageous from the viewpoint of both reactivity and stereoselectivity. The equilibrium between the *s-trans* and *s-cis* conformers is more on the side of the *s-cis* isomer for vinylallenes than it is for 1,3-dienes. Consequently, vinylallenes exhibit a higher reactivity.

Reich and coworkers[130] demonstrated that the reactions of vinylallenes with unsymmetrical dienophiles proceed predominantly via a transition state in which the largest substituents on both the allene moiety and the olefin are furthest apart. The regiochemistry is governed by these steric interactions, because the HOMO coefficients of the vinylallene at the sites of bond formation are very similar.

$$(53)$$
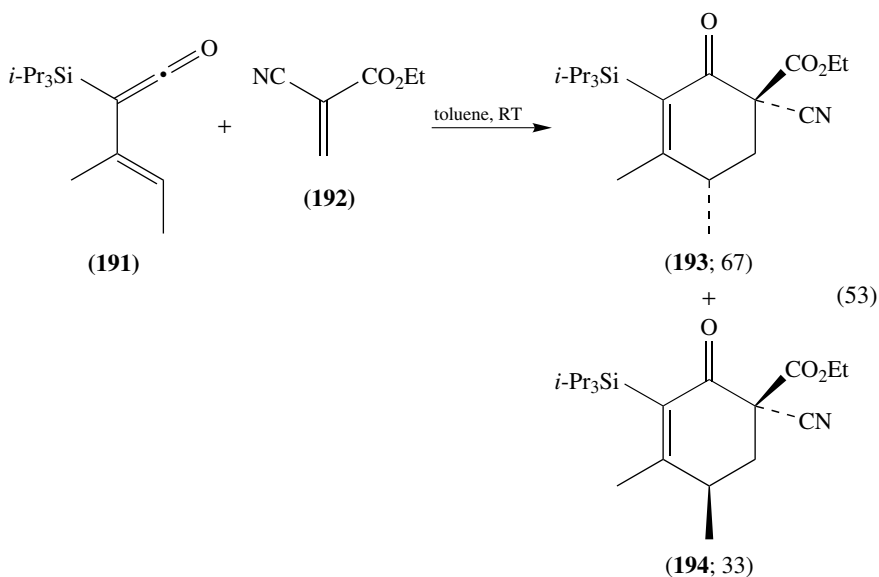
Krause and colleagues[131] reported the cycloadditions of several substituted vinylallenes with symmetrically as well as asymmetrically substituted olefins. The reactions proceeded at a reasonable rate at room temperature, affording adducts with high to complete facial, *endo* and regioselectivities. Vinylallene **195** proved highly reactive, even at 5 °C, affording dimer **196** as a 70 : 30 mixture of two isomers (equation 54). The regiochemistry was contrary to that generally observed (see above).

$$(54)$$
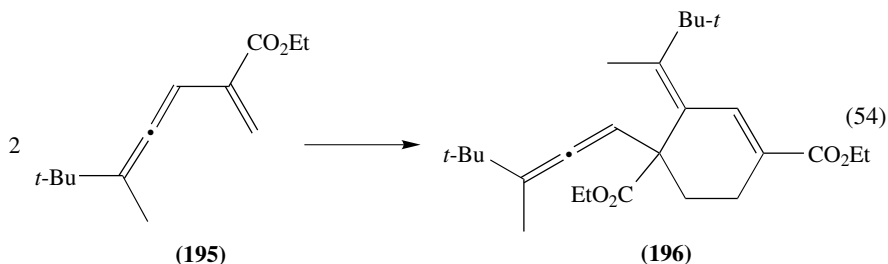
Murakami and colleagues[132] studied the Diels–Alder reactions of vinylallenes with alkynes catalyzed by a rhodium complex. When a vinylallene lacking substituents at the vinylic terminus was reacted with a terminal alkyne, 1,3,5-trisubstituted benzenes were obtained, the reaction between vinylallene **197** and 1-hexyne (**198**) being a representative example (equation 55). The reaction was proposed to proceed via a rhodacycle which afforded the primary Diels–Alder adduct via reductive elimination. Aromatization via isomerization of the exocyclic double bond led to the isolation of **199**.

The palladium catalyzed reactions of substituted vinylallenes with unactivated 1,3-butadienes proceeded with high selectivity[133]. A multistep mechanism, involving several palladacycles, was proposed to explain the high selectivities observed.

[Rh(cod)$_2$]OTf
P(OCH(CF$_3$)$_2$)$_3$
DME, RT

$$(55)$$

(197)   **(198)**   **(199)**
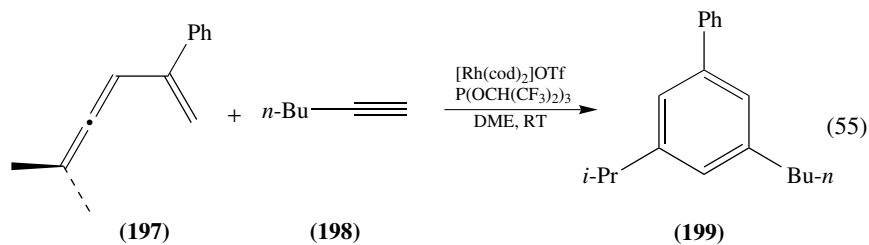
Spino and colleagues[134] studied the Diels–Alder reactions of vinylallenes aiming to synthesize six-membered rings with a tetrasubstituted exocyclic double bond, which were to be employed as precursors of quassinoids. Some representative results of their investigations have been summarized in Table 5 (equation 56). Due to the presence of two different substituents at the allene terminus of **200**, facial differentiation occurred, which resulted in non-equivalent amounts of geometrical isomers **201** and **202**. The major isomers obtained in each case were formed by *endo* attack of maleic anhydride **144** at the less hindered face of the diene.

toluene, RT or Δ

(200)   **(144)**   **(201)**

$$+$$ $$(56)$$

(202)
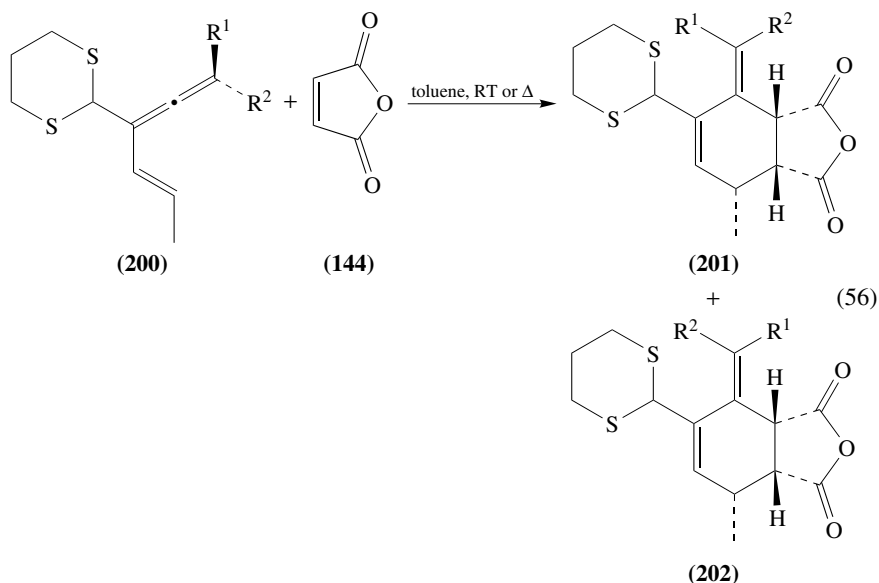
TABLE 5.   Isomer distribution for equation 56

Entry	R^1	R^2	**201/202**
1	*n*-pentyl	Me	75/25
2	*n*-pentyl	SiMe$_3$	<1/>49
3	2-(Methoxymethyloxy)pent-1-yl	Me	90/10

Allenes generally react with conjugated dienes to give [4 + 2] type of adducts in contrast with ketenes which generally react with dienes in a [2 + 2] kind of way. Some enhancement of reactivity is expected in comparison with olefins because of the significant amount of strain that allenes have. Semi-empirical calculations, however, have shown allene to be less reactive than ethylene due to higher deformation energies[135].

Gedanken and colleagues[136] investigated the Diels−Alder reactions of trichloromethyl allenyl sulfoxides 203 and cyclopentadiene under ultrasound irradiation. Allenes 203 are generally very sluggish in reactivity. However, when ultrasound was applied, the reactions of allenes 203 with cyclopentadiene were completed within 2 hours (equation 57). Mixtures of *endo* (204) and *exo* (205) isomers were obtained in all instances. When the γ-position of the allenyl sulfoxides was substituted, additional mixtures of *E* and *Z* isomers were obtained.

Kanematsu and coworkers studied the reactions of optically pure allene-1,3-dicarboxylates with furan[137] and cyclopentadiene[138]. The aluminum trichloride catalyzed reaction of 206 with cyclopentadiene proceeded at −78 °C with virtually complete *endo* selectivity and complete facial selectivity to afford 207 and 208 in a ratio of 98 : 2 (equation 58), cyclopentadiene approaching the double bond from the face opposite to the perpendicular carboxylate group.

$$\text{CH}_3\text{CN}, 0\,°\text{C} - \text{RT}$$

(1) **(203)**

R = H, Me, Ph

(204)

+

(205)

(57)
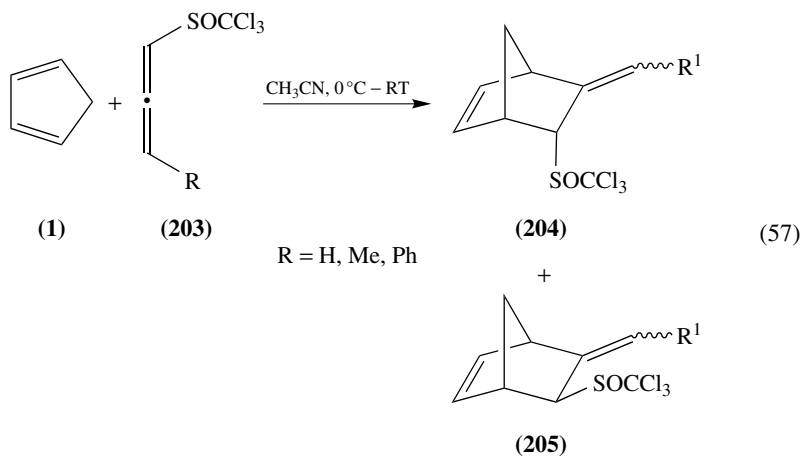
10. Diels−Alder reactions of fullerenes

The Diels−Alder chemistry of fullerenes has proven to be an important method for the preparation of novel organofullerenes. Consequently, a wide variety of cycloadducts have been reported[36]. In spite of the presence of 30 conjugated double bonds in [60]fullerene, it does not behave as a diene in Diels−Alder reactions. Instead, the carbon−carbon double bonds across two six-membered rings in [60]fullerene serve as dienophiles in reactions with predominantly electron-rich dienes. Although the strain of the π-orbitals and the electron-withdrawing ability of [60]fullerene make it reactive toward dienes, the loss of aromaticity of the two six-membered rings involved generally leads to retro Diels−Alder reactions at low temperatures. The well-explored reactions of [60]fullerene with *o*-quinodimethanes provide especially stable adducts as a consequence of the aromatization process which takes place during product formation. The reactions with heterocyclic *o*-quinodimethanes have been investigated much less[139].

$$\text{(58)}$$
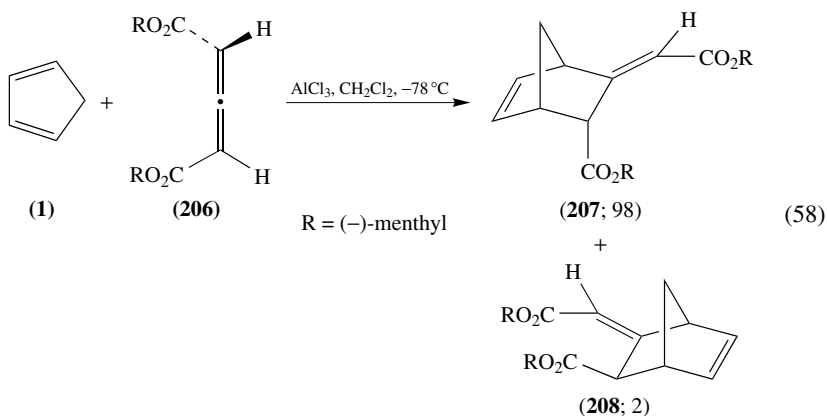
The trapping of *in situ* generated pyrimidine *o*-quinodimethanes **210a–d** with [60]fulle-rene **(209)** was investigated by Herrera and colleagues[140]. The reactions were conducted in refluxing *o*-dichlorobenzene and yielded adducts **211a–d** in yields ranging from 54% to 96%, based on the amount of consumed [60]fullerene (equation 59). According to

(**210a**; R = Me)
(**210b**; R = Ph)
(**210c**; R = *p*-MeC$_6$H$_4$)
(**210d**; R = *p*-ClC$_6$H$_4$)

$$\text{(59)}$$

o-dichlorobenzene, Δ

(**211a–d**)
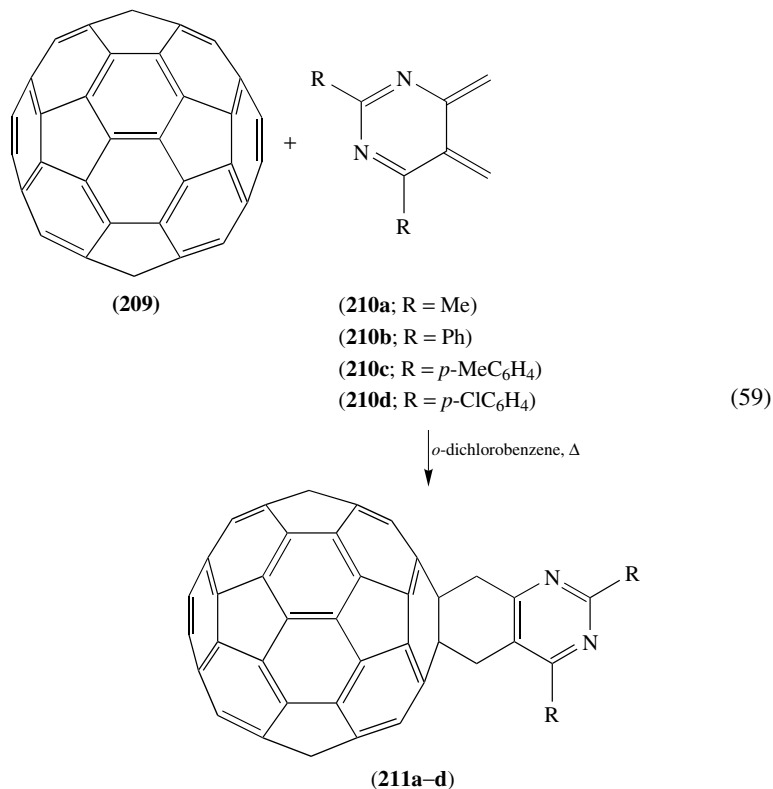
semi-empirical AM1 and PM3 calculations, these cycloadditions were controlled by the HOMOs of **210**.

The photo-induced single and double Diels–Alder reactions between [60]fullerene and 9-methylanthracene **(212)** which gave **213** and **214** were performed in the solid state by Mikami and colleagues (equation 60)[141]. The Diels–Alder reaction was considered to proceed following a photo-induced electron transfer from 9-methylanthracene to fullerene. The higher ionization potential of anthracene should explain its inreactivity toward the cycloaddition reaction with [60]fullerene.

$$(60)$$
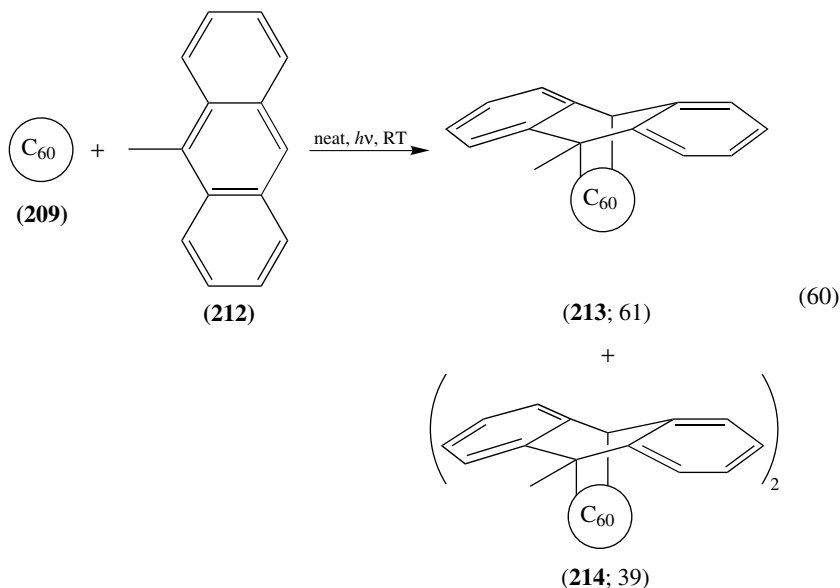
Cheng and coworkers[142] reported the first Diels–Alder reactions of fullerenes with dienes having an electron-withdrawing group at C(1). The reactions with [60]fullerene proceeded at elevated temperatures to afford the corresponding adducts with moderate yields. The adducts appeared to be more stable than the adducts of electron-rich dienes.

11. Diels–Alder reactions of resin-bound reagents

Solid phase chemistry has gained widespread use in recent years. Among the immense number of reactions that can be performed on the resin nowadays, the all-carbon Diels–Alder reaction still takes a minor place. The resin-bound Diels–Alder reactions reported in the literature between 1992 and 1997 have been reviewed recently[143].

Winkler and Kwak[144] recently prepared tricyclic ester **221** from **215** by means of three consecutive Diels–Alder reactions with **216**, **218** and **91b** to give **217**, **219** and **220**, respectively, followed by cleavage of the triple adduct **221** from the resin (equation 61). The overall yield was almost three times higher than when the same reaction sequence was performed in solution, thereby demonstrating the efficiency of resin-bound reactions in this case.

On the other hand, Hird and colleagues[145] studied the Diels–Alder reactions of resin-bound 2-amino-1,3-butadienes with several *N*-substituted maleimides and nitrostyrenes.
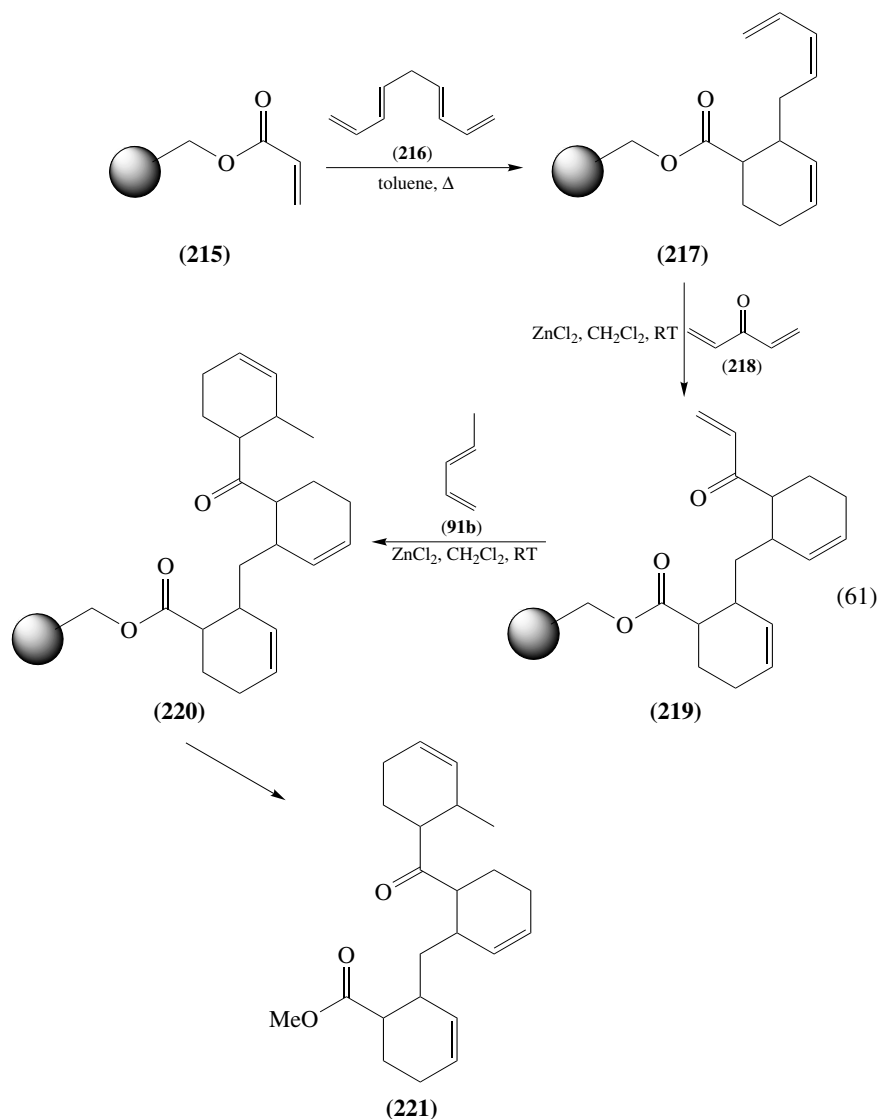
These reactions generally proceeded with lower *endo/exo* selectivities than the corresponding reactions in solution. In some cases, Michael adducts were isolated in minor amounts, possibly indicating a stepwise reaction.

Schlessinger and Bergstrom[146] reported some asymmetric Diels–Alder reactions of several polystyrene bound furans to which a chiral auxiliary had been attached with methyl acrylate. The adducts were obtained with de values of more than 99%, as was determined after cleavage of the adducts from the resin.

C. Chiral Auxiliaries

The synthesis of enantiomerically enriched compounds can be accomplished by application of chiral Lewis acids or chiral auxiliaries attached to either one of the reactants. The latter application[41,42] will be discussed in this section.

In most reported cases, the covalently bound chiral auxiliary has been attached to the dienophile via an acyl linkage, but there are also many examples known in which the auxiliary has been attached to the diene via an acyl, alkyl or heteroatom linkage, the first example of the latter being Trost's diene[147]. Lewis acids are often added to the reaction mixtures when the chiral auxiliary attached to the dienophile contains an additional Lewis basic site. This is not only to enhance the reaction rate, but especially to enhance the diastereofacial selectivity by complexing to the dienophile in a bidentate fashion. This makes the dienophile more conformationally rigid.

1. 1,3-Oxazolidin-2-ones as chiral auxiliaries

1,3-Oxazolidin-2-ones, introduced by Evans and coworkers[148] and usually synthesized from α-amino acids[149], have been applied in asymmetric syntheses with success, producing the target compounds with high de values.

Davies and coworkers[150], for example, used N-enoyl derivatives of a cis-1-aminoindan-2-ol based 1,3-oxazolidin-2-one **(222)** as chiral dienophiles in the Diels–Alder reactions with isoprene **(91a)** and piperylene **(91b)** which give **223** (equation 62). Their results have been summarized in Table 6. The reactions proceeded with high $endo/exo$ and regioselectivities. Bidentate co-ordination of the catalyst to both carbonyl groups kept the dienophile in a rigid conformation, which gave rise to the high de values observed.

$$(62)$$
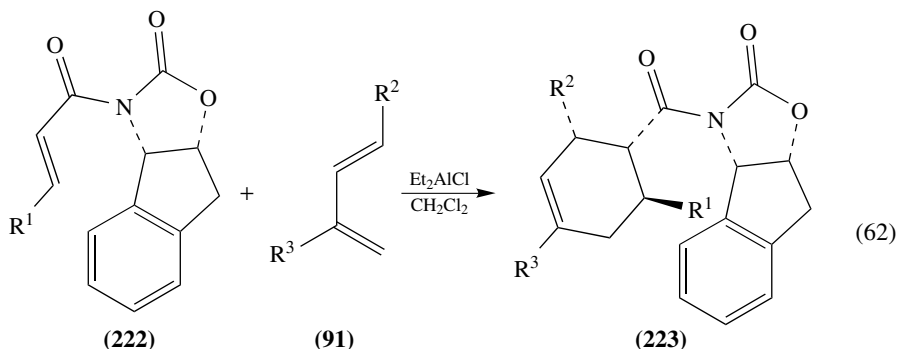
TABLE 6. Reaction data for equation 62

Entry	R^1	R^2	R^3	Diene	T (°C)	Yield (%)	$endo/exo$	de (%)
1	H	H	Me	**91a**	−70	85	—	87.5
2	H	Me	H	**91b**	−70	69	98/2	98.4
3	Me	H	Me	**91a**	−35	—	—	93.4
4	Me	H	Me	**91a**	−15	88	—	92.9
5	Me	Me	H	**91b**	−35	—	97/3	98.4
6	Me	Me	H	**91b**	−15	77	96/4	93.7

Okamura and coworkers[151] studied the base catalyzed Diels–Alder reactions between 3-hydroxy-2-pyrone (224) and chiral 1,3-oxazolidin-2-one based acrylate derivatives. Catalysis of the reaction between 224 and 225 by triethylamine gave fair to good de values, somewhat dependent on the solvent system used (equation 63, Table 7). Addition of 5% of water to the solvent isopropanol, for example, increased the de of the *endo* adduct 226 substantially. When the amount of water was increased, however, the triethylamine catalyzed reaction became less *endo* and diastereofacially selective, a small amount of *exo* 227 being obtained. Replacing triethylamine by the chiral base cinchonidine also improved the de, but now independently of the solvent system used.

Hintermann and Seebach[152] studied the reaction between cyclopentadiene and *N*-crotonyl-4-isopropyl-5,5-diphenyl-1,3-oxazolidin-2-one (228) using dimethylaluminum

(63)
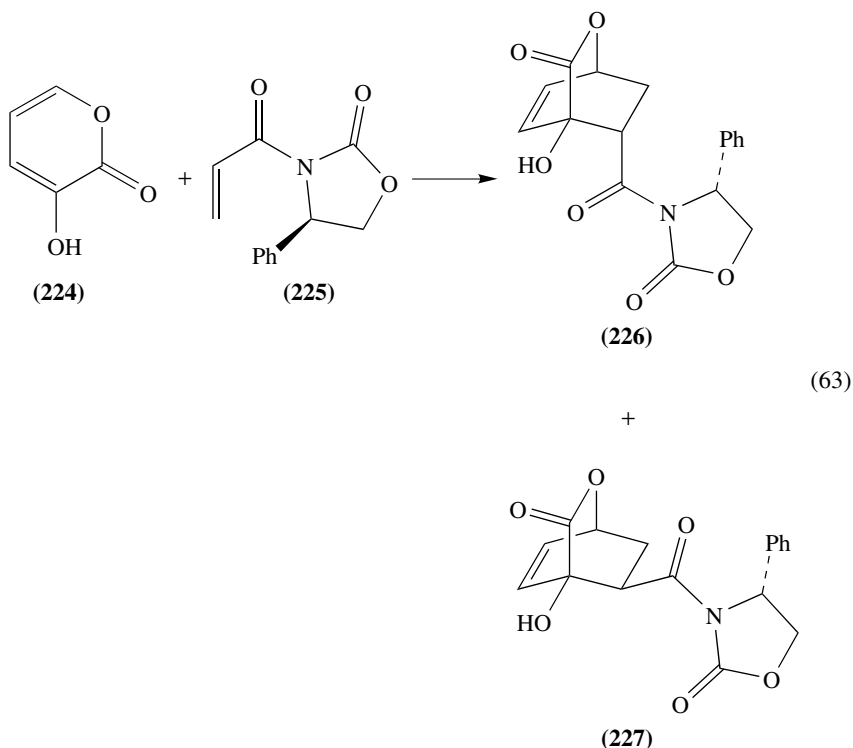
TABLE 7. Reaction data for equation 63

Entry	Base	Solvent	Yield (%)	226/227	% de 226
1	Et$_3$N	CH$_2$Cl$_2$	97	100/0	53
2	Et$_3$N	*i*-PrOH	100	100/0	69
3	Et$_3$N	*i*-PrOH : H$_2$O = 95 : 5	99	100/0	82
4	Et$_3$N	*i*-PrOH : H$_2$O = 80 : 20	87	88/12	61
5	Cinchonidine	*i*-PrOH	100	100/0	89
6	Cinchonidine	*i*-PrOH : H$_2$O = 95 : 5	93	100/0	95

chloride as the Lewis acid catalyst. The reaction proceeded with good yield (87%), almost complete *endo* selectivity (**229/230** = 98/2) and high diastereomeric selectivity (>90% de for **229**) (equation 64). Because the chiral dienophiles as well as the cycloadducts were generally more prone to crystallization than those containing Evans' chiral auxiliaries, use of **228** as a chiral auxiliary was stated to offer some advantages.
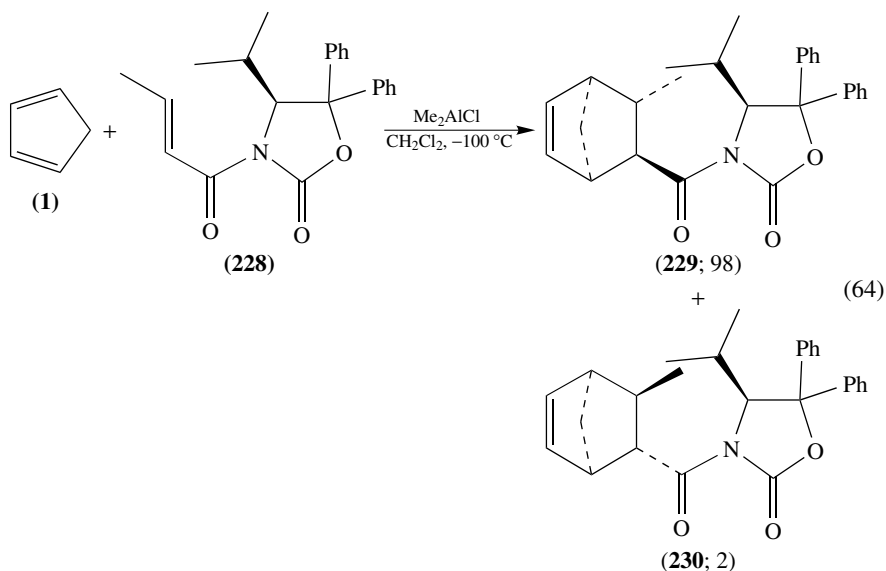
Sudo and Saigo[153] reported the application of *cis*-2-amino-3,3-dimethyl-1-indanol derived 1,3-oxazolidin-2-one **231** as a chiral auxiliary in asymmetric Diels–Alder reactions. The *N*-crotonyl and *N*-acryloyl derivatives were reacted with cyclopentadiene, 1,3-cyclohexadiene, isoprene and 2,3-dimethyl-1,3-butadiene, using diethylaluminum chloride as the Lewis acid catalyst. The reactions afforded the expected cycloadducts in moderate to high yields (33–97%) with high *endo* selectivities and high de values (92% to >98%).
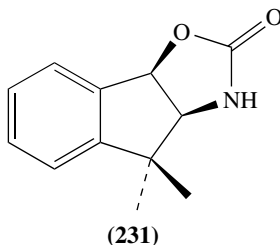
Cadogan and coworkers[154] employed camphor-derived 1,3-oxazolidin-2-ones **232** as chiral auxiliaries in Diels–Alder reactions between their *N*-enoyl derivatives and cyclopentadiene. The diethylaluminum chloride catalyzed reactions proceeded to give **233** with complete *endo* selectivities and high diastereofacial selectivities (Table 8, equation 65). When the angular methyl group in the chiral auxiliary was substituted by an ethyl group, the de increased to more than 95% for the adduct analogous to **233a**.

TABLE 8.   Yields and de of adducts **233**

Entry	R	Dienophile	T (°C)	Yield (%)	% de **233**
1	H	**232a**	−78	100	81
2	Me	**232b**	−78	92	>99
3	Ph	**232c**	−20	100	>99

(1)   **(232)**   **(233)**   (65)
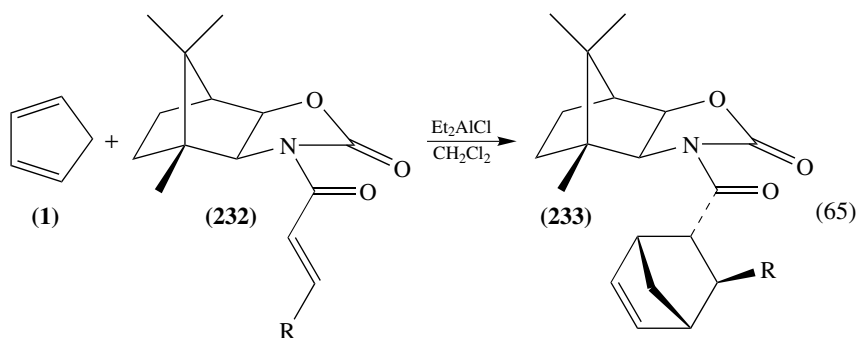
Kunieda and colleagues[155] used a similar kind of 1,3-oxazolidin-2-one **(234)** and studied the diethylaluminum chloride and boron trifluoride etherate catalyzed Diels–Alder reactions of its *N*-acryloyl and *N*-crotonyl derivatives with cyclopentadiene. The yields were high (80–100%), the reactions being almost completely *endo* selective. The diastereomeric excesses obtained ranged from 71% to more than 99%.

(234)
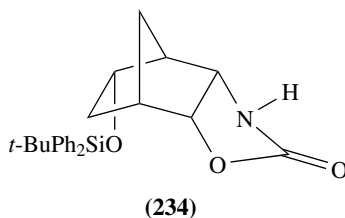
2. Carbohydrate based chiral auxiliaries

Carbohydrates have found widespread use as chiral auxiliaries in asymmetric Diels–Alder reactions[156]. A recent example is a study conducted by Ferreira and colleagues[157] who used carbohydrate based chiral auxiliaries in the Lewis acid catalyzed Diels–Alder reactions of their acrylate esters **235** with cyclopentadiene (equation 66). Some representative results of their findings, including the ratios of products **236** and **237**, have been summarized in Table 9. The formation of **236** as the main product when diethylaluminum chloride was used in dichloromethane (entry 3) was considered to be the result of an equilibrium between a bidentate and monodentate catalyst–dienophile complex. The bidentate complex would, upon attack by the diene, lead to **236**, whereas the monodentate complex would afford **236** and **237** in approximately equal amounts. The reversal of selectivity on changing the solvent from dichloromethane to toluene (entry 2 *vs* 3) remained unexplained by the authors.

(1) + **(235)** → **(236)** **(66)**

+

(237)
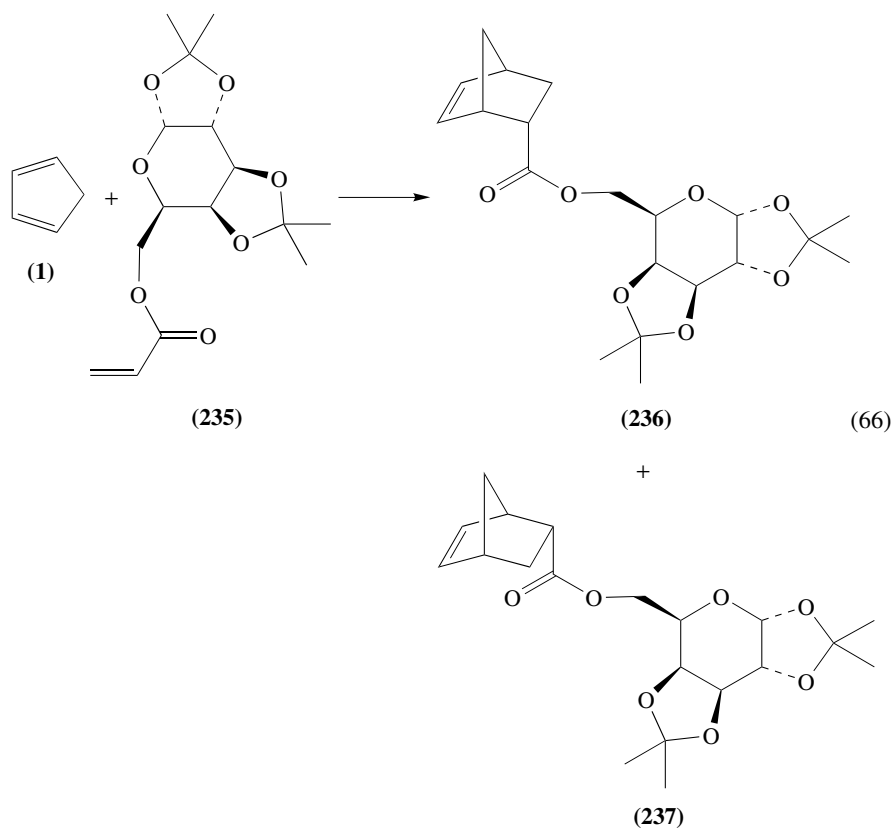
TABLE 9. Reaction data for equation 66

Entry	Solvent	Catalyst	$T(^{\circ}C)$	Yield (%)	endo/exo	236/237
1	CH_2Cl_2	none	0	85	85/15	60/40
2	Toluene	Et_2AlCl	−78	37	>98/<2	30/70
3	CH_2Cl_2	Et_2AlCl	−78	11	>98/<2	70/30
4	CH_2Cl_2	$EtAlCl_2$	−78	38	>98/<2	50/50
5	Toluene	$MgBr_2$	−78	78	83/17	50/50

Serrano and coworkers[158] reported some enantioselective syntheses of norbornene and cyclohexene nitroaldehydes via asymmetric Diels–Alder reactions with sugar-derived nitrodienes acting as chiral dienophiles. Dienes **238** and **242**, which were prepared from sugar-derived nitroalkenes and 1-acetoxy-1,3-butadiene, were employed in cycloaddition reactions with cyclopentadiene and gave **239** and **240**, and **243** and **244**, respectively (equation 67)[159]. Both reactions proceeded with complete site and diastereofacial selectivities and with almost complete *endo* selectivity. Cyclopentadiene approached the dienophiles from the face opposite to the sugar moiety. Under the reaction conditions applied, the *endo* adducts **240** and **244** rearranged to give the Cope rearranged products **241** and **245**, respectively.

$$S^1 = \text{D-}manno\text{-}(CHOAc)_4\text{-}CH_2OAc$$
$$S^2 = \text{D-}galacto\text{-}(CHOAc)_4\text{-}CH_2OAc$$

(67)
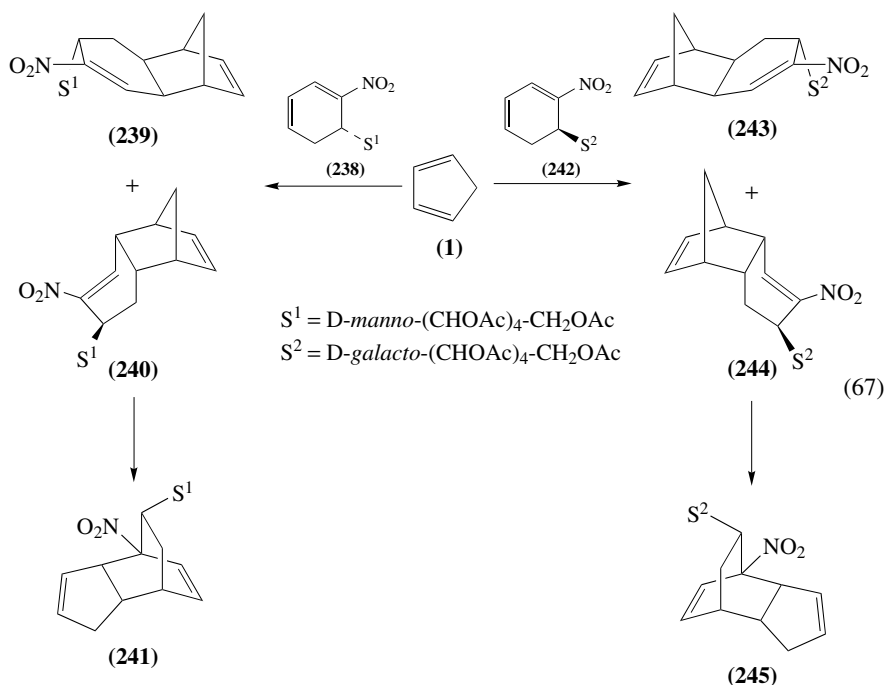
Cadogan and coworkers[160] developed a fructose-derived 1,3-oxazin-2-one chiral auxiliary which they applied in the Diels–Alder reactions of its *N*-enoyl derivatives **246** with cyclopentadiene using diethylaluminum chloride as the Lewis acid catalyst. The reactions afforded mixtures of *endo* **247** and *exo* **248** (equation 68). The catalyst binds to the chiral dienophile in a bidentate fashion (co-ordination to both carbonyl groups). As a consequence, the dienophile is constrained to a rigid conformation which accounts for the almost complete diastereofacial selectivities observed.

Stoodley and coworkers[161] studied the Diels–Alder reactions of substituted dienes having a chiral sugar moiety attached to C(1) via an *O*-glycosidic linkage with *N*-phenylmaleimide and tetracyanoethylene. They were able to reverse the diastereofacial selectivities of these reactions by anomerization of the sugar moiety. The *β*-anomers generally provided higher diastereofacial selectivities. The degree of facial selectivity was shown to be dependent on the steric bulk of the 2′ and 6′ hydroxyl protecting groups on the sugar moiety.

3. Sulfoxides as chiral auxiliaries

A wide variety of chiral sulfinyl substituents have been employed as chiral auxiliaries on both dienes[162] and dienophiles[163] in asymmetric Diels–Alder reactions. Carreño and colleagues[164], for example, used Diels–Alder reactions of (S_S)-2-(*p*-tolylsulfinyl)-1,4-naphthoquinone **(249)** to separate racemic mixtures of a wide variety of diene enatiomers **250a** and **250b** via kinetic resolution and to obtain enantiomerically enriched

tetracyclic quinones **251** and **252** after thermal elimination of the sulfoxide auxiliary group (equation 69). A representative overview of their work with *inner–outer* dienes has been given in Table 10.

(**246a**; R = H)
(**246b**; R = Ph)

$$CH_2Cl_2$$
$$-78\ ^{\circ}C\ or\ -20\ ^{\circ}C \quad | \quad Et_2AlCl$$

(68)

(**247a**; R = H)
(**247b**; R = Ph)

(**248a**; R = H)
(**248b**; R = Ph)
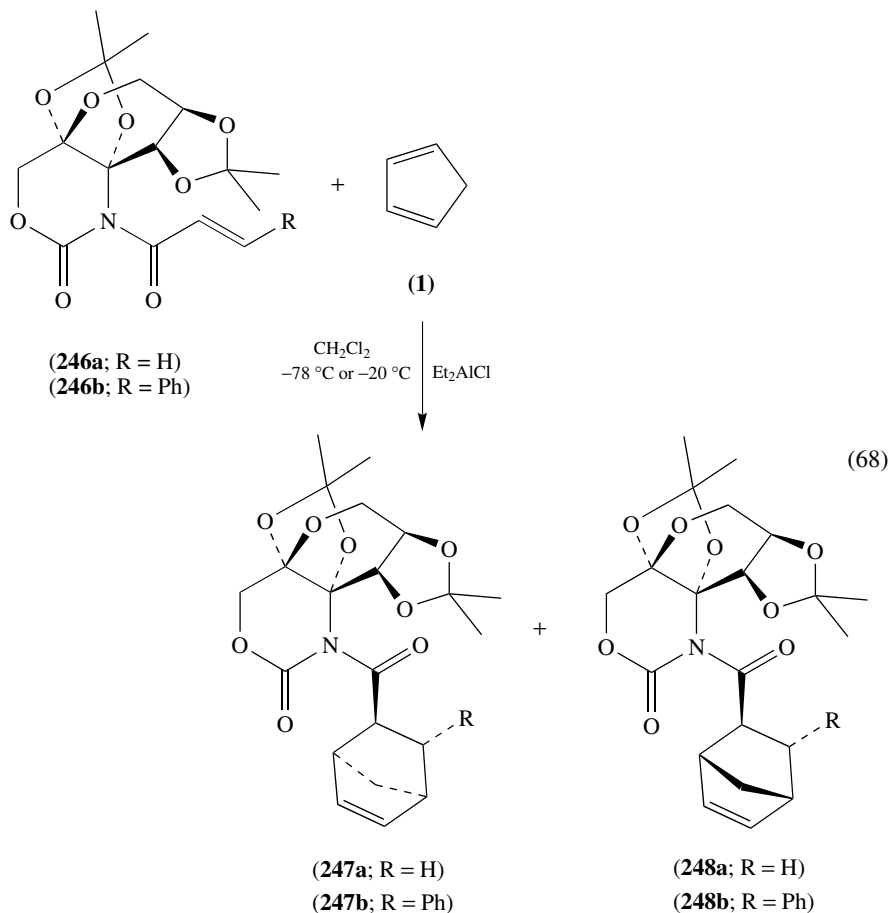
García Ruano and colleagues[165] studied the asymmetric Diels–Alder reactions of α-sulfinyl α,β-unsaturated esters with several dienes. In the reactions with cyclopentadiene, both reactivity and stereoselectivity were increased in the presence of zinc dihalides acting as catalysts. TiCl$_4$ was found to be the most efficient catalyst, however, allowing reactions to be conducted at low temperatures. Different models were proposed to explain the diastereofacial selectivities observed.

Diels–Alder reactions of chiral 1-sulfinyl-1,3-butadienes generally proceed very slowly, which requires the use of either long reaction times or high pressure to complete the reactions[166]. The reaction between diene **253** and *N*-methylmaleimide **117** (equation 70), for example, took 20 days in the absence of a Lewis acid and still 6 days when catalyzed

by SnCl$_4$. In the uncatalyzed reaction, the primary adduct **254** partially underwent a [2,3] sigmatropic rearrangement to **255**.

(69)
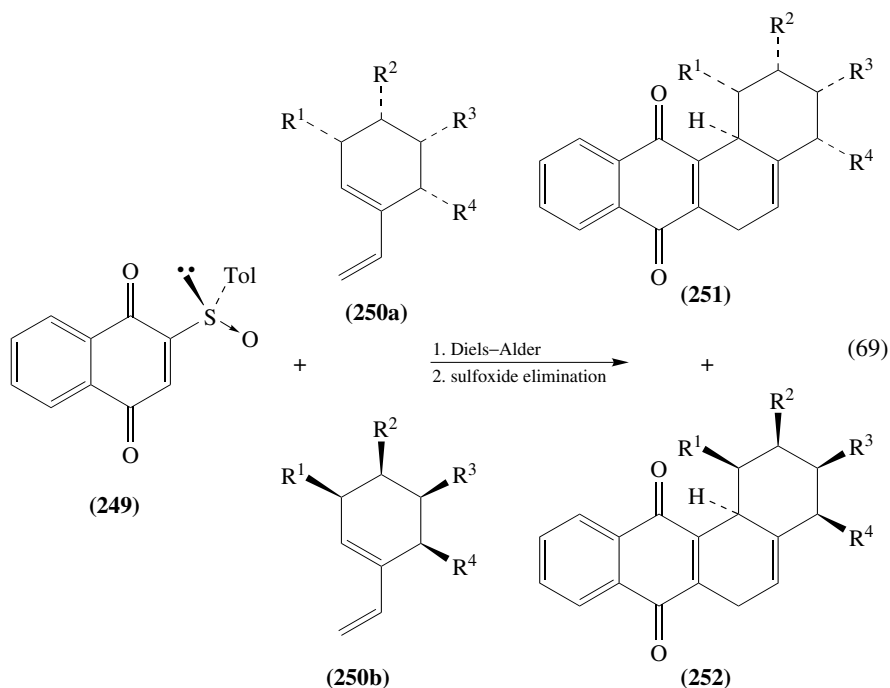
TABLE 10.   Reaction data for equation 69

Entry	R^1	R^2	R^3	R^4	Yield (%)	**251/252**	% ee **251**	% ee **252**
1	H	H	H	OH	73	100/0	20	—
2	H	H	H	OTBS	75	100/0	94	—
3	H	H	H	OMOM	61	100/0	92	—
4	H	Me	H	OH	69	100/0	20	—
5	OH	H	H	H	62	72/28	76	50
6	OMOM	H	H	H	61	100/0	94	—
7	H	H	OH	H	55	60/40	78	n.d.[a]
8	H	H	OMOM	H	53	70/30	86	n.d.[a]

[a]n.d. = not determined.

Fernández de la Pradilla and coworkers[167] studied the reactions of chiral sulfinyl and sulfonyl dienes such as **256** and **257** with *N*-phenylmaleimide. They found that the sulfinyl dienes showed facial selectivities opposite to those of the corresponding sulfonyl dienes, indicative of the powerful stereocontrol exerted by the sulfinyl moiety.

Aversa and colleagues[168] studied the facial selectivities in the reactions of (S_S)- and (R_S)-3-alkylsulfinyl-1-methoxy-1,3-butadienes with several dienophiles. Table 11 summarizes the results of the completely *endo* selective reaction of **258** with *N*-phenylmaleimide (**165**) and the effects of different catalysts on the diastereofacial selectivity of this reaction (equation 71)[168e]. In the case of the uncatalyzed reaction, the dienophile attacked the

(253)   (117)   (254)

(70)

(255)

(256)   (257)
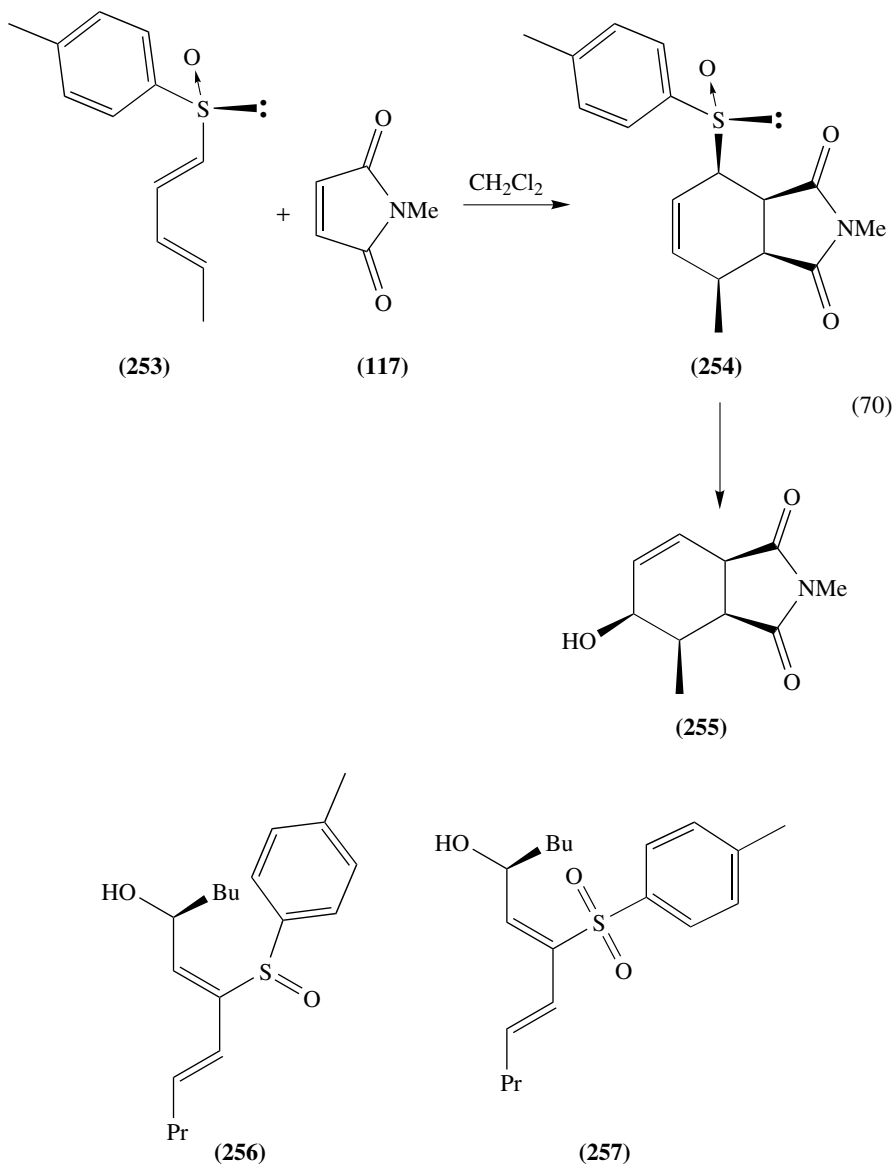
diene predominantly from the more electron-rich *re* face, opposite to the sulfinyl oxygen, the diene adopting the less sterically hindered conformation along the C−S bond. In the case of the Lewis acid catalyzed reactions, in which the Lewis acid co-ordinated to both the sulfinyl oxygen and one carbonyl oxygen on the dienophile, an additional diene conformation was stated to play a role. Depending on the size of the catalyst and the steric

requirements of the dienophile, the dienophile was now able to approach the diene from the *re* as well as the *si* face, which led to lower diastereofacial selectivities.

(258)   **(165)**   (71)

(260)   **(259)**
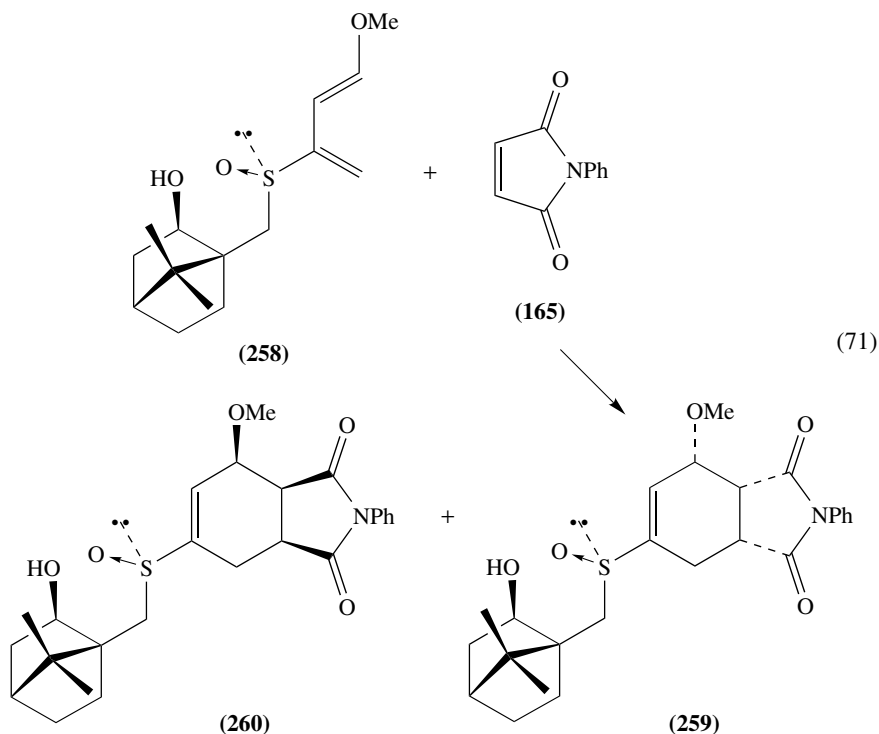
TABLE 11. Reaction data for equation 71

Entry	Catalyst	T (°C)	Yield (%)	**259/260**
1	none	25	80	85/15
2	none	−20	80	87/13
3	MgBr$_2$	0	83	80/20
4	BF$_3$·Et$_2$O	25	63	75/25
5	ZnCl$_2$	0	90	73/27
6	LiClO$_4$	−20	86	60/40
7	Eu(fod)$_3$	−20	90	36/64

Gosselin and colleagues[169] prepared Karahana ether **(264)**, starting with an asymmetric Diels–Alder reaction between chiral diene **261** and maleic anhydride. This reaction yielded diastereomers **262** and **263** in a 1 : 4 ratio (equation 72).

4. Cyclohexyl based chiral auxiliaries

Cyclohexyl based chiral auxiliaries have been widely employed in asymmetric syntheses[170]. Barluenga and coworkers[171] reported the first chiral 2-alkoxy-1,3-butadienes of

which the chiral auxiliary was either a *trans*-2-phenylcyclohexyl or a *trans*-2-mesitylcyclo-hexyl group. The reactions with *N*-phenylmaleimide and tetracyanoethene proceeded with moderate to high de values (60–90%). The auxiliary groups were stated to achieve better facial selectivities than menthol derived chiral auxiliaries.

$$(72)$$
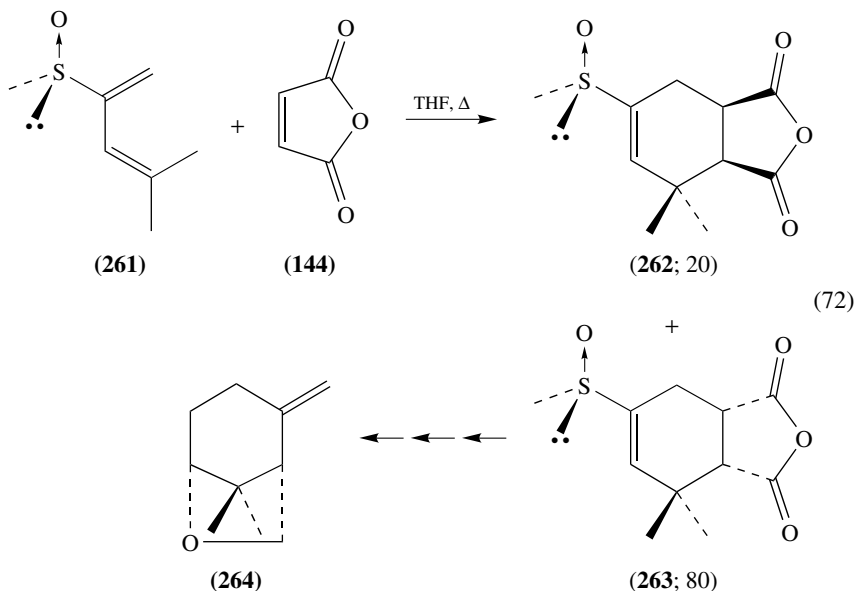
Brimble and coworkers[172] reported the asymmetric Diels–Alder reactions between quinones **265** bearing a menthol chiral auxiliary and cyclopentadiene (equation 73). When zinc dichloride or zinc dibromide was employed as the Lewis acid catalyst, the reaction proceeded with complete *endo* selectivity, but with only moderate diastereofacial selectiv-ity affording 3 : 1 and 2 : 1 mixtures of **266** and **267** (dominant diastereomer unknown), respectively. The use of stronger Lewis acids, such as titanium tetrachloride, led to the formation of fragmentation products. Due to the inseparability of the two diastereomeric adducts, it proved impossible to determine which one had been formed in excess.

Pericàs and coworkers[173] studied the *endo* selective reactions of 1-alkoxy-1,3-butadienes and 1-alkoxy-1,3-octadienes with maleic anhydride. They found that the *trans*-2-phenyl-cyclohexan-1-ol and 3-*exo*-(neopentyloxy)isobornan-1-ol based chiral dienes induced the highest facial selectivities. The relative transition state energies for the formation of the different diastereomers were calculated using semi-empirical methods (AM1).

Jones and colleagues[174] studied the influence of ligand substitution on the rates and diastereofacial selectivities of the Diels–Alder reactions between cyclopentadiene and 8-phenylmenthol based chiral acrylate-chromium complexes **268** (equation 74, Table 12). When the ligand co-ordinated to chromium was changed from CO to P(OPh)$_3$ to PPh$_3$, the diastereomeric excess of **269** was enhanced with concomitant increase of the reaction rate. This phenomenon was attributed to $\pi-\pi$ interactions between the aryl group and the enone system. These $\pi-\pi$ interactions were regarded as dipole–dipole interactions rather than $\pi-\pi$ stacking interactions because of the rate enhancement that was observed on changing the ligand.

(73)

(74)
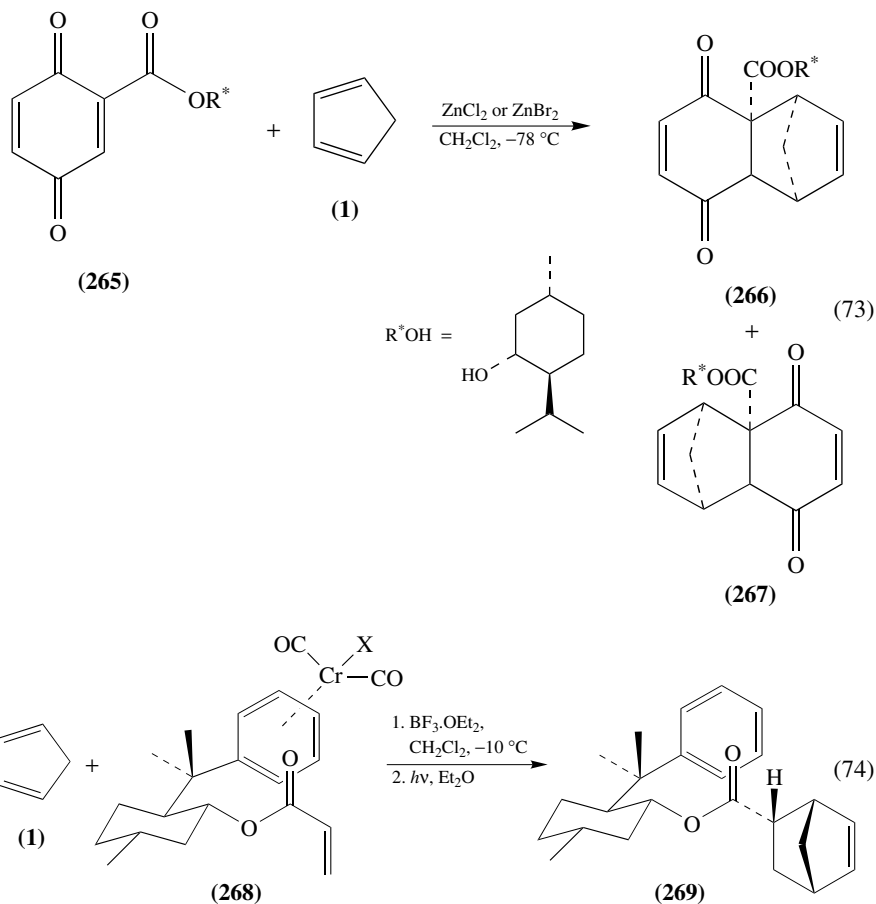
TABLE 12. *Endo/exo* ratio and % de of **269**

Entry	X	Dienophile	*endo/exo*	% de **269**
1	-(uncomplexed)	**268a**	92/8	93.9
2	CO	**268b**	90/10	90.2
3	P(OPh)$_3$	**268c**	92/8	92.7
4	P(OEt)$_3$	**268d**	92/8	92.3
5	PPh$_3$	**268e**	93/7	99.1

Taguchi and coworkers[175] studied the Lewis acid catalyzed asymmetric Diels–Alder reactions of chiral 2-fluoroacrylic acid derivatives with isoprene and cyclopentadiene. When a chiral 1,3-oxazolidin-2-one and diethylaluminum chloride were used as the chiral auxiliary and the Lewis acid catalyst, respectively, a de of 90% was observed for the reaction with isoprene. The reaction with cyclopentadiene afforded a 1 : 1 mixture of *endo* and *exo* isomers with de values of 95% and 96%, respectively. The *endo/exo* selectivity was improved by using 8-phenylmenthol as the chiral auxiliary. Thus, the reaction

of cyclopentadiene with **270** afforded **271** with complete *exo* selectivity and 95% de (equation 75). The diastereoselectivity dropped when the fluoro atom was substituted by a chloro atom or a methyl group. The high de observed in the case of the fluoro substituent was tentatively attributed to bidentate chelation of the Lewis acid catalyst to both the acrylate carbonyl and the fluoro atom.

(75)
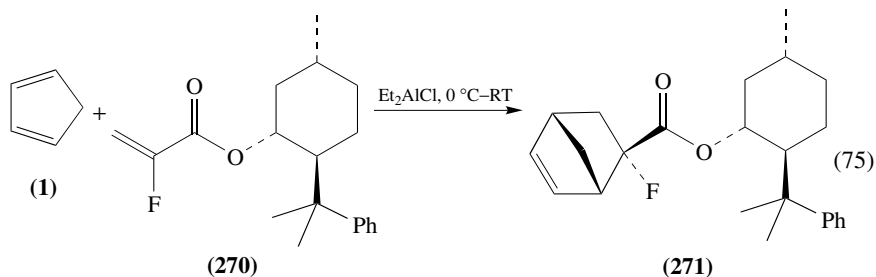
5. Pantolactone based chiral auxiliaries

Brimble and coworkers[176] studied the asymmetric Diels–Alder reactions of cyclopentadiene with chiral naphthoquinones **272** bearing different chiral auxiliaries. The highest *endo* and facial selectivities were obtained using zinc dichloride as the Lewis acid catalyst and (−)-pantolactone as the chiral auxiliary. Thus, the reaction between cyclopentadiene and **272** afforded a 98 : 2 mixture of **273** and **274** (equation 76). The chiral auxiliary was removed easily by lithium borohydride reduction.

(76)
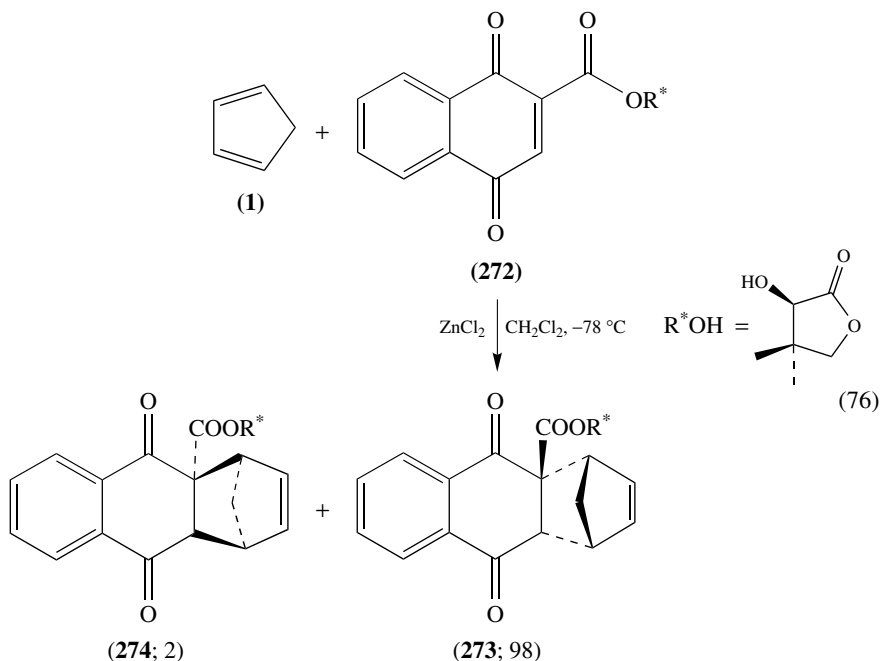
Hansen and colleagues[177] used (+)-pantolactone as a chiral auxiliary to achieve asymmetric induction in the first step toward their synthesis of *cis*-perhydroisoquinoline **278**. The titanium tetrachloride catalyzed reaction between 1,3-cyclohexadiene (**275**) and chiral acrylate **276** proceeded with high diastereofacial selectivity to give **277** (94% de) in 75% yield (equation 77).
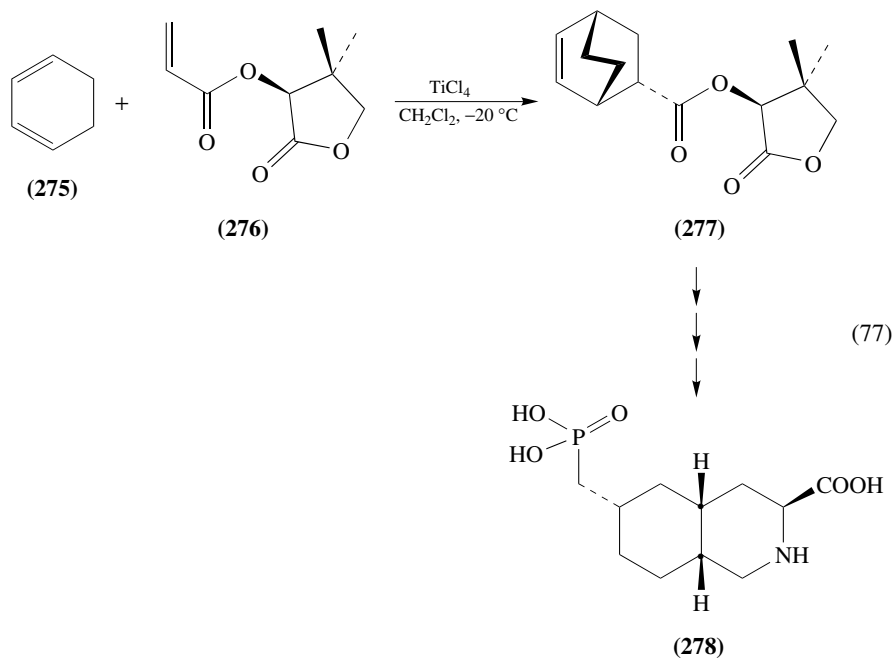
Markó and colleagues[178] studied the Eu(hfc)$_3$ catalyzed *inverse electron demand* Diels–Alder reactions between (−)-pantolactone derived chiral α-pyrones **279** and vinyl ethers and thio ethers **280**. This auxiliary proved superior to other auxiliaries in these reactions. The reactions generally proceeded with high yields, affording the *endo* adducts **281** with de values generally above 95%. The de proved independent of the chirality or achirality of the Lewis acid employed, as (+)-Eu(hfc)$_3$, (−)-Eu(hfc)$_3$ and Eu(fod)$_3$ all afforded the same diastereomer with >95% de (equation 78, Table 13).
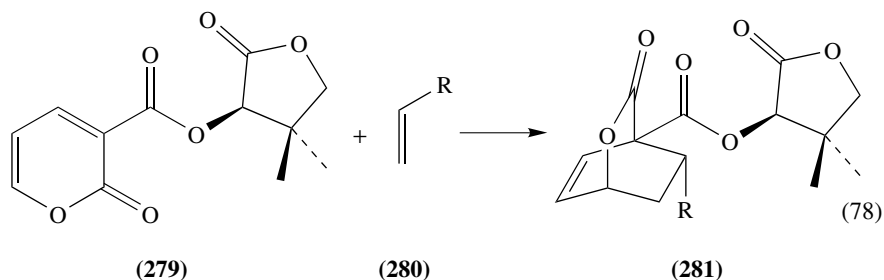
TABLE 13. Reaction data for equation 78

Entry	R	Dienophile	Catalyst	Yield (%)	% de **281**
1	OEt	**280a**	(+)-Eu(hfc)$_3$	97	>95
2	OEt	**280a**	(−)-Eu(hfc)$_3$	91	>95
3	OEt	**280a**	Eu(fod)$_3$	94	>95
4	OBu	**280b**	(+)-Eu(hfc)$_3$	84	>95
5	OBu	**280b**	Eu(fod)$_3$	95	>95
6	SBu	**280c**	(+)-Eu(hfc)$_3$	87	>95
7	SPh	**280d**	(+)-Eu(hfc)$_3$	91	75

6. Sultam based chiral auxiliaries

Oppolzer and colleagues performed pioneering work on the application of chiral sultam based dienophiles in asymmetric Diels–Alder reactions. The bornanesultam based dienophiles provided excellent de values in the Lewis acid mediated Diels–Alder reactions with a wide variety of dienes[179]. The efficiency of the simpler toluene-2,α-sultam based dienophiles was also studied[180]. Chiral auxiliary **282** proved superior to **283** and **284** in the aluminum Lewis acid catalyzed Diels–Alder reactions of its *N*-acryloyl derivative with cyclopentadiene, 1,3-butadiene and isoprene, affording the adducts with >90% de.

(282)   **(283)**   **(284)**
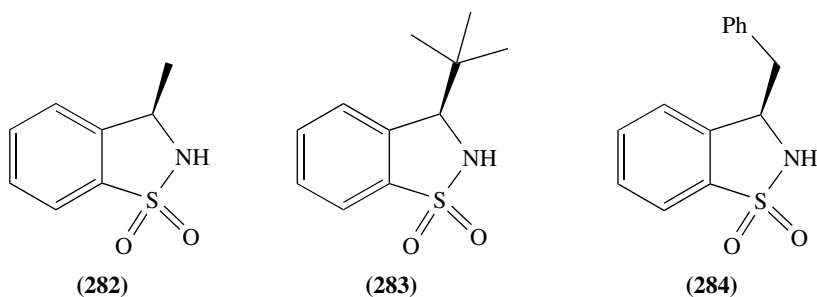
Chan and colleagues[181] studied the efficiency of tricyclic sultam **285** in asymmetric Diels–Alder reactions which gave adducts like **286** (equation 79). Some of their results have been summarized in Table 14. The *endo* selectivities were high in all cases, whereas the diastereofacial selectivities depended on the catalyst and the reaction conditions employed.

(1)   **(285)**   **(286)**   (79)
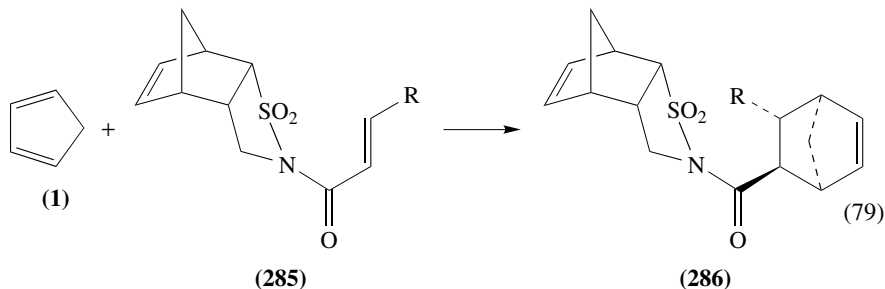
TABLE 14.   Reaction data for equation 79

Entry	R	Dienophile	Lewis acid (equiv.)	T (°C)	Yield (%)	*endo/exo*	% de **286**
1	H	**285a**	—	−20	80	>90/<10	0
2	H	**285a**	SnCl$_4$ (0.5)	−78	87	98/2	88
3	Me	**285b**	ZnBr$_2$ (10)	20	88	91/8	24
4	Me	**285b**	TiCl$_4$ (0.8)	−78	90	97/3	88

7. Other chiral auxiliaries

Breitmaier and colleagues[182] used asymmetric Diels−Alder reactions between chiral dienes such as **287** and anthraquinone **288** to synthesize anthracycline precursors such as **289** (equation 80). The reactions generally proceeded with high yields and excellent de values (>98%). The high facial selectivity was attributed to $\pi-\pi$ stacking between the phenyl ring and the diene unit, because replacement of the phenyl ring by a cyclohexane ring induced a dramatic drop in the facial selectivity.

(80)
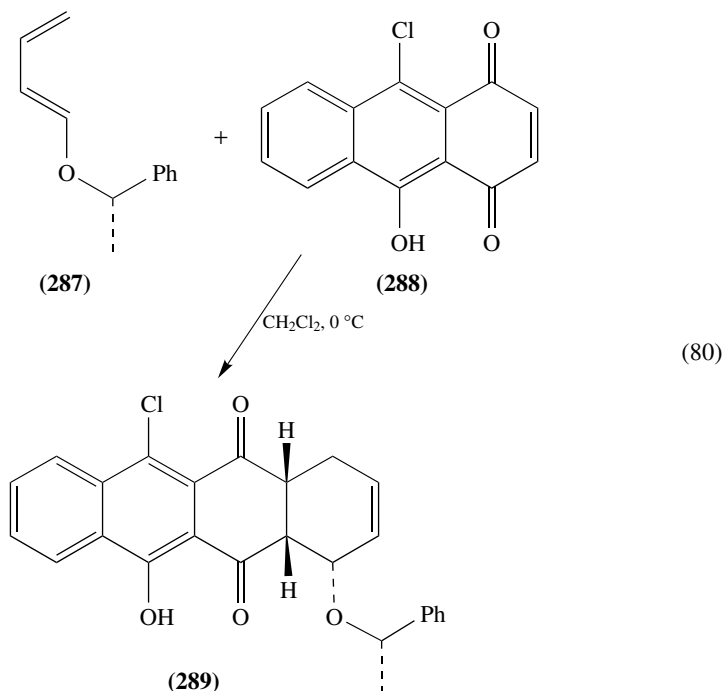
The $\pi-\pi$ stacking model has originally been used by Trost and colleagues to explain the stereoselectivity found in cycloadditions of chiral 1,3-butadien-1-yl *O*-methylmandelate[147]. In a more recent paper[183a], they retreated from this model because of a molecular mechanics study of the Diels−Alder reactions of this diene. Their results supported an earlier statement of Siegel and Thornton[183b] based on experimental results indicating that the orientation of the phenyl group is perpendicular to the diene plane in the transition state. In the sterically favored perpendicular conformation, the dienophile (quinone) will

approach the diene from the side opposite to the perpendicular phenyl group for steric reasons and also to avoid electrostatic repulsions between the electron-rich phenyl ring and one of the oxygen atoms on the quinone. This explanation seems more appropriate to explain the stereochemical results[184].

Vogel[185] used 3-aza-6,8-dioxabicyclo[3.2.1]octane based chiral dienophiles to prepare anthracyclines and anthracycline derivatives.

Bloch and Chaptal-Gradoz[186] studied the diastereofacial selectivities of the thermal and Lewis acid catalyzed Diels−Alder reactions of chiral 2-substituted 1,3-butadienes **290** with methyl acrylate and methyl vinyl ketone which gave adducts **291−294**) (equation 81). The allylic stereocenter contained either a free or protected hydroxyl group. The unprotected dienes afforded the "para" adducts with high de values, probably due to hydrogen bonding of the hydroxyl group to the carbonyl group on the dienophile which approached the diene from the face opposite to the phenyl group. The absence of this interaction caused the de values to be low for the protected dienes. The sharp increase in de observed when boron trifluoride etherate was added to the reaction mixture was proposed to originate from selective attack on the diene conformer which minimized the interaction between the co-ordinated Lewis acid and the protective group R^3 (Table 15).

Crisp and Gebauer[187] studied the *endo* selective Diels−Alder reactions of chiral dienes **295** with maleic anhydride. They found that the diastereofacial selectivity was dependent

(**11b**; $R^3 = $ OMe)
(**100**; $R^3 = $ Me)

(**290**)

(**291a–b**)   (**292a–b**)

(81)

(**293a–b**)   (**294a–b**)
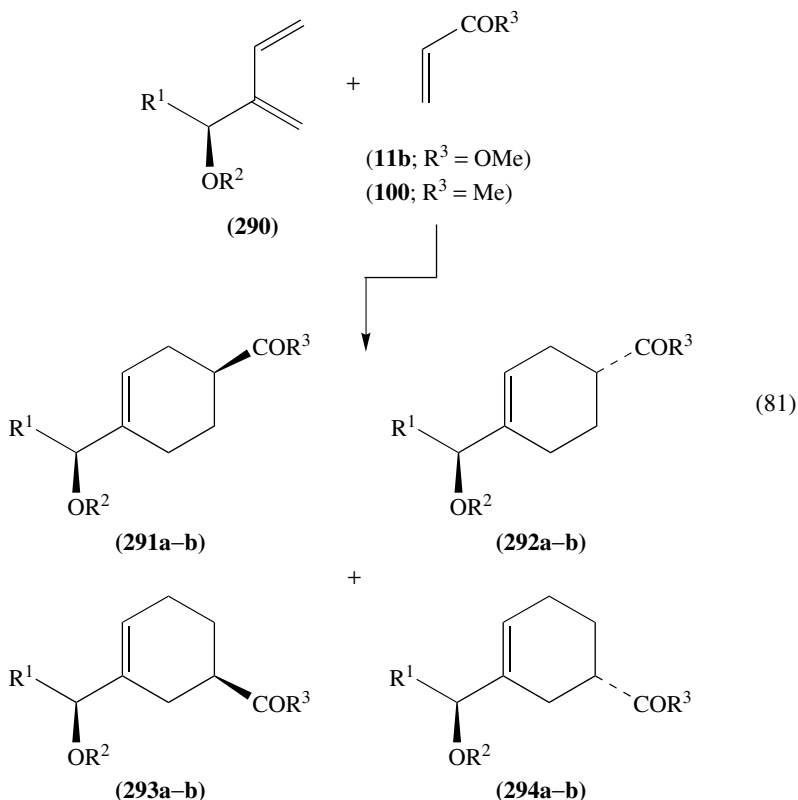
TABLE 15.   Reaction data for equation 81

Entry	R^1	R^2	R^3	Catalyst	Yield (%)	"para"/"meta"	**291/292**
1	n-C_6H_{13}	H	OMe	—	83	67/33	80/20
2	n-C_6H_{13}	TBDMS	OMe	—	87	70/30	45/55
3	n-C_6H_{13}	TBDMS	Me	$BF_3 \cdot Et_2O$	66	100/0	12/88
4	Ph	H	OMe	—	72	69/31	80/20
5	Ph	TMS	Me	—	70	67/33	45/55
6	Ph	TMS	Me	$BF_3 \cdot Et_2O$	78	100/0	>5/<95

on the size of R^1 and independent of the size of R^2. A transition state conformation was proposed in which the 1,2- and 1,3-eclipsing interactions were minimized. This conformation involved a perpendicular orientation of the R^1OCH_2 unit with respect to the diene system, thereby shielding one face of the diene. A maximum de of 76% was obtained for $R^1 = SiPh_2Bu$-t.

(295)
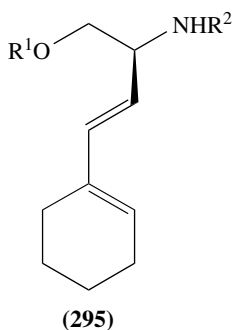
Roos and Balasubramaniam[188] tuned imidazolidin-2-one chiral auxiliaries in order to obtain reasonable reactivities in the Diels–Alder reactions of their 3-N-enoyl derivatives with relatively unreactive acyclic dienes. When 1-N-methyl substituted imidazolidin-2-ones were used as chiral auxiliaries, the corresponding 3-N-enoyl derivatives proved to lack sufficient reactivity to react with dienes beyond the highly reactive cyclic variants, irrespective of the reaction conditions applied. It was rationalized that the probable reason for this is the donor capacity of the 1-N-methyl group and it was therefore 'replaced' by a benzoyl group. The reactions of 3-N-enoyl derivatives **296a** and **296b** with cyclopentadiene afforded adducts with excellent *endo/exo* selectivities and high diastereomeric excesses (*endo/exo* = 90/10 and 98/2, respectively; >99 de in both cases) and moderate to good diastereomeric excesses in the reactions with isoprene and piperylene (**91a–b**) leading to **297** (equation 82, Table 16). *Endo* attack of the diene occurred at the C_α-*si* face of the dienophile having adopted a preferred *s-cis* conformation.

Taguchi and colleagues[189] studied the reactions of axially chiral maleimide and anilide derivatives **298** and **300** with cyclopentadiene (equation 83). The reaction of **298** with cyclopentadiene, catalyzed by diethylaluminum chloride, proceeded quantitatively with almost complete *endo* and diastereofacial selectivities to give **299** and **301**, respectively. The reaction of **300** with cyclopentadiene was catalyzed by iodine and proceeded via a cationic iodocyclization intermediate. The reaction afforded a mixture of *endo* and *exo* isomers in a ratio of *endo/exo* = 97/3, the *endo* isomer being obtained with 97% de.

TABLE 16.   Yields and de of **297**

Entry	R^1	R^2	Diene	R^3	Dienophile	Yield (%)	% de **297**
1	Me	H	**91b**	CO$_2$Bu-t	**296a**	68	66
2	H	Me	**91a**	CO$_2$Bu-t	**296a**	50	64
3	H	Me	**91a**	CO$_2$Me	**296b**	61	38

(82)

(83)
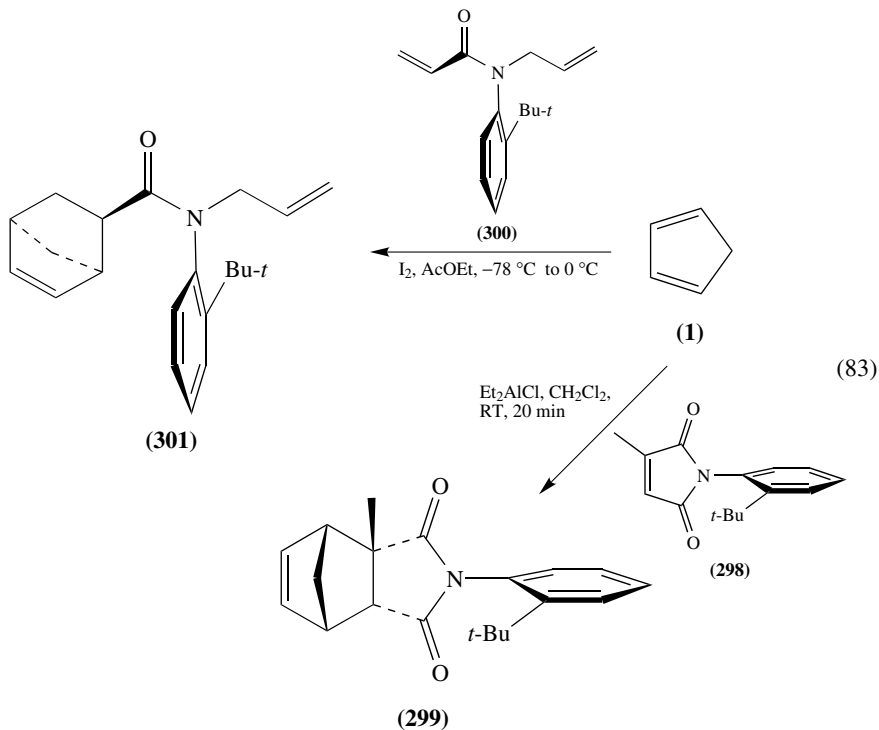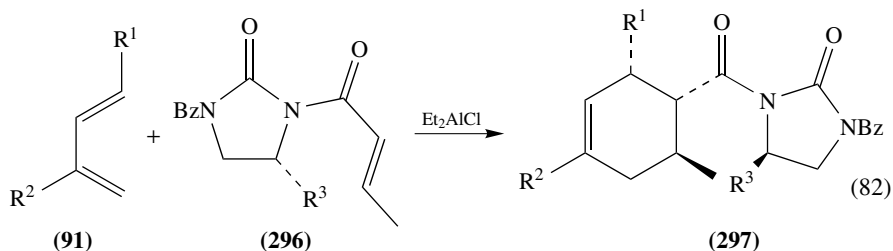
The applicability of axially chiral 1,1′-binaphthalene-8,8′-diol in asymmetric Diels−Alder reactions was studied by Fuji and colleagues[190]. They studied the Lewis acid catalyzed reaction of the unsymmetrically substituted maleate ester of 1,1′-binaphthalene-8,8′-diol **302** with cyclopentadiene. The diastereoselectivity proved to depend strongly on the Lewis

acid used. Diethylaluminum chloride and tin(IV) tetrachloride, for example, induced opposite diastereoselectivities. The best results were obtained using titanium catalysts (78–100% de for the *endo* adducts). It was proposed that these catalysts bind to **302** via tridentate co-ordination to both carbonyl groups and the hydroxyl group, thereby keeping the dienophile in a rigid conformation.

Cis-1-(arylsulfonamido)indan-2-ols have been shown to be excellent chiral auxiliaries for asymmetric Diels–Alder reactions[191]. Some results obtained in the Lewis acid catalyzed Diels–Alder reaction of 1-(*p*-toluene sulfonamido)indan-2-yl acrylate (**303**) with cyclopentadiene (equation 84) have been depicted in Table 17. The reaction conducted in the absence of a Lewis acid did not afford any facial selectivity and only moderate *endo/exo* selectivity. However, when a Lewis acid was added, excellent de values and almost complete *endo* selectivities (cf. **304**) were observed, almost independent of the type and amount of Lewis acid added.

(**302**)

(84)

(**1**)   (**303**)   (**304**)
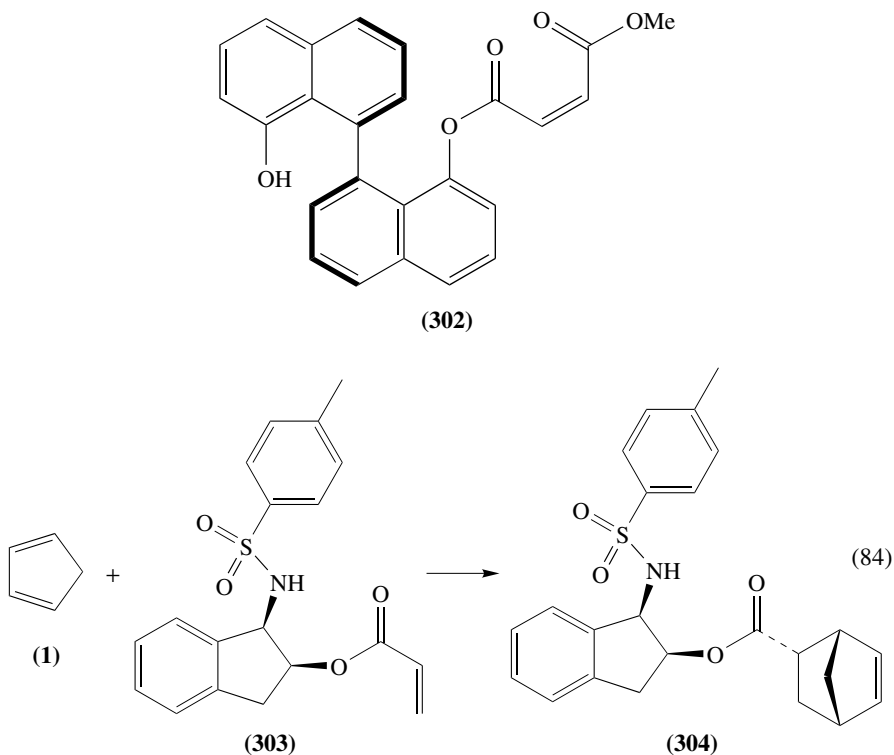
The Diels–Alder chemistry of chiral amino-1,3-butadienes has recently been reviewed[34] and has been the subject of several studies since. For instance, Enders and Klatt studied the reactions between chiral diene **305** carrying (*S*)-2-methoxymethylpyrrolidine as the chiral auxiliary[192] and substituted (*E*)-β-nitrostyrenes **306a–e**[193]. The reactions proceeded with moderate yields (26–60%). Hydrolysis of the intermediate enamines **307a–e** through diastereoselective protonation afforded ketones **308a–e** with high enantiomeric purities (95–99% ee) and high diastereoselectivities (75–95%) (equation 85).

TABLE 17. Reaction data for equation 84

Entry	Lewis acid (equiv.)	$T\,(^{\circ}C)$	Yield (%)	*endo/exo*	% de **304**
1	none	0	85	80/20	0
2	$BF_3 \cdot OEt_2$ (1.0)	−78	85	>99/<1	76
3	$BF_3 \cdot OEt_2$ (2.0)	−78	91	>99/<1	80
4	$TiCl_4$ (1.0)	−78	83	>99/<1	76
5	$TiCl_4$ (2.0)	−78	87	>99/<1	86
6	Et_2AlCl (2.0)	−78	80	>99/<1	54
7	$SnCl_4$ (2.0)	−78	85	>99/<1	72

(**306a**; R = H)
(**306b**; R = *p*-Me)
(**306c**; R = *p*-F)
(**306d**; R = *p*-OMe)
(**306e**; R = 3,4-OCH$_2$O)

(**305**)

Et_2O, −78 °C to 20 °C

(85)

silica gel
Et_2O/H_2O

(**307a−e**)

(**308a−e**)
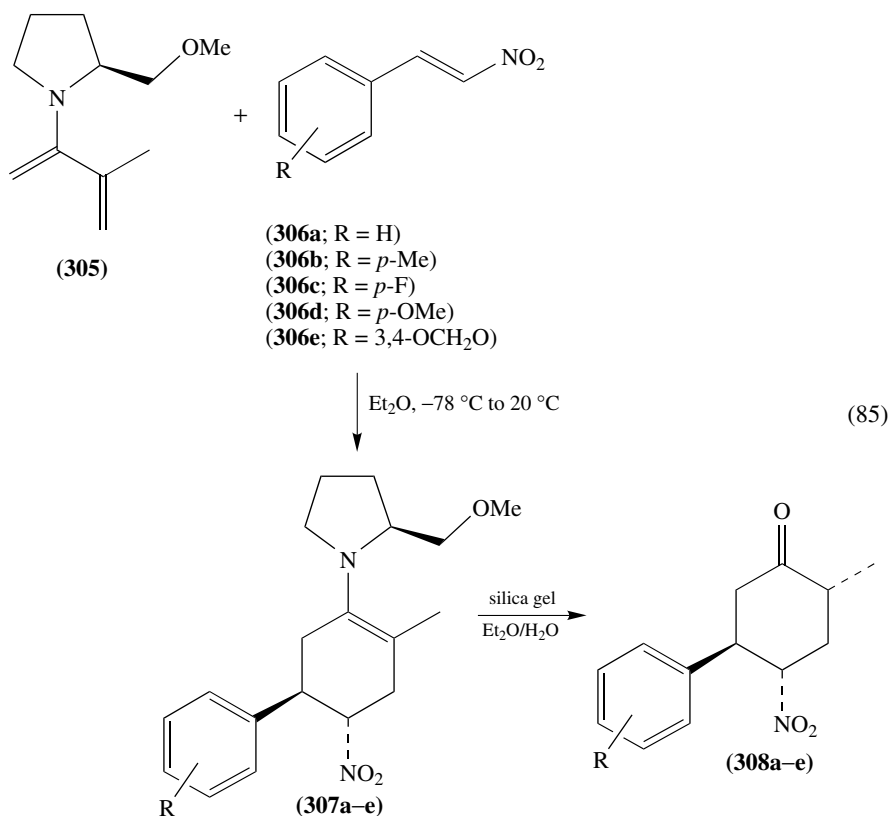
Barluenga and coworkers[194] recently extended the scope of the reaction between nitroalkenes and dienes like **305** by varying the substituents on the nitroalkene as well as on the diene. The 4-nitrocyclohexanone derivatives were generally obtained with good yields and very high enantiomeric excesses. This Diels−Alder strategy was used to synthesize cyclic β-amino acids[195].

Kozmin and Rawal[196] examined the reactions of chiral diene **309** with various dienophiles. Using this strategy, cyclohexenones were obtained with very high ee values (86−98%). Thus, the reaction of **309** with methacrolein **(310)** afforded adduct **311**, which

was converted in two steps to enantiomerically enriched **312** (equation 86). The major adduct was said to arise through a transition state in which the larger group on the dienophile was placed in the open pocket of the chiral pyrrolidine.
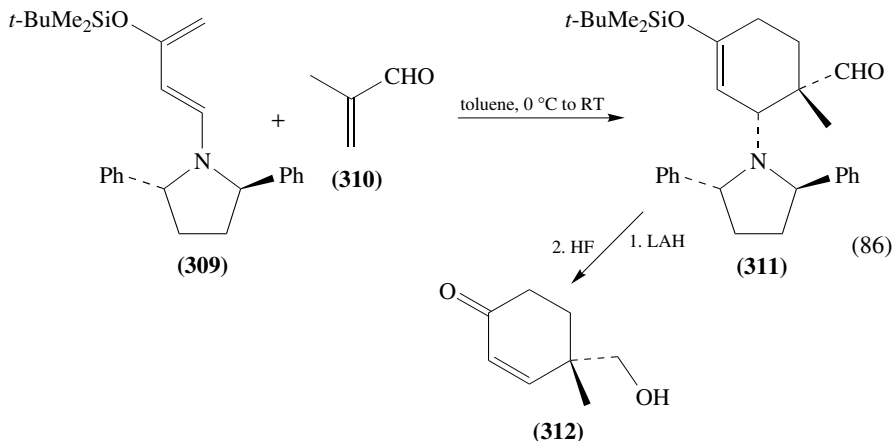
Arai and coworkers[197] reported the utilization of a chiral pyrrole sulfoxide as a chiral auxiliary in the asymmetric Diels−Alder reactions of its *N*-cinnamoyl and *N*-crotonyl derivatives **313** with cyclopentadiene which gave **314−317** (equation 87). The results have been summarized in Table 18. The yield as well as the *endo/exo* selectivity and the de proved to depend on the type and amount of Lewis acid used.

Nieman and Keay[198] reported the use of *cis,cis*-spiro[4,4]nonane-1,6-diol as a new chiral auxiliary to be used in asymmetric Diels−Alder reactions. Their best results in a series of reactions between chiral acrylates and cyclopentadiene were obtained when the pivalate ester of *cis,cis*-spiro[4,4]nonane-1,6-diol was used as the chiral auxiliary. When **318** was treated with cyclopentadiene, the expected *endo* adduct **319** was obtained with more than 97% de (equation 88).

Murray and colleagues[199] developed some 2,5-diketopiperazines as new chiral auxiliaries and examined their asymmetric induction in the Diels−Alder reactions of their *N*-acryloyl derivatives with several dienes. Some of their results with dienophile **320** have been summarized in Table 19 (equation 89). When the benzyl group on **320** was substituted by an isopropyl or *t*-butyl group, the diastereofacial selectivity dropped dramatically. It was proposed that $\pi-\pi$ stacking between the phenyl group and the electron-poor double bond provided a more selective shielding of one face of the double bond in this special case.

TABLE 18.   Reaction data for equation 87

Entry	R	Dienophile	Lewis acid (equiv.)	Yield (%)	*endo/exo*	% de **314**
1	Ph	**313a**	BF$_3$ · Et$_2$O (1.0)	0	—	—
2	Ph	**313a**	ZnCl$_2$ (1.0)	60	77/23	38
3	Ph	**313a**	AlCl$_3$ (1.0)	99	95/5	>99
4	Ph	**313a**	AlCl$_3$ (2.0)	84	59/41	11
5	Ph	**313a**	Yb(OTf)$_3$ (0.2)	33	80/20	80
6	Ph	**313a**	Yb(OTf)$_3$ (1.0)	61	69/31	89
7	Me	**313b**	Yb(OTf)$_3$ (1.0)	93	92/8	93
8	Me	**313b**	AlCl$_3$ (1.0)	100	91/9	92

(87)

(88)
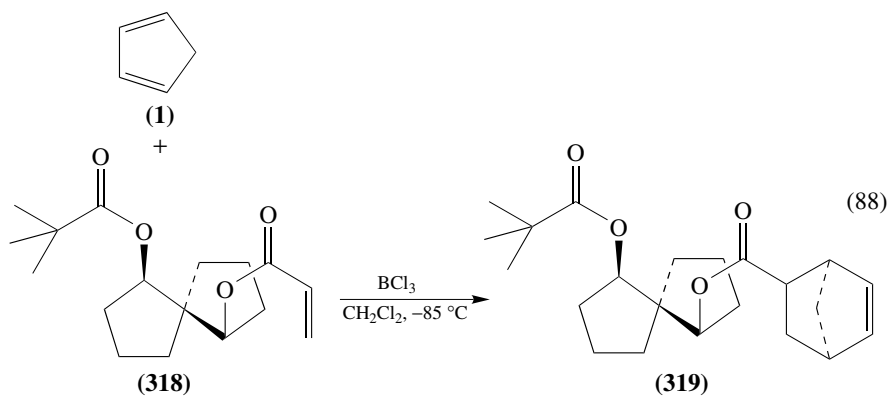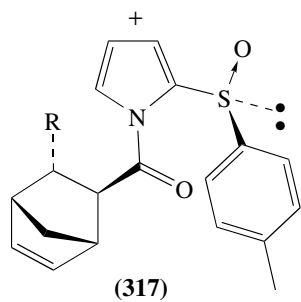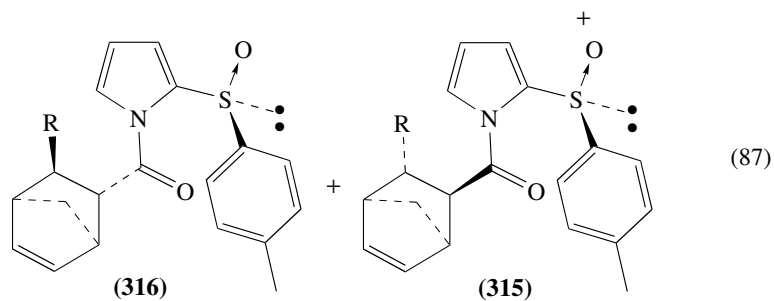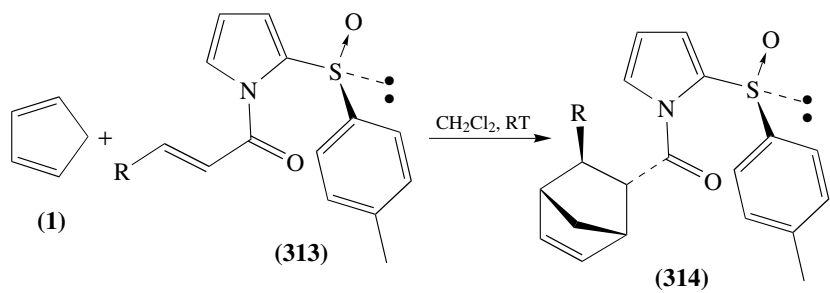
TABLE 19.   Reaction data for equation 89

Entry	n	R^1	R^2	Yield (%)	*endo/exo*	% de **321**
1	1	H	H	78	90/10	98
2	2	H	H	88	99/1	97
3	0	Me	Me	92	—	92
4	0	H	Me	94	—	100

(89)

(320)   **(321)**
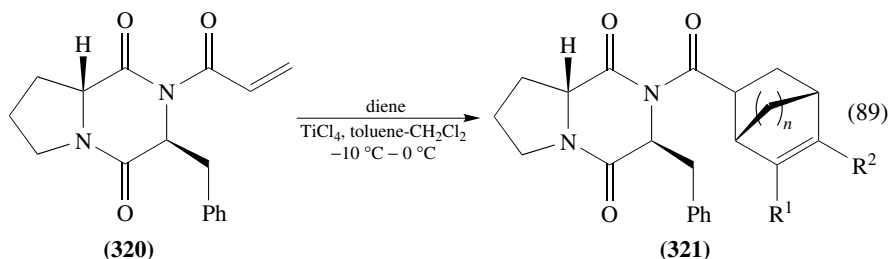
D. Chiral Lewis Acid Catalysts

The most important development within the field of Diels−Alder chemistry during the past two decades must be considered to be the design and application of chiral Lewis acid catalysts. From the mid '80s on, the number of literature reports about the design and application of chiral Lewis acids in the synthesis of chiral Diels−Alder adducts from achiral precursors grew exponentially, but it started to level off and decrease again in the mid '90s. Several excellent reviews about the application of chiral Lewis acids in Diels−Alder reactions have been published[41,43,44]. In this section, the recent literature about the chiral Lewis acid catalyzed all-carbon Diels−Alder reactions of dienes with dienophiles is reviewed, which, as such, has not been reviewed before.

In order to undergo Lewis acid catalysis, the dienophile or diene reacting in the Diels−Alder reaction must be conjugated with a group which can be complexed by a Lewis acid. In nearly all cases, this is a carbonyl functionality on the dienophile. This complexation leads to a lowering of the LUMO energy of the dienophile and to a relative increase of the LUMO coefficient at the β-carbon atom. This results in higher *endo* and regioselectivities.

High enantioselectivities can only be obtained if the chiral Lewis acid−carbonyl complex adopts a well-defined rigid conformation in the transition state. Lewis acid−carbonyl complexes exist as either σ or π complexes (Figure 4)[200]. Main group, early transition metal and lanthanide types of Lewis acids are believed to co-ordinate in a σ fashion. Electron-rich transition metal complexes prefer to give π-type of complexes with electron-poor carbonyl groups. The overwhelming majority of Lewis acids which catalyze Diels−Alder reactions belong to the former category.

α,β-Unsaturated carbonyl compounds to which a Lewis acid has been complexed in an η^1 fashion can adopt four conformations, as depicted for aldehydes in Figure 5. The terms *syn* and *anti* refer to the relative orientation of the Lewis acid with respect to the carbonyl substituent with the highest priority. In the case of aldehydes, the *anti* conformations are preferred. This has been shown for several BF_3−aldehyde complexes which proved to have a B−O−C−C dihedral angle of about $180°$[201]. The stereoelectronic control in the

η^1 complex (σ bonding) η^2 complex (π bonding)
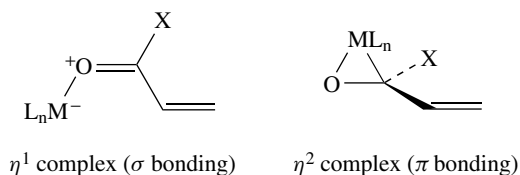
FIGURE 4. η^1 and η^2 types of co-ordination of a Lewis acid to a carbonyl group

syn s-trans   *anti s-trans*   *syn s-cis*   *anti s-cis*
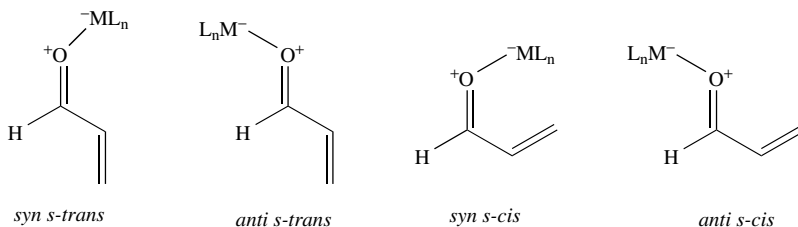
FIGURE 5. Important conformations of Lewis acid complexed aldehydes

formation of η^1 Lewis acid–carbonyl complexes has recently been discussed by Fu and colleagues[202]. In the case of esters, complexation of the Lewis acid occurs preferentially *anti* to the alkoxy group, as was demonstrated by X-ray crystallographic studies[202,203]. Lewis acids complex to amide carbonyls in an *anti* fashion with respect to the R_2N moiety, because *syn* complexation is strongly disfavored by allylic strain[200].

The enone system has to preferably adopt an *s-cis* or *s-trans* conformation in the transition state. Which one is favored may depend on the nature of the Lewis acid. It is generally accepted that Lewis acid complexation dramatically stabilizes the *s-trans* conformation[204]. The *s-cis* conformation, however, may be the more reactive conformation. The dienophile may react selectively in this conformation, if the *s-trans* and *s-cis* conformations are in equilibrium.

Stereoselective complexation of the chiral Lewis acid together with a preferred *s-cis* or *s-trans* conformation of the dienophile generally cause selective shielding of one face of the dienophile. Corey and coworkers[205] explained the high enantioselectivities observed with their chiral Lewis acid by hydrogen bridge formation between a formyl hydrogen and a chiral alkoxy ligand, based on X-ray crystallographic results.

The types of dienophiles which have been studied most are acrylic aldehydes, acrylates and 3-acryloyl-1,3-oxazolidines. The latter have been used predominantly in copper, magnesium, zinc and lanthanide catalyzed reactions in which the chiral Lewis acid binds in an η^2 fashion to the dienophile (complexation to both carbonyls).

1. Chiral aluminum catalysts

The chiral Lewis acid catalyzed cycloaddition of methacrolein **310** to cyclopentadiene predominantly affording *exo* cycloadduct **322** together with some **323** has been extensively investigated. The application of menthoxyaluminum dichloride **(324)** as the chiral catalyst in this reaction represents one of the earliest examples of a chiral Lewis acid catalyzed Diels–Alder reaction[206] (equation 90). The authors confirmed their results in 1987, but the ee was revised from 72% to 57%[207].

(1)   (310)   (2S-322)   (2R-323)   (90)
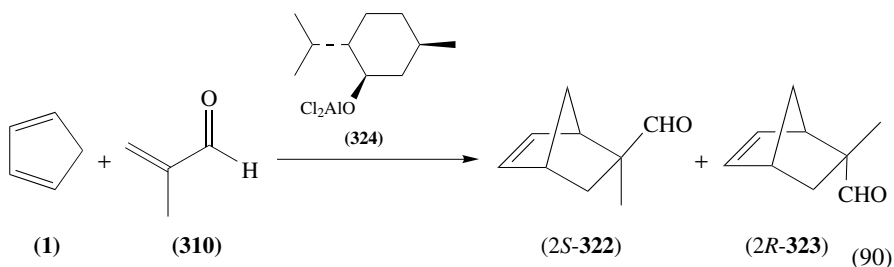
Kagan and coworkers studied the reaction between cyclopentadiene and **310** in the presence of aluminum alcoholates of chiral diols and their chiral mono ethers[208]. Among the various diols studied, only 1,1-diphenyl-1,2-propanediol **(325)** gave satisfactory results. Optimization by variation of the dienophile/catalyst ratio, aging of the catalyst and variation of the temperature ultimately resulted in a maximum of 86% ee at $-100\,^{\circ}$C.

(325)

(326)
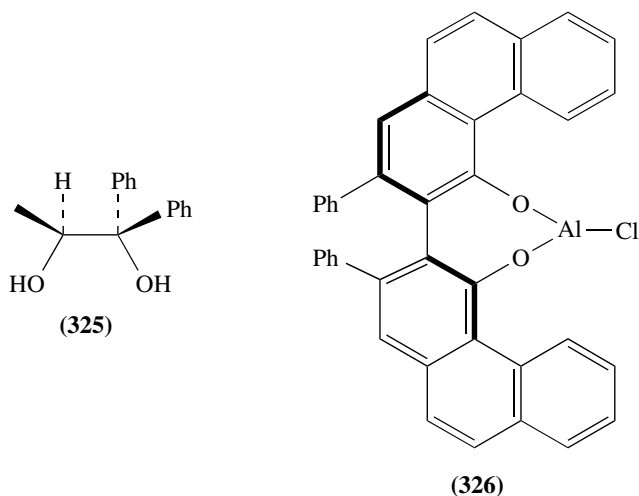
A very high asymmetric induction was observed when the reaction between cyclopentadiene and methacrolein was performed using 0.5 mol% of binaphthol catalyst **326**[209]. Diels–Alder adduct (2R)-**322** was formed with up to 97.8% ee within 4 h at $-80\,^{\circ}$C.

Mayoral and colleagues[210] studied the same reaction catalyzed by a menthoxyaluminum catalyst supported on silica gel and alumina. The catalyst was prepared by treatment of the solid support with diethylaluminum chloride and (−)-menthol. The silica-supported catalyst proved more active than the alumina-supported catalyst. The reaction rates and enantioselectivities depended strongly on the amount of (−)-menthol used. The highest ee obtained was 31% at 81% conversion (*endo*/*exo* = 10/90).

Recently, Diels–Alder reactions between cyclopentadiene and menthoxyaluminum dichloride–acrolein complexes were investigated by means of combined AM1/AM3 calculations and the results were compared to full AM1 results[211].

The asymmetric Diels–Alder reaction of cyclopentadiene with methyl acrylate **11b** has been studied using several types of catalysts. The asymmetric induction of various

dialkoxyaluminum chloride catalysts was studied by Hermann and coworkers, who also showed the dependence of the composition of the catalyst in solution on aging time. The best results were obtained employing ligand **328**, the reaction affording **327** with an ee of 70% in a yield of 49% (equation 91)[212].

$$(91)$$

(1)   **(11b)**   (2S-**327**)
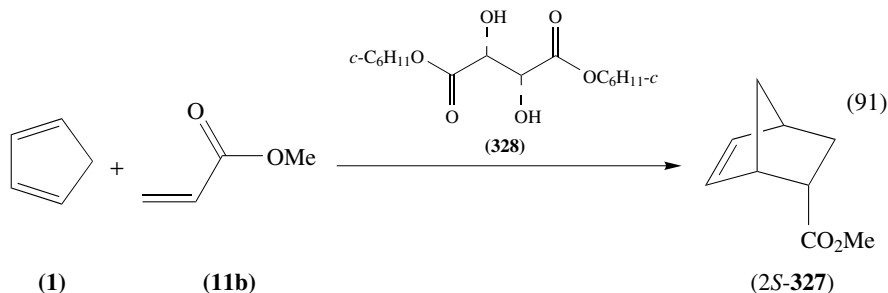
Catalyst **329**, prepared from trimethylaluminum and 3,3′-bis(triphenylsilyl)-1,1′-bi-2-naphthol, allowed the preparation of the *endo* cycloadduct (2S)-**327** with 67% ee. The use of non-polar solvents raised the ee, but lowered the chemical yield[213]. Recently, it was reported that the reaction to form **327** exhibited autoinduction when mediated by catalyst **326**[214]. This was attributed to a co-operative interaction of the cycloadduct with the catalyst, generating a more selective catalytic species. A wide variety of carbonyl ligands were tested for their co-operative effect on enantioselectivity. Sterically crowded aldehydes such as pivaldehyde provided the best results. Surprisingly, 1,3-dicarbonyl compounds were even more effective than monocarbonyl compounds. The asymmetric induction increased from 82 to 92% ee when di(1-adamantyl)-2,2-dimethylmalonate was added while at the same time the reaction temperature was allowed to increase by 80 °C, from −80 °C to 0 °C.

(329)
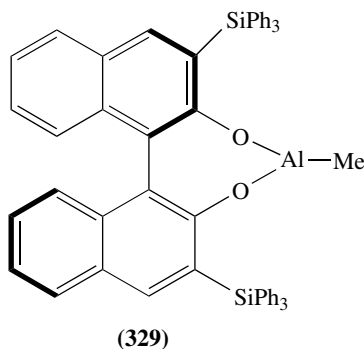
Catalyst **329** was also applied in the asymmetric Diels−Alder reaction of methyl propiolate **14** with cyclopentadiene, yielding cycloadduct **330** with 55% ee (equation 92)[213].

Corey and colleagues[215] prepared chiral aluminum complexes from chiral bis(sulfonamides) and trimethylaluminum. These were successfully applied in the cycloadditions of 3-acryloyl-1,3-oxazolidin-2-one **(17a)** with substituted cyclopentadienes. Thus, the reaction of 3-acryloyl-1,3-oxazolidin-2-one with 5-(benzyloxymethyl)cyclopentadiene **(331)** afforded **332** with 94% ee (equation 93). A transition state was proposed based on the X-ray structure of the chiral catalyst and on NMR data of the 1 : 1 complex between **333**

and **17a**[216]. The cycloaddition was the first step in the enantioselective synthesis of a key intermediate used to synthesize prostanoids[217].

$$(92)$$

(1)   **(14)**   **(1R-330)**

$$(93)$$

(17a)   **(331)**   **(2S-332)**
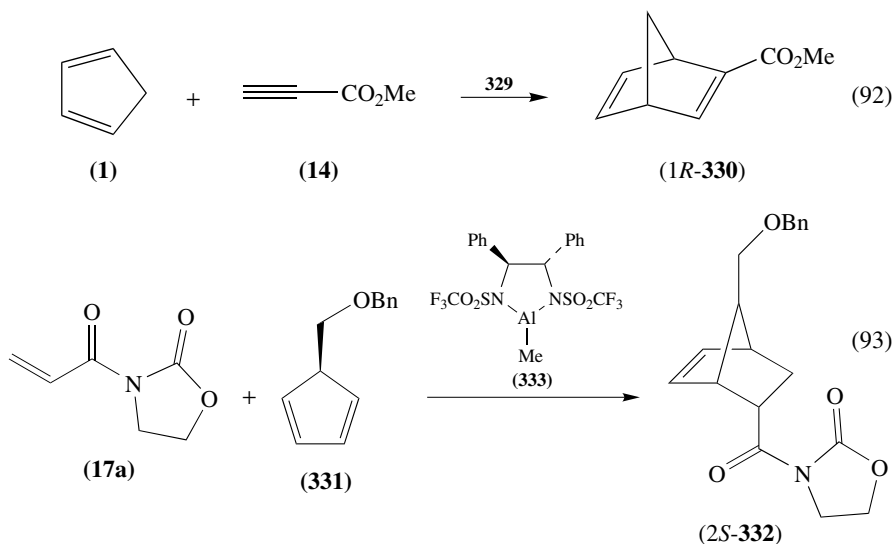
When catalyst **333** was applied in the cycloaddition reaction of 2-methoxy-1,3-butadiene **(334)** with *N*-(*o*-tolyl)maleimide **(335)**, the corresponding cycloadduct **337a** was obtained with only 58% ee. However, an ee of 95% was observed when catalyst **338** and *N*-(*o*-*t*-butylphenyl)maleimide **(336)** were employed (equation 94). The *meta* methyl substituents on the phenyl groups of catalyst **338** proved crucial for producing **337** with high enantio-selectivity. In contrast, the Diels–Alder reaction of maleic anhydride with 2-methoxy-1,3-butadiene using catalyst **338** afforded a racemic adduct. These results were considered to result from a different complexation behavior of the catalyst in the case of maleic anhydride in comparison with *N*-arylmaleimides[218].

$$(94)$$

(334)   **(335**; R = *o*-tolyl)   **(337a**; R = *o*-tolyl)
            (336; R = *o*-*t*-butylphenyl)   **(337b**; R = *o*-*t*-butylphenyl)
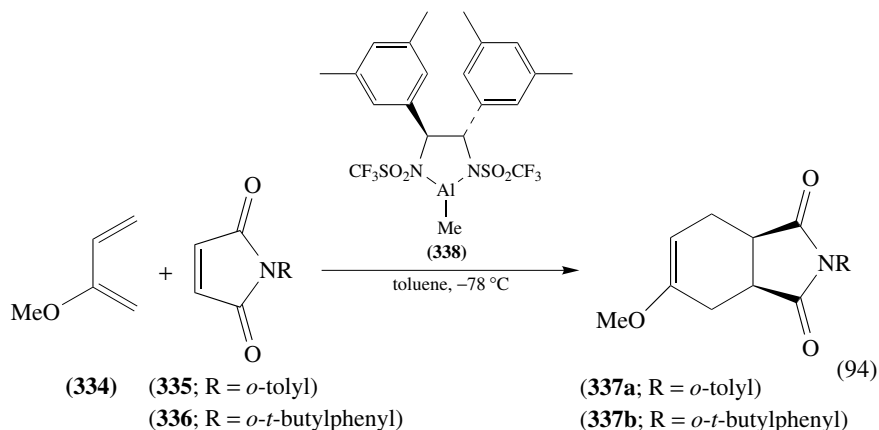
The reaction between diene **339** and **336** afforded cycloadduct **340** with 95% ee when catalyst **338** was used (equation 95). Adduct **340** was used as a precursor for the marine natural products gracillins B and C[219].

(95)
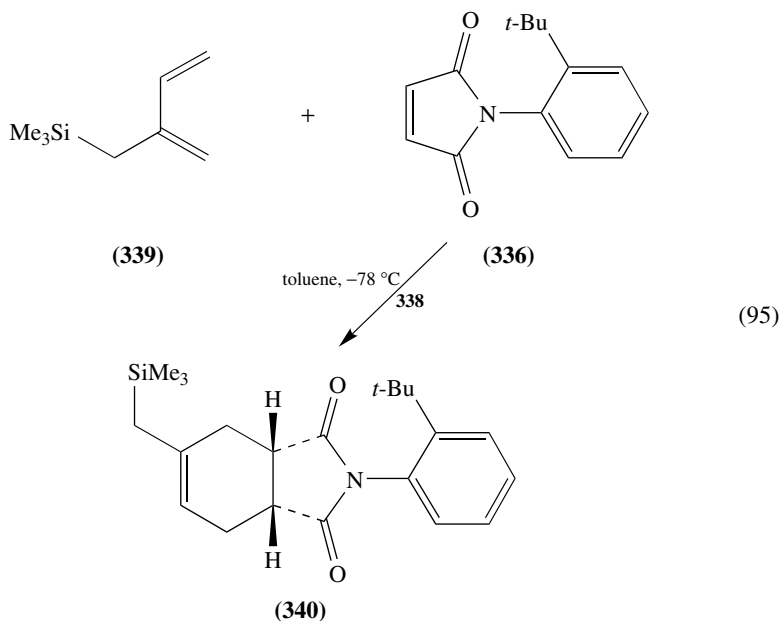
2. Chiral boron catalysts

Chiral boron catalysts had already been widely used in a variety of reactions before they were applied in Diels–Alder reactions[220]. Boron catalysts were first employed in the Diels–Alder reactions of quinones with electron-rich dienes. Kelly and coworkers[221] found that stoichiometric amounts of a catalyst prepared from BH_3, acetic acid and 3,3′-diphenyl-1,1′-bi-2-naphthol (**344**) catalyzed the reaction of 1-acetoxy-1,3-butadiene (**341**) with juglone (**342**) to afford cycloadduct **343** with 98% ee (equation 96). The reaction was supposed to proceed via a spirocyclic borate complex in which one face of the double bond of juglone was effectively shielded from attack by the diene.

A similar approach was followed by Yamamoto and colleagues[222]. A chiral boron catalyst prepared from trimethyl borate and various (R,R)-tartaric diamides **347** effectively catalyzed the cycloaddition of juglone to 1-triethylsilyloxy-1,3-butadiene (**345**) to give cycloadduct **346** with high enantioselectivity (equation 97).

The application of chiral boron catalysts in the cycloadditions of α,β-unsaturated aldehydes and acrylic acid derivatives has been investigated most.

Kaufmann and colleagues examined the asymmetric induction of chiral boron complexes **348** and **349**, obtained through reaction of $HBBr_2 \cdot SMe_2$ with pinene[223] and 1,1′-bi-2-naphthol[224], respectively, in the cycloaddition of cyclopentadiene with methacrolein (equation 98). A low ee (28%) was found when employing catalyst **348**, but the ee was greatly improved to 90% using catalyst **349**. The X-ray structure of **349** showed the molecule to have a propeller-like shape with an interesting C_3 symmetry.

(96)

(97)

(98)
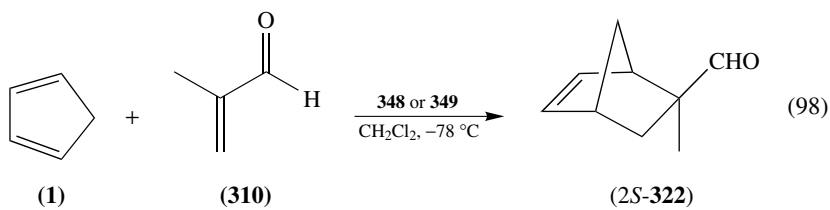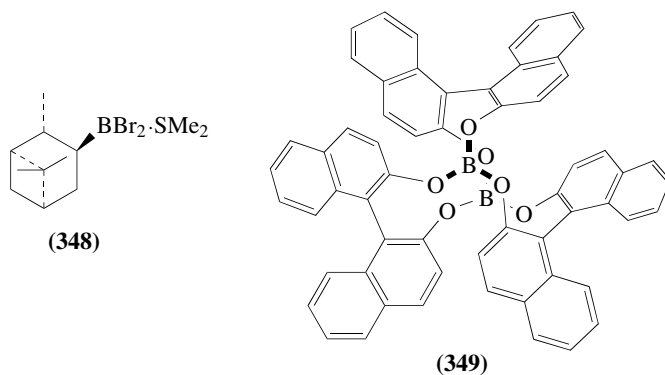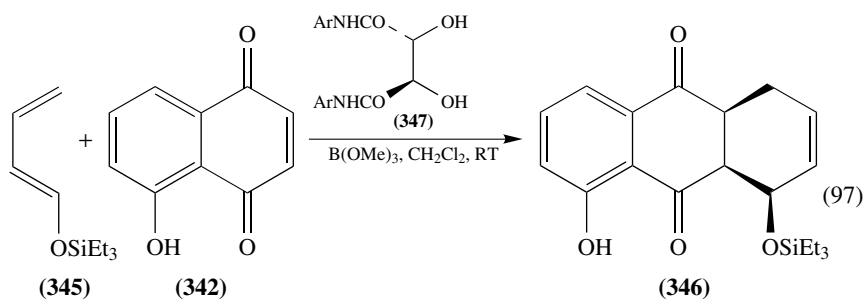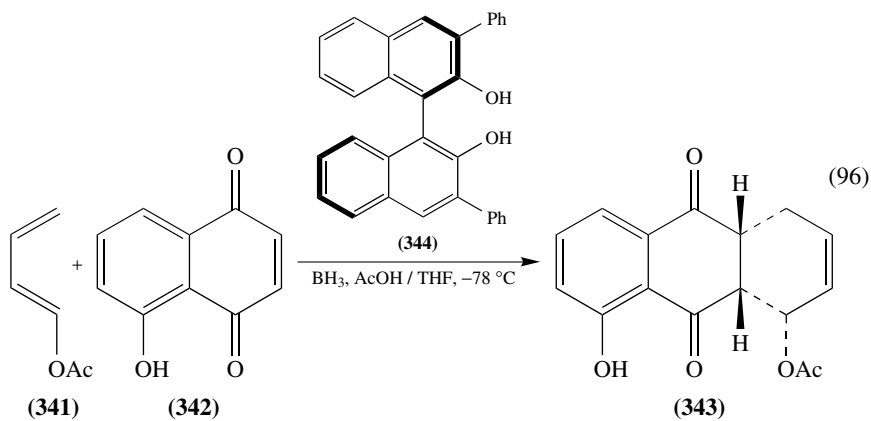
Hawkins and Loren[225] reported simple chiral arylalkyldichloroborane catalysts **352** which were effectively used in the cycloadditions of acrylates **11b** and **350** to cyclopentadiene, affording adducts **351a** and **351b**, respectively (equation 99). A crystal structure of the molecular complex between methyl crotonate and the catalyst allowed the authors to rationalize the outcome of the reaction. One face of methyl crotonate is blocked by $\pi-\pi$ donor–acceptor interactions, as becomes clear from the structure of complex **353**. The cycloadduct of methyl acrylate and cyclopentadiene (5 equivalents) was obtained with 97% ee, using the same catalyst. Three years later, the authors reported that the cycloadduct was obtained with 99.5% ee in the presence of 10 equivalents of cyclopentadiene[226].

(99)

(1)

(11b; R = H)
(350; R = Me)

(351a; R = H)
(351b; R = Me)

(353)
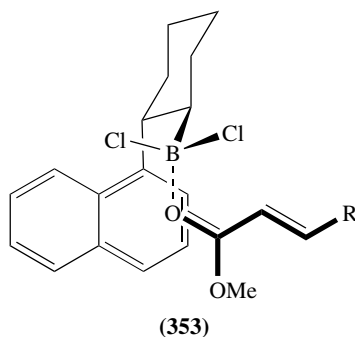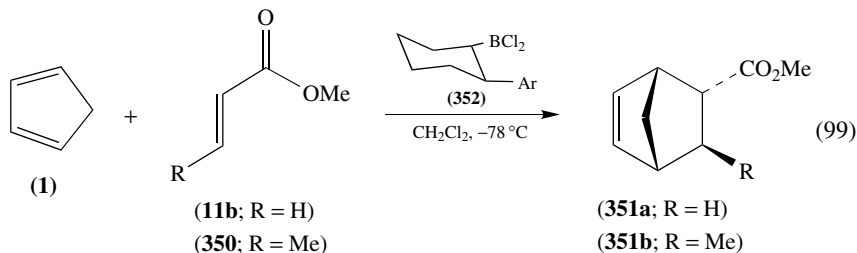
Kobayashi and colleagues[227] prepared chiral boron reagent **355** from BBr_3 and chiral prolinol derivative **354** (equation 100). This catalyst afforded the *exo* Diels–Alder adduct of cyclopentadiene and methacrolein with 97% ee (equation 101). In the same way, norbornene (2R)-**357** was obtained from **356** and cyclopentadiene.

(100)

(354)

(355)
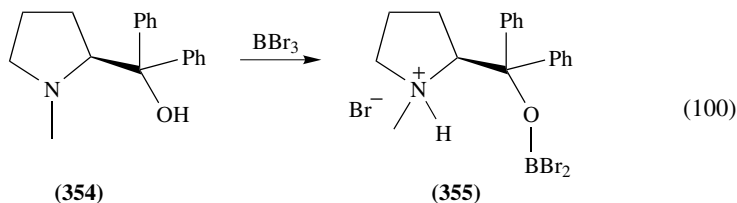
Chiral 1,2,3-oxazaborolidines simply obtained from α-amino acid derived sulfonamides and borane were first applied in Diels–Alder reactions by Taliasu and Yamamoto[228], and Helmchen and colleagues[229]. Yamamoto prepared catalysts from α-aminobutyric acid derived arylsulfonamides and found that the enantioselectivity of the reaction between

methacrolein and 2,3-dimethyl-1,3-butadiene (358) increased with increasing bulkiness of the arylsulfonyl group. Cycloadduct 359 was obtained with a maximum of 74% ee using catalyst 360 (equation 102).

(101)

(1)

(310; R = Me)
(356; R = Et)

(2R-322; R = Me, 97% ee)
(2R-357; R = Et, 73% ee)

(102)

(358)   (310)   (359; 74% ee)

(360)

(361a; R = H)
(361b; R = Me)
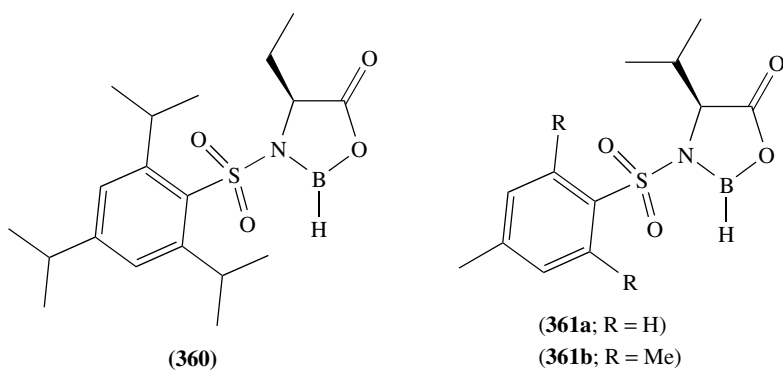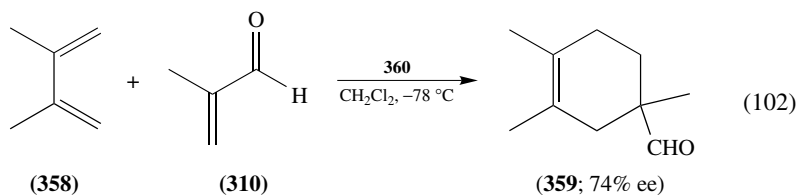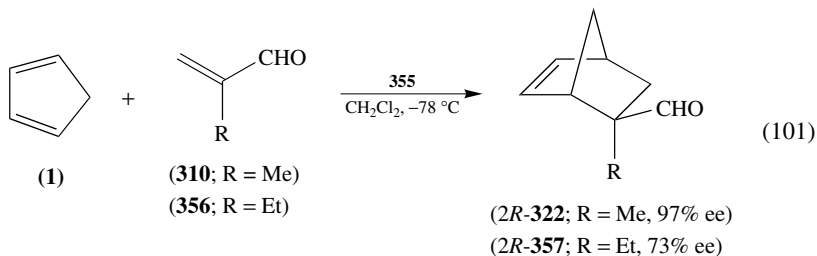
Helmchen and colleagues used equimolar amounts of L-valine derived oxazaborolidine 361a to catalyze the reaction of methacrolein with cyclopentadiene (equation 103). Cycloadduct 322 was obtained with 64% ee[229]. The enantioselectivity was increased to 86% ee by using 60 mol% of 361a and donor solvents like THF. The same catalyst afforded the *endo* cycloadduct of crotonaldehyde and cyclopentadiene with 76% ee.

(103)

(1)   (310)   (2R-322; 64–86% ee)
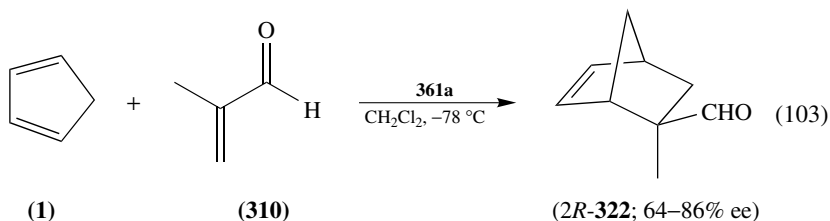
The cycloaddition reaction of crotonaldehyde (**362**) with cyclopentadiene in the presence of 20 mo1% of catalyst **361b** afforded cycloadduct **363** with 58% yield (*endo/exo* = 97/3) and 72% ee (equation 104)[230].

$$(104)$$

(**1**)　　　　　　　　　(**362**)

(2*S*-**363**; 72% ee)
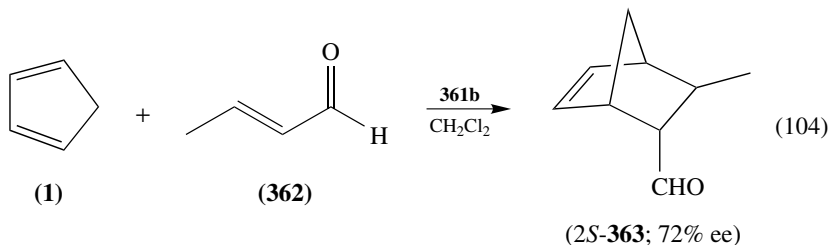
Interestingly, Corey and coworkers[231] showed that the main adduct in the reaction of methacrolein with cyclopentadiene was (2*S*)-**322** (92% ee) when catalyst **364**, derived from ($\alpha S, \beta R$)-β-methyltryptophan and *n*-butylboric acid, was used.

(**364**)
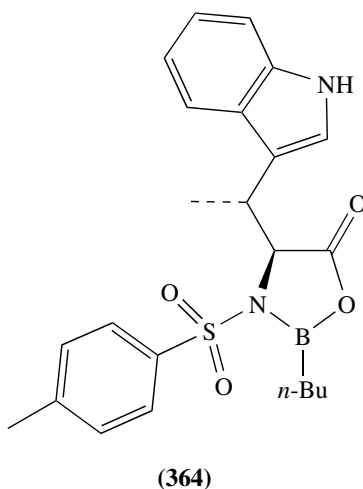
The effect of changing the position of the electron-donating atom in the side chain R of oxazaborolidine catalysts **367** was studied systematically for the reaction between cyclopentadiene and methacrolein. The enantioselectivity proved to be controlled by the presence of electron-donor atoms at positions 2 and 4 of the side chain. The effect was especially apparent in the formation of **366** from cyclopentadiene with α-bromoacrolein (**365**) (equation 105, Table 20), which is more electron-poor than methacrolein[232].

These results were rationalized by application of a transition state model for the reaction catalyzed by **367d** (Figure 6). A strong donor–acceptor interaction was envisaged between the oxygen atom of the benzyloxymethyl group and the carbonyl carbon of the complexed dienophile. In addition, a $\pi-\pi$ stacking interaction between the aromatic ring and the olefinic double bond was proposed. Because of these interactions, one of the dienophile faces is selectively blocked for approach by cyclopentadiene.

Very high enantioselectivities were obtained in the reaction between cyclopentadiene and α-bromoacrolein using (S)-tryptophan derived oxazaborolidine catalyst (S)-**369b**. The Diels–Alder adduct (2R)-**366** was obtained with at least 99% enantiomeric excess[233].

$$(105)$$

(1)   **(365)**   **(2R-366)**
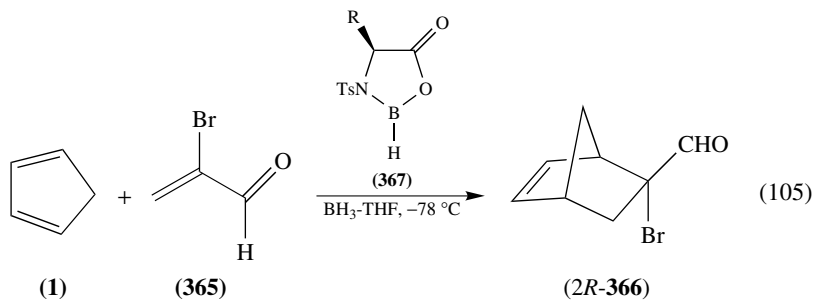
TABLE 20.   Reaction data for equation 105

Entry	R	Catalyst	*endo/exo*	% ee
1	Bn	**367a**	5/95	55
2	p-MeOC$_6$H$_4$CH$_2$	**367b**	4/96	72
3	p-PhCH$_2$OC$_6$H$_4$CH$_2$	**367c**	4/96	81
4	PhCH$_2$OCH$_2$	**367d**	4/96	81
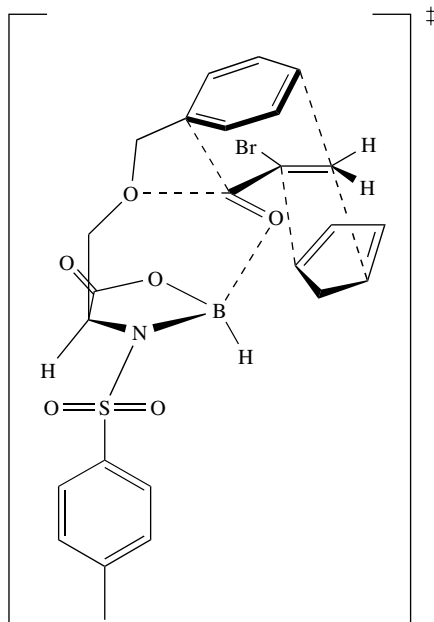
FIGURE 6. Model of the *exo* transition state to form **366** using **367d** as the catalyst

Catalyst (*S*)-**369a** was applied in the cycloaddition of isoprene to α-bromoacrolein to yield cycloadduct **368** with 76% yield and 92% ee (equation 106).

(91a)   (365)   (*S*-368)   (106)
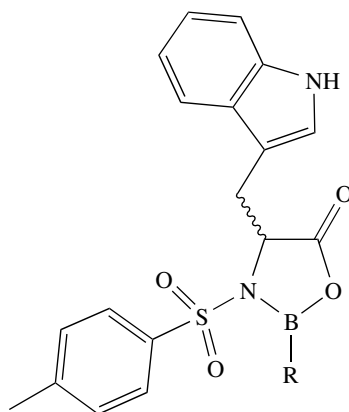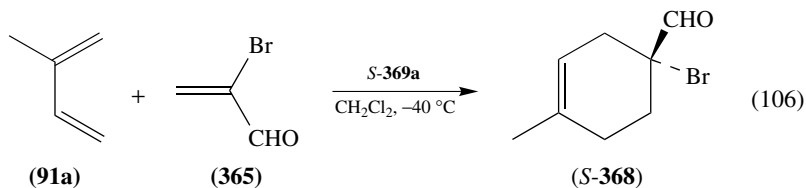
(**369a**; R = H)
(**369b**; R = *n*-Bu)

Catalyst (*R*)-**369b** catalyzed the cycloaddition of α-bromoacrolein to 5-(benzyloxyme-thyl)cyclopentadiene (**331**) to give adduct **370** with 82% yield and 92% ee (equation 107)[231,233]. Cycloadduct **370** has been used in prostaglandin synthesis.

(331)   (365)   (2*S*-370)   (107)
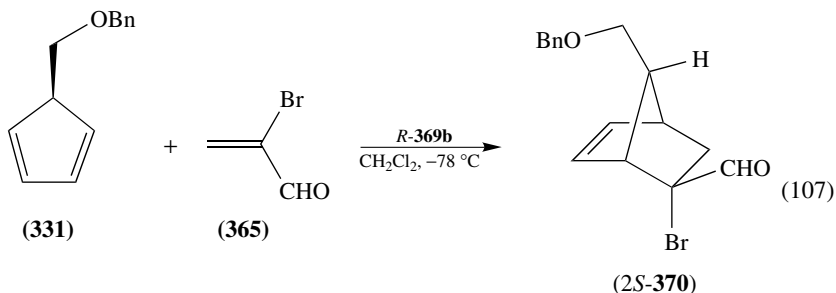
Marshall and Xie[234] used equimolar amounts of (*S*)-**369a** in the cycloaddition of α-bromoacrolein to diene **371** to prepare adduct **372**, a precursor for a subunit of the antitumor antibiotic kijanimycin. In this cycloaddition, the *endo* adduct was formed exclusively with 88% yield and 72% ee (equation 108).

$$(108)$$
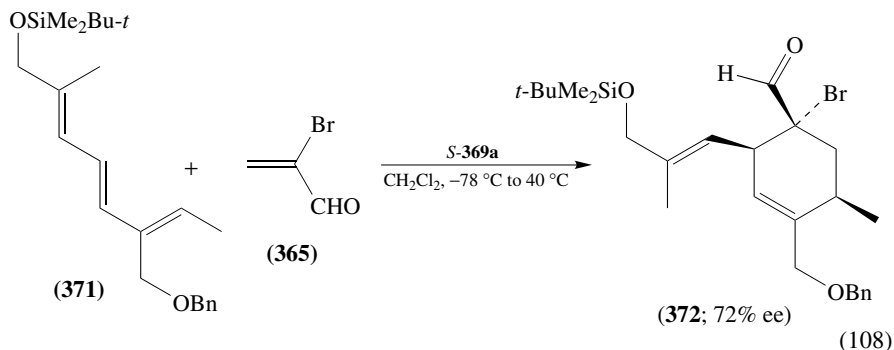
Furan reacted with α-bromoacrolein in the presence of 10 mol% of catalyst **364** to give the Diels–Alder adduct **373** in 98% yield with 92% ee (equation 109)[235]. Cycloadduct **373** has been applied in further synthesis[236]. The related catalyst (*S*)-**369b** proved much less effective in this reaction.

$$(109)$$
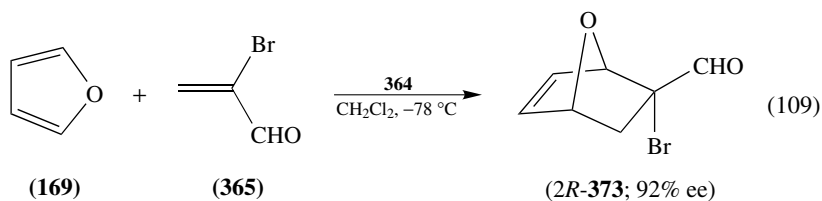
Two other applications of catalyst **364**, i.e. in cycloaddition reactions of α-substituted acroleins with dienes **374** and **376**, have been depicted in equations 110 and 111[237]. Cycloadducts **375** and **377** have been used as precursors in the syntheses of cassiol and gibberellic acid, respectively. The use of catalysts **364** and **369b** in cycloadditions with acrolein resulted in low enantioselectivities with opposite face selectivities.

Cross-linked polymers bearing *N*-sulfonyl amino acids as chiral ligands were converted to polymer bound oxazaborolidine catalysts by treatment with borane or bromoborane. In the cycloaddition of cyclopentadiene with methacrolein, these catalysts afforded the same enantioselectivities as their non-polymeric counterparts[238].

$$(110)$$

$$(111)$$

(376)   **(365)**   (2*R*-**377**; 99% ee)
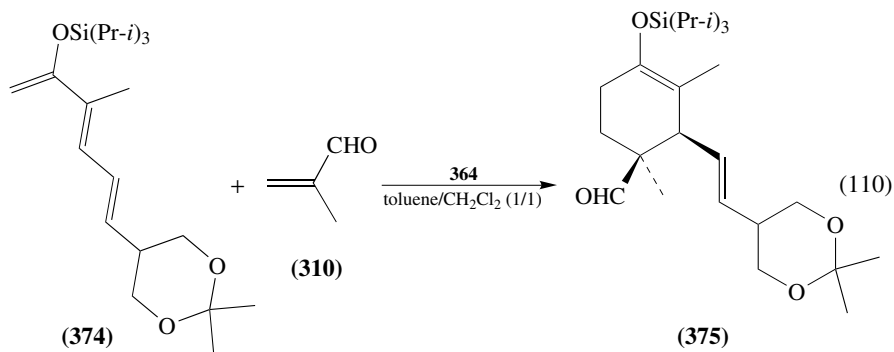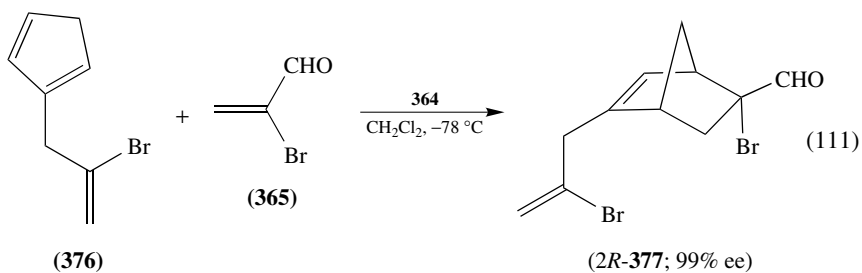
Yamamoto and colleagues developed achiral boron catalysts **379** and **380a–b** derived from monoacylated tartaric acid and BH_3–THF as shown for **379** in equation 112. The cycloaddition of cyclopentadiene to acrylic acid **(381)** afforded *endo* **382** with 78% ee and 93% yield when catalyst **379** was employed (equation 113)[239].

$$(112)$$

(378)   **(379)**

(380a; X = H)

380b; X =

380c; X =

$$(113)$$

(1)   (381)   (2R-382; 78% ee)
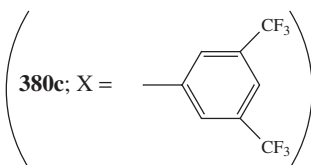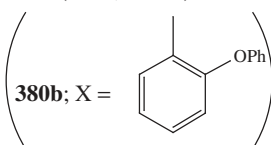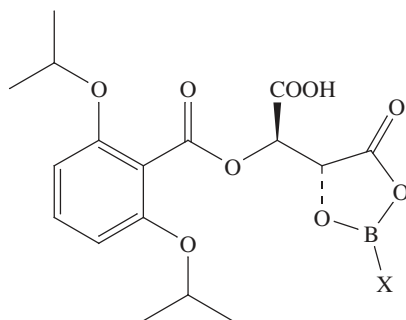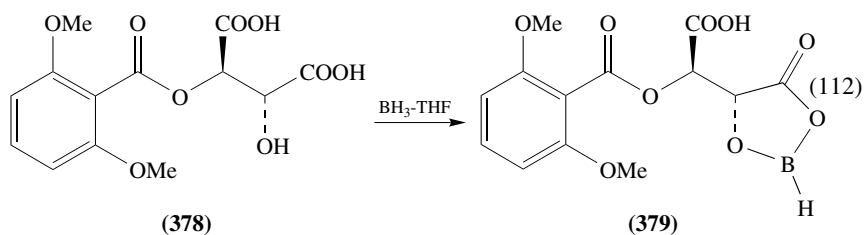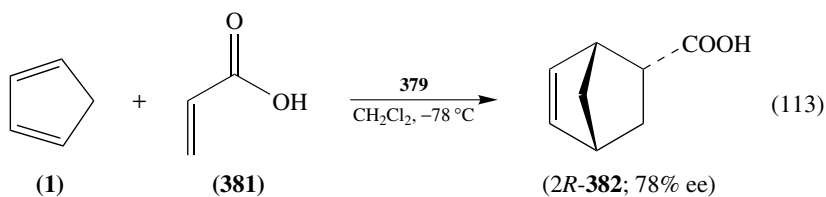
The asymmetric induction by catalyst **379** was extensively studied in the cycloadditions of simple dienes with substituted α,β-unsaturated aldehydes. It proved that α-substitution on the dienophile increased the enantioselectivity, whereas β-substitution dramatically decreased it. In the case of substrates having both α- and β-substituents, high enantioselectivities were observed[240].

Yamamoto and coworkers found that the Diels–Alder reactions of α-bromo-α,β-enals with dienes were also efficiently catalyzed by catalysts **380a** and **380b**[241]. The highest enantioselectivity and yield (98% ee, 100% yield) were obtained in the reaction of cyclopentadiene with α-bromoacrolein using 10 mol% of **380b** (equation 114). The same enantioselectivity was observed in the reaction between cyclopentadiene and **383**, which afforded adduct **384**. Catalyst **380a**, having a hydrogen substituted boron atom, afforded high ee values with other dienes. A model of the catalyst–dienophile complex (**385**) was proposed in which effective shielding of the *si* face of the co-ordinated unsaturated aldehyde arose from $\pi-\pi$ stacking of the 2,6-diisopropoxybenzene ring with the double bond of the unsaturated aldehyde[242].

$$(114)$$

(1)   (365; R = H)   (2S-366; R = H, 98% ee)
             (383; R = Me)   (2S-384; R = Me, 98% ee)

(385)
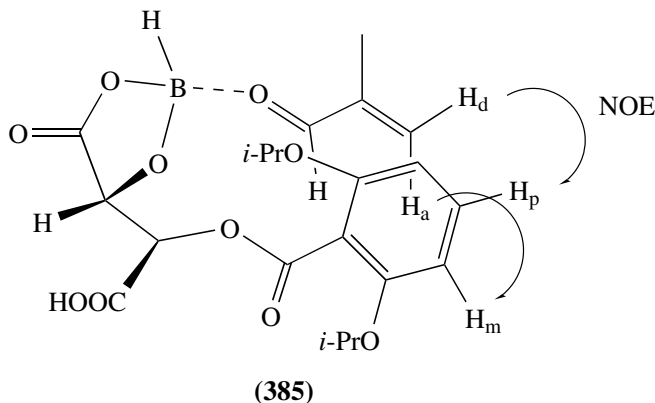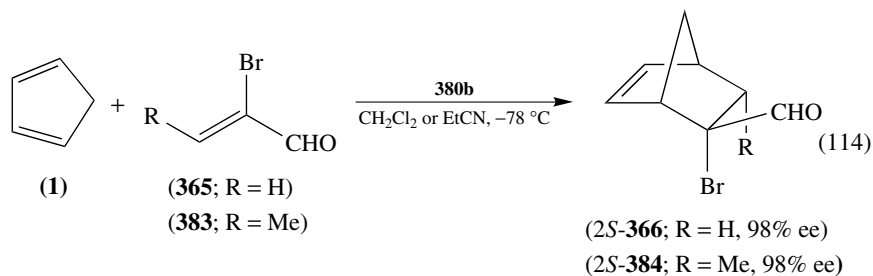
Simple chiral tartrate derived dioxaborolidine **386** induced a moderate enantioselectivity in the cycloaddition reaction of cyclopentadiene with α-bromoacrolein (equation 115)[243].

(115)

(1)   (365)   (2R-366)
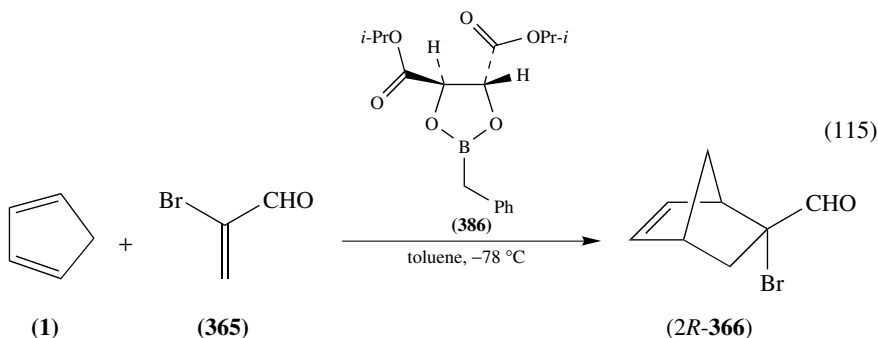
Yamamoto and colleagues showed that very high enantioselectivities and yields were obtained in the cycloadditions of cyclopentadiene with several α-substituted acrylic aldehydes using binaphthol catalyst **387** (equation 116).

(116)

(1)   (310; R = Me)   (2R-322; R = Me, >99% ee)
      (365; R = Br)   (2R-366; R = Br, >99% ee)
      (356; R = Et)   (2R-357; R = Et, 92% ee)
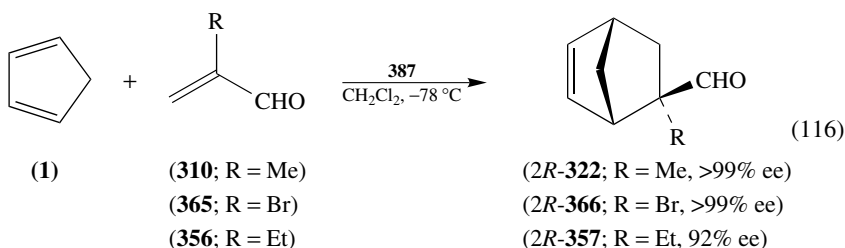
The high stereopreference was rationalized by considering complex **388** in which an attractive $\pi-\pi$ donor–acceptor interaction favors co-ordination of the dienophile to the face of the boron center which is *cis* to the 2-hydroxyphenyl substituent. Hydrogen bonding of the hydroxyl proton of the 2-hydroxyphenyl group to an oxygen of the adjacent B−O bond played an important role in the asymmetric induction. Protection of this hydroxy functionality with a benzyl group caused reversal of enantioselectivity in the cycloaddition of cyclopentadiene with methacrolein (model **389**)[244].

Further improvement of catalyst **387** resulted in the development of catalyst **393**, as demonstrated by the formation of **391** and **392** from dienophiles **390** and cyclic dienes which gave good results with less reactive dienes and dienophiles (equation 117, Table 21)[245].

Reilly and Oh explored the asymmetric induction of chiral catalysts derived from bis(dichloroborane) **397** in the cycloaddition of cyclopentadiene with α-bromoacrolein and methacrolein. *N*-Tosyltryptophan (**394**) and chiral diols **395** and **396** were employed as chiral ligands[246,247]. The application of chiral *N*-tosyltryptophan afforded the best results (equation 118, Table 22).

Corey and coworkers[205b,c,248] reported the reactive cationic oxazaborinane catalyst and afforded **398a** which promoted cycloadditions between cyclopentadiene and several α,β-enals good enantioselectivities. Excellent results were obtained in cycloadditions of several modestly reactive dienes to α-bromoacrolein in the presence of catalyst **398b** having tetra[3,5-bis(trifluoromethyl)phenyl]borate as the counterion (Table 23).

(**387**)

(**388**)

(**389**)
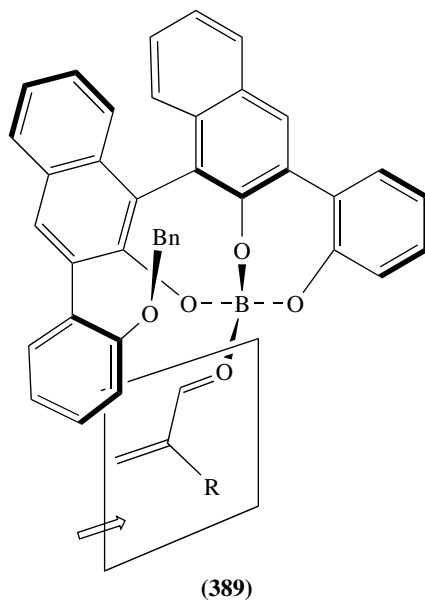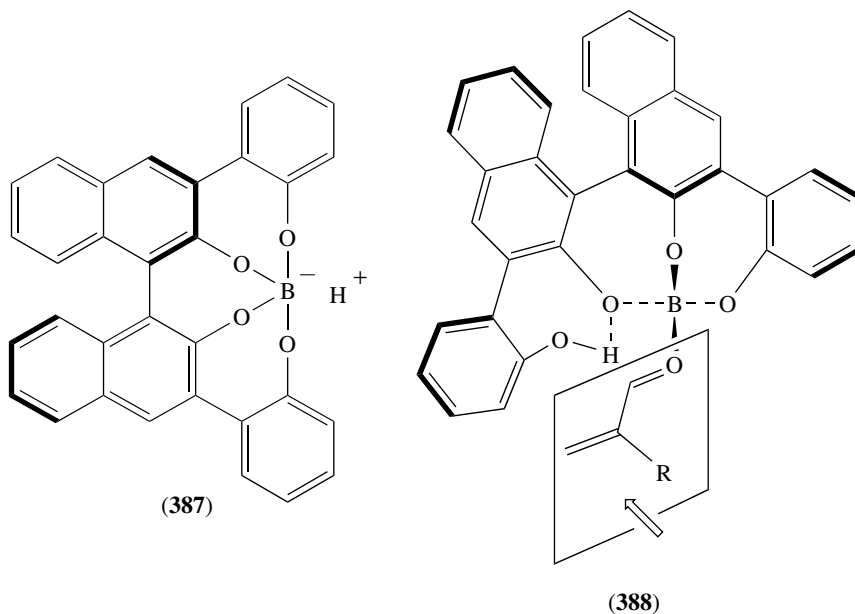
Recently, Yamamoto and coworkers[249] reported the first examples of chiral induction in the cycloadditions of cyclopentadiene to propargylic aldehydes **402** using catalysts **380c, 387** and **393** (equation 119). The cycloadditions were stated to proceed via *exo* transition states and were accelerated by coordination of the Lewis acid to the carbonyl group.

Later, Corey and colleagues reported that this reaction (with R = TMS, TES, Me_2PhSi and Bu_3Sn) was effectively catalyzed by **398b**, with which ee values of 80–87% were obtained[250].

$$(117)$$
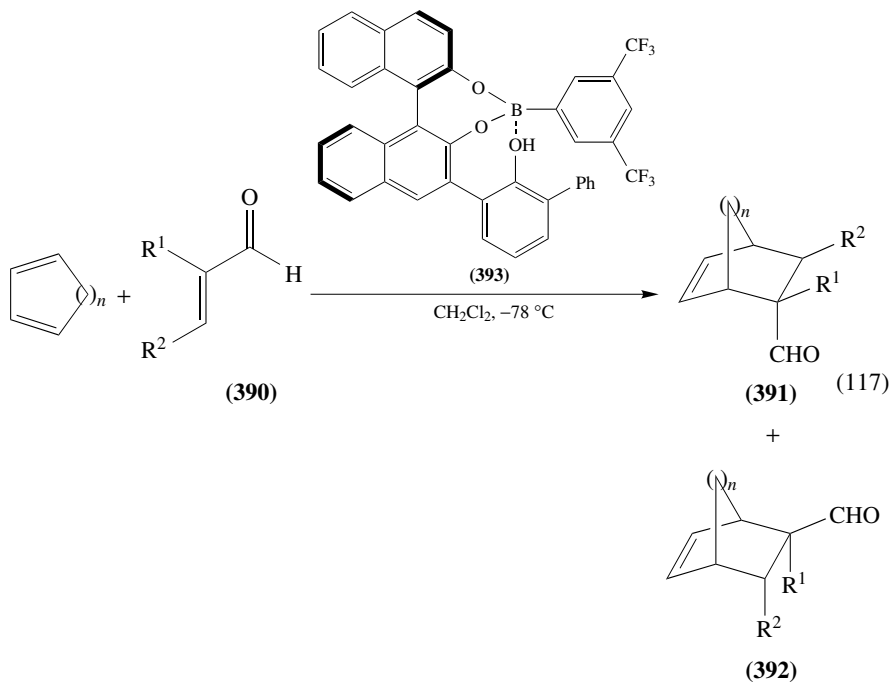
TABLE 21.   Reaction data for equation 117

Entry	n	R^1	R^2	Dienophile	**391/392**	% ee (major)
1	1	Me	H	**310**	—	99 (S)
2	1	Br	H	**365**	10/90	>99 (R)
3	2	Br	H	**365**	90/10	95
4	1	Me	Me	**390a**	2/98	96
5	1	H	H	**390b**	97/3	95 (S)
6	2	H	H	**390b**	100/0	96 (S)
7	1	H	Me	**362**	90/10	95 (S)
8	1	H	CO_2Et	**390c**	98/2	95 (R)

3. Chiral titanium catalysts

Chiral titanium catalysts have generally been derived from chiral diols. Narasaka and colleagues[251] developed an efficient catalyst, **406**, prepared from $TiCl_2(OPr\text{-}i)_2$ and a (+)-tartaric acid derived 1,4-diol. These authors found that *N*-crotonyl-1,3-oxazolidin-2-one (**404**) reacted with cyclopentadiene in the presence of 10 mol% of **406** to give cycloadduct **405** with up to 91% ee (equation 120)[252].

(394)   (395)   (396)

(118)

(1)   (397)
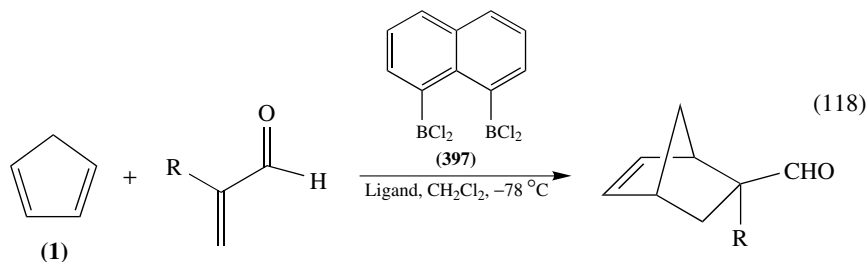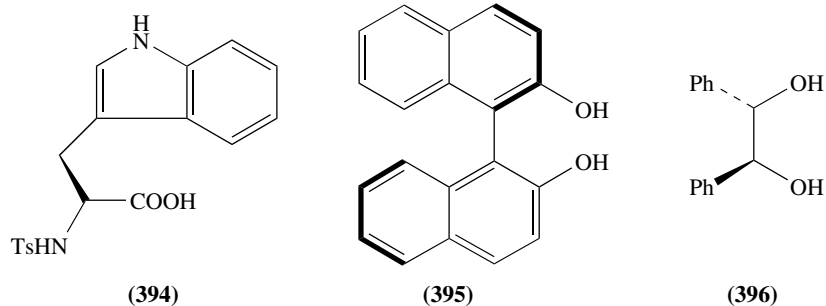
TABLE 22.   Reaction data for equation 118

Entry	R	Dienophile	Ligand	Ligand/397	Yield (%)	*endo/exo*	% ee
1	Br	**365**	**394**	1	84	8/92	22 *(exo)*
2	Me	**310**	**394**	1	46	37/63	100 *(endo)*
3	H	**390b**	**394**	1	53	94/6	62 *(endo)*
4	Br	**365**	**395**	1	81	14/86	36 *(exo)*
5	Br	**365**	**395**	2	81	20/80	28 *(exo)*
6	Br	**365**	**396**	2	83	20/80	—

(399)   (*R*-400)

(2*R*-401)
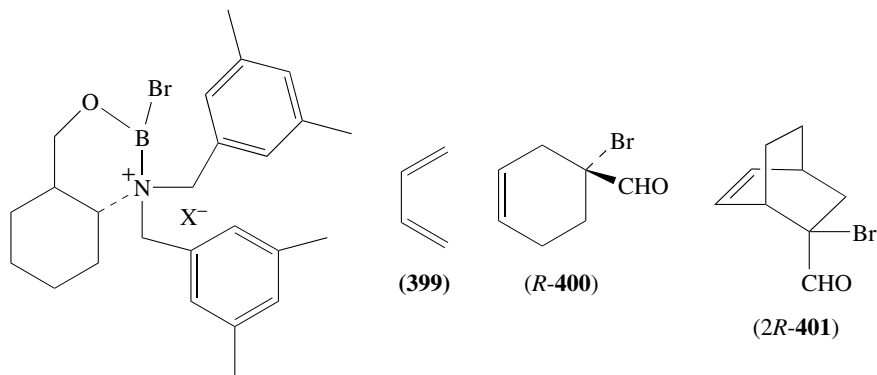
(398a; X = BBr₄)
(398b; X = B[C₆H₃-3,5-(CF₃)₂]₄)

TABLE 23. Reaction data for the cycloaddition reactions between α-bromoacrolein and several dienes

Entry	Diene	Product	Yield (%)	*endo/exo*	% ee
1	**399**	**400**	99	—	94
2	**91a**	**369**	99	—	96
3	**275**	**401**	99	4/96	93
4	**1**	**366**	99	9/91	98

(119)

(**402a**; R = H)   (**403a**; R = H)

(**402b**; R = Me)   (**403b**; R = Me)

(**402c**; R = CO$_2$Et)   (**403c**; R = CO$_2$Et)

(120)

(2S-**405**; 91% ee)
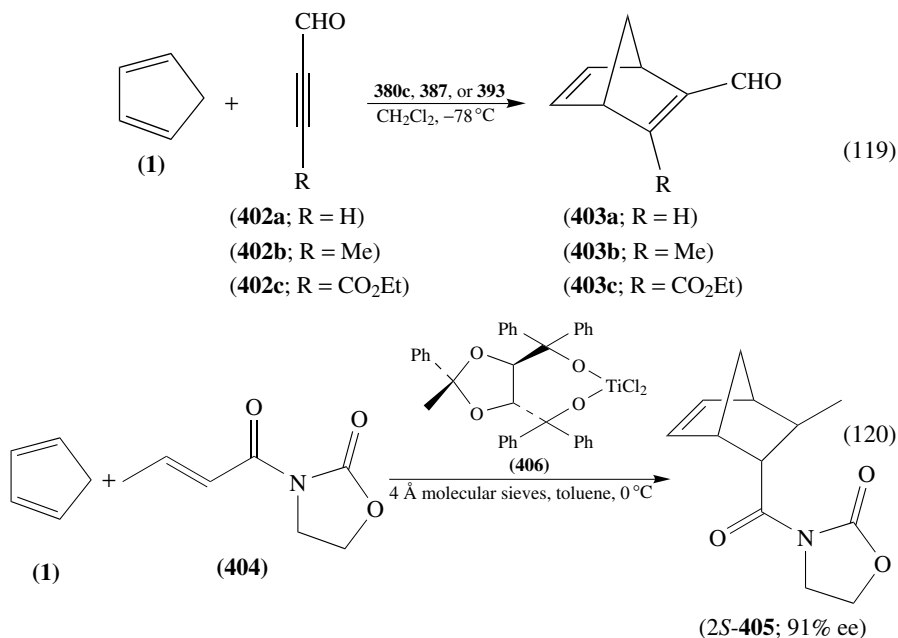
The catalyst was prepared from the corresponding chiral diol and TiCl$_2$(OPr-i)$_2$ at room temperature in the presence of 4 Å molecular sieves. Without molecular sieves, stoichiometric amounts of the titanium complex were required to obtain an equally high enantioselectivity. A remarkable solvent effect was observed. Various cycloadducts were only obtained with high optical yields when non-polar solvents were employed[252,253]. For example, 4-substituted 4-cyclohexene-1,2-dicarboxylate derivatives **408** were obtained with ee values ranging from 91 to 94% in the reactions of **91a**, **399** and **407** with **17b** in toluene/

petroleum ether (equation 121).

Narasaka and Yamamoto applied catalyst **406** in the cycloaddition of 1-acetoxy-3-methyl-1,3-butadiene (**409**) to 3-boryl propenoic acid derivative **410** (equation 122). Cycloadduct **411** was employed in the total synthesis of (+)-paniculide[254].

Corey and colleagues studied the chiral induction of various analogs of **406** in which the phenyl groups on the tertiary carbinol unit were replaced by other aromatic groups. The use of 3,5-xylyl groups (catalyst **412**) gave the best results. Cycloadduct **413**, for example, was obtained with 95% ee in the presence of this catalyst[255].

(121)

(**91a**; R = Me)
(**399**; R = H)
(**407**; R = SEt)

(**17b**)

4 Å mol. sieves,
toluene, petroleum ether | **406**

(**408**; R = H, Me, SEt; 91−94% ee)

(122)

(**409**)

(**410**)

4 Å mol. sieves, RT | **406**

(**411**; 94% ee)

(412)   **(413)**
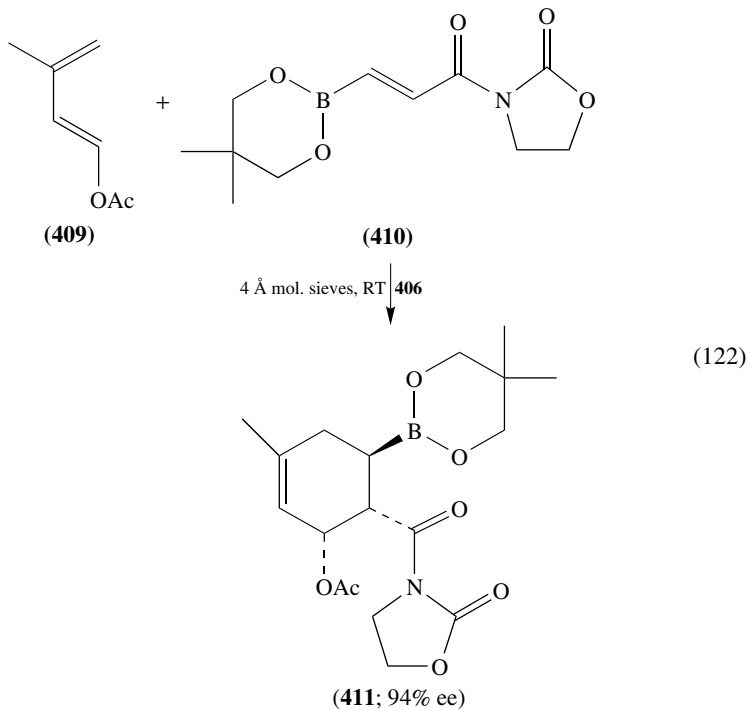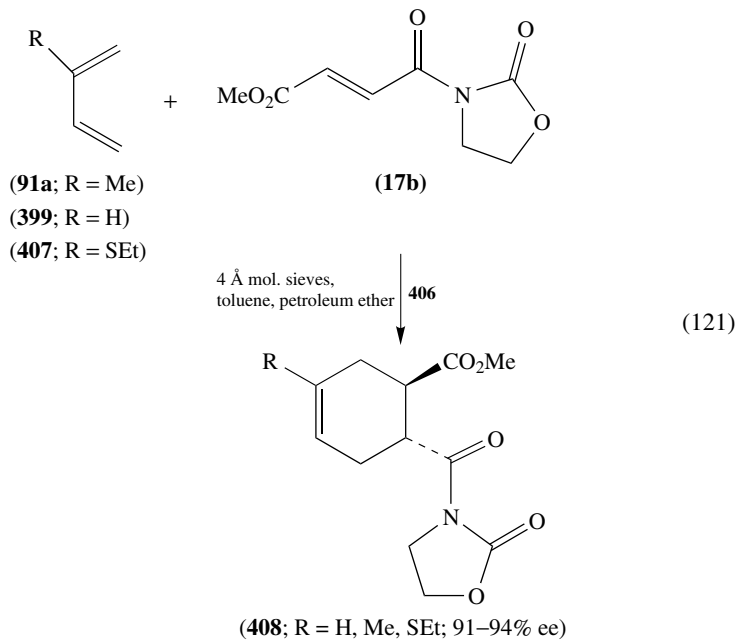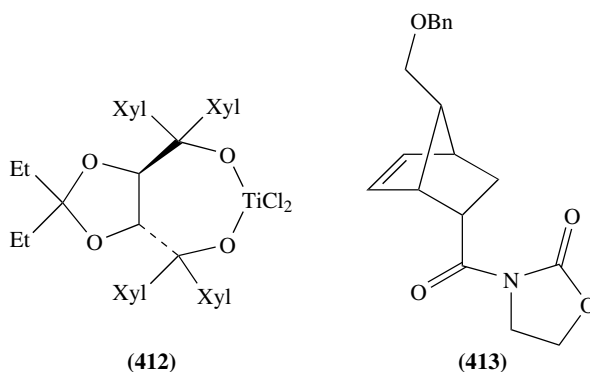
Engler and colleagues[256] demonstrated that the way in which catalyst **406** is prepared has a strong effect on the regioselectivity and enantioselectivity of quinone Diels–Alder reactions. The most effective catalyst was prepared from a 1 : 1 : 1 mixture of titanium tetrachloride, titanium tetraisopropoxide and chiral diol **416**. The cycloadditions of 2-methoxy-1,4-benzoquinones such as **414** with simple dienes to give adducts like **415** proceeded with high yields and enantioselectivities of up to 80% ee using this catalytic system (equation 123).

(123)

(91b)   **(414)**   **(415; 80% ee)**
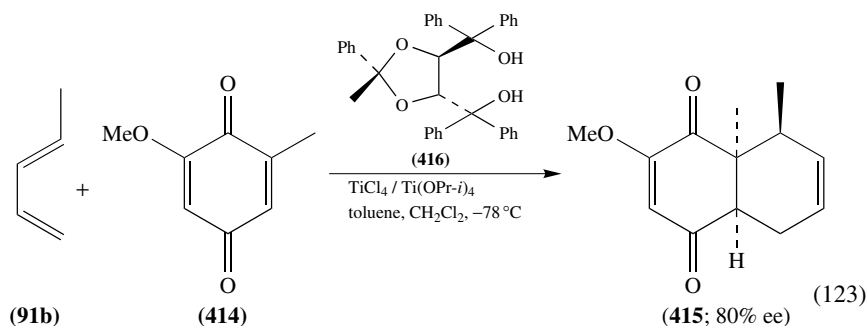
Binaphthol catalyst **417** proved effective in the cycloadditions of 1-alkoxy-1,3-butadienes with methacrolein and 1,4-naphthoquinone[257]. More recently, it was found that the use of molecular sieves was essential for the *in situ* preparation of the catalyst, but also that this had dramatic effects on the enantioselectivity[258]. In the presence of molecular sieves, the cycloaddition of juglone **(342)** with 1-acetoxy-1,3-butadiene was catalyzed by 10 mol% of **417** to give cycloadduct **343** with only 9% ee. In the absence of molecular sieves, the enantiomeric excess increased to 76–96% (equation 124).

Monochlorotitanium complex **418**, prepared from (1R,2S)-N-(2,4,6-trimethylbenzenesulfonyl)-2-amino-1-indanol and titanium tetraisopropoxide followed by treatment with titanium tetrachloride effectively catalyzed the cycloaddition of α-bromoacrolein to cyclopentadiene, affording **366** with 93% ee (equation 125)[259]. Catalyst **418** induced an ee of 90% in the reaction of isoprene with α-bromoacrolein.

Yamamoto and colleagues prepared chiral titanium catalyst **420** from titanium tetraisopropoxide and chiral binaphthol **419** (equation 126). This catalyst gave high asymmetric inductions in various Diels–Alder reactions of α,β-unsaturated aldehydes with cyclopentadiene and 1,3-cyclohexadiene[260].

(124)

(125)
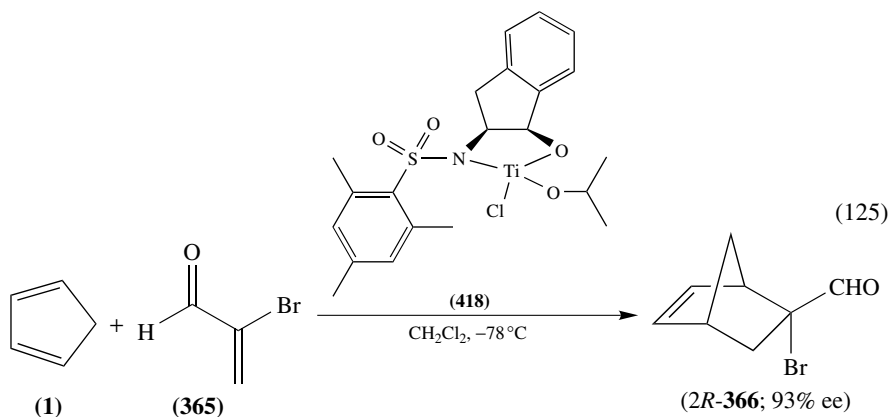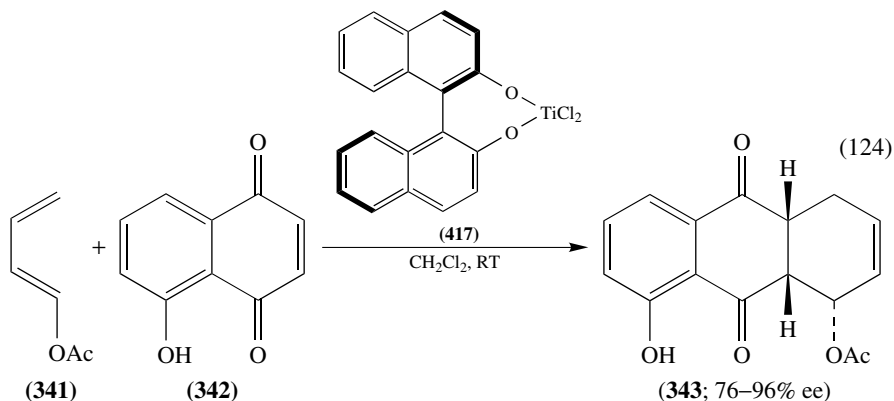
Chiral metallocene complex $[(S)$-1,2-ethylenebis(η^5-tetrahydroindenoyl)]Ti(OTf)$_2$ **422a** and its zirconium analog **422b** efficiently catalyzed the cycloadditions of 1,3-oxazolidin-2-one based dienophiles **17a** and **404** with cyclopentadiene which gave **421** and **405**, respectively[261]. The *endo* selectivity was highest in dichloromethane, whereas the enantioselectivity was higher in nitroalkane solvents (equation 127, Table 24).

4. Chiral copper(II) catalysts

Evans and coworkers[262] demonstrated the utility of bis(oxazolidine)copper(II) complexes **425** as Lewis acid catalysts in Diels–Alder reactions of *N*-enoyl-1,3-oxazolidin-2-ones **423** with cyclopentadiene, which gave adducts **424** (equation 128, Table 25). Their best results were obtained using catalyst **425c**. Surprisingly, only 30% ee was obtained in the reaction between cyclopentadiene and **17a** when catalyzed by **425a**. Similar results were obtained for the thiazolidine-2-thione analogs of the *N*-enoyl-1,3-oxazolidin-2-ones.

The enantioselectivities observed were rationalized by the transition state depicted in Figure 7. Copper(II) has a high propensity for 4-co-ordinacy. In this case, two co-ordination sites are occupied by the bidentate ligand, the substrate binding to the two remaining binding sites. Cyclopentadiene approaches the dienophile from the side opposite

to the *t*-butyl group. The transition state model was supported by results from stereodif-
ferentiating experiments using chiral (*R*)- and (*S*)-1,3-oxazolidin-2-ones[262,263].

(419)

azeotropic removal of *i*-PrOH $\vert$ Ti(OPr-*i*)$_4$, CH$_2$Cl$_2$ (126)

(420)
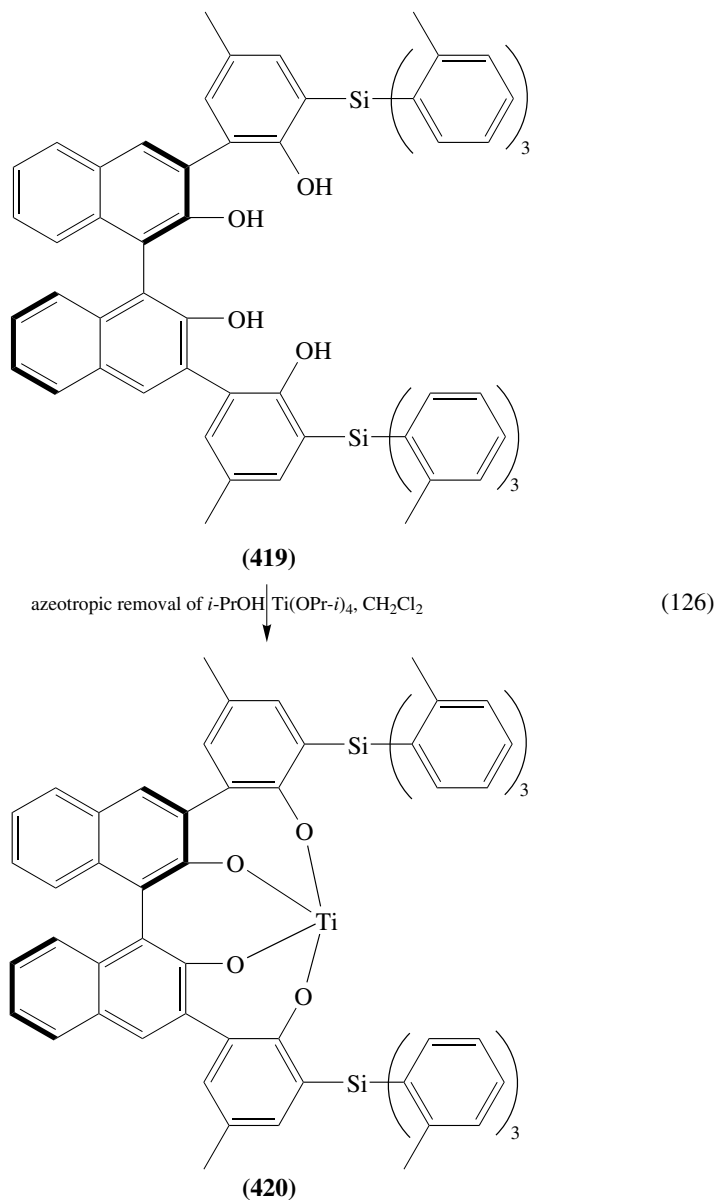
Afterwards, the authors found that catalyst **426** with SbF$_6{}^-$ as the counterion demon-
strated higher inductions in the reactions of substituted *N*-acryloyl-1,3-oxazolidin-2-ones

428 with several dienes, e.g. with cyclopentadiene to form **429** (equation 129, Table 26)[264]. This counterion effect had already been observed in the utilization of tridentate bis(oxazolidinyl)pyridine based copper(II) complexes **427** in Diels–Alder reactions of α-substituted acroleins. Catalyst **427d**, for example, proved about 20 times more reactive and induced higher ee values than catalyst **427a** (equation 130, Table 27)[264,265]. Catalysts **425c** and **427** were compared with their Zn(II) analogs[265]. It was concluded that they are superior to their Zn(II) counterparts as chiral Lewis acids in the Diels–Alder reactions of cyclopentadiene with substituted N-acryloyl-1,3-oxazolidin-2-ones.
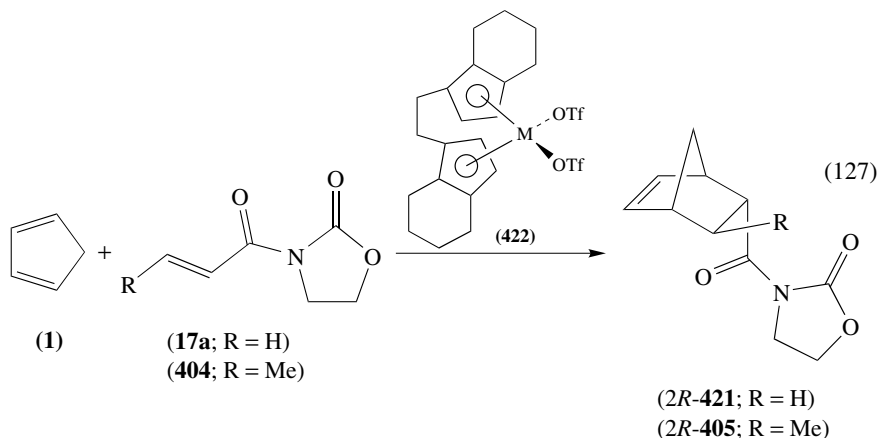
TABLE 24. Reaction data for equation 127

Entry	M (mol%)	Catalyst	R	Solvent	T (°C)	endo/exo	% ee
1	Ti (10)	**422a**	H	CH_2Cl_2	0	90/10	0
2	Ti (10)	**422a**	H	CH_3NO_2	0	88/12	88
3	Ti (5)	**422a**	H	CH_3NO_2	−30	88/12	89
4	Zr (1)	**422b**	H	CH_2Cl_2	−78	97/3	30
5	Zr (5)	**422b**	H	$(CH_3)_2CHNO_2$	−78	86/14	92
6	Zr (5)	**422b**	Me	$(CH_3)_2CHNO_2$	−78	94/6	95

Davies and colleagues[266] studied the use of copper(II) complexes of chiral bis(oxazolidine) **430** as catalysts in the cycloadditions of cyclopentadiene to substituted N-acryloyl-1,3-oxazolidin-2-ones. They observed high endo and enantioselectivities. Again, the highest enantioselectivities were observed using SbF_6^- as the counterion, although differences were small this time: ee values of 92 and 95% were obtained for the triflate and SbF_6^- based catalysts, respectively.

The effect of the ligand bite angle on the enantioselectivity in the copper(II) catalyzed Diels–Alder reaction of cyclopentadiene with N-acryloyl-1,3-oxazolidin-2-one was studied using spiro bis(oxazolidine) based complexes **431a–d** (Table 28)[267,268]. The data show that the enantioselectivity and endo selectivity increase with increasing bite angle θ which is related to the angle Φ and n. Substitution of the dimethyl moiety on **430** with a cyclopropyl moiety (**431a**) induced an increase in enantioselectivity, which is in agreement with the expected increase in bite angle.

$$(128)$$
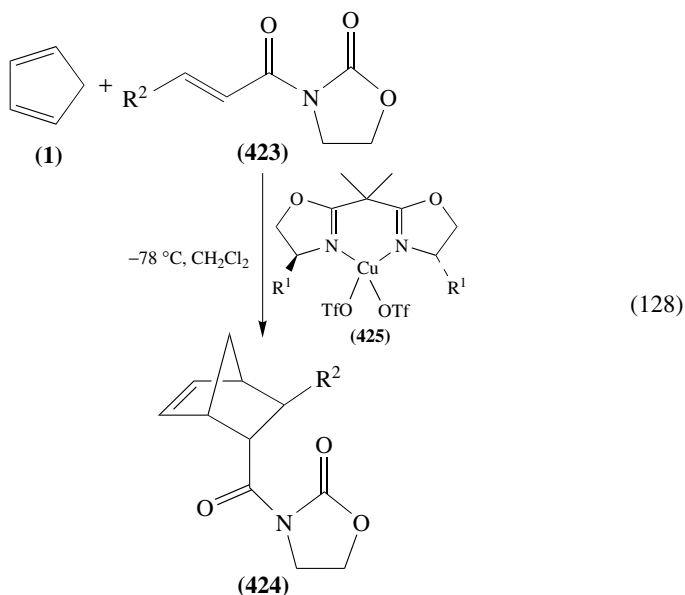
TABLE 25.   Reaction data for equation 128

Entry	R^1	Catalyst	R^2	Dienophile	Adduct	*endo/exo*	% ee
1	Ph	**425a**	H	**17a**	**421**	—	30
2	*i*-Pr	**425b**	H	**17a**	**421**	—	58
3	*t*-Bu	**425c**	H	**17a**	**421**	—	98
4	*t*-Bu	**425c**	Me	**404**	**405**	96/4	97
5	*t*-Bu	**425c**	CO₂Et	**423a**	**424a**	94/6	95
6	*t*-Bu	**425c**	Ph	**423b**	**424b**	90/10	90
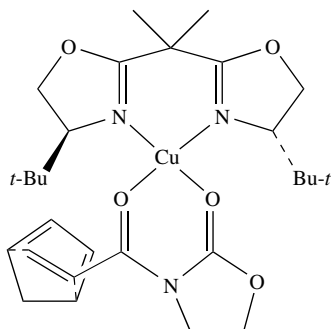
FIGURE 7. Transition state model for the reaction between cyclopentadiene and **17a** catalyzed by **425c**

(**425c**; X = OTf)
(**426**; X = SbF₆)

(**427a**; X = OTf)
(**427b**; X = BF₄)
(**427c**; X = PF₆)
(**427d**; X = SbF₆)

$$\text{(129)}$$

(**1**)   (**428**)   (**429**)
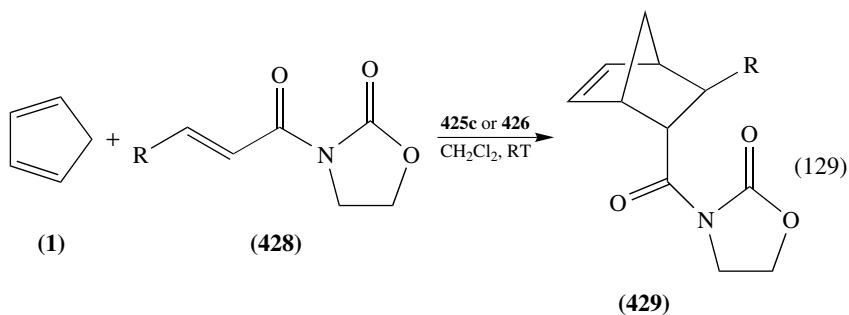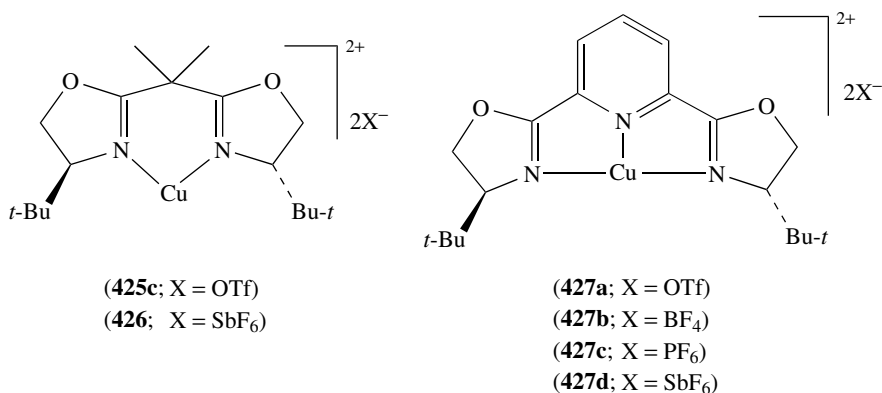
TABLE 26. Reaction data for equation 129

Entry	R	Dienophile	Catalyst	Time (h)	Yield (%)	% ee
1	Me	**404**	**425c**	8	95	94
2	Me	**404**	**426**	8	98	96
3	Ph	**423b**	**425c**	24	85	99
4	Ph	**423b**	**426**	24	96	96
5	Cl	**428**	**425c**	24	10	53
6	Cl	**428**	**426**	24	96	95

Ghosh and coworkers[269] reported high enantioselectivities using catalyst **432** in the cycloadditions of cyclopentadiene to several *N*-enoyl-1,3-oxazolidin-2-ones (equation 131). Recently, complex **425c** was successfully applied in the cycloaddition of *N*-acryloyl-1,3-oxazolidin-2-one to furan (equation 132)[270,271] and 1-acetoxy-2-methyl-1,3-butadiene[272].

$$\text{(130)}$$

(**1**)
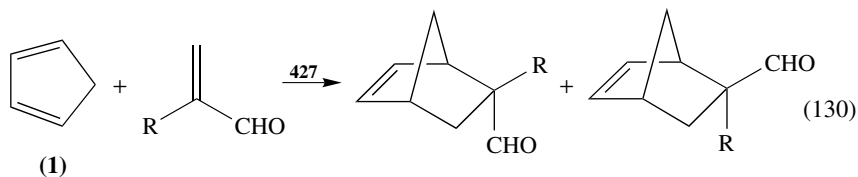
TABLE 27. Reaction data for equation 130

Entry	Catalyst	R	Dienophile	Time (h)	T (°C)	*endo/exo*	% ee (major)
1	**427a**	H	**390b**	116	−20	97/3	85
2	**427a**	Br	**365**	60	−40	3/97	87
3	**427a**	Me	**310**	120	−20	4/96	85
4	**427d**	H	**390b**	18	−20	94/6	85
5	**427d**	Br	**365**	12	−78	2/98	96
6	**427d**	Me	**310**	8	−40	3/97	92
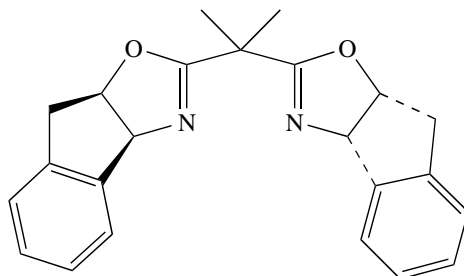
(430)
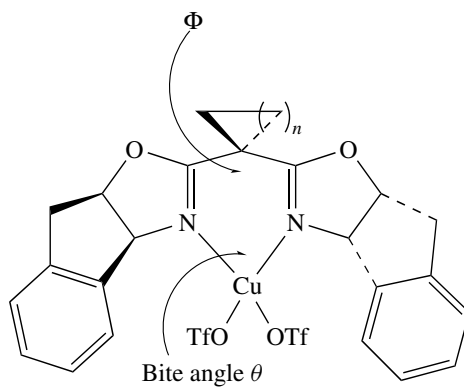
(**431a**; $n = 1$)

(**431b**; $n = 2$)

(**431c**; $n = 3$)

(**431d**; $n = 4$)

TABLE 28.   Influence of bite angle θ of catalyst **431** on the *endo* selectivity and enantioselectivity of the cycloaddition reaction between cyclopentadiene and *N*-acryloyl-1,3-oxazolidin-2-one

Entry	Complex	ϕ (°)	*endo/exo*	% ee (*endo*)
1	**431a**	110.6	98/2	96.3
2	**431b**	108.0	97/3	92.0
3	**431c**	105.8	97/3	89.5
4	**431d**	103.7	96/4	83.0
5	**430.Cu(OTf)₂**	104.7	98/2	82.5

(**1**)

(**17a**; R = H)
(**404**; R = Me)
(**423a**; R = CO₂Et)

(131)

(**432**)

(*R*-**421**; R = H, 99% ee)
(*R*-**405**; R = Me, 84% ee)
(*S*-**424a**; R = CO₂Et, 94% ee)

(**169**)   (**17a**)   **425c**
                              CH₂Cl₂, −78 °C

(132)

(**433**, 97% ee)
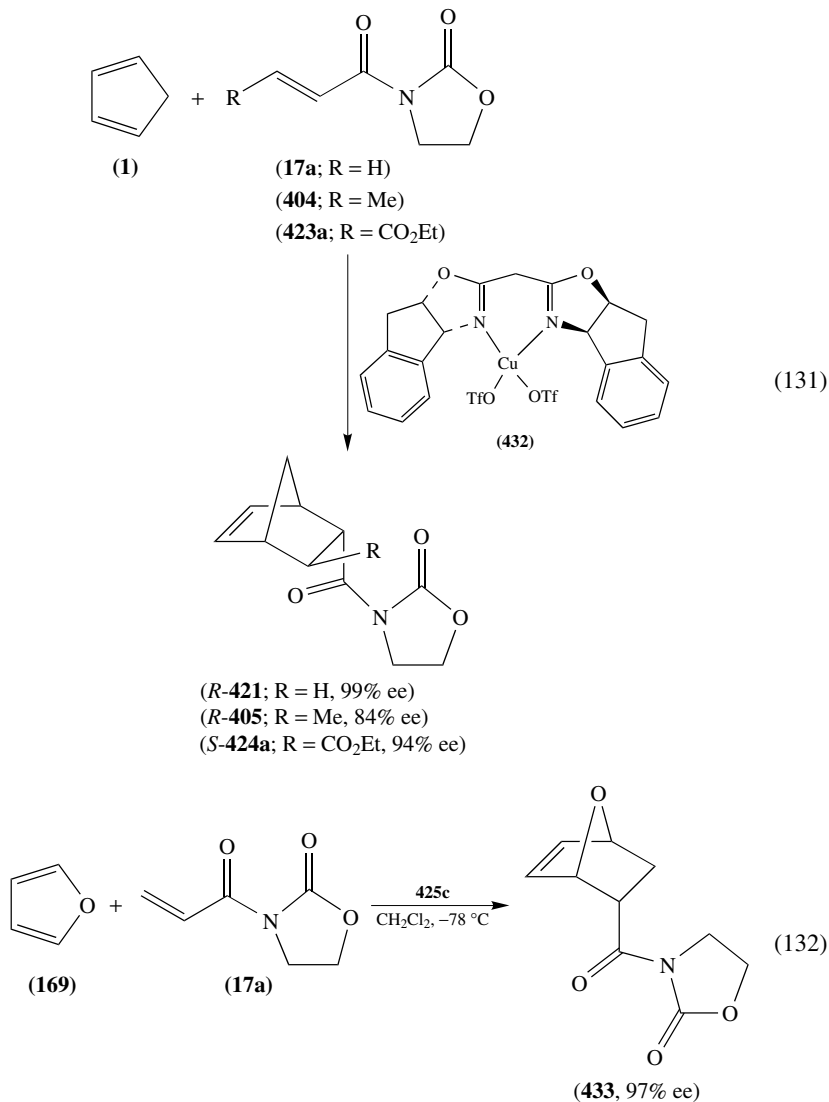
Evans and colleagues[263] demonstrated the effectiveness of copper(II) catalyst **436** in the Diels–Alder reactions of cyclopentadiene with several *N*-enoyl-1,3-oxazolidin-2-ones and their dithio analogs **434** (equation 133). The adducts **435** were obtained with good yields (83–98%) and high ee values (83–94%).

(133)
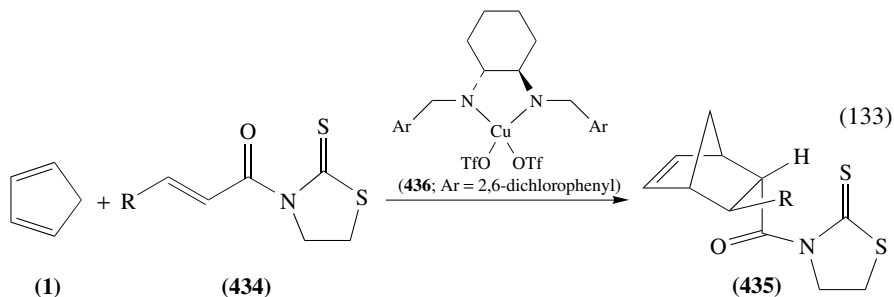
Copper(II) complexes of amino acids have been explored as chiral Lewis acid catalysts in the Diels–Alder reaction of 3-phenyl-1-(2-pyridyl)-2-propen-1-one with cyclopentadiene. The best results were obtained using *N*-methyl-*L*-tryptophan, but more interestingly, the highest ee values for the major *endo* adduct were achieved in aqueous solution[273].

5. Other chiral Lewis acids

Chiral magnesium(II) Lewis acids with chiral bis(oxazolidine) ligands **437** and **438** induced high enantioselectivities in the cycloaddition reactions of cyclopentadiene with several *β*-substituted *N*-acryloyl-1,3-oxazolidin-2-ones[274]. Interestingly, the enantioselectivities observed when employing the catalyst derived from **437** were opposite to those observed when employing the corresponding Cu(II) catalyst. Moderate to high enantioselectivities in the same cycloadditions were obtained using a magnesium(II) complex derived from oxazolidine **439**[275] and several other magnesium(II) catalysts[276,277] derived from ligands **438** and **440**. Recently, the magnesium triflate and magnesium perchlorate complexes of ligands **438, 441** and **442** were examined in the presence and absence of achiral auxiliaries (water, tetramethylurea), which can co-ordinate to the Lewis acid. Interestingly, the magnesium perchlorate based intermediates were tetrahedral in the absence of an achiral auxiliary, but became octahedral after the addition of two equivalents of the achiral ligand. The reaction of cyclopentadiene with *N*-acryloyl-1,3-oxazolidin-2-one afforded *endo* (2*S*)-**421** in the absence of an achiral auxiliary, and *endo* (2*R*)-**421** in the presence of an achiral auxiliary. Thus, by tuning the chiral ligand and achiral auxiliary, both enantiomers were obtained with ee values of more than 90%[278].

Takacs and colleagues[279] investigated a series of zinc, magnesium and copper catalysts of 1,2- 1,3- and 1,4-bis(oxazolidine) ligands **443–445** in the reaction of cyclopentadiene with *N*-acryloyl-1,3-oxazolidin-2-one. It was demonstrated that the different metal catalysts required different distances between the oxazolidine moieties to induce the highest enantioselectivities. Ligand **445**, a 1,4-bis(oxazolidine), proved best for zinc triflate, whereas 1,3-bis(oxazolidine) ligand **444** gave the best results with magnesium triflate and copper triflate. On account of these results, five chiral 1,4-bis(oxazolidine) ligands, each bearing a bicyclic backbone, were examined in the zinc and copper triflate catalyzed Diels–Alder reaction between cyclopentadiene and *N*-acryloyl-1,3-oxazolidin-2-one. At room temperature, ee values of up to 80% were achieved. Surprisingly, the non-C_2-symmetric bis(oxazolidine) **446**, bearing a *meso* backbone, belonged to the more efficient ligands[280].

(437)

(438)

(439)

(440)

(441)

(442)
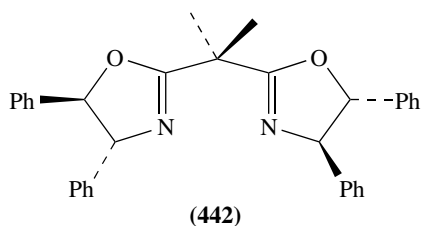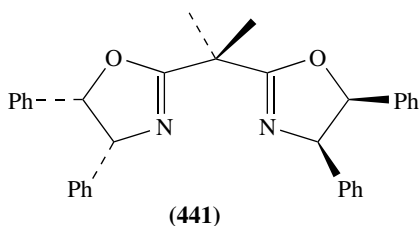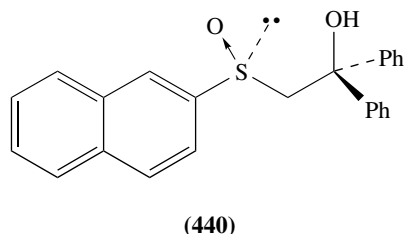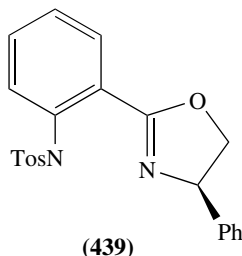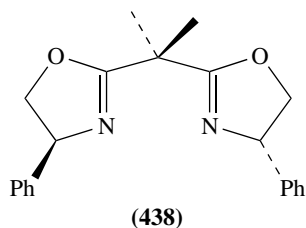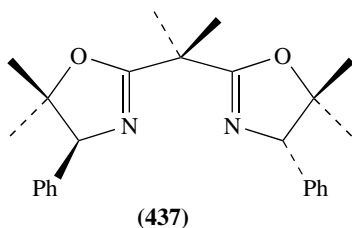
The cationic aqua complexes of the C_2-symmetric *trans*-chelating tridentate ligand **447** proved also highly effective chiral catalysts. The complexes involving the metal(II) perchlorates of iron, cobalt, nickel, copper and zinc produced the main *endo* adduct of cyclopentadiene and *N*-acryloyl-1,3-oxazolidin-2-one with very high ee values[281].

The Diels–Alder reaction of ethyl 2-benzoylacrylate **(450)** with cyclopentadiene was effectively catalyzed by magnesium(II) complexes of bis(oxazolidine) **448** and oxazolidine **449** (equation 134). When the catalysts were prepared in refluxing acetonitrile, adduct **451** was obtained with virtually complete *endo* selectivity for the ethoxycarbonyl group and up to 87% ee[282].

High ee values were achieved in the cycloadditions of α-bromoacrolein to various dienes using iron catalyst **452**[283].

Chiral rhodium[284] and ruthenium catalysts[285,286] have been reported to catalyze the Diels–Alder reaction of methacrolein with cyclopentadiene. Several bis(oxazolidine) and 2-pyridyl-1,3-oxazolidine ligands were used as chiral ligands. The adducts were obtained with only moderate enantioselectivities.

Recently, a palladium(II) complex with a chiral (*S*)-BINAP ligand was shown to induce an excellent enantioselectivity in the model reaction of *N*-acryloyl-1,3-oxazolidin-2-one with cyclopentadiene[88].

Several chiral lanthanide(III) Lewis acid catalysts, derived from chiral binaphthols, have been used in the cycloaddition reactions of cyclopentadiene with substituted *N*-acryloyl-1,3-oxazolidin-2-ones. A catalyst derived from ytterbium triflate, (*R*)-binaphthol
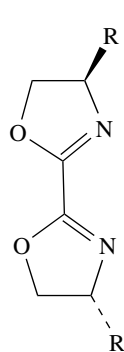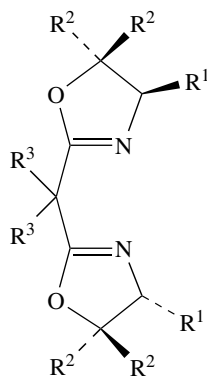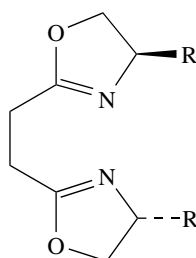
(**443**)   (**444**)   (**445**)
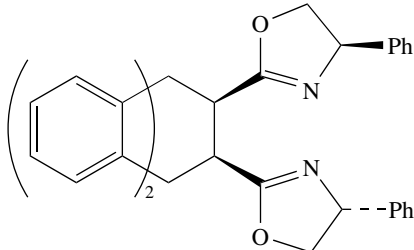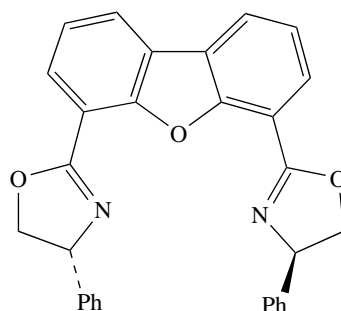
(**446**)   (**447**)
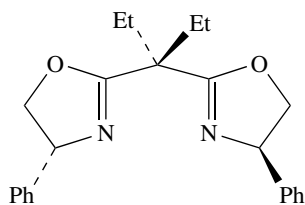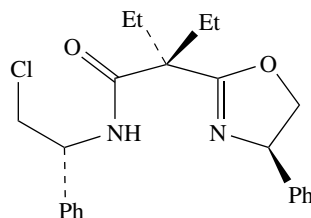
(**448**)   (**449**)

R, R^1 = Bn, CHPh$_2$, Ph, t-Bu
R^2, R^3 = H, Me

and cis-1,2,6-trimethylpiperidine demonstrated high chiral inductions[287]. The analogous scandium catalyst **453**, the structure of which has been proposed on account of spectroscopic data, also demonstrated high ee values in these cycloadditions[288].

Kobayashi and colleagues[289] showed that the selectivity of other lanthanide (Ln) triflates diminished with the increase of the ionic radius, as has been illustrated in Table 29 (equation 135). It was also found that the activity of the catalysts in solution diminished in time and with increasing temperature. Aging was prevented in the presence of the

(134)

(1)   (450)   (451)

(452)   (453)

(1)   (404)   (2S-405)   (135)
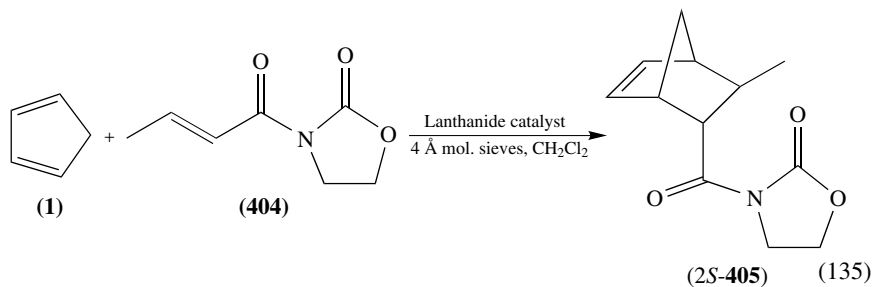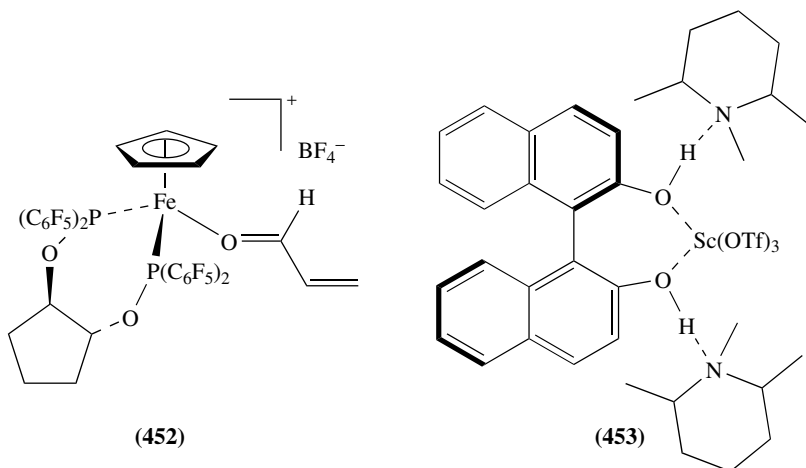
TABLE 29.   Reaction data for equation 135

Entry	Ln	Ionic radius (Ln^{+3}) (pm)	Yield (%)	endo/exo	% ee (endo)
1	Lu	85	60	89/11	93
2	Yb	85.8	77	89/11	93
3	Tm	87	46	86/14	75
4	Er	88.1	24	83/17	69
5	Ho	89.4	12	73/27	25
6	Y	89.3	6	70/30	20
7	Gd	93.8	0	—	—

dienophile. Interestingly, the enantioselectivity was reversed by adding diketonic achiral ligands like acetylacetone and 3-phenylacetylacetone to the reaction mixture.

An ytterbium binaphthol catalyst was successfully applied in the cycloaddition reactions of 3-carbomethoxy-2-pyrone **(454)** with *O*- and *S*-substituted olefins like **455** and **280d**. Upon heating, the products lost carbon dioxide to yield chiral cyclohexadienes **456** (equation 136). *S*-substituted olefins generally gave higher ee values than the corresponding *O*-substituted ones.

(454)

(455; R = OAc)
(280d; R = SPh)

Yb(OTf)$_3$
(*R*)-BINOL
i-Pr$_2$NEt, CH$_2$Cl$_2$

CO$_2$Me

−CO$_2$

(136)

CO$_2$Me

R

(456a; R = OAc, 85% ee)
(456b; R = SPh, >95% ee)
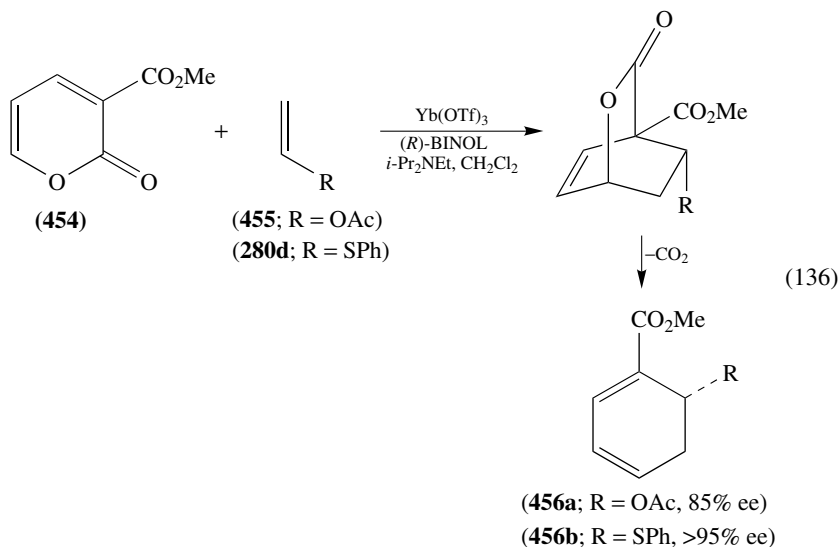
IV. [6 + 4] CYCLOADDITION REACTIONS

Thermally allowed [6 + 4] cycloadditions offer the attractive features of high stereoselectivity and rapid increase of molecular complexity. The limiting feature of many higher-order processes, however, is a lack of periselectivity that translates directly into the relatively low chemical yields of the desired cycloadducts.

Due to the high conformational demands which are imposed on higher-order cycloadditions, fulvenes, heptafulvenes and tropones have been mostly applied in uncatalyzed [6 + 4] cycloadditions. The scope of metal-promoted cycloadditions, however, is much broader due to the preorganized orientation of the reactants which are both co-ordinated to the metal center.

Fulvenes can participate as either 6π or 2π reactants in reactions with dienes. The controlling orbitals in the reaction of a fulvene with an electron-deficient diene are the fulvene HOMO, having a nodal plane through the exocyclic double bond, and the diene LUMO (Figure 8). This dictates the participation of fulvenes merely as 2π partners. When an electron-donating substituent is present at C(6), however, the NHOMO (Next Highest Occupied Molecular Orbital) energy (Figure 8) is raised sufficiently to permit a [6 + 4] cycloaddition to prevail[291]. LUMO controlled reactions with electron-rich dienes will produce [6 + 4] adducts because of the large LUMO coefficients at C(2) and C(6).

These phenomena can be illustrated by the cycloaddition reactions of fulvenes with electron-deficient α-pyrones. In general, the Diels−Alder reactions of electron-deficient dienes such as **458** with 6-alkyl substituted fulvenes favor addition across one of the endocyclic
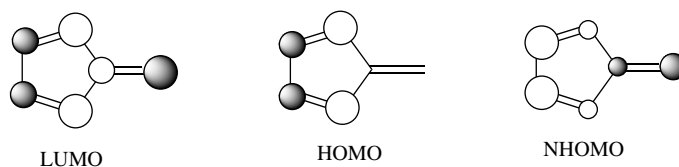
FIGURE 8. Relative frontier orbital coefficients of fulvene

double bonds of the fulvene unit to yield the [4 + 2] adduct[292]. When **458** was reacted with electron-rich fulvene acetal **457**, however, [6 + 4] cycloadduct **460** was obtained in 54% yield by elimination of carbon dioxide from the intermediate cycloadduct **459** (equation 137)[293].

(137)
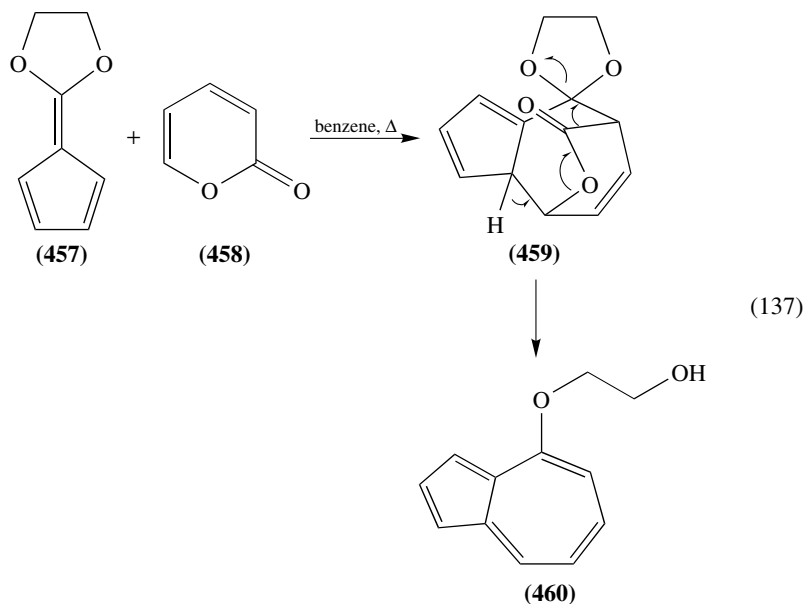
Niggli and Neuenschwander[294] studied the reaction of fulvene **(461)** with cyclopentadiene. The main product fraction consisted of three 1 : 1 adducts, as illustrated in equation 138. Diels – Alder Adducts **462** and **463** resulted from attack of cyclopentadiene at the endocyclic and exocyclic double bonds of fulvene, respectively. The formation of **464** was rationalized by a [6 + 4] cycloaddition reaction followed by two [1,5] hydrogen shifts. It was stated that due to the absence of electron-donating and electron-withdrawing groups on both triene and diene, fulvene may have reacted via its HOMO as well as its LUMO.

Liu and colleagues[295,296] studied the cycloaddition reactions between electron-deficient 8,8-disubstituted heptafulvenes **466** and electron-rich 6,6-disubstituted fulvenes. The substituted heptafulvene reacted as the trienophile in this case. Only when 6,6-dimethylfulvene **(465)** and heptafulvenes **466a–b** were used as the triene and trienophiles, respectively,

and the reactions were performed at ambient temperature, were [6 + 4] cycloadducts **467** and **470** obtained along with [8 + 2] cycloadducts **468** and **469b** (equation 139). At higher temperatures, the [8 + 2] and [4 + 2] adducts were the only adducts isolated. When 8,8-diphenylfulvene was used, no [6 + 4] adducts were isolated, even when the reaction was performed at room temperature. This is probably due to insurmountable steric hindrance in the transition state. The reaction produced predominantly [8 + 2] and [4 + 2] adducts, the latter becoming more significant at higher reaction temperatures.

(**461**)   (**1**)   (**462**; 47)   +   (**463**; 41)   (138)

+

(**464**; 13)
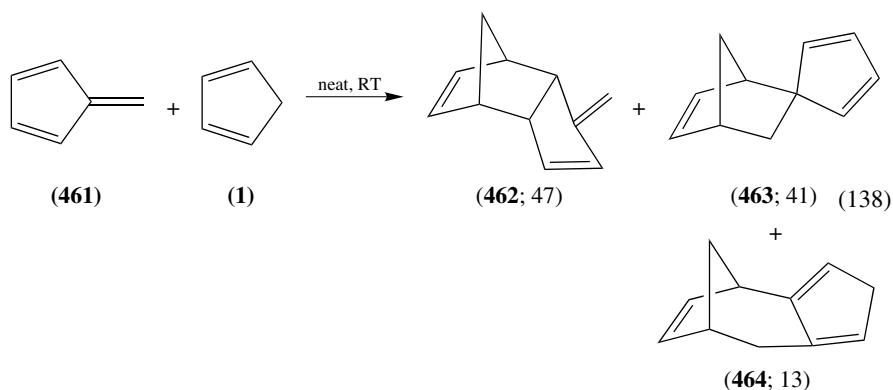
[6 + 4] Cycloaddition reactions using tropone or another cyclic triene as the 6π partner have been abundantly described in the literature. It has been found that virtually all metal-free [6 + 4] cycloadditions of cyclic trienes afford predominantly *exo* adducts. This has been rationalized by consideration of the HOMO–LUMO interactions between the diene and triene partners. An unfavorable repulsive secondary orbital interaction between the remaining lobes of the diene HOMO and those of the triene LUMO develops during an *endo* approach. The *exo* transition state is devoid of this interaction (Figure 9).

The periselectivity of the tropone–diene cycloaddition is dependent on the reaction temperature. The *exo* [6 + 4] cycloadduct is considered to be the *kinetic* product, the *endo* [4 + 2] cycloadduct being the *thermodynamic* product[291].

Mahon and colleagues[297] studied the cycloaddition reactions of substituted *cis*-1,2-isopropylidenedioxycyclohexadienes. The reaction of tropone (**471**) with cyclohexadiene **472**, for example, afforded the expected *exo* cycloadduct **473** with good yield (equation 140).

Hisano and coworkers[298] prepared tricycle **476** by reaction of cyclopentadienone **475** with cyclooctatetraene (**474**) in refluxing benzene (equation 141). Cyclized [4 + 2] cycloadduct **477** was isolated as a by-product.

Takeshita and colleagues[299] studied the reactions of 3-bromo-1,5-azulenequinone (**478**) and 3-bromo-1,7-azulenequinone (**484**) with benzo[*c*]furan (**479**) and 1,3-diphenylbenzo[*c*]furan (**485**) by analogy with the reactions previously described by Scott and Adams[300]. The reaction of **478** with **479** afforded a mixture of four cycloadducts (equation 142), three stereoisomeric [2 + 4]/[6 + 4] tandem adducts (**480–482**) and one [2 + 4]/[2 + 4]/[6 + 4] triple adduct (**483**). No mono adduct was isolated, indicative of a fast follow-up cycloaddition. The [6 + 4] cycloadditions all proceeded in an *exo* fashion, whereas the [4 + 2] cycloaddition proceeded in an *endo* fashion for **480** and **483**, and in an *exo* fashion for **481** and **482**. The reaction of **478** with **485** afforded a mixture of [4 + 2] adducts and [4 + 2]/[8 + 4] tandem adducts.

(139)

(465)

+

(466a; R^1 = R^2 = CN)
(466b; R^1 = CN, R^2 = CO$_2$Me)

$\xrightarrow{\text{CHCl}_2, \text{ RT}}$

(467a; 5)
(467b; 0)

$\xrightarrow{\text{[1,5] H-shift}}$

(470a; 49)
(470b; 26)

(468a; 46)
(468b; 24)

+

(469b; 50)
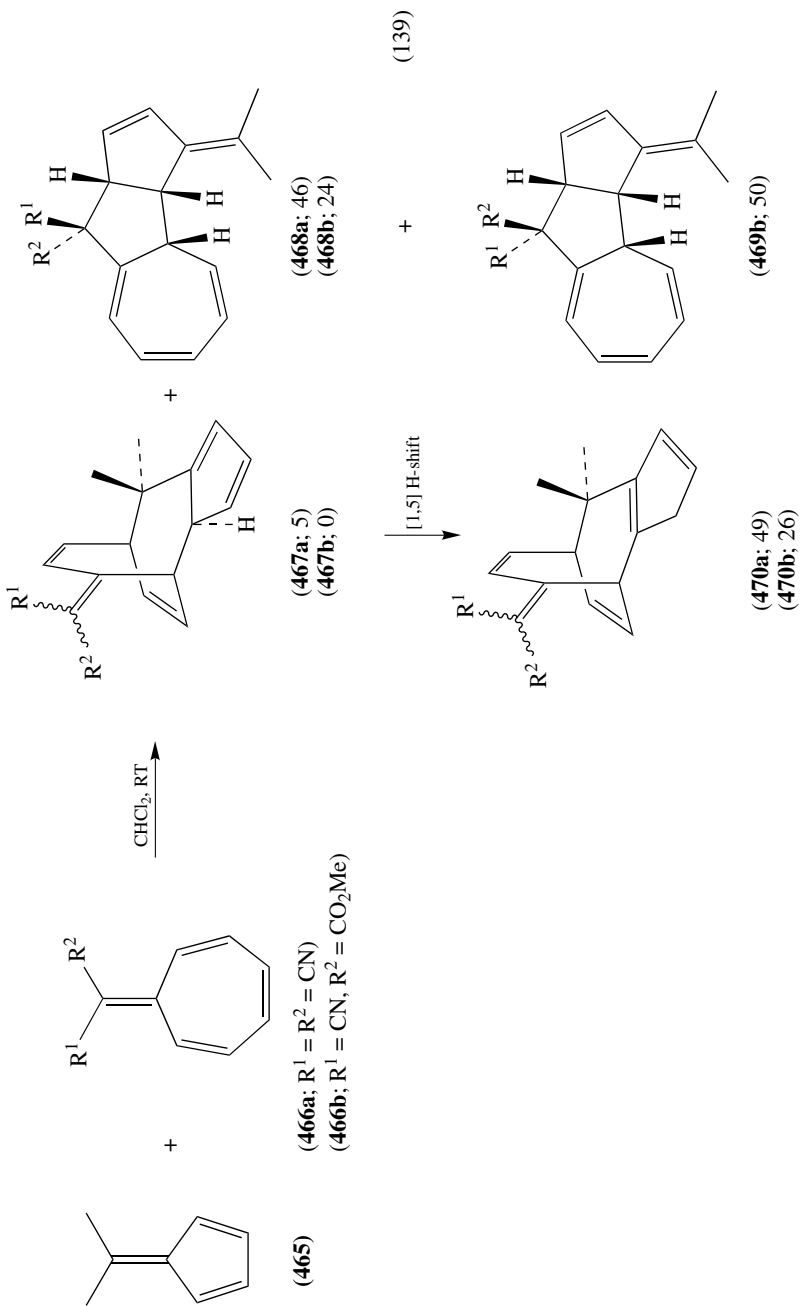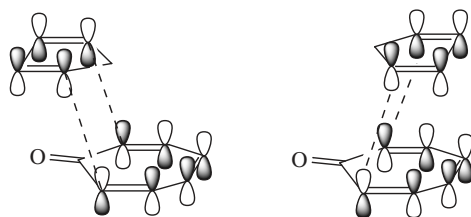
FIGURE 9. *Endo* and *exo* approach of cyclopentadiene to tropone

(140)

(471) **(472)** **(473)**

+

(474) **(475)**

PhH, Δ

(141)

+

(477) **(476)**
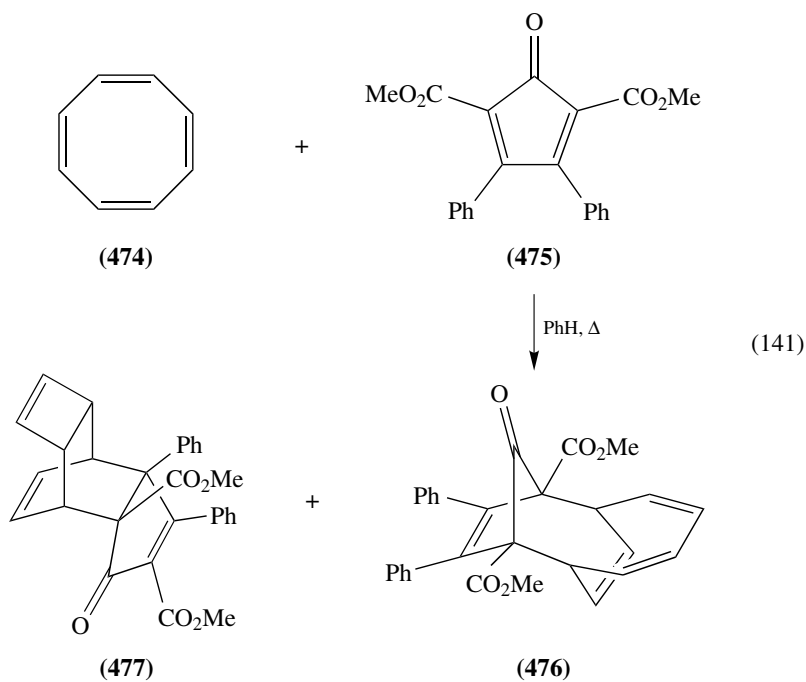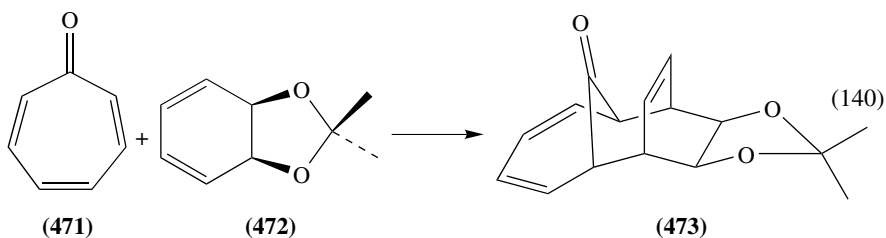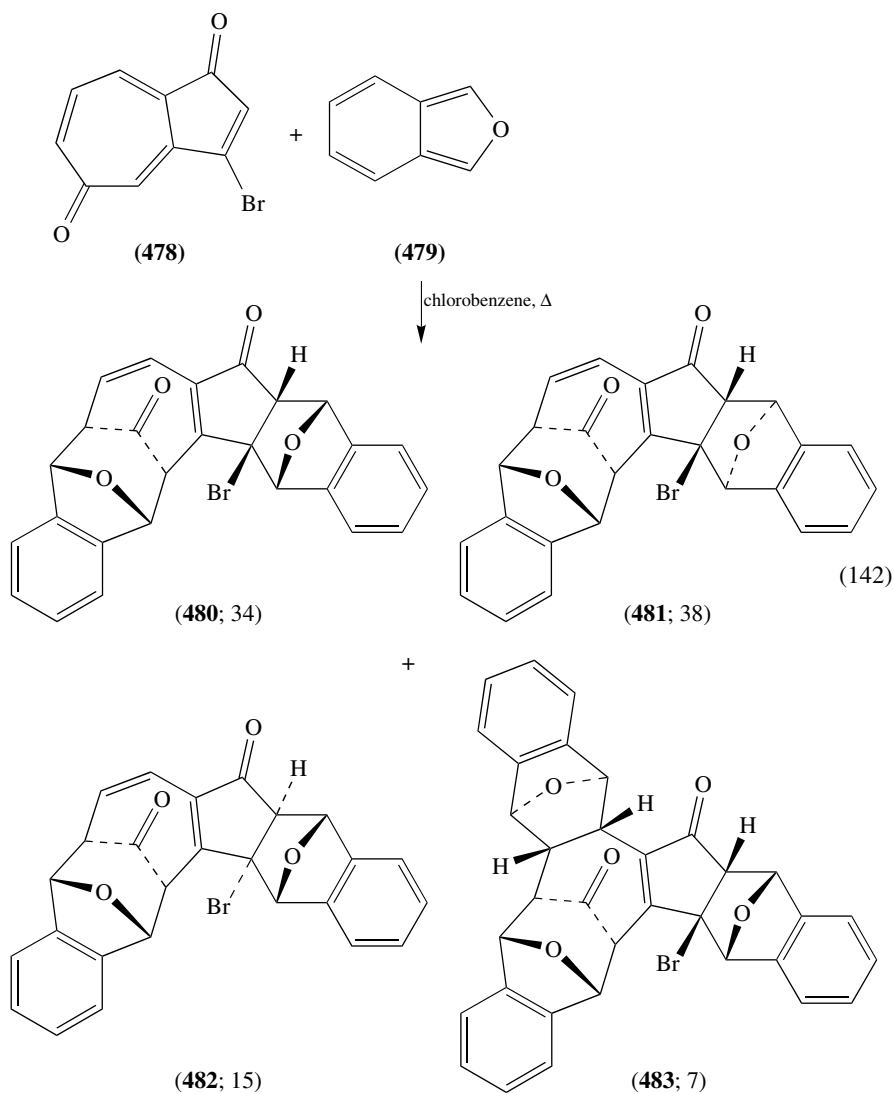
The reactions of **484** with **479** and **485** produced two tandem [4 + 2]/[6 + 4] adducts in both cases. The [6 + 4] cycloadditions proceeded in an *exo* fashion. The Diels–Alder reaction proceeded in an *endo* fashion for **479**, whereas *endo* and *exo* Diels–Alder adducts **486** and **487** were observed for **485** (equation 143).

Gandolfi and coworkers[301] studied the periselectivity in the reactions of substituted cyclopentadienones with *N*-aryl-8-azaheptafulvenes. The reactions proved to produce mainly [6 + 4] cycloadducts, along with some [8 + 2] and [4 + 2] cycloadducts, as illustrated by the reaction between azaheptafulvene **488** and cyclopentadienone **489** which

afforded adducts **490–493** (equation 144). By means of cycloreversion experiments, Gandolfi and colleagues were able to determine that the formal [8 + 2] cycloadduct **491** was formed by a [3,3] sigmatropic rearrangement of the [6 + 4] adduct **490**.

(484)   **(485)**

chlorobenzene, Δ

(143)

(487)   **(486)**
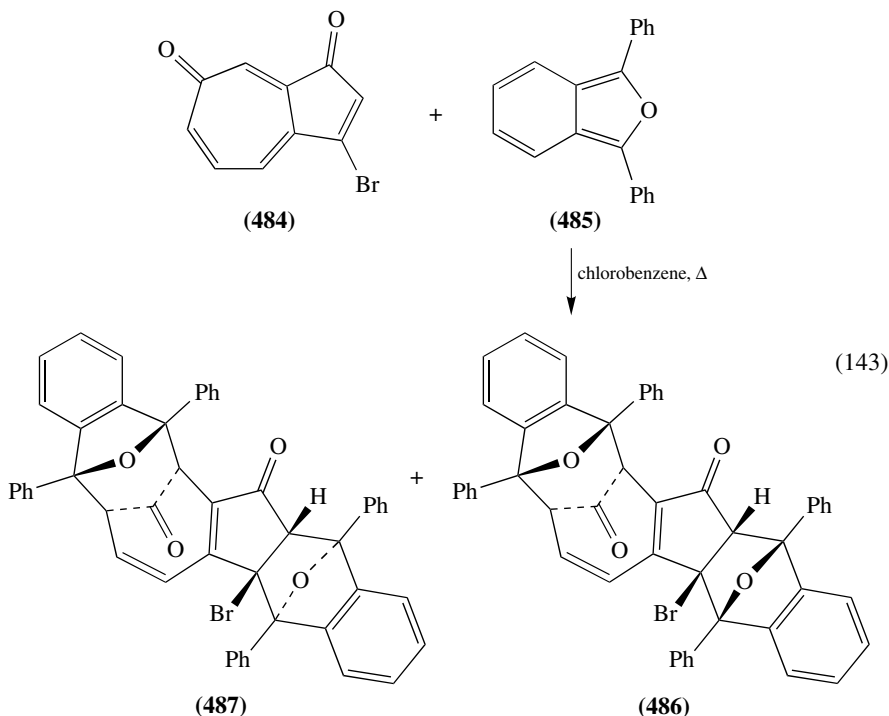
The use of transition metal templates represents a particularly intriguing strategy to selectively accomplish [6 + 4] cycloadditions, as was shown first in the Kreiter laboratories[302]. Chromium(0) has emerged as the metal of choice in this kind of cycloaddition reaction which is either thermally or photochemically activated[291].

Two mechanisms have been proposed which primarily differ in the way in which the initial co-ordinatively unsaturated intermediates are generated. In mechanism 1, a light-induced CO dissociation from **494** to **495** occurs, whereas a light-induced hapticity slippage from η^6 (**494**) to η^4 (**499**) occurs in mechanism 2 (equation 145). Co-ordination of a diene to **495** or **499** affords complexes **496** and **500**, respectively, which then undergo an intramolecular reaction to give **497** and **501**, respectively. Ring closure finally affords the complexed adduct **498**. Stufkens and coworkers[303] have demonstrated that mechanism 1 is the likely pathway for these processes in low-temperature matrices and in liquid noble gas solutions. Kreiter and colleagues[304] demonstrated that this mechanism also holds in THF at 203 K.

Rigby and coworkers obtained some conflicting results. When electron-rich dienes were employed, exposure of the reaction mixtures to a blanket of CO after photolysis led to increased yields, which is in support of mechanism 1 (the **497** to **498** step).

When electron-deficient dienes were used, however, it proved that vigorously flushing the solution with an inert gas during photolysis resulted in higher reaction yields. This may indicate that the reaction can also proceed according to mechanism 2. A pathway according to **494 → 499 → 500 → 501 → 497 → 498** could then explain the positive effect of a CO blanket in the case of electron-rich dienes[305].

(144)
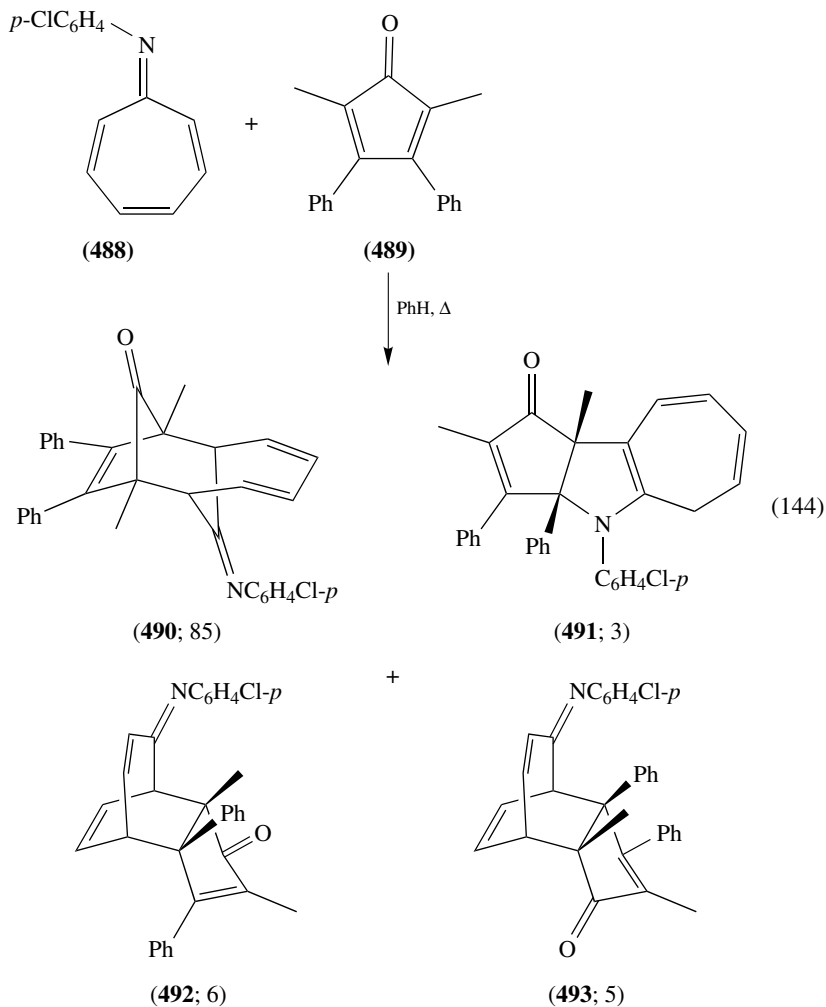
In concurrence with the thermal metal-free version, diastereoselection is virtually complete in the metal mediated cycloaddition. In contrast to thermal, metal-free [6 + 4] cycloaddition reactions, however, the metal mediated reactions of trienes are known to furnish exclusively *endo* products. This is in agreement with both mechanisms,

(145)
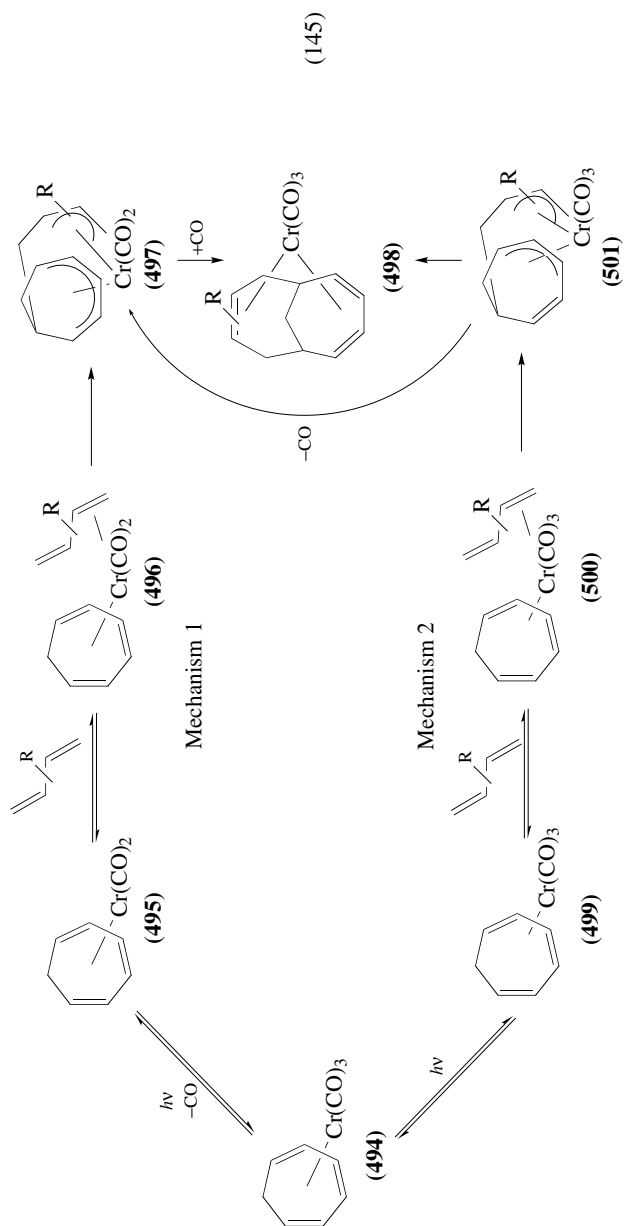
because neither **497** nor **501** is capable of accommodating an *exo* orientated diene component.

In contrast with the metal-free cycloaddition again, the efficiency of metal mediated cycloaddition reactions is relatively insensitive to the electronic nature of the reactants. This has been nicely demonstrated by Rigby and colleagues[305] who treated complex **494** with a 1 : 1 mixture of methyl sorbate **(502)** and 1-trimethylsilyloxy-1,3-butadiene **(50)**. The reaction proceeded in 90% yield and afforded **503** and **504** in a 46 : 54 ratio (equation 146).

Rigby and colleagues also demonstrated that the regioselectivities in the reactions of 1- and 2-substituted dienes with 1-substituted cycloheptatrienes, which do not proceed under metal-free conditions, were generally high. In the case of 1-substituted dienes, this may be completely attributed to steric hindrance. 2- And 3-substituted cycloheptatrienes hardly showed any regioselectivity[305].

$$CO_2Me$$

$$OSiMe_3$$

(494)   **(502)**   **(50)**

2. P(OMe)$_3$ | 1. *h*ν   (146)

$$OSiMe_3$$

$$MeO_2C$$

(504; 54)   **(503**; 46)
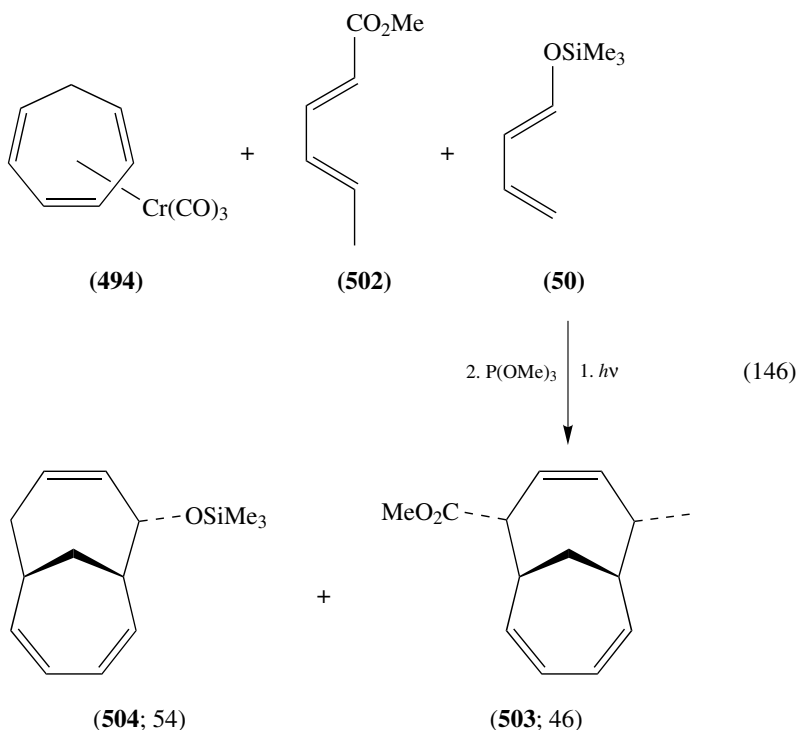
By attaching a chiral auxiliary to the diene unit, Rigby and colleagues[305] were able to obtain cycloadducts with high diastereomeric excesses. Their best results were obtained using chiral camphorsultam based sorbate **506**. The reaction with **494** afforded **507a** with 74% yield and 84% de (equation 147). The analogous reaction using **505** as the triene component afforded **507b** (equation 147) with 75% yield and 75% de. Adduct **507b** was used to prepare the C5–C11 segment of streptovaricin D[306].

A diastereoselectivity of 85% was obtained in the reaction of **494** with chiral diene **508** (equation 148)[307]. This reaction showed once again the high reactivity of two unactivated reactants toward cycloaddition in the presence of chromium(0). Cycloadduct **509** was considered to be a model precursor for the convergent synthesis of the unusual sesterpene cerorubenol (**510**).

When the reactions of **494** with some dienes were carried out under thermal conditions, the adducts were obtained metal-free. This suggested the possibility of effecting these transformations using a catalytic amount of an appropriate Cr(0) source. Rigby and colleagues showed that the reaction between cycloheptatriene **511** and 1-acetoxy-1,3-butadiene (**341**) can be catalyzed by employing a catalytic amount of **513** (equation 149). The yield of **512** was 36% in this instance, whereas a yield of 20% was obtained when a catalytic amount (10 mol%) of **494** was used as the catalyst[305,308].

(**494**; R = H)
(**505**; R = Me)

(**506**)

2. P(OMe)₃ | 1. *hv*

(147)

(**507a**; R = H)
(**507b**; R = Me)
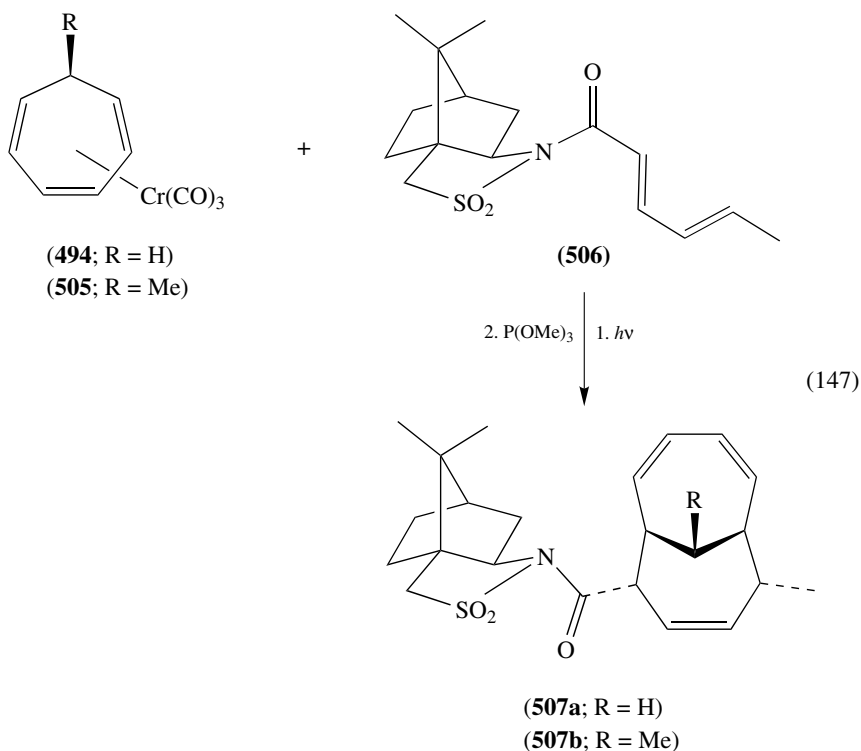
Rigby and coworkers[305,309] also performed metal mediated [6 + 4] cycloadditions of heterocyclic trienes and tropones with various dienes. In concurrence with the all-carbon trienes, the electronic nature of the diene partners generally had little influence on the cycloaddition efficiency. The only reported exceptions are the reactions of thiepin-1,1-dioxides. Lower yields were observed in the reactions involving electron-deficient dienes in comparison with the reactions with electron-rich dienes. The reaction of complex **514**

with diene **50** to give **516,** for example, proceeded with a yield of 78%, whereas the reaction with diene **515** afforded adduct **517** with only 38% yield (equation 150).

1. $h\nu$, 0 °C
2. P(OMe)$_3$

Cr(CO)$_3$

(494)   **(508)**   **(509)**

(148)

(510)

OAc

Cr(CO)$_2$PPh$_3$

(513)

n-Bu$_2$O, Δ

+

OH

H   H

OAc

(511)   **(341)**   **(512)**

(149)
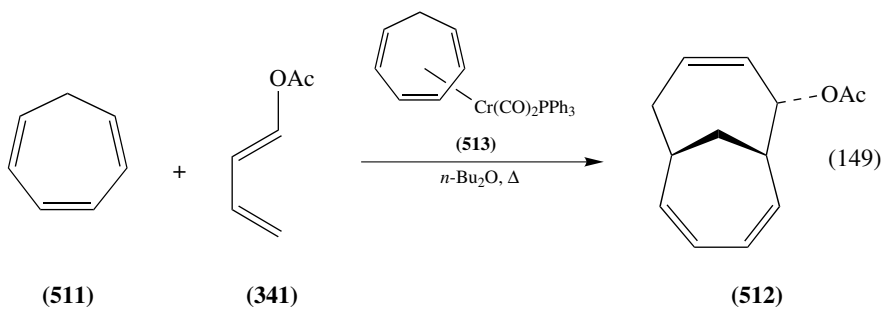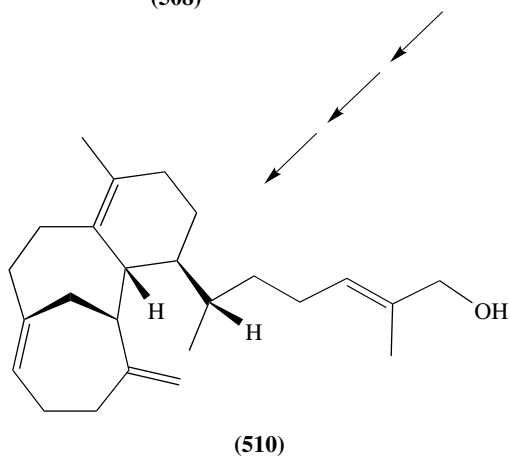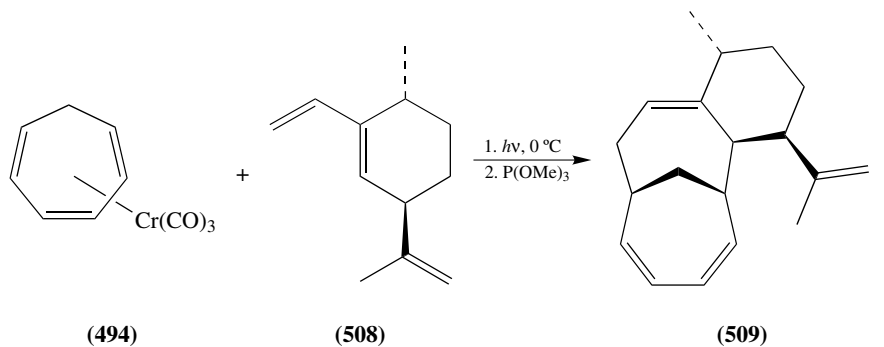
A recent application of the metal mediated [6 + 4] cycloaddition reaction is the synthesis of nine-membered carbocycles by a sequential [6 + 4] cycloaddition-pinacol rearrangement, as employed by Rigby and Fales[310].

(517) **(514)**

(150)

(516)
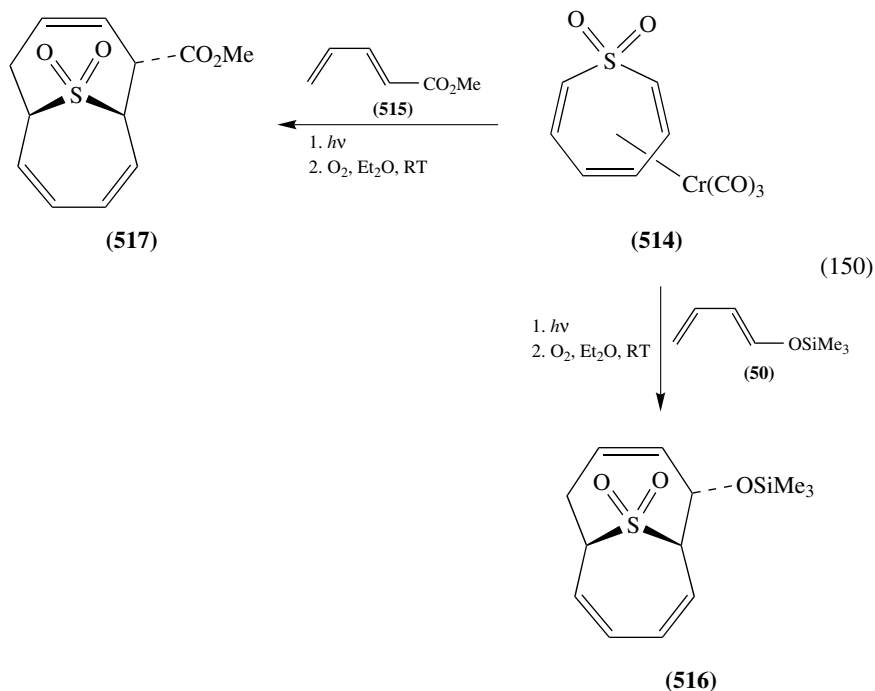
V. [8 + 2] CYCLOADDITION REACTIONS

The thermally allowed [8 + 2] cycloaddition reactions may be considered as the 10π analogs of the Diels−Alder reaction in which the diene component has been replaced by a tetraene component. Like trienes in the [6 + 4] cycloaddition reactions, the 8π tetraenes must satisfy certain requirements concerning geometry in order to be able to participate in an [8 + 2] cycloaddition. For example, tetraenes **518** and **519** can undergo an [8 + 2] cycloaddition, whereas an [8 + 2] cycloaddition with **520** is virtually impossible. Due to its fixed π-system, **519** is more reactive in cycloaddition reactions than **518** and is therefore more often encountered in the literature. [8 + 2] Cycloadditions have been applied only

(518) **(519)** **(520)**
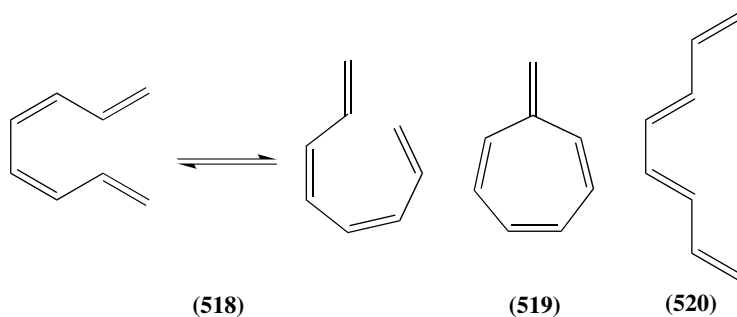
occasionally in organic synthesis. The reaction often proceeds with accompanying [4 + 2] and, in the case of a diene being the tetraenophile, [6 + 4] cycloaddition reactions.

Nair and coworkers have described the [8 + 2] cycloaddition reactions of 2H-cyclohepta[b]furan-2-ones such as **521** in several reports[311]. The reactions of **521** with alkenes yield azulene derivatives upon extrusion of carbon dioxide. Table 30 summarizes the results of the reactions between **521** and some 6,6-disubstituted fulvenes **522** (equation 151)[311b]. In the case of 6,6-dialkyl fulvenes **522a–c**, the [8 + 2] cycloadducts **523** were the major adducts obtained, the Diels–Alder adducts **524** only being formed in trace amounts.

(151)
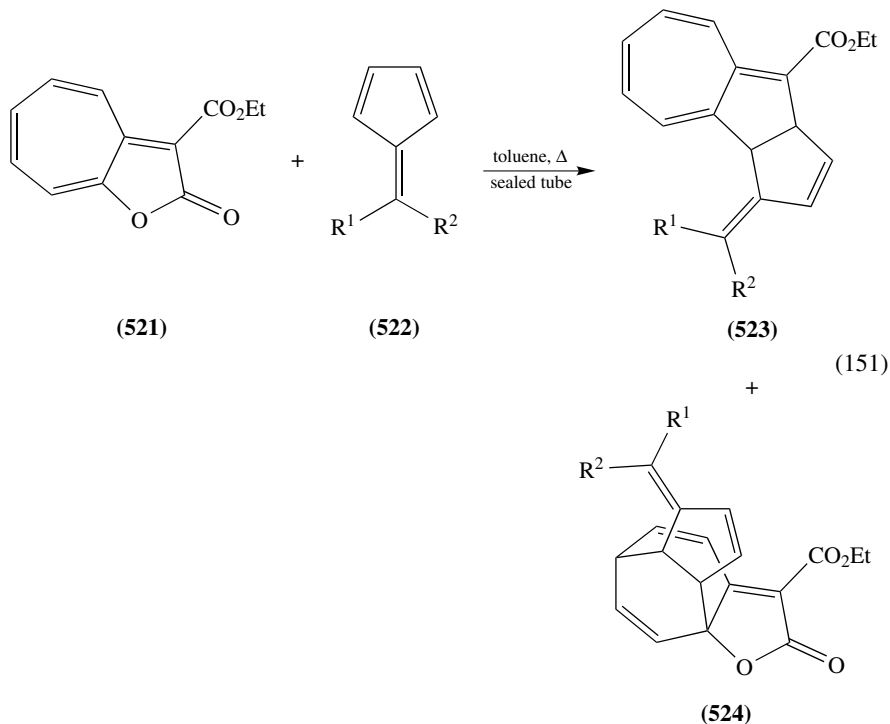
When cycloalkyl pentafulvenes **522e–g** were employed, [8 + 2] and [4 + 2] cycloadducts were produced in approximately equal amounts. The [4 + 2] cycloadduct became the major cycloadduct in the reaction of **521** with 6,6-diphenylfulvene **522d**. Semi-empirical

TABLE 30.   Yields of products in the reaction of **521** with **522**

Entry	R^1	R^2	Fulvene	Yield **523** (%)	Yield **524** (%)
1	Et	Et	**522a**	87	trace
2	Me	Et	**522b**	68	trace
3	Me	i-Bu	**522c**	80	trace
4	Ph	Ph	**522d**	16	60
5	$-(CH_2)_4-$		**522e**	46	43
6	$-(CH_2)_5-$		**522f**	39	31
7	$-(CH_2)_6-$		**522g**	37	31

calculations indicated that the $[8 + 2]$ adduct is probably formed via a reaction of the HOMO of **521** with the LUMO of fulvene **522**, whereas the Diels–Alder adduct is produced via interaction of the NLUMO of **521** with the fulvene HOMO. The Diels–Alder reactions must therefore be classified as being *inverse electron demand* Diels–Alder reactions.

The reactions of **521** with 1,3-dienes were found to proceed exclusively in an $[8 + 2]$ addition mode. The reactions were completely site and regioselective, as exemplified by the reaction between **521** and 2-methyl-1,3-pentadiene **(525)** which gave **526** after loss of CO_2 (equation 152). The regiochemistry observed was in agreement with the frontier orbital coefficients calculated with semi-empirical methods.

(521)   **(525)**   **(526)**   (152)
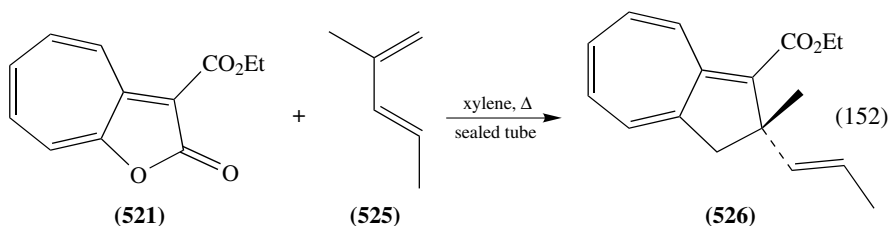
The $[8 + 2]$ cycloaddition reactions between substituted cyclohepta[*b*]furan-2-ones and enamines have been described by Kuroda and coworkers[312]. The cycloaddition reactions proceeded with concomitant elimination of carbon dioxide and amine. Thus, the reaction between **527** and enamine **528** afforded $[8 + 2]$ cycloadduct **529** with good yield (equation 153)[312c].

(527)   **(528)**   **(529)**   (153)
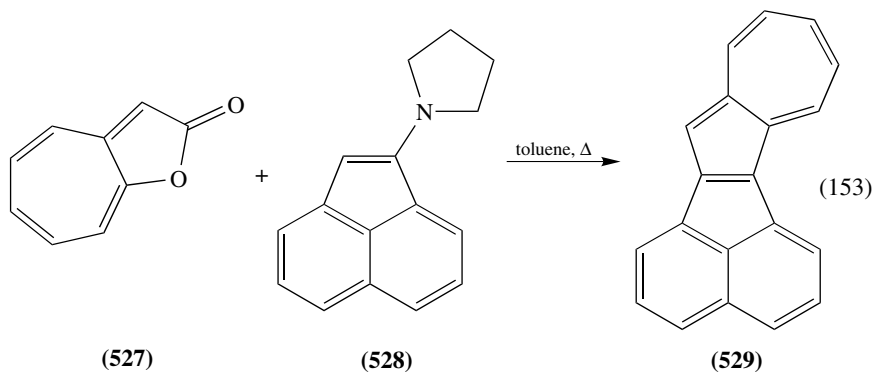
Nozoe and colleagues[313] performed $[8 + 2]$ cycloaddition reactions between substituted cyclohepta[*b*]furan-2-ones and vinyl ethers, vinyl acetates, dihydrofurans and dihydropyrans, which resulted in the formation of various substituted azulenes. They also investigated the reactions with acetals. These afforded the corresponding vinyl ethers at high reaction temperatures by elimination of one mole of alcohol[314]. For example, acetal **530** gave enol **531** upon heating, which reacted with cyclohepta[*b*]furan-2-ones **532** to give **533** (equation 154). In the same way, Nozoe and colleagues[315] prepared 2-alkoxyazulene derivatives by reacting orthoesters, which generate ketene acetals upon heating, with cyclohepta[*b*]furan-2-ones.

(154)
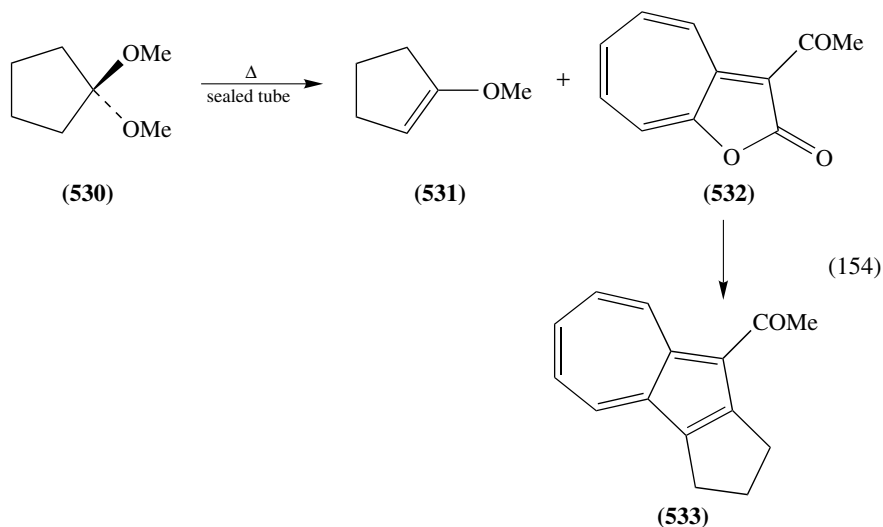
Daub and colleagues studied the [8 + 2] cycloaddition reactions of electron-rich 8-substituted heptafulvenes with a wide variety of acceptor substituted alkenes. 8-Methoxyheptafulvene **(534)** proved to give the best results, the more electron-rich heptafulvenes being less reactive toward [8 + 2] cycloaddition reactions and more prone to oxidative dimerization[316]. The reactions of 8-methoxyheptafulvene with acceptor substituted polyenophiles **535** can in principle produce up to 8 diastereomers. The reactions proved, however, highly regioselective, the *exo* and site selectivities being moderate to good, and afforded mixtures of **536**, **537** and **538** (equation 155, Table 31)[317].

The regioselectivity observed was in agreement with the calculated orbital coefficients for the HOMO of heptafulvene **534** and the LUMOs of the polyenophiles. The largest coefficient in the HOMO of **534** is at C(8). The reactions of nitroethene and (*E*)-*β*-nitrostyrene with **533** (entries 4 and 5) afforded merely *exo* adducts, the two isomers arising from attack of the polyenophile at the two different sites of **534**.

The reactions of **534** with substituted quinones produced mixtures of regioisomers. The substituent effect on the regioselectivity of the [8 + 2] cycloaddition reactions was said to be dependent on steric as well as electronic effects. Equation 156 shows the reaction between **534** and 2-methylbenzoquinone **(539)**. The reaction afforded a mixture of two regioisomeric adducts **540** and **541**, which were transformed to azulenes **542–545** under the reaction conditions applied[318].

Daub and colleagues have also described the cycloaddition reaction of **534** with [60]fullerene **(209)** (equation 157)[319] and [70]fullerene[320], which were the first [8 + 2] cycloaddition reactions with fullerenes described in the literature. Reaction with [60]fullerene afforded **546** as the main product with a yield of more than 90%. On the basis of the results of previous cycloadditions performed with fullerenes, it was assumed that it was a 6,6-double bond which had reacted with **533**, [60]fullerene adding to the less hindered site of **534**.

[8 + 2] Cycloaddition reactions of indolizines such as **547** can generally be performed with moderately electron-poor alkenes only, because alkenes with strong acceptor substituents predominantly give Michael adducts. The cycloaddition of 2-methylindolizine

(547) with 1-cyclobutene-1,2-dicarbonitrile (548), for example, proceeded to give the dehydrogenated adduct 549, whereas the reaction with *cis*-3-hexene-2,5-dione (550) afforded solely the Michael adduct (equation 158)[321].

(155)
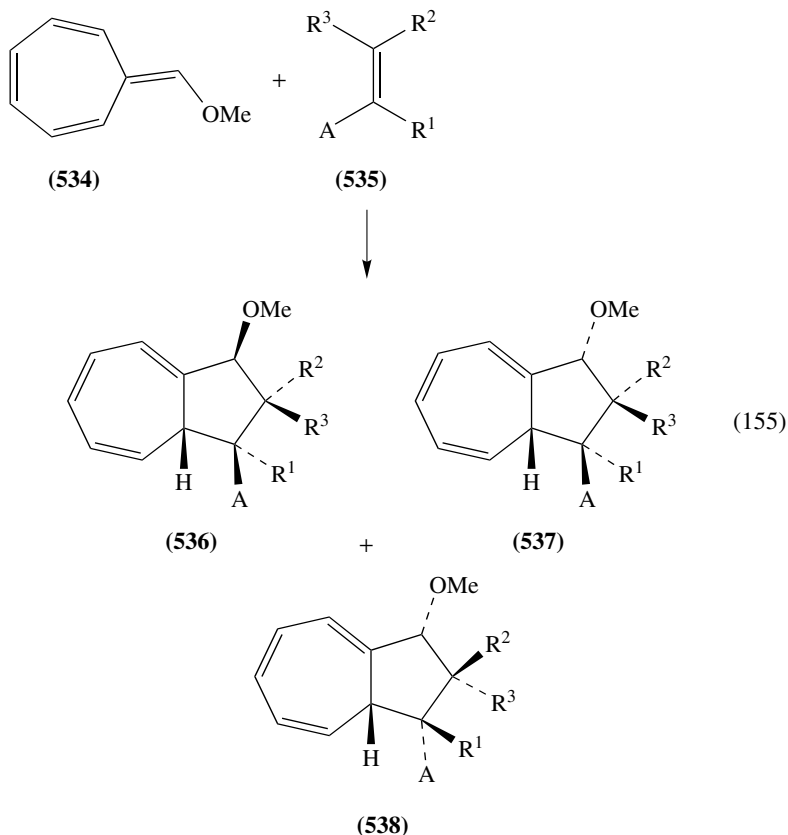
TABLE 31.   Yields and product distributions in the reaction of 534 with 535

Entry	A	R^1	R^2	R^3	Yield (%)	536/537/538
1	CN	CN	CF_3	CF_3	85	33/67/0
2	CN	CN	Ph	H	100	12/68/20
3	CN	CN	$p\text{-}O_2NC_6H_4$	H	94	12/65/23
4	NO_2	H	Ph	H	98	10/90/0
5	NO_2	H	H	H	100	28/72/0

Tominaga and coworkers[322] prepared dimethyl dibenzo[*a,h*]cycl[3.2.2]azine-1,2-dicarboxylate (553) by an [8 + 2] cycloaddition reaction of 1-cyanoisoindolo[2,1-*a*]isoquinoline (552) with dimethyl acetylenedicarboxylate (57), followed by elimination of HCN. A small amount of acetic acid was added to improve the yield of the reaction from 1% to 26%. The double adduct 554 was isolated in minor amounts (equation 159).

(**534**)

(**540**; 81)

+

(**539**)

(**541**; 19)

(156)

(**542**; 67)   +   (**543**; 13)

(**544**; 13)   (**545**; 7)

(534)

(209)

toluene, RT (157)

(546)

(551)

(550)

(547)

(548)

(549)

(158)

(552)   **(57)**   **(553)**

(159)

+

(554)
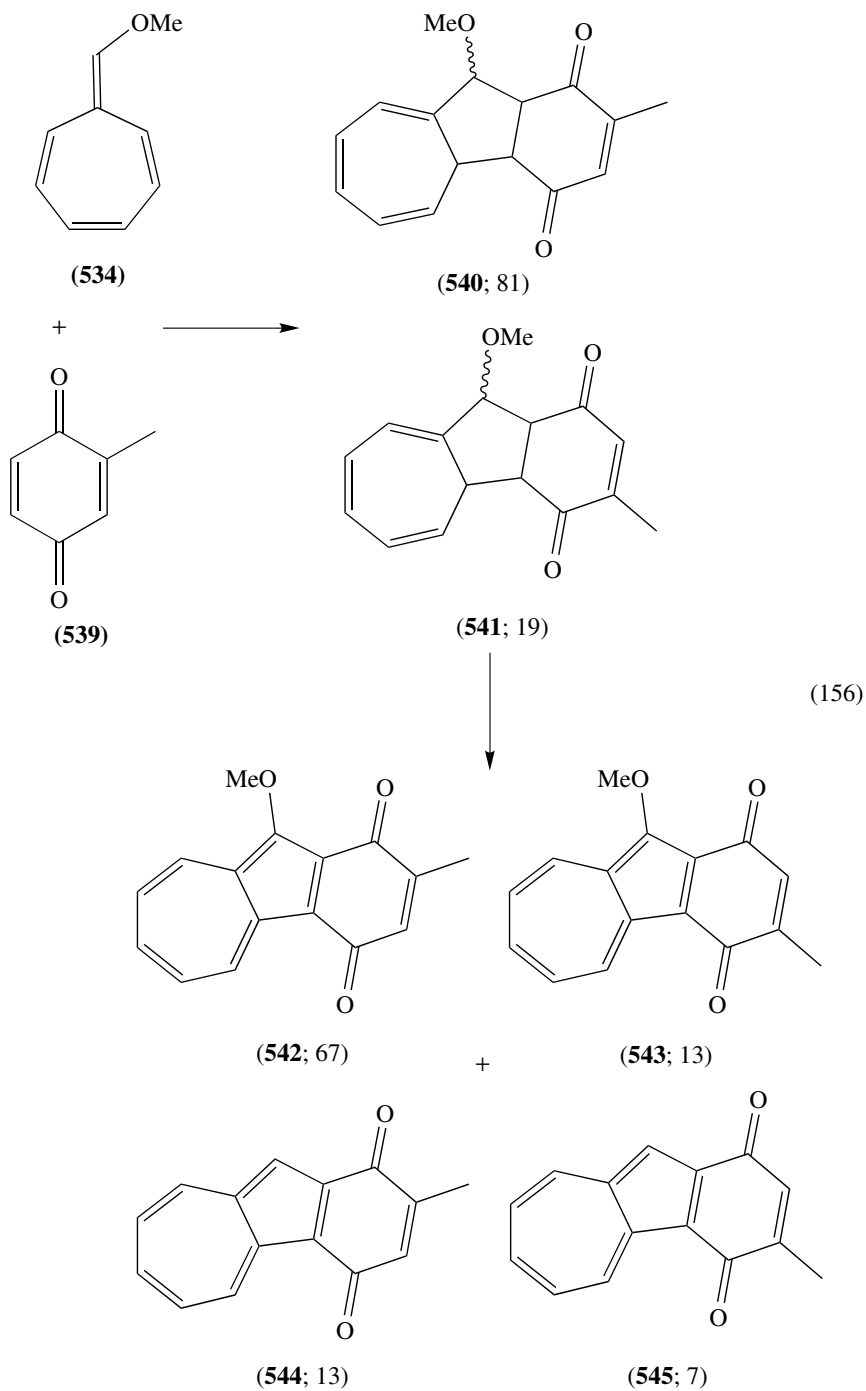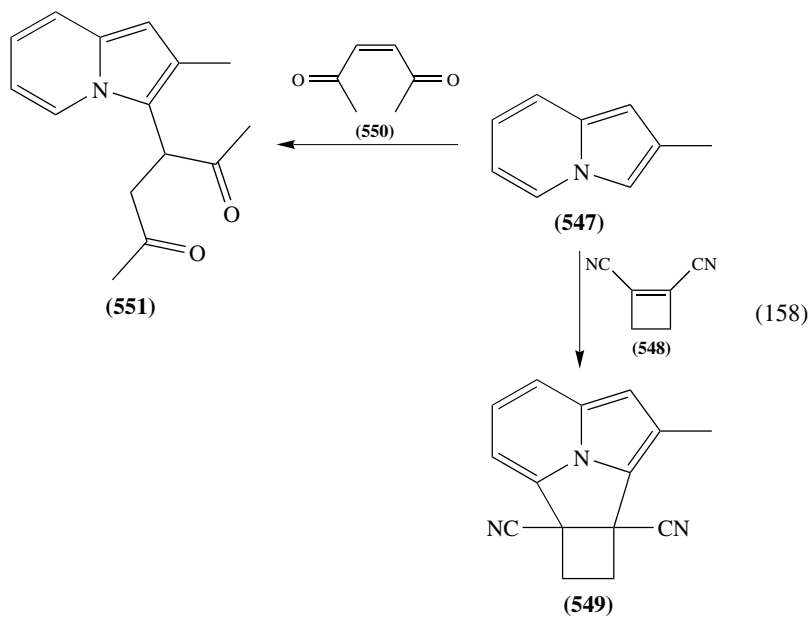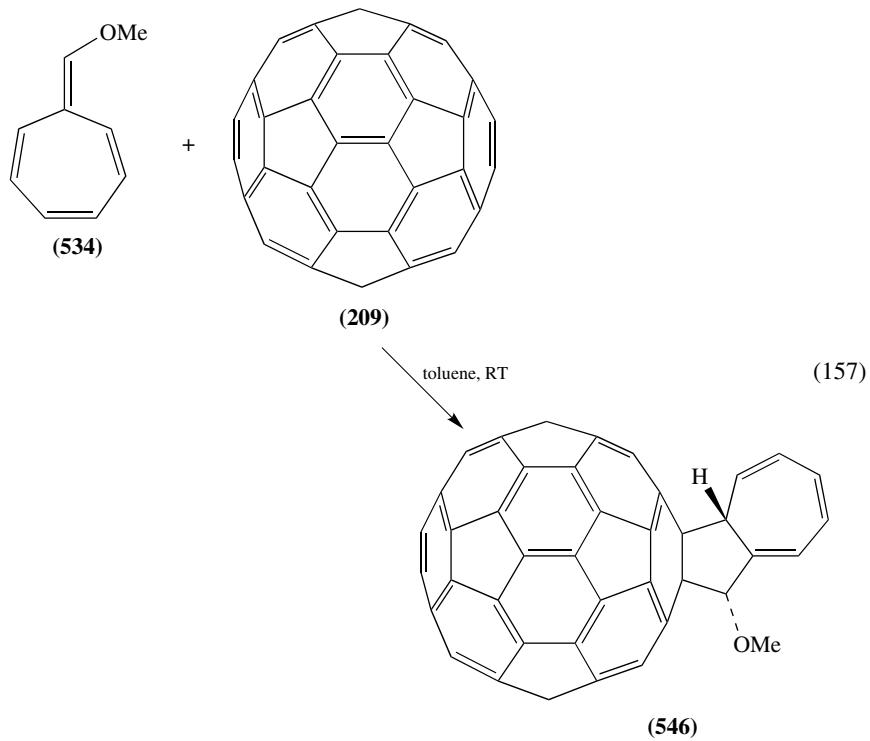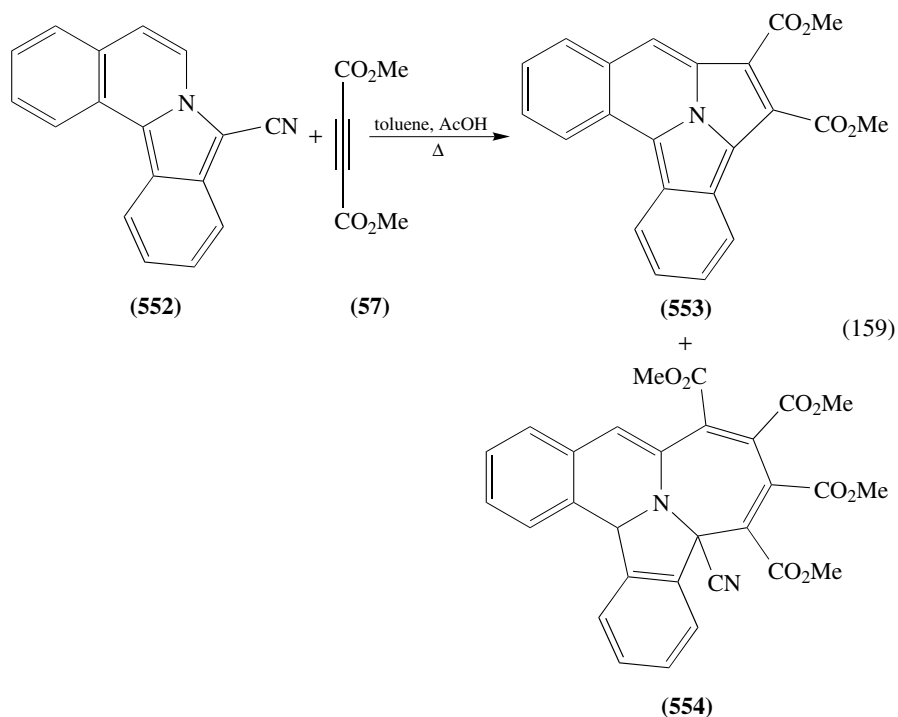
Jug and colleagues performed quantum mechanical SINDO1 and AM1 calculations of the transition states for the, in some cases experimentally still unknown, [8 + 2] cycloaddition reactions of indolizine **(555a)** and 6-nitroindolizine **(555b)** with nitroethene, methyl acrylate, acrylonitrile, ethene and dimethylvinylamine to give **556a** and **556b**, respectively (equation 160)[323]. They found that most [8 + 2] cycloaddition reactions should proceed concertedly, i.e. no intermediate and second transition state were found. Only the reactions of nitroethene (D = H, A = NO_2) with **555a** and **555b**, and the reaction of dimethylvinylamine (D = NMe_2, A = H) with **555b** were classified as being two-step processes. The experimentally observed reactions of nitroalkenes with indolizines, however, were Michael additions, which corresponds to only the first step of the two-step process.

(160)

(**555a**; R = H)   (**556a**; R = H)
(**555b**; R = NO_2)   (**556b**; R = NO_2)
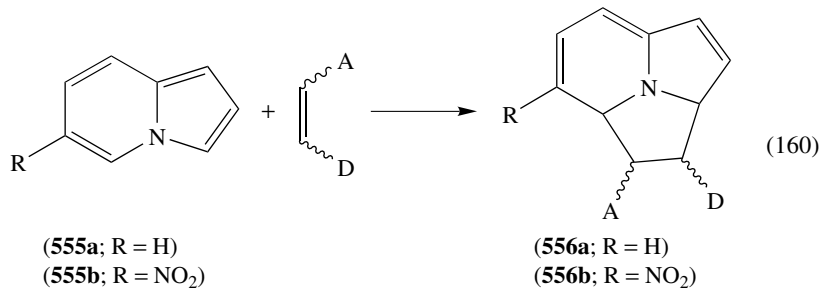
VI. [2 + 2 + 2] CYCLOADDITION REACTIONS

Even more than [6 + 4] and [8 + 2] cycloaddition reactions, the [2 + 2 + 2] cycloaddition reactions require a very well preorganized orientation of the three multiple bonds with respect to each other. In most cases, this kind of cycloaddition reaction is catalyzed by transition metal complexes which preorientate and activate the reacting multiple bonds[111,324]. The rarity of thermal [2 + 2 + 2] cycloadditions, which are symmetry allowed and usually strongly exothermic, is due to unfavorable entropic factors. High temperatures are required to induce a reaction, as was demonstrated by Berthelot, who described the synthesis of benzene from acetylene in 1866[325], and Ullman, who described the reaction between norbornadiene and maleic anhydride in 1958[326]. As a consequence of the limiting scope of this chapter, this section only describes those reactions in which two of the participating multiple bonds are within the same molecule.

Most metal mediated [2 + 2 + 2] cycloadditions involve two triple bonds which coordinate to a metal center to form a reactive metallocyclopentadiene species (*vide infra*). The corresponding reactions involving at least two double bonds and an intermediate metallocyclopentane species are almost completely limited to norbornadiene systems. These reactions can be considered as homo Diels–Alder reactions.

The most efficient catalysts for the homo Diels–Alder reactions of norbornadiene were found to be cobalt[327] and nickel[328] complexes. The general mechanistic pathway that has been proposed for these reactions has been depicted in equation 161[329]. According to this mechanism, co-ordination of norbornadiene and the olefin or acetylene to the metal center gives **557**, which is in equilibrium with metallocyclopentane complex **558**. Then, insertion of the olefin or acetylene in the metal–carbon bond takes place to form **559**. Reductive elimination finally liberates the deltacyclane species.

(161)
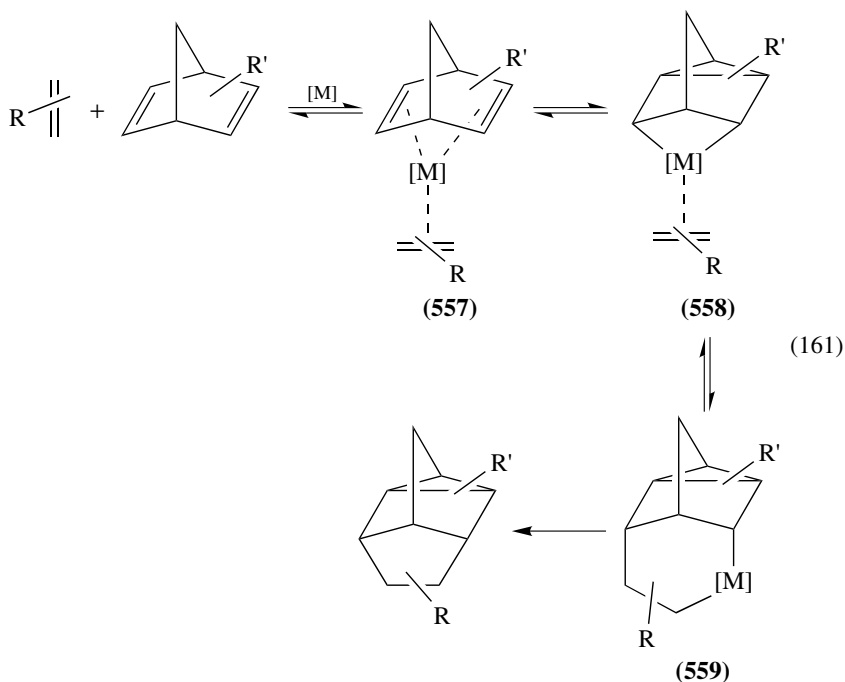
Lautens and colleagues[328] found 5 mol% Ni(COD)$_2$/2PPh$_3$ to be the most efficient catalytic system for the cycloaddition between methyl vinyl ketone **(100)** and norbornadiene **(560)**. The adducts **561** and **562** were obtained with 99% overall yield and with an *exo/endo* ratio of >95/<5 (equation 162).
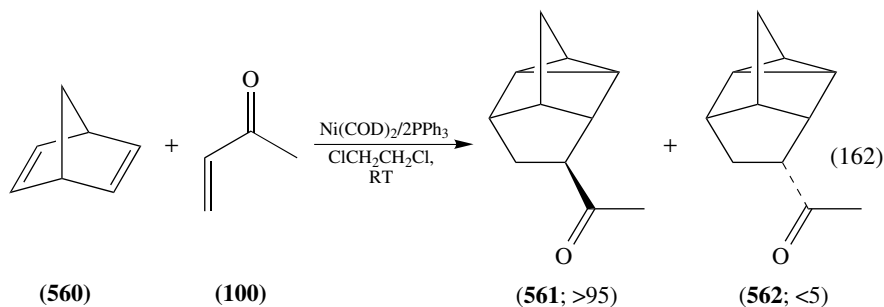
Unlike thermal homo Diels−Alder reactions in which *endo* adducts predominate[330], the nickel catalyzed reactions of acyclic electron-deficient dienophiles afford the *exo* isomers as the major cycloadducts. This has been explained by unfavorable steric interactions within intermediate **559** leading to the *endo* adduct. Cyclic dienophiles, on the contrary, give predominantly the *endo* isomer, which has again been explained by unfavorable steric interactions within *exo* **559**. The preferred conformation of the dienophile, *s-cis* or *s-trans*, has also been suggested to play a role[328].

The regiochemistry of nickel mediated cycloadditions of substituted norbornadienes has been investigated in detail. The regioselectivity, *exo/endo* selectivity and site selectivity seem to depend strongly on the substituents on both diene and dienophile. Tetracyanoethene, for example, reacted with 2-acetyloxymethyl substituted norbornadiene on the distal side[331].

The reactions between norbornadiene **563** and unsymmetrical dienophiles can, in principle, produce up to 8 cycloadducts. Lautens and colleagues[328] reported that **564** was the main regioisomer found in the reactions of **563** with the range of dienophiles examined (equation 163, Table 32). When the PPh$_3$ ligand was replaced by P(OPr-*i*)$_3$, however, **566** became the main product in the reaction of **563** with methyl vinyl ketone. The *endo/exo* selectivity depended strongly on the olefinic substituent and the regiochemical course of the reaction. The reaction of methyl vinyl ketone with 2-methoxynorbornadiene, which proceeded more slowly than the reaction with **563**, gave the regioisomer analogous to **566** as the major isomer, whereas the reaction with 2-trimethylsilylnorbornadiene afforded the adduct analogous to **565** as the major product. An adduct analogous to **567** was not obtained in any instance.

[2 + 2] Adducts were obtained as exclusive adducts or as by-products in the nickel mediated reactions of some substituted norbornadienes with various dienophiles. The formation of these products was considered to result from an intermediate metallocyclopentane species built up of the metal center, the dienophilic double bond and one of the double bonds of the norbornadiene moiety.

The cobalt mediated homo Diels−Alder reaction of norbornadiene **(560)** with phenyl acetylene **(568a)**, affording a phenyl substituted deltacyclene, demonstrated the potential of low-valent cobalt complexes as catalysts[332]. Lautens and coworkers[327] extended the scope of this reaction and were able to synthesize a wide range of substituted deltacyclenes from alkynes **568** (equation 164, Table 33). The low-valent cobalt(I) or cobalt(0) species to be used was prepared *in situ* by reduction of Co(acac)$_3$ with Et$_2$AlCl. Monosubstituted

acetylenes **568a–e** and **198** were more reactive than disubstituted acetylenes **568f–h**. The reactions between diphenylacetylene (**568g**) and norbornadiene did not take place at room temperature. Bis(trimethylsilyl)acetylene (**568h**) did not react, not even on prolonged heating at 60 °C. Dimers of norbornadiene were obtained instead.

(163)
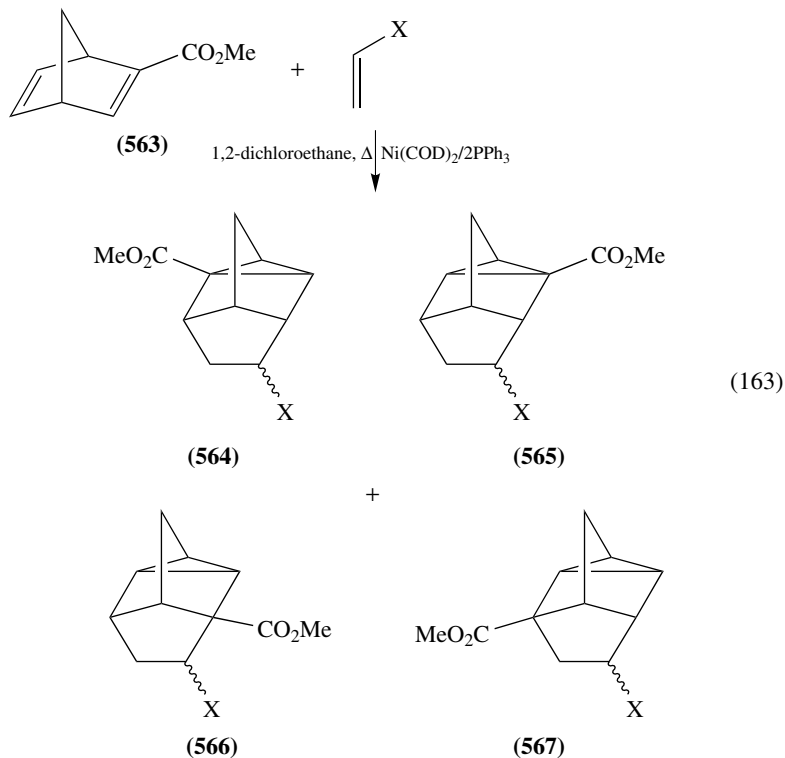
TABLE 32. Reaction data for equation 163

			Relative yield (*exo/endo*)			
Entry	X	Yield (%)	**564**	**565**	**566**	**567**
1	CN	94	100 (30/70)	—	—	—
2	SO$_2$Ph	75	66 (>95/<5)	33 (>95/<5)	—	—
3	COMe	84	70 (75/25)	10 (42/58)	20 (0/100)	—

The possibility of asymmetric induction in these reactions was probed by adding chiral phosphine ligands to the cobalt complex. Brunner and colleagues[333] found an ee of 98.4% for the adduct of norbornadiene and phenylacetylene using a cobalt complex based on the chiral bidentate phosphine NORPHOS (**570**). They extended their studies to include a variety of other bidentate phosphines and different acetylenes, reaching enantioselectivities of more than 99%[334]. Buono and coworkers[335] obtained high enantioselectivities (up to 97% ee) using a cobalt(II) iodide complex and amino acid based chiral phosphine ligand **571**. Chiral phosphine **572** induced an ee of 82% in the reaction of norbornadiene

with phenylacetylene, as reported by Lautens and coworkers[327,336]. The highest enantios-electivity (91% ee) with 1-hexyne was found when phosphine **573** was employed as the chiral ligand.

$$(164)$$

(560)   **(568)**   **(569)**
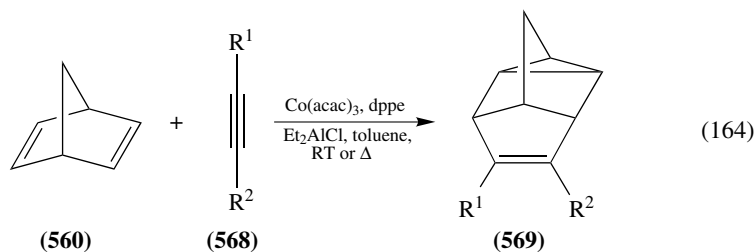
TABLE 33.   Reaction data for equation 164

Entry	R^1	R^2	Alkyne	$T(^\circ C)$	Yield (%)
1	Ph	H	**568a**	RT	100
2	n-Bu	H	**198**	RT	91
3	i-Pr	H	**568b**	RT	58
4	i-Bu	H	**568c**	RT	50
5	$(CH_2)_3OTBDMS$	H	**568d**	RT	90
6	$SiMe_3$	H	**568e**	RT	50
7	Et	Et	**568f**	60	65
8	Ph	Ph	**568g**	60	58
9	TMS	TMS	**568h**	60	0

(570)   **(571)**

(572)   **(573)**
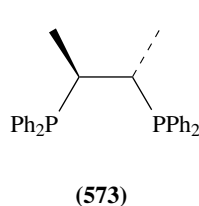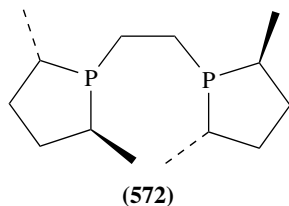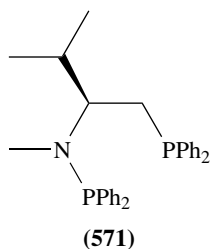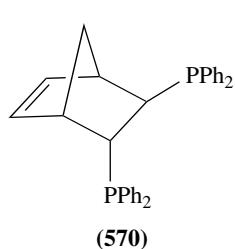
The regioselectivity in the reactions of 7-substituted norbornadienes with substituted acetylenes generally proved low. The reactions of **563** and 2-methoxynorbornadiene with 1-hexyne (**198**) did not proceed. With 2-trimethylsilylnorbornadiene (**574**), adducts **575** and **576** were obtained, albeit in low to moderate yields (equation 165). The best regios-electivity (**575/576** = 92/8) was obtained when the reaction was performed at room

temperature and $Co(acac)_3$ was used as the pre-catalyst[327]. The low yields and the formation of acetylene trimers suggested that 2-substituted norbornadienes do not co-ordinate well to the active cobalt complex.

$$(574) \qquad (198) \qquad (575)$$

$$+ \qquad (165)$$

$$(576)$$
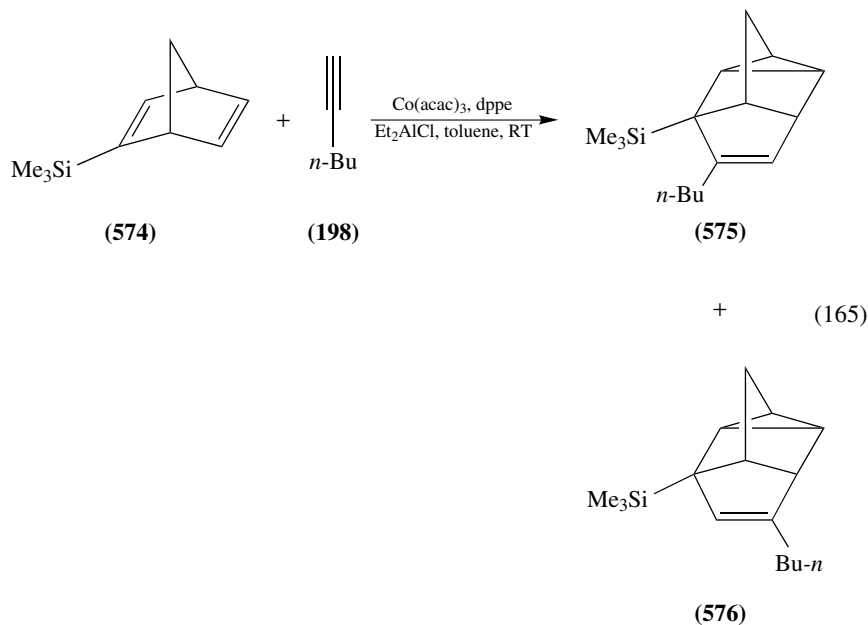
Cobalt, as its $CpCo(CO)_2$ complex, has proven to be especially suited to catalyze $[2 + 2 + 2]$ cycloadditions of two alkyne units with an alkyne or alkene. These cobalt-mediated $[2 + 2 + 2]$ cycloaddition reactions have been studied in great detail by Vollhardt[337]. The generally accepted mechanism for these cobalt mediated cycloadditions, and similar transition metal mediated cycloadditions in general, has been depicted in equation 166. Consecutive co-ordination of two triple bonds to $CpCo(CO)_2$ with concomitant extrusion of two molecules of carbon monoxide leads to intermediates **578** and **579** via monoalkyne complex **577**. These react with another multiple bond to form intermediate **580**. The conversion of **578** to **580** is said to be kinetically favored over that of **579** to **580**. Because intermediates like **580** have never been isolated, it is still unclear whether the next step is a Diels−Alder reaction to form the final product or an insertion to form **581**. The exact circumstances might determine which pathway is followed.

Vollhardt and colleagues have explored the reactions between diynes and enamines[338−341]. The reactions between symmetrically substituted alkynes and alkyne tethered uracil derivatives proceeded in moderate yields, producing adducts with predominant *anti* configurations[342−343]. On the other hand, the reactions between diynes and uracil derivatives produced predominantly *syn* isomers.

The attachment of chiral sugar-derived auxiliaries to the uracil unit generally induced low diastereoselectivities. Only in the reaction between diyne **582** and uracil **583** was a high *syn* and diastereoselectivity observed, complex **584** being obtained as the major diastereomer (equation 167).

The cobalt mediated $[2 + 2 + 2]$ cycloadditions of α,ω-diynes with indole were only accomplished when the nitrogen atom was substituted with an electron-withdrawing

(166)

group[338a]. Furthermore, the CpCo(CO)$_2$ complex proved inefficient in these reactions. When CpCo(C$_2$H$_4$)$_2$ was used, however, the reactions proceeded well.

THF, Δ | CpCo(C$_2$H$_4$)$_2$

(167)
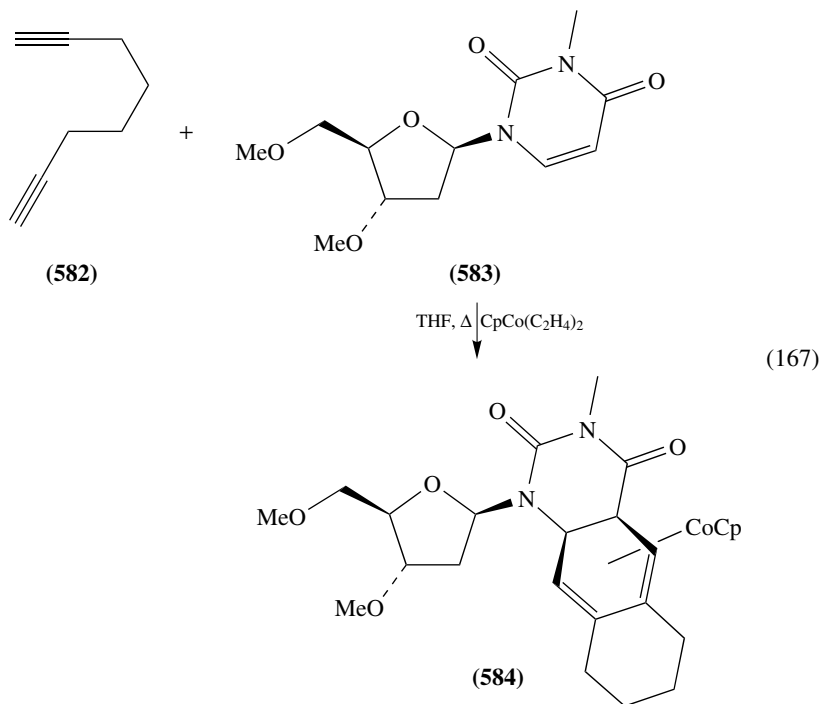
Vollhardt and colleagues[338b] studied the regiochemistry in these cycloaddition reactions. When the α,ω-diynes had large substituents at both termini, the reaction with N-phenylsulfonylindole did not afford any adduct due to steric hindrance. When smaller substituents were present, the cycloaddition proceeded in such a way that the larger substituent was distant from the phenylsulfonamide moiety, as illustrated for the reaction of **585** with **586** (equation 168). *Anti* **587** and *syn* **588** were obtained in a 61 : 39 ratio.

A formal synthesis of γ-lycorane was accomplished by Vollhardt and colleagues by employing a [2 + 2 + 2] cycloaddition between enyne **589** and **568h** (equation 169)[344]. The reaction afforded a mixture of *syn* and *anti* adducts **590** and **591** in a 80 : 20 ratio when the reaction was conducted at room temperature. When the reaction was conducted in refluxing **568h**/THF (1 : 1, v/v), a *syn:anti* ratio of 60 : 40 was obtained. A small amount of [2 + 2] adduct **592** was also isolated. This product became the dominant product when the enamide double bond was substituted. The additional steric hindrance probably prevented the enamide double bond from participating in the cycloaddition reaction.

Vollhardt and colleagues also investigated the [2 + 2 + 2] cycloadditions of alkyne tethered furans **593a** and thiophenes **593b** with alkynes[345]. The reactions with **568h** proceeded to generate the expected cycloadducts **594a** and **594b** (equation 170). These species,

however, underwent heterolytic ring opening in most cases and provided the rearranged compounds **595a** and **595b** through a series of ring-closure/ring-opening sequences.

Malacria and coworkers[346] prepared phyllocladane and kaurane types of diterpenes by means of $[3 + 2]/[2 + 2 + 2]/[4 + 2]$ cascade reaction sequences. A representative example of such a reaction sequence has been outlined in equation 171. The five-membered ring of **598** was built by a 1,3-dipolar cycloaddition between **596** and an all-carbon 1,3-dipole generated from **597**. The reaction of **598b** with **568h** afforded benzocyclobutene **599**. The intramolecular $[4 + 2]$ cycloaddition afforded diastereomers **600** and **601** in a 5 : 1 ratio. It is noteworthy that the exocyclic double bond in **598b** neither participates in the $[2 + 2 + 2]$ cycloaddition reaction nor isomerizes under the reaction conditions applied.

(168)

(**585**)   (**586**)

(**587**; 61)   (**588**; 39)
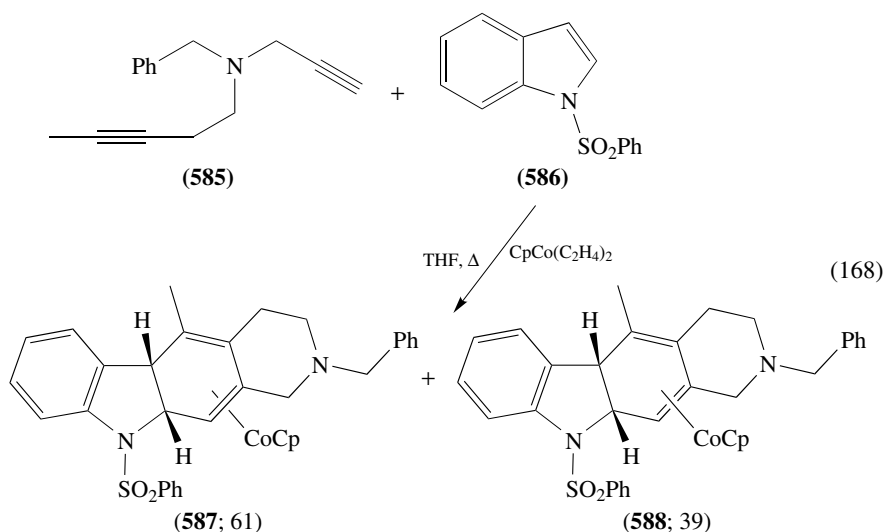
The kaurane type of adduct **601** became the major product when the methylene group at C(12) was replaced by a carbonyl group and substituents were present at C(15). Repulsive steric interactions between the substituents at C(15) and H(1) prevented the formation of phyllocladane type of compounds like **600**[347].

In a similar way, Malacria and colleagues accomplished the formation of the stemodan skeleton by a tandem $[2 + 2 + 2]/[4 + 2]$ cycloaddition process[348].

Apart from cobalt, other metals have also been shown to be able to catalyze $[2 + 2 + 2]$ cycloaddition reactions. Grigg and coworkers[349], for example, used a Pd(0) complex to catalyze $[2 + 2 + 2]$ cycloadditions.

Tsuda and coworkers[350] used nickel(0) complexes to effect the $[2 + 2 + 2]$ cycloadditions between two alkyne units and one alkene unit and employed this strategy to synthesize copolymers. Thus, the reaction of diyne **602** with *N*-octylmaleimide (**603**) catalyzed by Ni(CO)$_2$(PPh$_3$)$_2$ afforded copolymer **604** with a maximum yield of 60% and a GPC molecular weight of as high as 35,000, which corresponds to $n = 64$ (equation 172). The *exo,exo*-bicyclo[2.2.2]oct-7-ene moiety of **604** arises through the reaction of the initially formed $[2 + 2 + 2]$ adduct with another equivalent of *N*-octylmaleimide.

(589)   **(568h)**

CpCo(CO)$_2$,THF, Δ

(590)   **(591)**   (169)

+

(592)
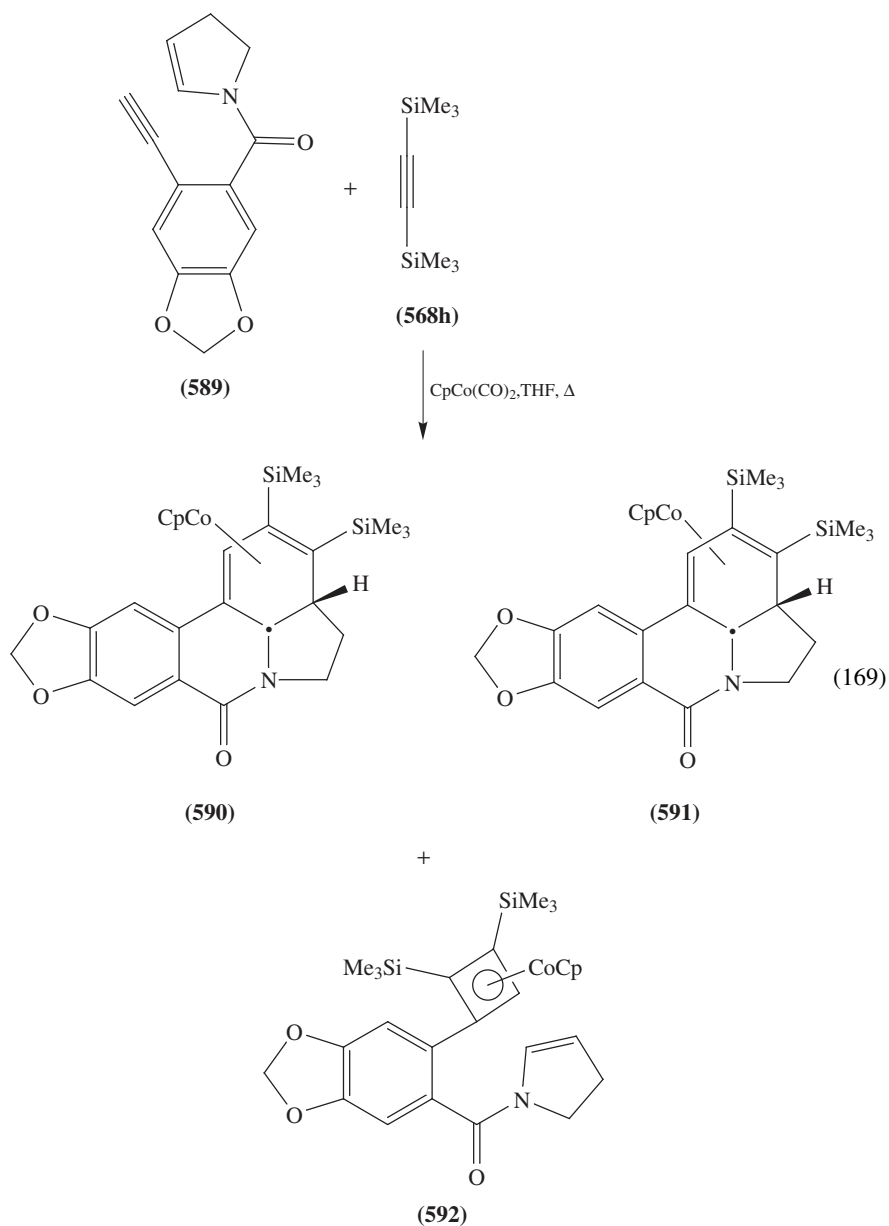
Ikeda and coworkers[351] performed [2 + 2 + 2] cycloadditions of diynes with α,β-enones using NiCl$_2$/Zn (1 : 10) as the catalytic couple. In these reactions, nickel dichloride

reacts with zinc to afford a Ni(0) species and zinc dichloride. The best catalytic results were obtained when 1.5 equivalents of zinc dichloride and triethylamine were added to the reaction mixture. Thus, methyl vinyl ketone (**100**) reacted with diyne **605** to afford the aromatized adduct **606** as the exclusive product (equation 173). The two abstracted hydrogen atoms proved to be incorporated into another molecule of methyl vinyl ketone.

When trimethylsilyl substituted diyne **607** was reacted with methyl vinyl ketone, the reaction proceeded with complete regioselectivity and without aromatization to afford **608** with 56% yield (equation 174). The regioselectivity observed was considered to result from a metallacyclopentene intermediate which was built up of the nickel atom, the double bond of methyl vinyl ketone and the less substituted triple bond of **607**.

(**593a**; X = O)   (**568h**)   (**594a**; X = O)
(**593b**; X = S)   (**594b**; X = S)

(170)

(**595a**; X = O)
(**595b**; X = S)
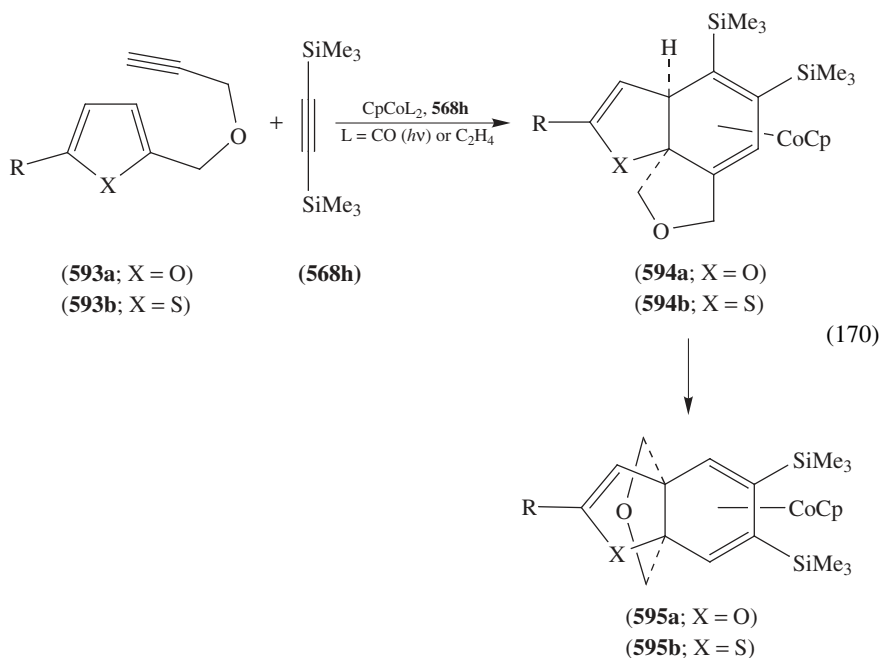
Rothwell and colleagues[352] studied the titanium mediated [2 + 2 + 2] cycloaddition of alkenes with monoynes and diynes. Among the reactions studied, the reaction between styrene (**29**) and diyne **609** in the presence of titanium catalyst **610** proved cleanest (equation 175). The reaction yielded **614** via a [2 + 2 + 2] cycloaddition followed by a titanium mediated suprafacial [1,5] H-shift involving **611**–**613**. The *cis* relationship between the trimethylsilyl group and the phenyl group indicated that the initially formed titananorbornene **611** had an *endo* stereochemistry.

The authors had evidence to believe that the addition of **29** to the titanacyclopentadiene complex proceeded in a Diels–Alder type of way, i.e. in a concerted manner instead of a stepwise manner via a titanacycloheptatriene intermediate.

Kotha and Brahmachary[353] prepared some constrained α-amino acids using a rhodium mediated [2 + 2 + 2] cycloaddition reaction. The indane type of α-amino acids were synthesized by reacting diynes with monoynes using Wilkinson's catalyst[354]. Thus, the reaction of diyne **615** with **616** afforded α-amino acid derivative **617** (equation 176).

(171)

(172)

(173)

(174)

[Ti] = Ti(OAr)$_2$, ArO = 2,6-diphenylphenoxide
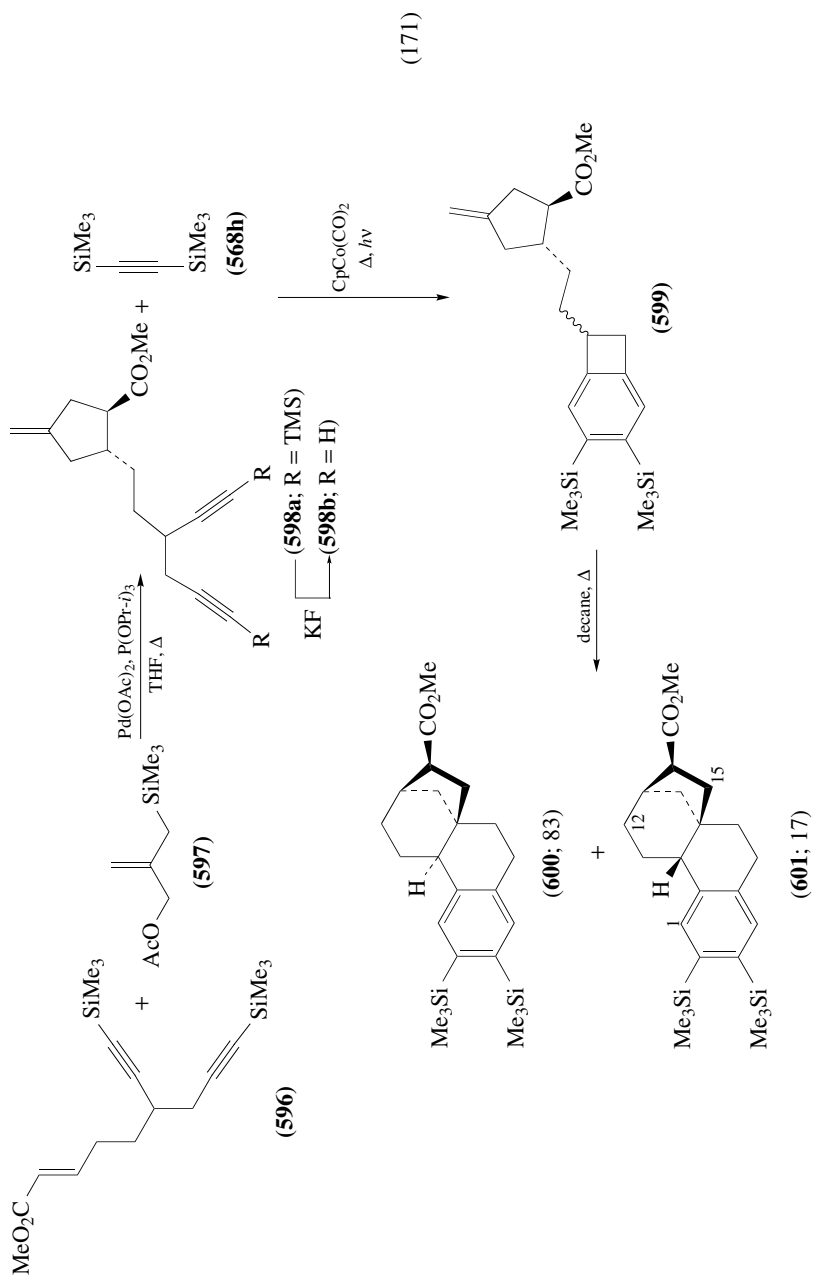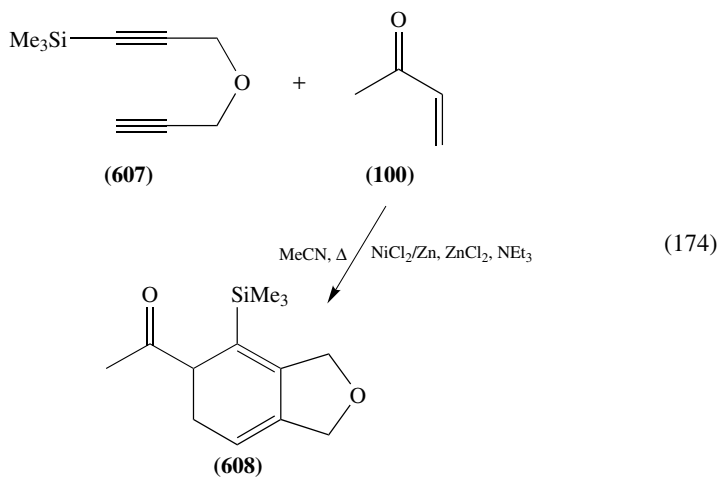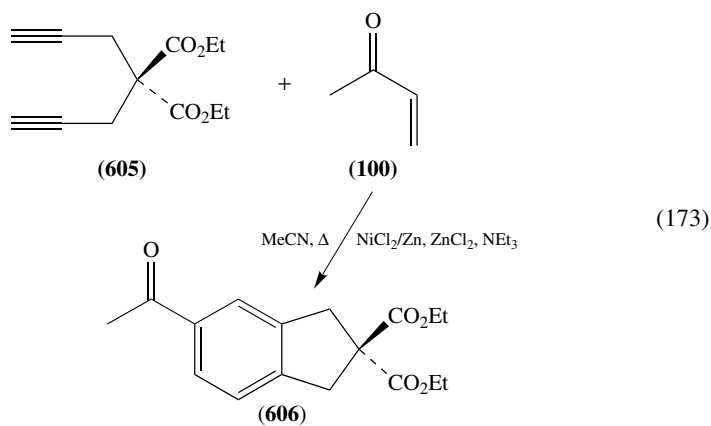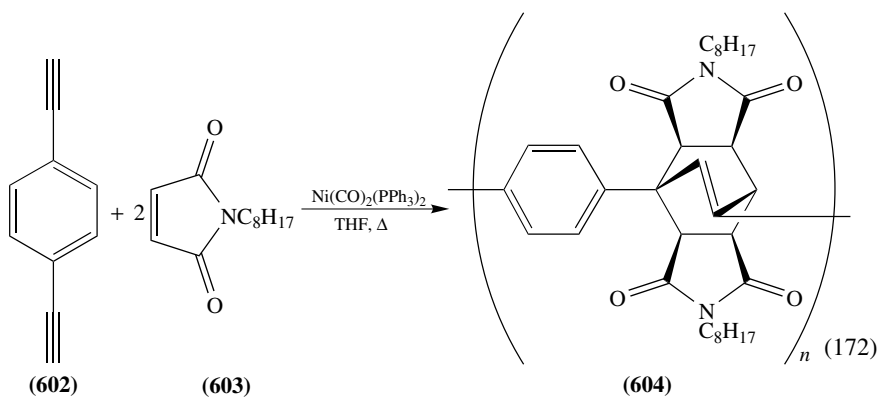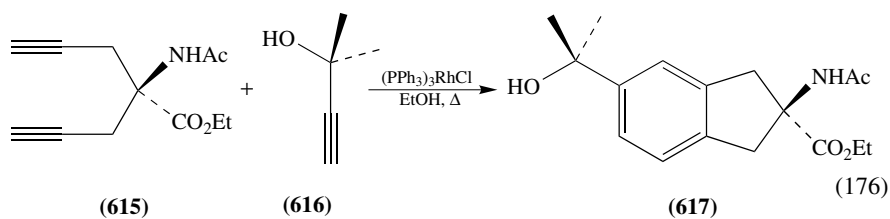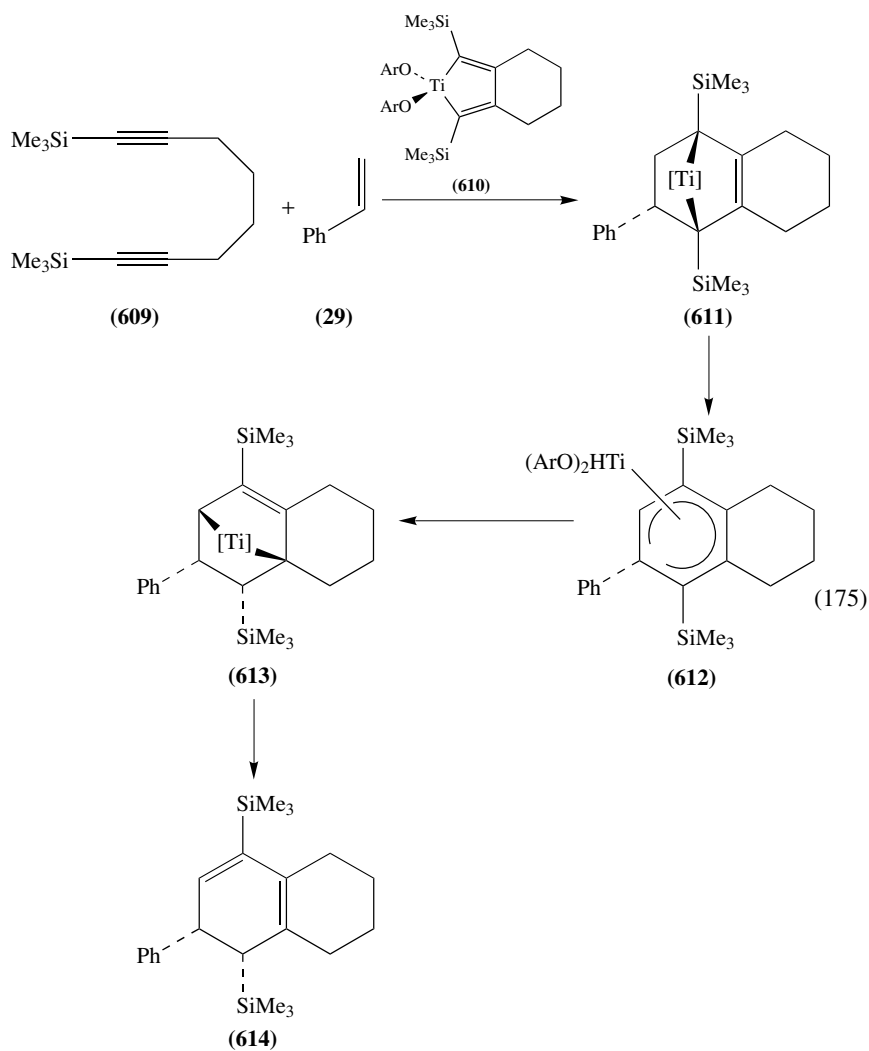
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CHAPTER **6**

Cycloaddition to give heterocycles

GERHARD V. BOYD

*Department of Organic Chemistry, The Hebrew University of Jerusalem, Jerusalem
91904, Israel*

I. INTRODUCTION

The formation of heterocycles by cycloaddition reactions of conjugated dienes is the subject of this chapter. Almost the entire account is devoted to the Diels–Alder reaction of dienes with heterodienophiles to yield six-membered ring compounds (equation 1). Many such reactions have been reported and there is a plethora of reviews. Some[1a–p] are general; others are cited at appropriate places in the text. This account is highly selective, concentrating on recent work with particular regard to the stereochemistry of these processes.

$$\text{(1)}$$
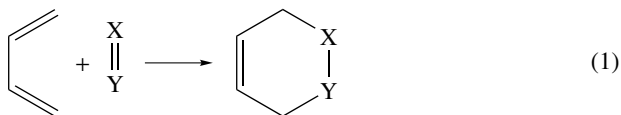
Some addition reactions leading to five-membered ring compounds are described at the end.

II. ADDITION TO CARBONYL COMPOUNDS

Dienes do not react with carbonyl compounds unless the latter are activated by electron-withdrawing substituents such as carboxyl groups. Cyclohexa-1,3-diene, for example, adds diethyl mesoxalate (1) at 120 °C to form 2 (equation 2)[2]. Other cycloadditions of this ester with various dienes, which were carried out in a sealed tube at 130–135 °C, are shown in equations 3 and 4[3]. It is noteworthy that no product was isolated from the action of diethyl mesoxalate on cyclopentadiene; it was suggested[3] that the cycloadduct reverted to its components at the high temperature required for the reaction.

(1)   (2)

(2)

78%

(3)

80%   7%

(4)

The presence of electron-donating substituents in the diene enables it to react with simple aldehydes: thus both acetaldehyde and benzaldehyde add to 1-methoxy-1,3-butadiene at 50–65 °C under high pressure (20 Kbar) to give dihydropyrans as 70 : 30 mixtures of *cis-* and *trans-*isomers (equation 5)[4]. The combination of electron-rich diene/electron-poor dienophile makes it possible to perform the reaction under milder conditions. 2-Alkyl-1-ethoxy-1,3-butadienes and diethyl mesoxalate afford dihydropyrans almost quantitatively (equation 6)[5].

R = Me or Ph

(5)

$$R + 1 \longrightarrow \text{(dihydropyran product)} \qquad (6)$$

An outstandingly reactive diene is 1-methoxy-3-(trimethylsilyloxy)-1,3-butadiene ('Danishefsky's diene') **4**, prepared by the action of trimethylsilyl chloride on the ketone **3** in the presence of zinc chloride/triethylamine (equation 7)[6]. The reaction of diethyl mesoxalate with Danishefsky's diene gives the dihydropyran **5**; with the (trimethylsilyloxy)dienes **6** and **7**, mixtures of dihydropyrans are obtained, in which the 'meta-isomers' predominate (equations 8 and 9)[7].

$$ \text{(3)} + Me_3SiCl \longrightarrow \text{(4)} \qquad (7) $$

(3)   **(4)**

(5)

$$ \text{(6)} \xrightarrow{\ 1\ } \text{'meta-'} + \text{'para-'} \qquad (8) $$

(6)

'meta-'

'para-'

'meta-'

+

'para-'

(9)
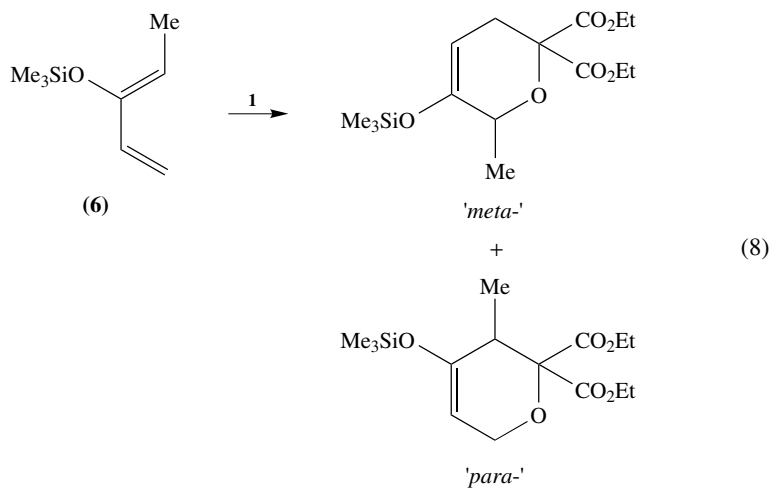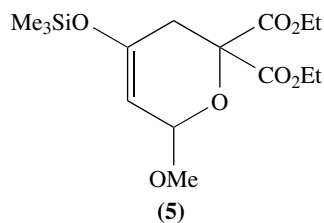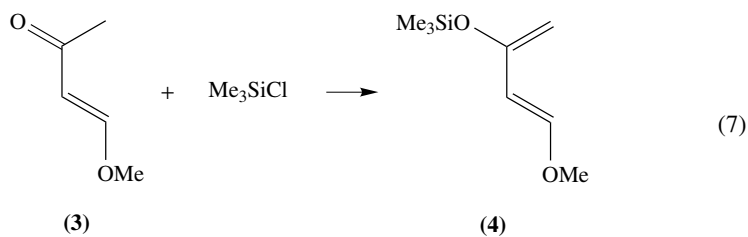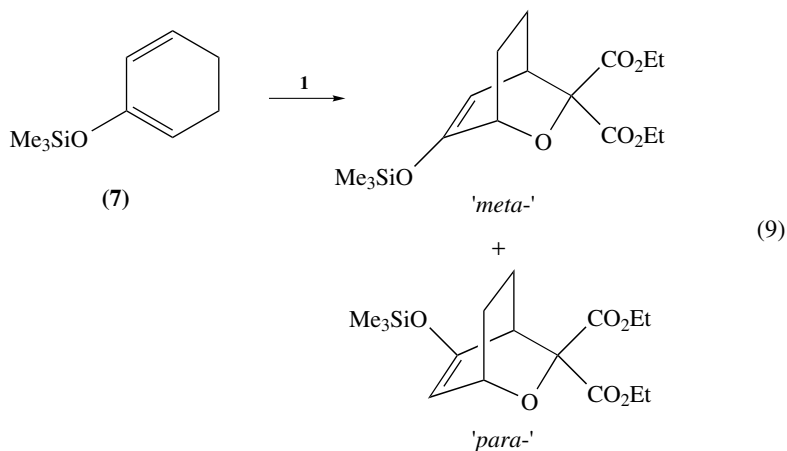
Equation 10 shows an example of the synthesis of a chiral functionalized hexapyra-noside from diethyl mesoxalate and the butadienyl ether of a protected sugar[8a,b].

(10)
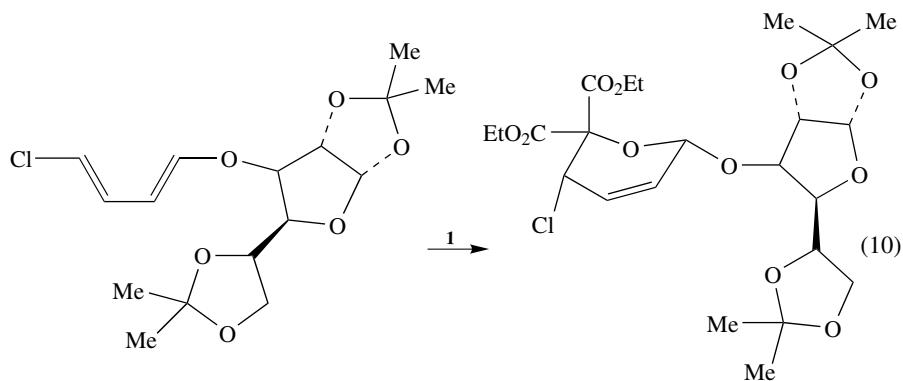
Other carbohydrate syntheses include the formation of dihydropyrans from diethyl mesoxalate and 1-methoxybutadienes (e.g. equation 11)[9]. The butadiene **8**, which is activated by the presence of two alkoxycarbonylamino groups, adds to diethyl mesoxalate in DMF during 44 h at 180 °C in an autoclave to give the cycloadduct **9** in 34% yield (equation 12)[10].

(11)

$$\text{(8)} \quad + \quad \mathbf{1} \quad \longrightarrow \quad \text{(9)} \tag{12}$$
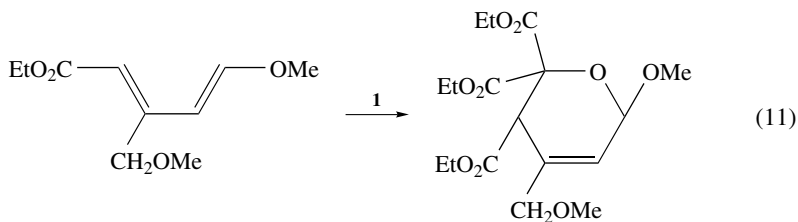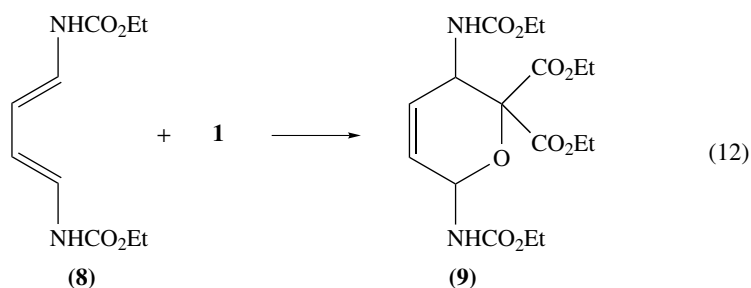
In recent years, much work has been done on catalyzed and asymmetric cycloaddition reactions. In the presence of 5 mol% bismuth trichloride, the simple dienes **10** ($R^1 = R^2 = H$; $R^1 = H$, $R^2 = Me$; or $R^1 = Me$, $R^2 = H$) react with diethyl mesoxalate to afford mixtures of the cycloadducts **11** and the products **12** of an ene-reaction (equation 13)[11,12]. 1,3-Cyclohexadiene and ethyl glyoxylate give solely the *endo* adduct **13** in 50% yield (equation 14)[12].

$$\tag{13}$$

$$\tag{14}$$
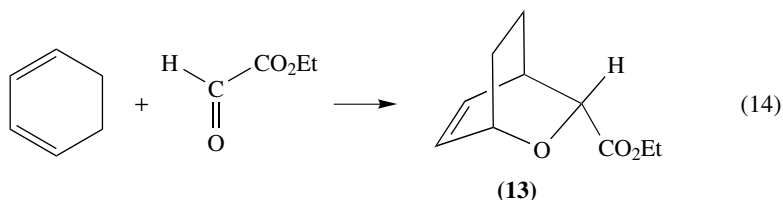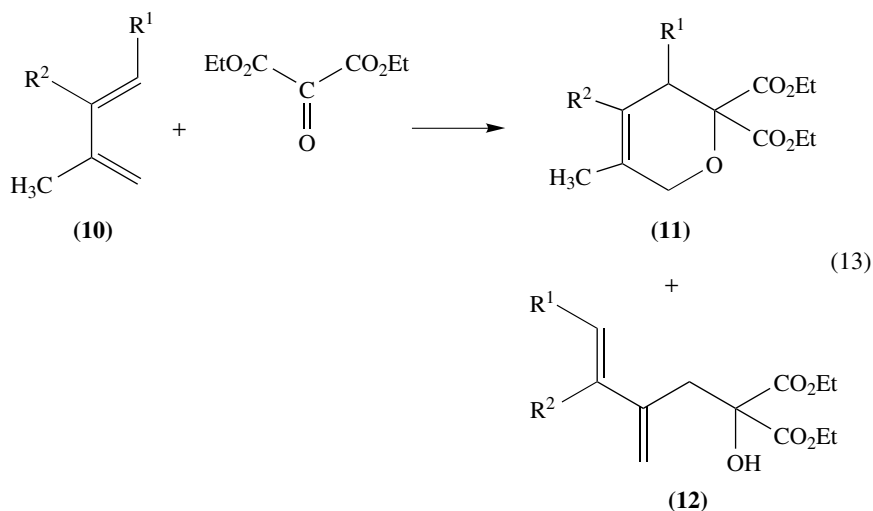
The first report of a cycloaddition reaction in the presence of an optically active catalyst[13] appeared in 1983[14a]. The dienes **14** add to benzaldehyde in the presence of 1 mol% of the chiral lanthanide NMR shift reagent Eu (hfc)$_3$, i.e. tris[3-(heptafluoropropyl-hydroxymethylene)-(+)-camphorato]-europium(III), to give, after treatment with trifluoroacetic acid, the dihydro-γ-pyrone **15** enriched in the (*R*)-enantiomer, the degree of

asymmetric induction depending on the nature of the group R (equation 15)[14].

(15)

For R = Me : 18% ee
For R = *i*-Pr : 28% ee
For R = *t*-Bu : 38% ee
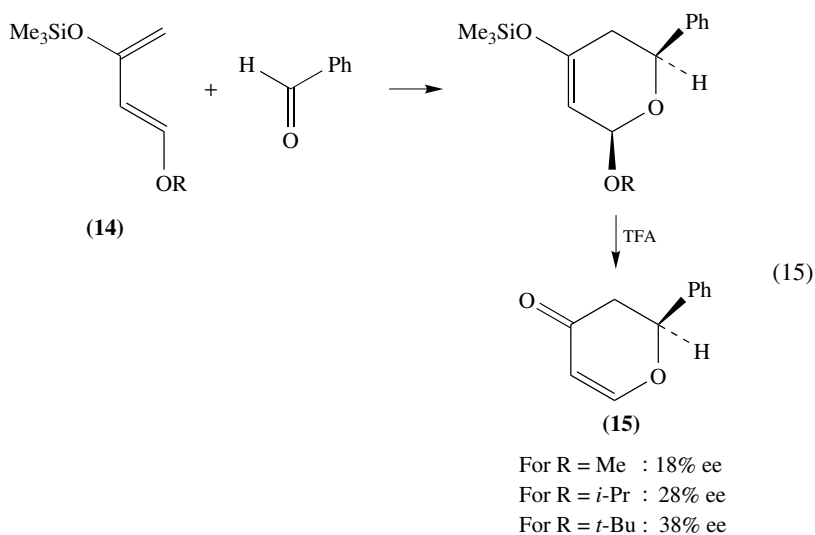
The 1,3-butadiene **16**, which contains the chiral auxiliary *l*-menthyl group, reacts with benzaldehyde in the presence of Eu(hfc)₃ to yield a mixture of the diastereomeric products **17** and **18** (equation 16); the butadiene **19** similarly affords a mixture of **20** and **21** (equation 17). It is seen that for the combination *l*-menthyl auxiliary/chiral catalyst the facial selectivity is much higher than for the combination *d*-menthyl auxiliary/chiral catalyst, which points to an 'interactivity' between the chiral auxiliary and the chiral catalyst[14].

(16)

(17)

8 parts

+ (16)

(18)

92 parts

(19) + H-C(=O)-Ph

(i) Eu(hfc)$_3$
(ii) Et$_3$N/MeOH

(20)
41 parts

+ (17)

(21)
59 parts
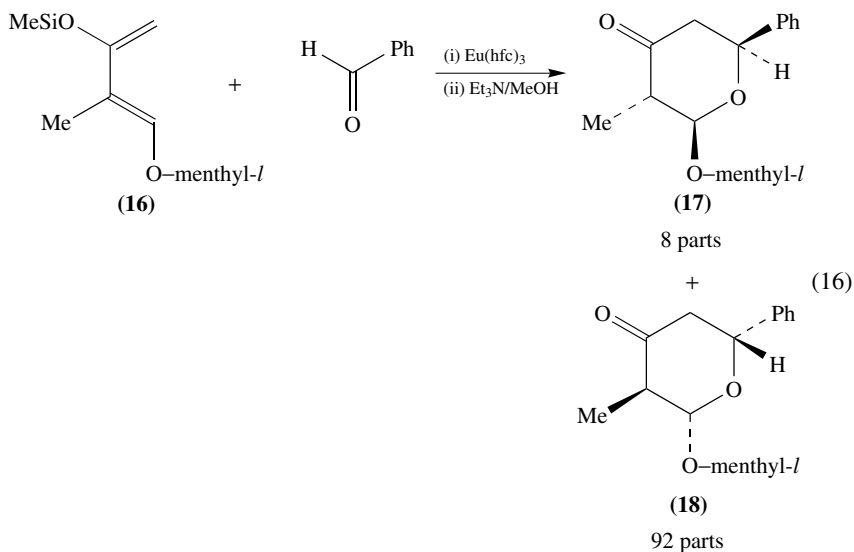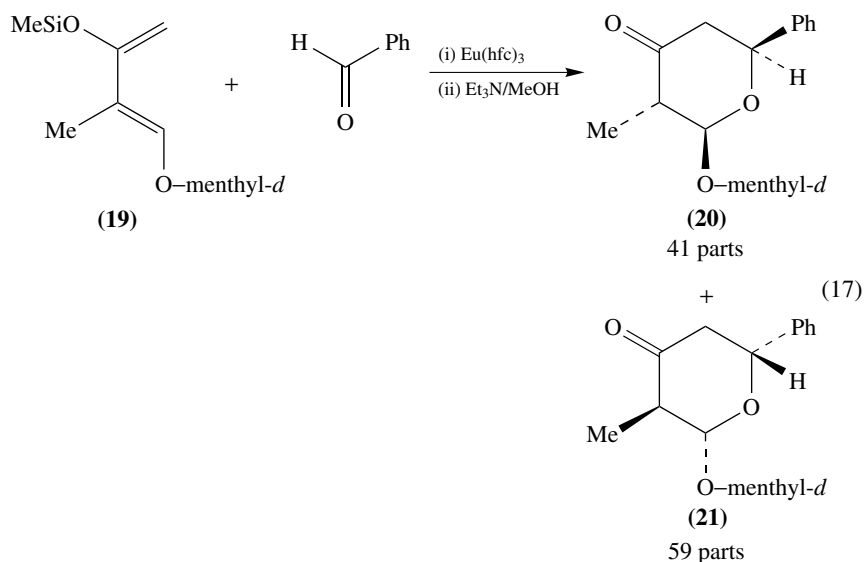
The chiral copper(II) bisoxazoline compounds **22** (R^1 = t-Bu or Ph, Tf = trifluorome-thanesulfonyl) catalyze the enantioselective reactions of 2,3-dimethylbuta-1,3-diene with glyoxylic esters HCO$_2$R^2 (R^2 = Me, Et or i-Pr) to yield mixtures of Diels–Alder and ene products, **23** and **24**, the proportions of which depend on the structure of the chiral ligand, the nature of R^2 and the temperature of the reaction (equation 18). Thus, ethyl glyoxylate and the diene in the presence of (R)-**22** (R^1 = Ph) at −30 °C gave the (S)-dihydropyran **23** (R^2 = Et) (13%) in 85% enantiomeric excess (ee), together with 7% of the ene-product **24** (R^2 = Et)[15]. Treating 1,3-cyclohexadiene with ethyl glyoxylate in the presence of 5 mol% (S)-**22** (R^1 = t-Bu) in nitromethane led to the smooth formation of the cycloadduct **25** in 66% yield and 97% ee[16].

(22)

(24)

+ (18)

(23)

(25)
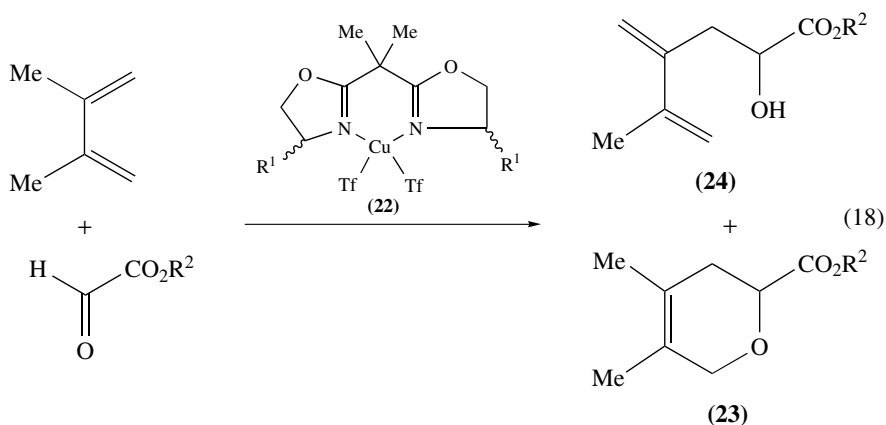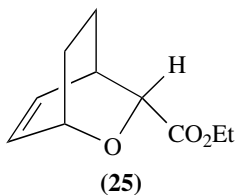
Under the influence of 20 mol% of the chiral aluminum complex (S)-**26**, 2,3-dimethyl-1,3-butadiene adds to ethyl glyoxylate in dichloromethane at $-78\,°C$ to room temperature during 20 h to produce a mixture of the cycloadduct **23** (R^2 = Et) (73% yield, 97% ee) and the ene product **24** (R^2 = Et) (9% yield, 88% ee)[17]. The analogous aluminum complexes (R)-**27** and (S)-**27** (Ar = Ph or 3,5-xylyl) (10 mol% in toluene) catalyze the Diels–Alder reaction of benzaldehyde with the diene **28** to give, after the addition of trifluoroacetic acid, the dihydropyrone **29** in 95% ee, accompanied by a small amount of the corresponding *trans*-isomer (equation 19)[18].

(S)-**(26)**   (R)-**(27)**   (19)

(28)   **(29)**
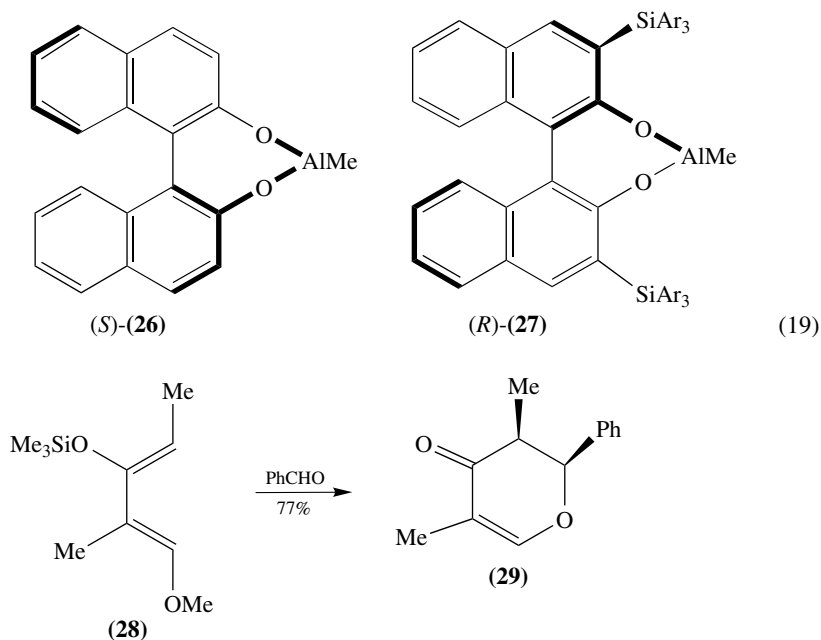
Benzaldehyde reacts with the diene **28** in the presence of 20 mol% of the chiral boric acids **30** (R = n-Bu, Ph or 2-MeOC$_6$H$_4$), obtained from alkylboric acids and the appropriate derivatives of tartaric acid, at $-78\,°C$ for 4–9 h to afford the *cis*-products **29** in 56–95% yields and 87–97% ee[19,20]. Benzaldehyde, cinnamaldehyde and various aliphatic aldehydes (n-hexanal, n-heptanal etc) add directly to Danishefsky's diene **4** in ether at $-30\,°C$ in the presence of the (R,R)-salen chromium complexes **31** (X = Cl, N$_3$, F or BF$_4$) and 4 Å molecular sieves to afford the cycloadducts **32** (e.g. R = Ph, PhCH=CH) in 70–93% ee[21].

(30)

(31)

(32)

(33)
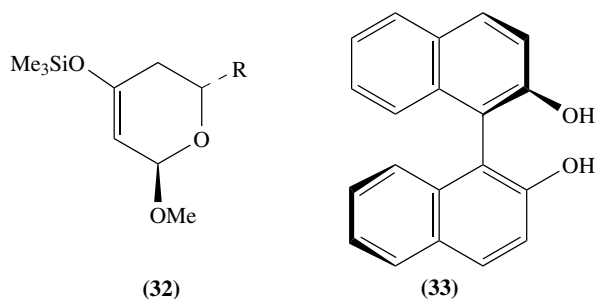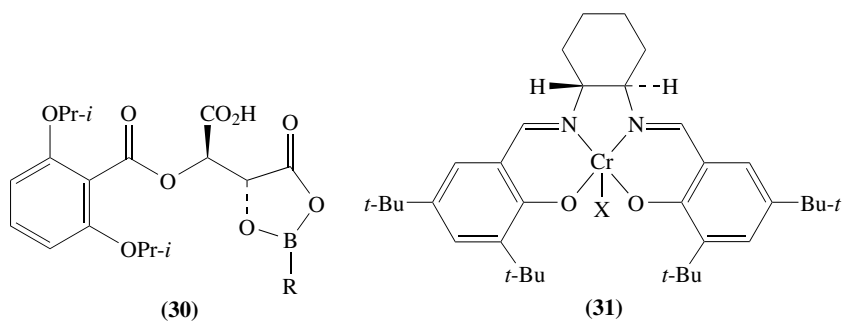
It has been shown[22] that the reaction of the diene **4** with aldehydes RCHO in the presence of a catalyst prepared from (*R*)-BINOL **(33)** and Ti(OPr-*i*)$_3$, which affords the dihydro-γ-pyrones **35** in good yields and high ee, proceeds by a two-step sequence via the open-chain adducts **34**, which cyclize to the products on treatment with trifluoroacetic acid (equation 20).

(4)   (34)   (35)   (20)
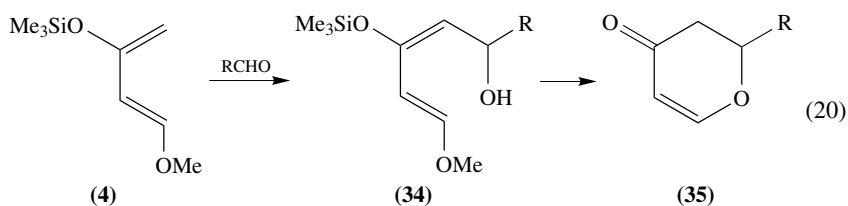
The carbonyl group of *p*-benzoquinone is capable of adding to dienes on irradiation to yield the spiro-compounds **36** (equation 21)[23].

(36)   (21)
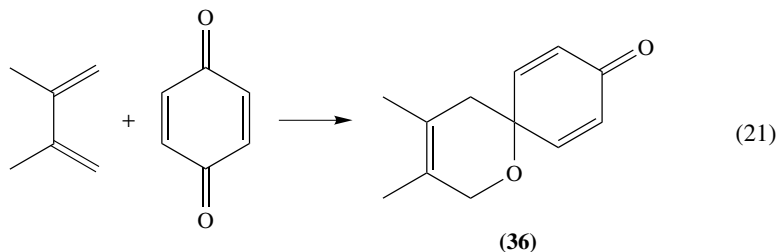
The ketene **37** reacts with 2-methoxybutadiene to afford a 63% yield of the rearranged methylenedihydropyran **38** (equation 22)[24]. In contrast, dimethylketene and 1-methoxy-butadiene form a 'normal cycloadduct', the cyclobutanone **39** (equation 23)[24].

(22)

(23)
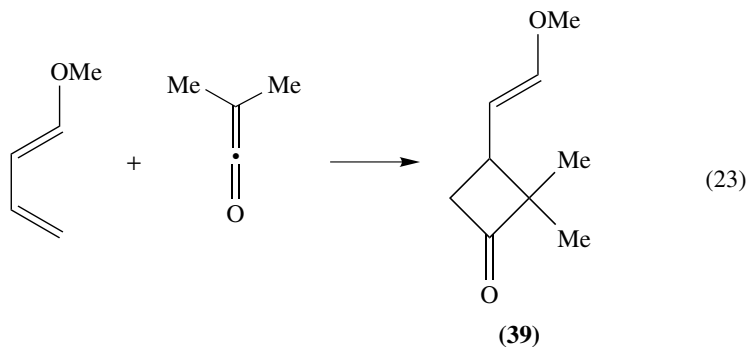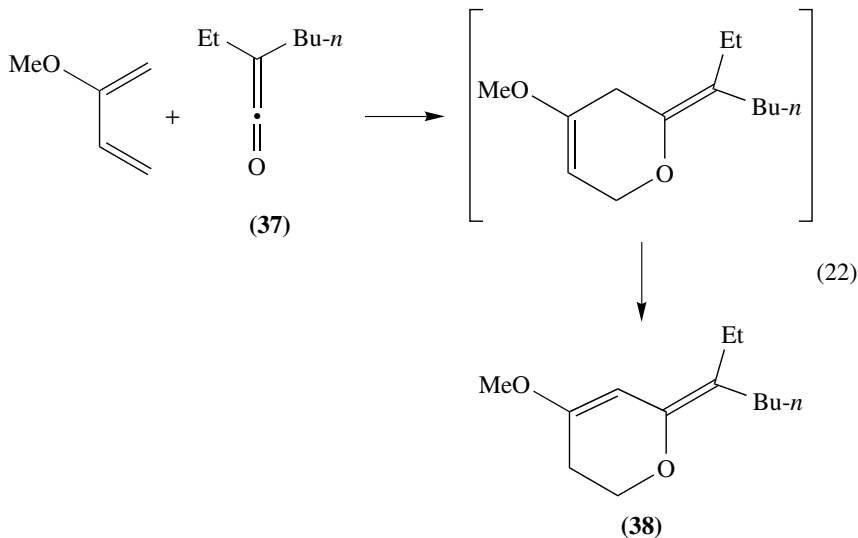
III. ADDITION TO C=S COMPOUNDS

Thiocarbonyl compounds are more reactive dienophiles than their carbonyl counter-parts.

Thioketones, such as thiofluorenone, hexafluorothioacetone and perfluorocyclobutanone, add to a variety of 1,3-dienes to give dihydrothiapyrans (e.g. equation 24)[25]. Styrene yields a 1 : 2 adduct with hexafluorothioacetone (equation 25)[25]. The reactions of thioace-tophenone and thiobenzophenone with isoprene and 2-chlorobutadiene yield mixtures of regioisomers in quantitative yields (e.g. equation 26)[26].

(24)

(25)

(26)
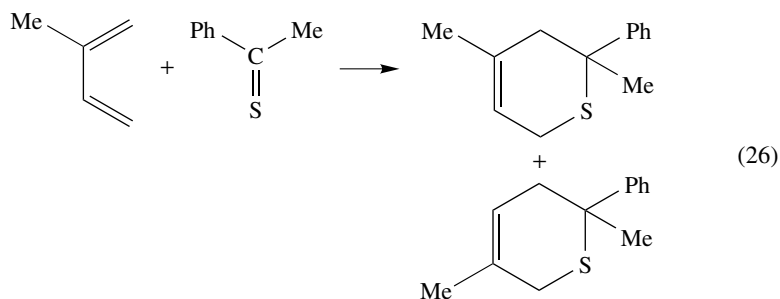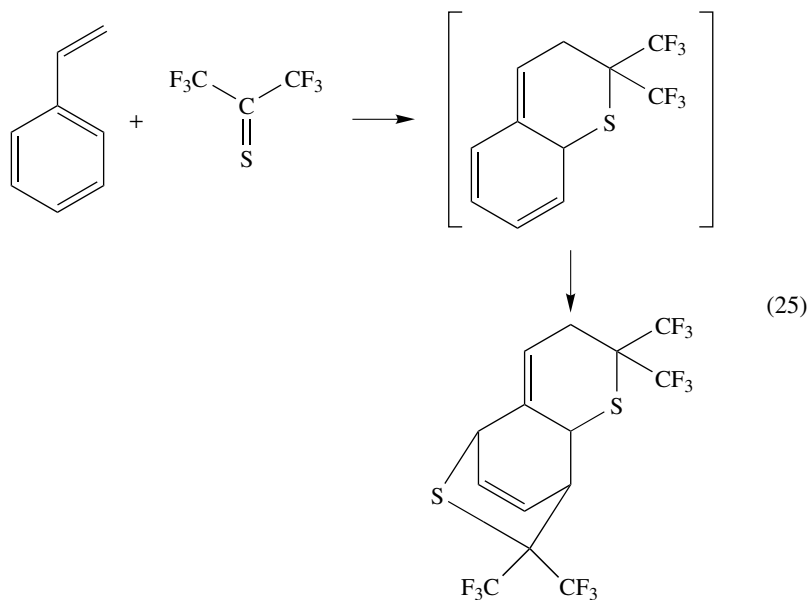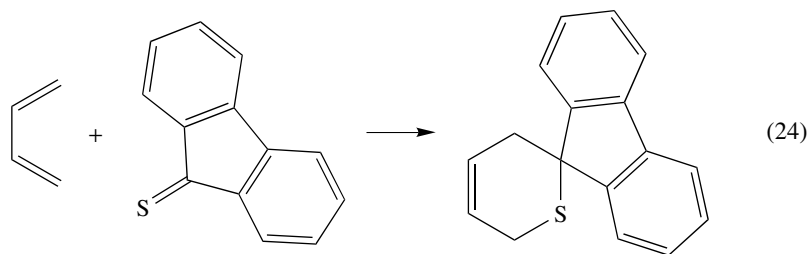
Thiophosgene forms the unstable cycloadduct **40** with cyclopentadiene, which was characterized by oxidation to the sulfone **41** with *m*-chloroperbenzoic acid (equation 27)[27].

Bis(trifluoromethyl)thioketene **(42)** is sufficiently stable to handle. It readily adds to 2,3-dimethyl-1,3-butadiene to yield **43** (equation 28)[28], 1,2,4,7-(tetrakis)methylenecyclooctane gives **44** (equation 29)[29] and cyclooctatetraene affords **46** via the valence isomer **45** (equation 30)[30].
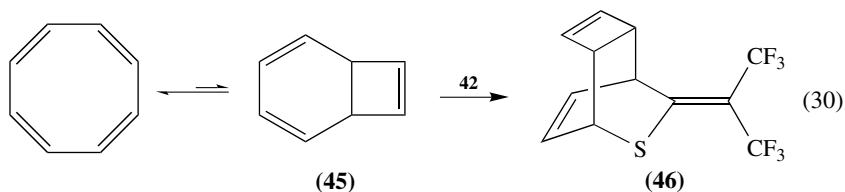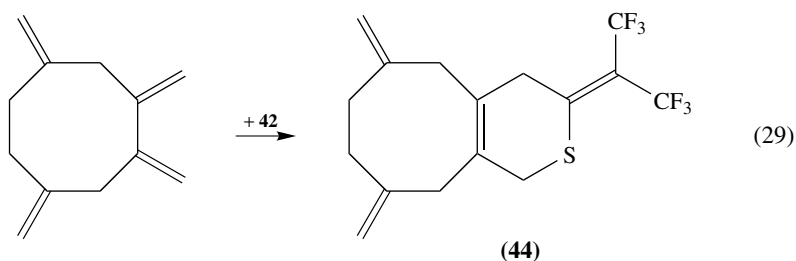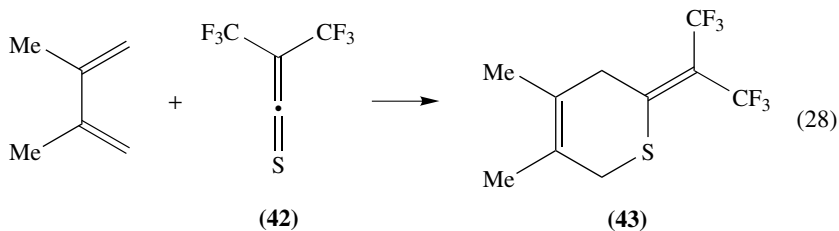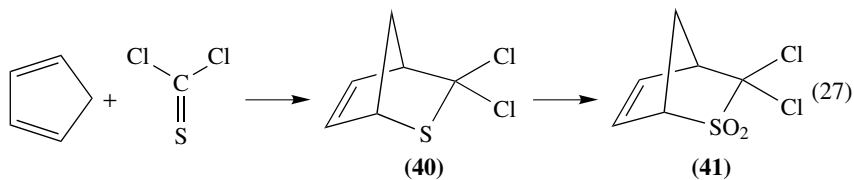
The dithio esters **48** (R = Me, Ph or OEt) are generated by treatment of the salts **47** with bases; they are trapped as Diels–Alder adducts in the presence of dienes (equation 31)[31]. Penta-1,3-diene gave mainly the regioisomers **49** in this reaction (equation 32)[31].

The cycloaddition of chlorosulfines to dienes may give mixtures of geometrically isomeric products (equation 33)[32]. A mixture of *exo-* and *endo*-cycloadducts is obtained from thiofluorenone *S*-oxide and cyclopentadiene (equation 34)[32].

Dichlorosulfine **(50)**, prepared by oxidation of thiophosgene with *m*-chloroperbenzoic acid, is a powerful dienophile. It reacts with cyclopentadiene in pentane at −40 °C to give the cycloadduct **51** (equation 35)[32].

(31)

(32)

(49)

R = Me, Ph, OEt

78%   70%   (33)

exo-

+   (34)

endo-

(50)   **(51)**   (35)
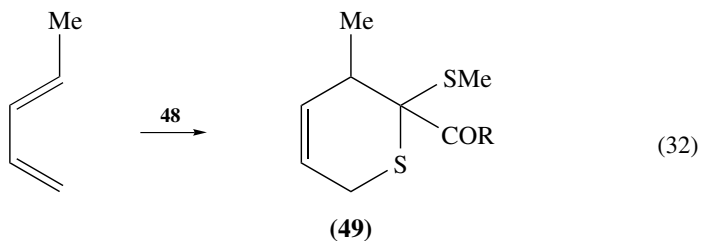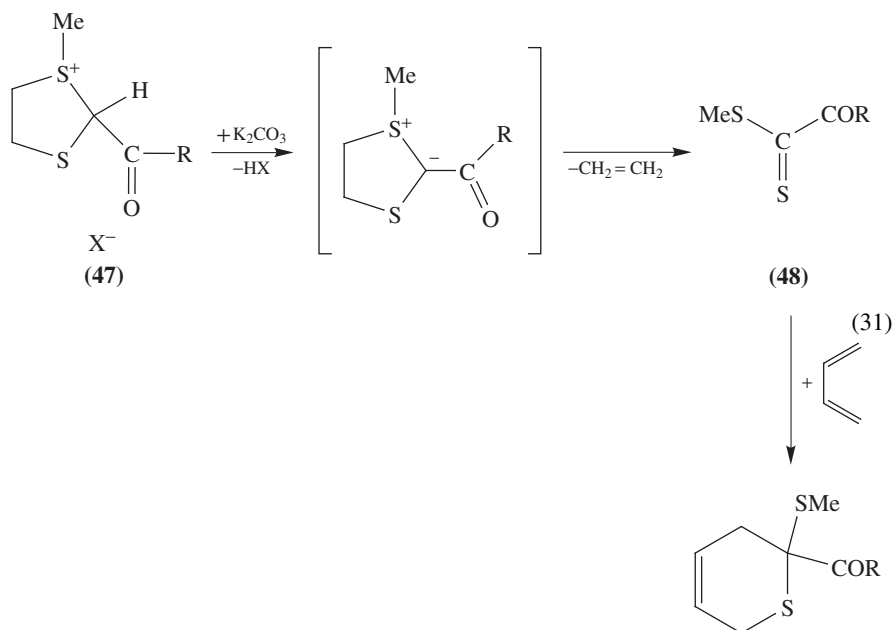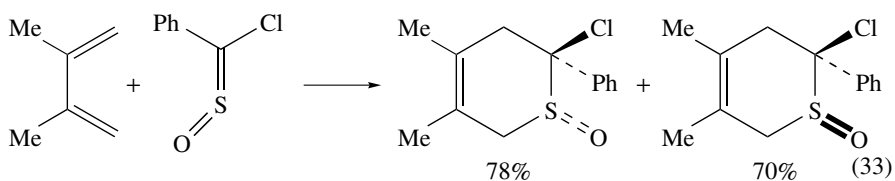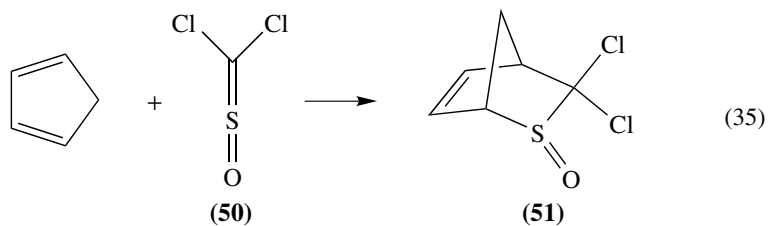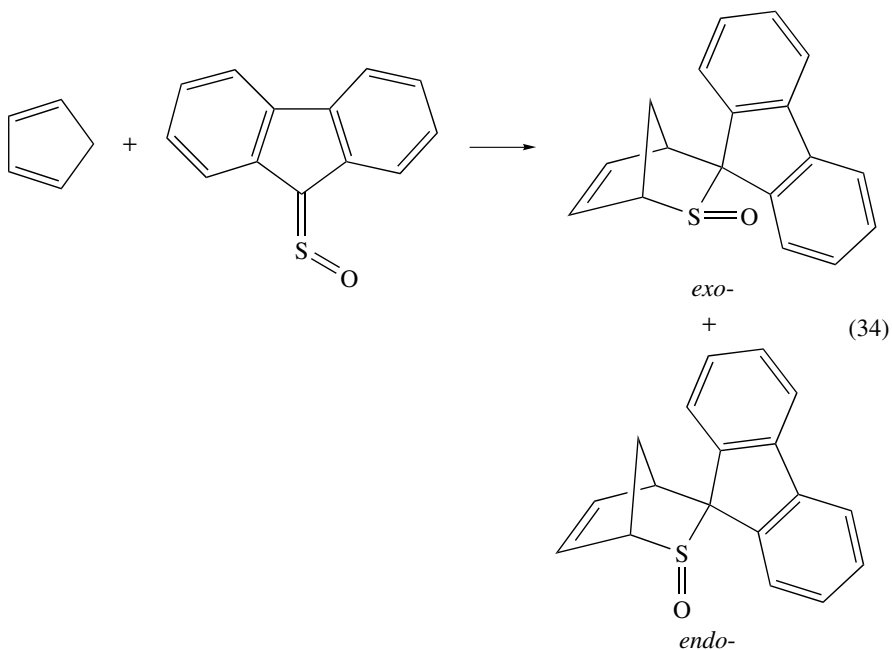
10-Chloro-10-sulfinylcamphor **(52)** reacts with 2,3-dimethyl-1,3-butadiene during one week at 70 °C to yield solely the diastereomer **53** (equation 36)[33]. Addition of the optically active sulfoximinosulfines **54a** and **54b** to the above diene during 16 h at room temperature gave in each case a single diastereomer **55a**, **55b** in 40 and 66% yields, respectively (equation 37); hence, complete asymmetric induction was observed[33].

(52)   **(53)**   (36)

(37)

(54a) R = Me **(55a)** R = Me

(54b) R = Ts **(55b)** R = Ts
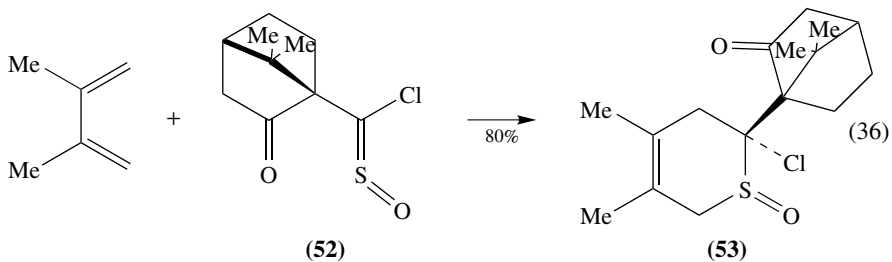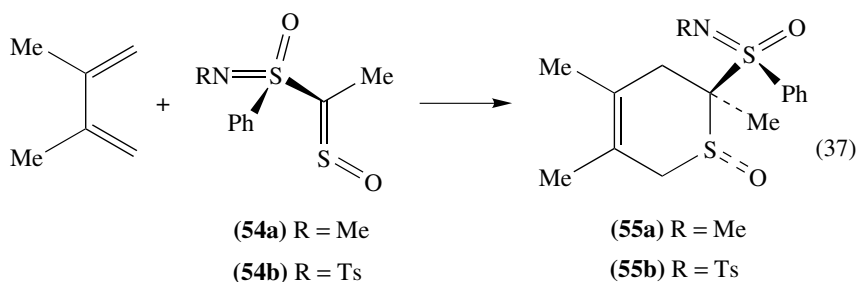
Reactions of the sulfonylsulfines **56** (e.g. $R^1 = R^2 = $ Bn; $R^1 = $ Me, $R^2 = $ Ph; $R^1 = $ CPh$_3$, $R^2 = $ Ph etc.) derived from (S)-proline with 2,3-dimethyl-1,3-butadiene afford dihydrothiopyran S-oxides **57** with asymmetric induction of up to 40% (equation 38)[34]. Methyl cyanodithioformate **58** is a very reactive dienophile; with cyclopentadiene it forms a mixture of 40 parts of the *endo*-adduct **59** and 60 parts of the *exo*-isomer **60** (equation 39)[35].

(56) **(57)** (38)

(58) **(59)** **(60)** (39)
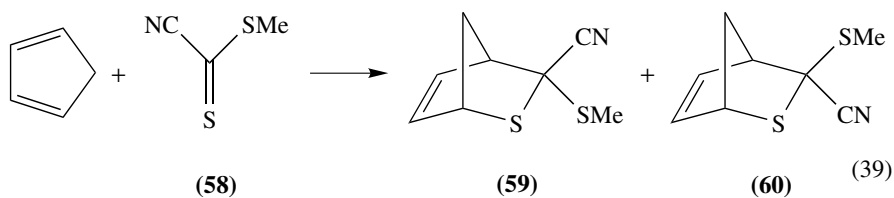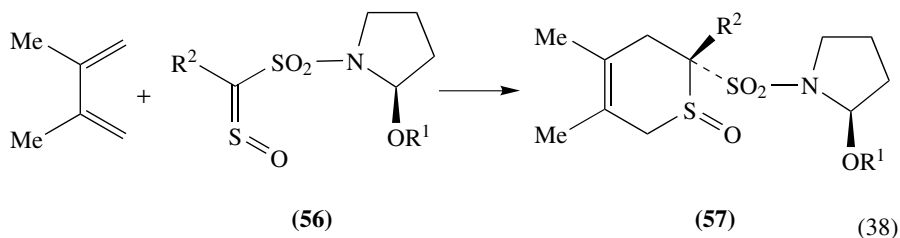
Cyanothioformamides NC−CS−NR^1−COR^2 ($R^1 = $ Ph or 4-O$_2$NC$_6$H$_4$; $R^2 = $ CF$_3$ or Ph) comprise another class of reactive dienophiles (e.g. equation 40)[36]. The trithiocarbonate **61** adds to cyclopentadiene to yield **62** (equation 41)[37]. Trithiocarbonate *S,S*-dioxides **63** ($Ar^1 = $ 4-MeC$_6$H$_4$ or 4-ClC$_6$H$_4$; $Ar^2 = $ Ph or 4-ClC$_6$H$_4$) react instantly with cyclopentadiene to afford mixtures of *endo*- and *exo*-cycloadducts **64** and **65**, respectively, in which the former predominate (equation 42)[38]. The adducts produced from acyclic dienes are unstable; they readily eliminate arylsulfinic acids to yield thiopyrans (equation 43)[38].

(40)

$$(41)$$

$$(42)$$

$$(43)$$
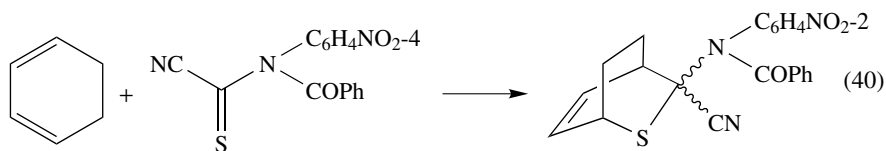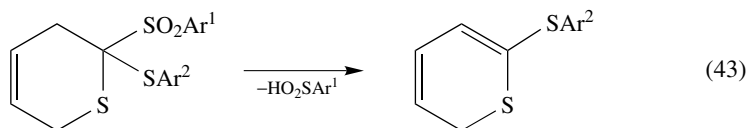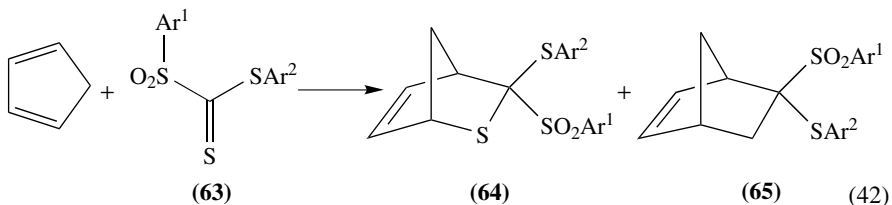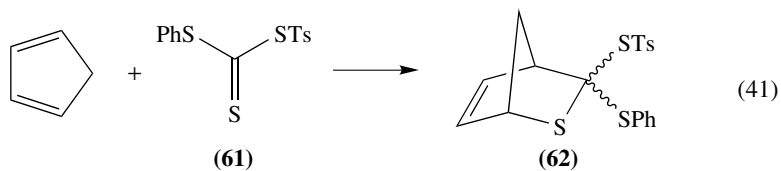
The thione S-imide **66** adds to isoprene to afford solely the regioisomer **67** (equation 44); in contrast, the imide functions as a 1,3-dipole **68** in the reaction with cyclopentadiene to yield **69** (equation 45)[39].

$$(44)$$

$$(45)$$
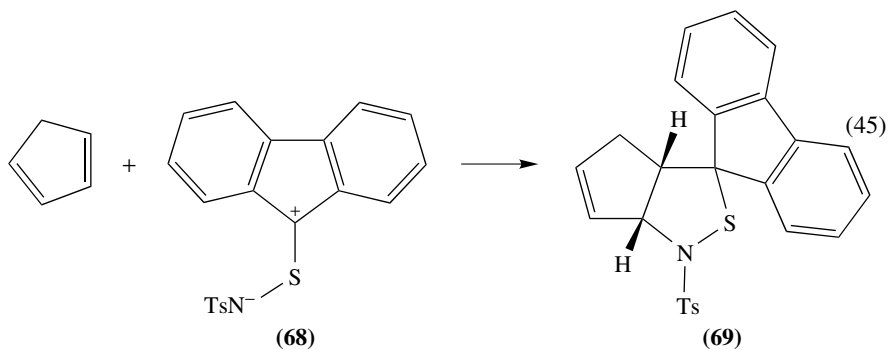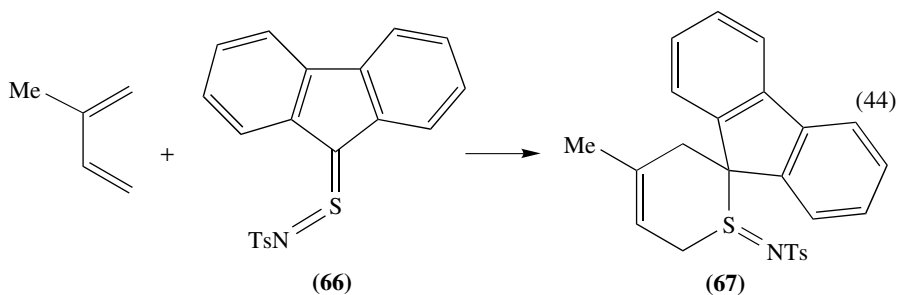
IV. ADDITION TO IMINES AND CYANIDES

The cycloaddition of dienes to imines to form tetrahydropyridines (equation 46) has been investigated extensively[40]. Ordinary imines are not sufficiently reactive to add to dienes; they have to be activated by the presence of electron-withdrawing substituents. Thus the triester **70** adds to cyclopentadiene under atmospheric pressure to form **71** (equation 47). The reactions with other dienes (cyclohexadiene, isoprene or 2,3-dimethylbuta-1,3-diene) require high pressures[41].

(46)

(47)

(70) **(71)**
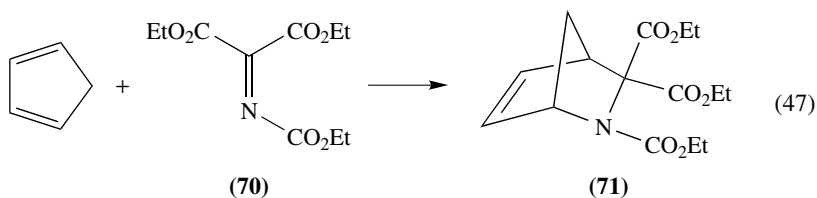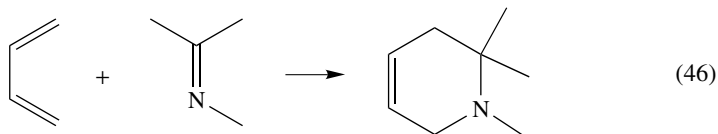
The sulfonylimine **72** reacts with cyclopentadiene in benzene at 0 °C to afford solely the *exo*-adduct **73** in 84% yield (equation 48)[42]. The unstable imine **75**, formed from the phosphorus compound **74** and ethyl glyoxylate by an aza-Wittig reaction, adds to dienes *in situ* (equation 49)[43].

(48)

(72) **(73)**
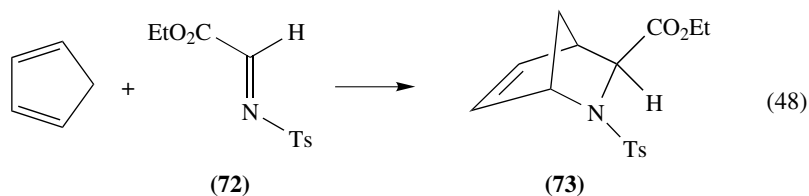
Simple imines undergo Diels–Alder reactions in the presence of suitable catalysts. Lanthanide triflates, which are stable in water, are especially effective. Thus in the presence of 10 mol% of ytterbium or scandium triflate, Danishefsky's diene **4** reacts with benzylideneaniline in acetonitrile at 0 °C to give the dihydropyridone **76** quantitatively (equation 50)[44]; analogous products are obtained from **4** and furylideneaniline, benzylidenebenzylamine and pentylidenebenzylamine[45]. In a one-pot version of the reaction, a mixture of an aldehyde, an amine and the diene **4** in acetonitrile containing magnesium sulfate is treated with 10 mol% ytterbium triflate to afford the dihydropyridone in *ca* 80% yield[45]. Even phenylglyoxal monohydrate can be employed[44].

In the reaction of benzylideneaniline with cyclopentadiene, the imine functions as an azadiene to yield the rearranged Diels–Alder adduct **77** (equation 51)[44,45a]. In a study of the effect of various Lewis acids (ZnCl$_2$, TiCl$_4$, Et$_2$AlCl and SnCl$_4$) on diastereoselective cycloadditions of Danishefsky's diene to the imines **79**, obtained from the chiral aldehydes **78** (R = MeO or Cl), it was found that SnCl$_4$ was the most effective, giving the optically active products in high yields and excellent ee values (equation 52)[46].

(49)

(50)

(51)

(52)
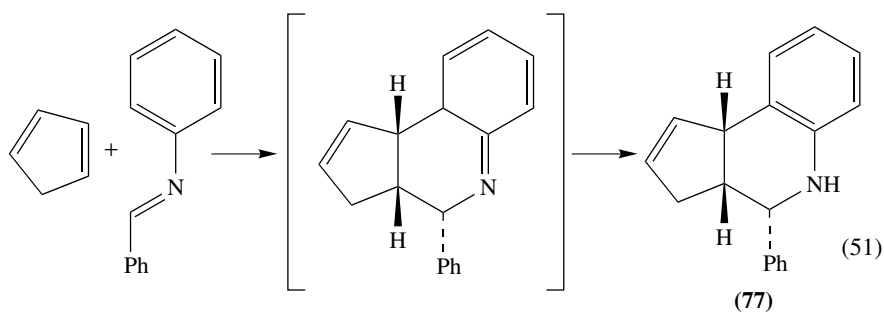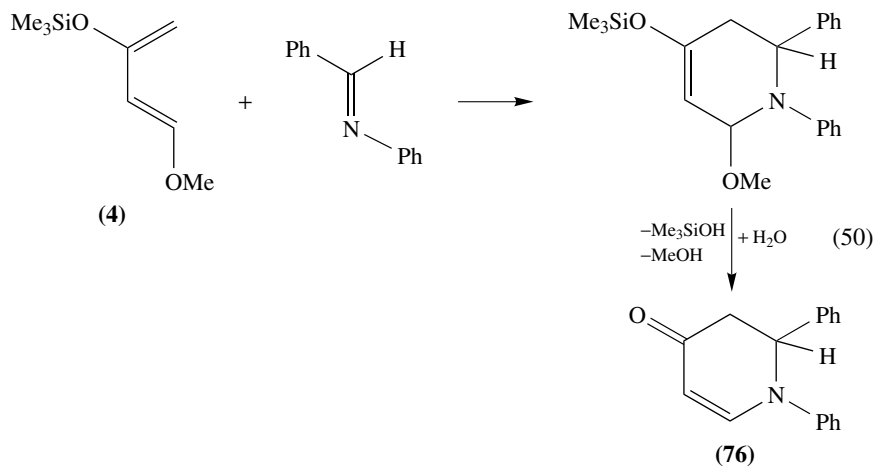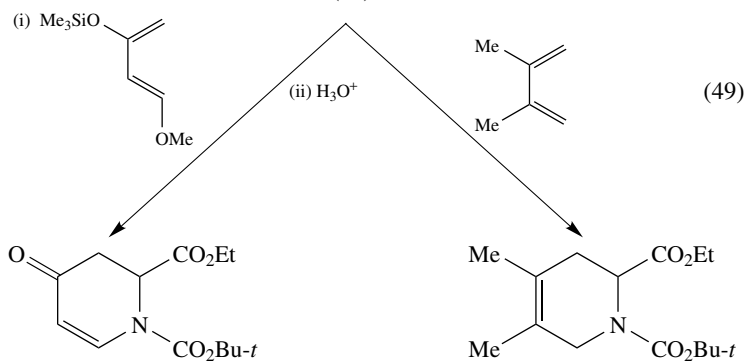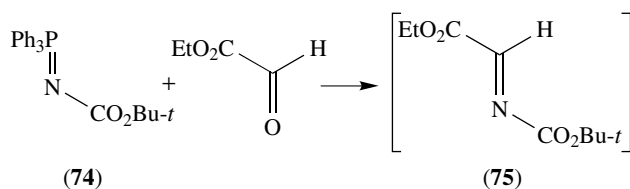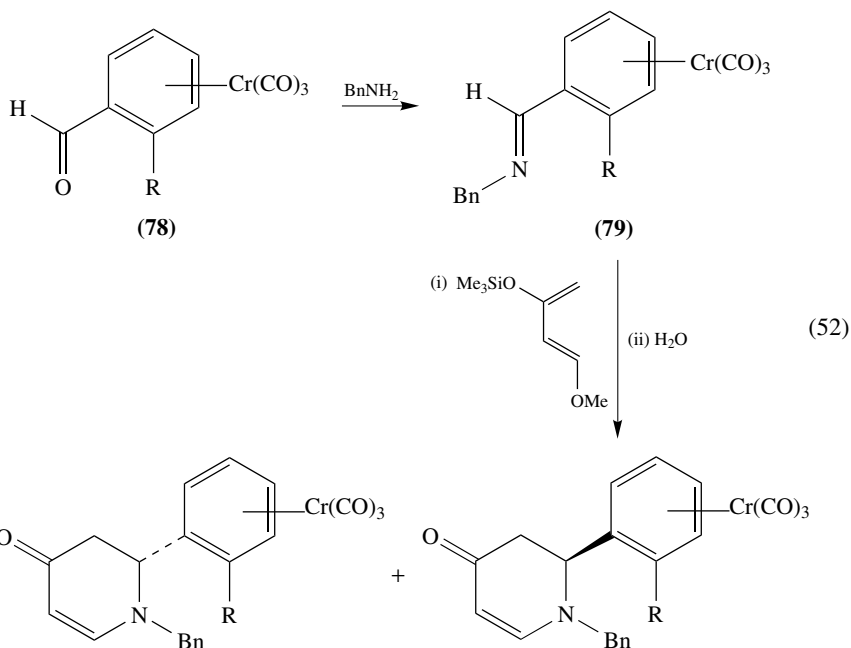
A moderate degree of diastereoselectivity was observed for the reaction of the *N*-[(1*R*)-(−)-camphor-10-ylsulfonyl]imine **80** [R = (1*R*)-(−)-camphor-10-yl] with Danishefsky's diene to yield, after treatment with concentrated hydrochloric acid, a 1 : 1.86 mixture of the dihydropyridones **81** and **82** (equation 53). In the presence of Ti(OPr-*i*)$_4$, the ratio was 1 : 2.33; with Et$_2$AlCl it was reversed to 1.44 : 1[47].

(53)
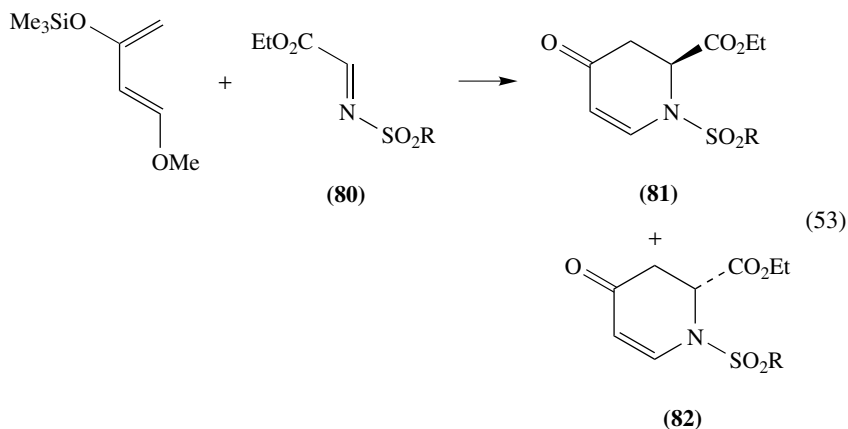
The imine **83** derived from (*R*)-phenylethylamine adds to cyclopentadiene in the presence of trifluoroacetic acid and a catalytic amount of water to afford a 97 : 3 mixture

of *exo-* and *endo-*isomers **84** and **85**, respectively, each of which was produced in high diastereomeric excess (equation 54). The reaction of **83** with cyclohexa-1,3-diene proceeded analogously, giving a 92 : 8 mixture of *exo-* and *endo-*cycloadducts[48].

(83)   **(84)**

(54)

+

(85)
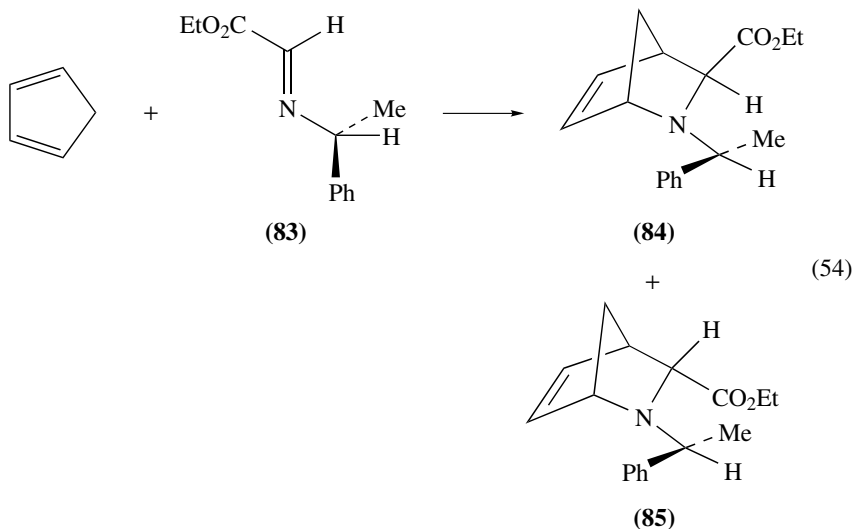
The action of the valine derivatives **87** on the diene **86** under EtAlCl$_2$ catalysis resulted in a mixture of cycloadducts **88**, which on hydrolysis with aqueous methanolic sodium carbonate furnished a mixture of the dihydro-2-pyridones **89** and **90** and the esters **91** and **92**. In the case of imines derived from aliphatic aldehydes, e.g. **87** (R = Pr), all four types of product were isolated, whereas imines from aromatic aldehydes, **87** (R = Ph, 3-ClC$_6$H$_4$ etc.), gave only the esters **91** and **92** (equation 55). All products were formed in yields of 64–84% and in high de[49].

The optically active catalyst **93**, formed from triphenyl borate and (*R*)-binaphthol, catalyzes the asymmetric reaction of the dienes **94** (R^1 = H or Me) with the imines **95** (R^2 = Ph, 3-pyridyl or cyclohexyl). The products **96** are formed in greater than 80% ee (equation 56). Treatment of the diene **94** (R^1 = H) (Danishefsky's diene) with the chiral imine **97** leads to the diastereomers **98** and **99** in the ratio 99 : 1 (equation 57)[50].

Under the influence of zinc chloride, Danishefsky's diene **4** reacts with simple imines to give dihydro-γ-pyridones **100** (e.g. R^1 = *n*-Bu, Ph, Bn; R^2 = Pr, *i*-Pr, Ph) in 62–76% yields (equation 58)[51]. In contrast, the Et$_2$AlCl-catalyzed reaction of the diene **86** with benzylidenemethylamine **(101)** results in the formation of the dihydro-α-pyridone **102** (equation 59)[52].

The first step in the total synthesis of the alkaloid (±)-ipalbidine **104** was the reaction of the diene **103** with Δ^1-pyrroline (equation 60)[53]. The proportions of *threo-* and *erythro-*dihydro-α-pyridones, **106** and **107**, respectively, produced in the diethylaluminium chloride-catalyzed reactions of the α-benzyloxyimines **105** (R = *n*-C$_5$H$_{11}$, *i*-Pr or *t*-Bu) with the diene **86** (equation 61), depend on the nature of R and the amount of imine used[54].

MeO

OMe +

OSiMe₃

(86)

R

N   CO₂Bu-*t*

Me   Me

(87)

⟶

MeO   R

N   CO₂Bu-*t*

Me₃SiO   OMe

Me   Me

(88)

↓

MeO   R

N   CO₂Bu-*t*

O

Me   Me

(89)

+

MeO   R

N   CO₂Bu-*t*

O

Me   Me

(90)

(55)

+

MeO   R

HN   CO₂Bu-*t*
CO₂Me

Me   Me

(91)

+

MeO   R

HN   CO₂Bu-*t*
CO₂Me

Me   Me

(92)

O·B—OPh
O

(93)

Me₃SiO

R¹

OMe

(94)

+

R²   H

N
Bn

(95)

(i) **93**
⟶
(ii) H₂O

O   R²

H

R¹   N   Bn

(96)

(56)

(94) R^1 = H   **(97)**   **(98)**

                                                                    +   (57)

                                                                   (99)

(4)   **(100)**   (58)

(86)   **(101)**   **Me$_3$SiO   OMe**   **(102)**   (59)
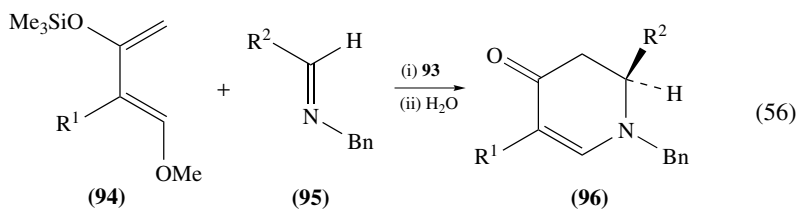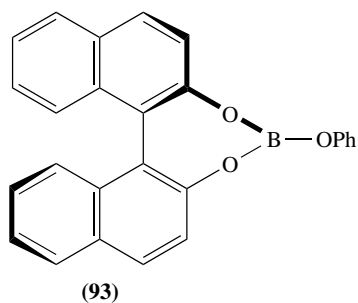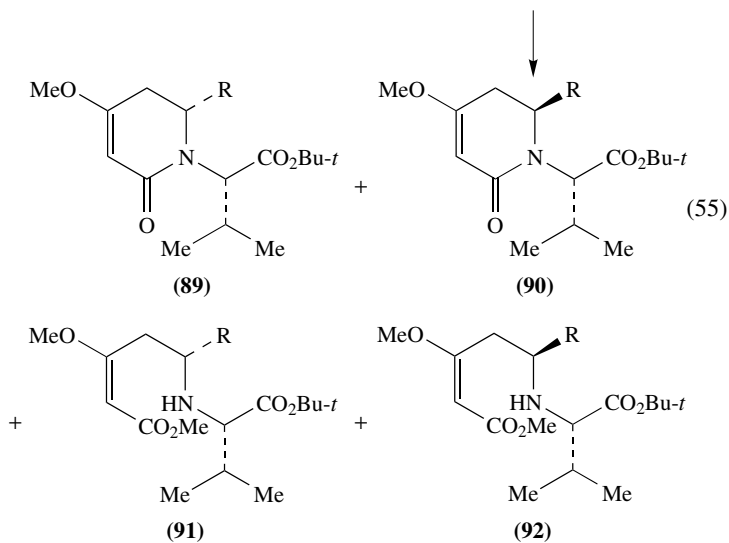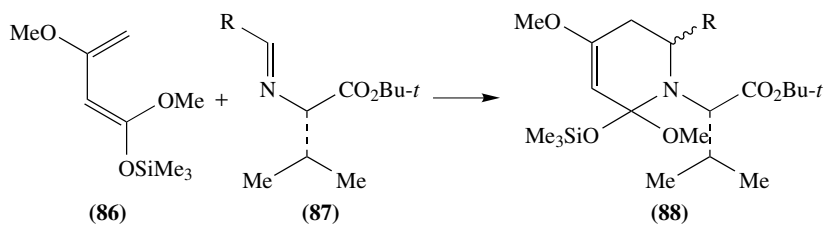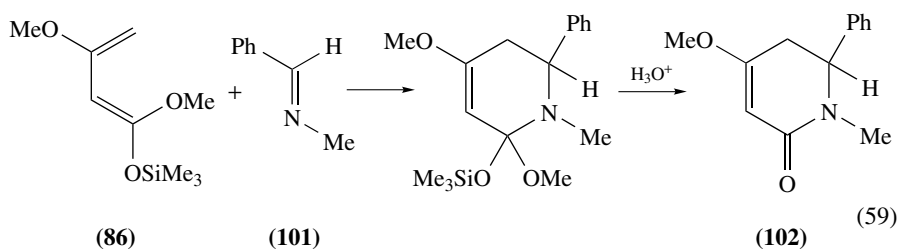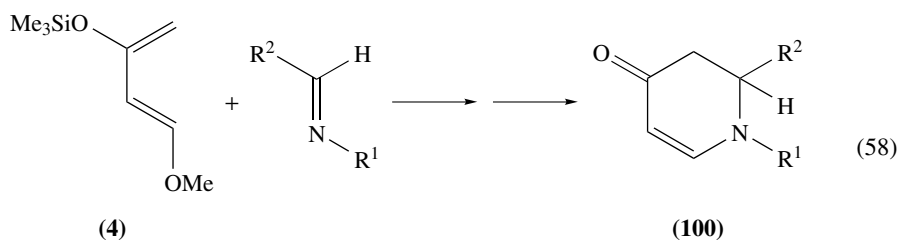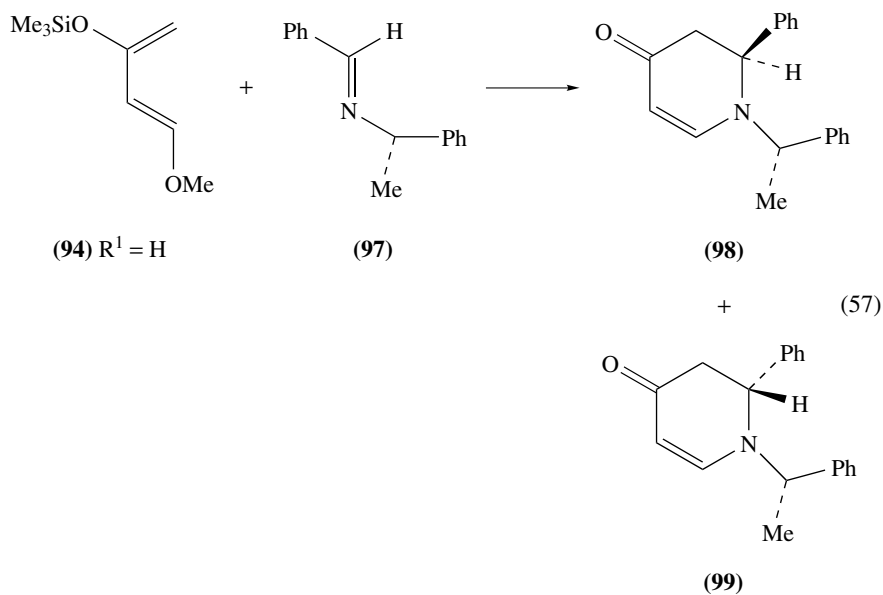
Diastereoselectivities of up to 90% were observed for the cycloadditions of *N*-galactosy-limines **108** (Piv = pivalyl; R = 2-furyl, 2-thienyl-, 4-FC$_6$H$_4$, 4-ClC$_6$H$_4$ or 3-pyridyl) to isoprene in the presence of zinc chloride to form the tetrahydropyridines **109** and **110** (equation 62)[55].

The enantioselective (76–90% ee) formation of the dihydro-γ-pyridones **113** from various imines **112** (R = Ph, 3,5-xylyl or 3-pyridyl) and Danishefsky's diene **4** in the presence of 4 Å molecular sieves and one equivalent of a catalyst prepared from triphenyl

borate or a trialkyl borate and (*R*)-Binaphthol **111** in dichloromethane has been reported (equation 63)[56]. Similarly, the chiral zirconium complex **114** (L = 1-methylimidazole) catalyzes the reaction of the diene **4** with the Schiff's base **115** in toluene at −45 °C to yield, after hydrolysis, 88% of the optically active dihydropyridone **116** in 90% ee (equation 64)[57].
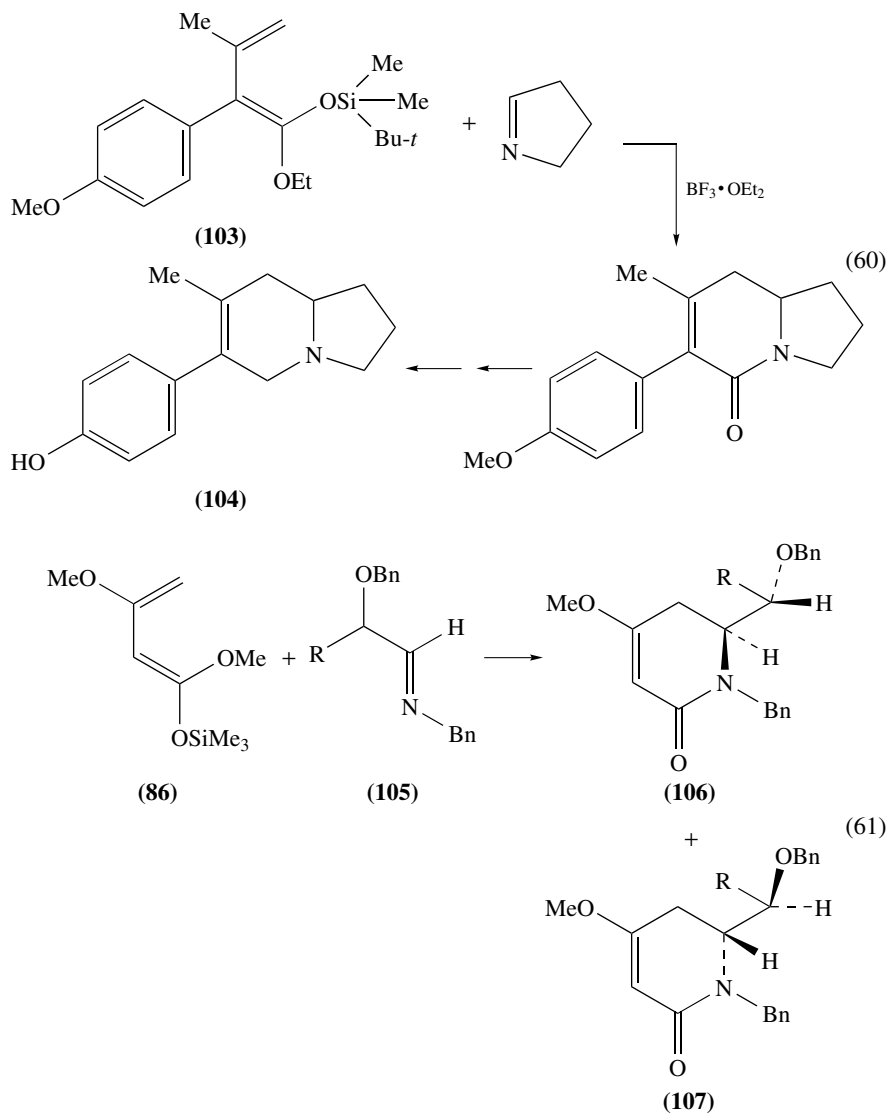
In a study of the Lewis-acid catalyzed formation of optically active dihydro-γ-pyridones **118** from the imines **117** (R = Ts, Ph, Bn or CO₂Et) and the diene **4** in the presence of chiral Lewis acids, it was found that only the tosyl compound reacted diastereoselectively,

giving the product in 68% yield and 80% de (equation 65)[58]. In the presence of 0.1
equivalent of diethylaluminum chloride, cyclopentadiene adds the chiral imine **119** to
give a mixture of the diastereomers **120** and **121** in the ratio 12 : 88 (equation 66)[59].

(108)

(62)

(110)   +   **(109)**

(111)

(4)   **(112)**   **(113)**   (63)

(114)

(64)

(115)   (116)

(65)

(117)   (118)

(119)   (120)   (66)

(121)
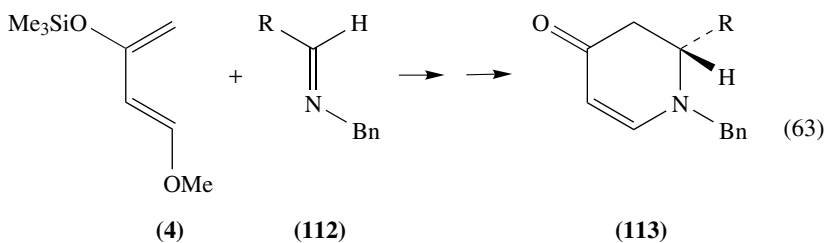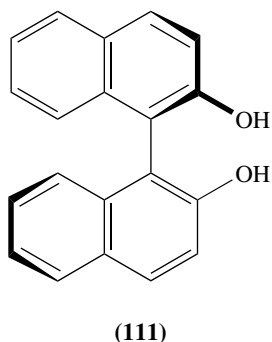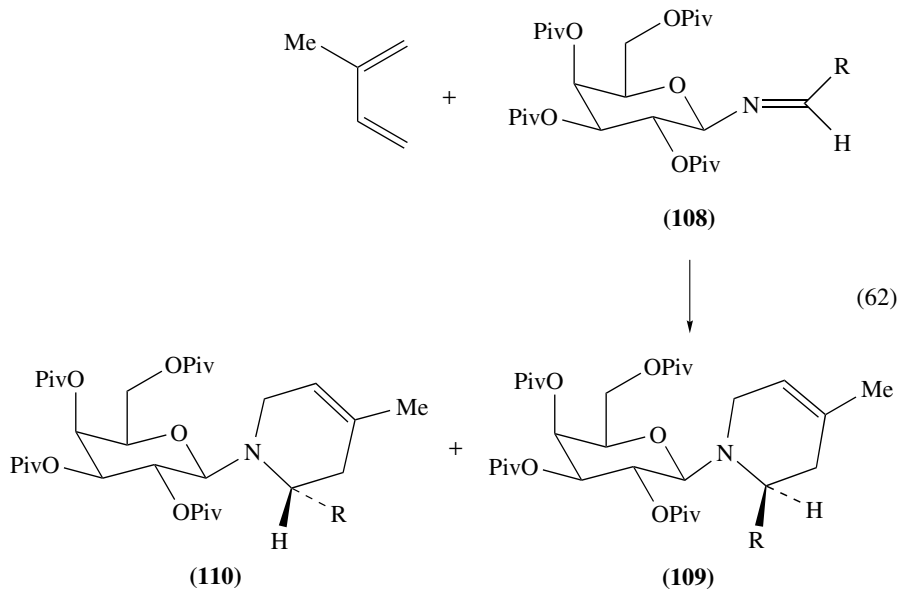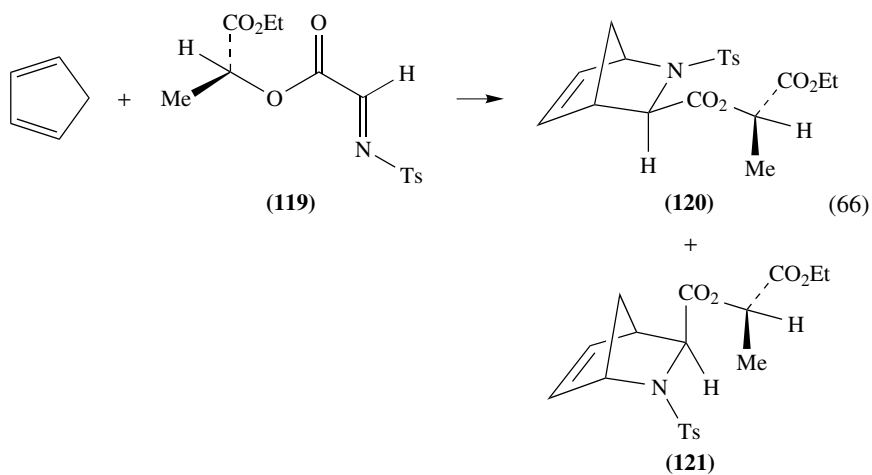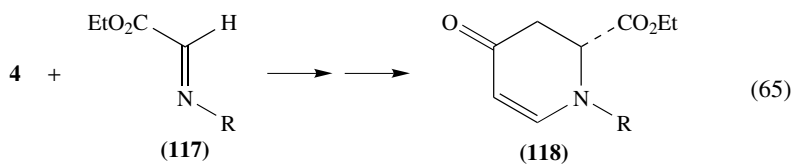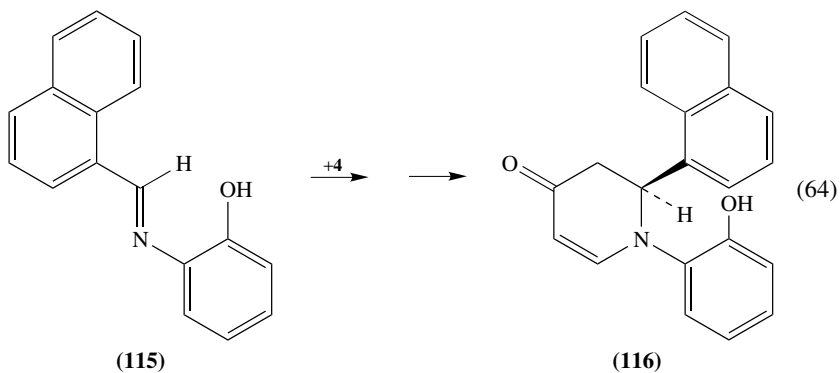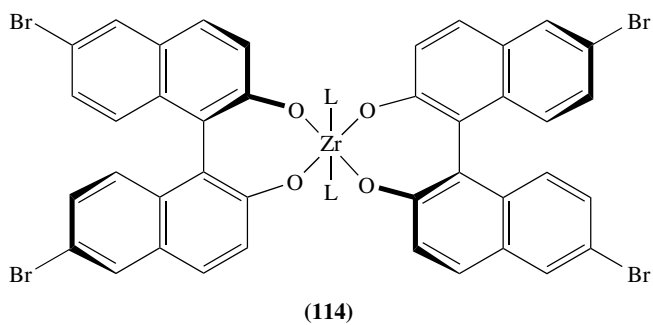
Imines **123**, generated from α-arylethylamines **122** (Ar = Ph, 4-BrC$_6$H$_4$ or 4-O$_2$NC$_6$H$_4$) and aqueous formaldehyde, react with cyclopentadiene *in situ* at room temperature to afford mixtures of the bridged dihydropyridines **124** and **125** (equation 67), whose relative configurations were deduced by ^{1}H NMR experiments and their absolute configurations assigned by reference to the X-ray structure of the aziridinium derivative **126** (equation 68)[60].
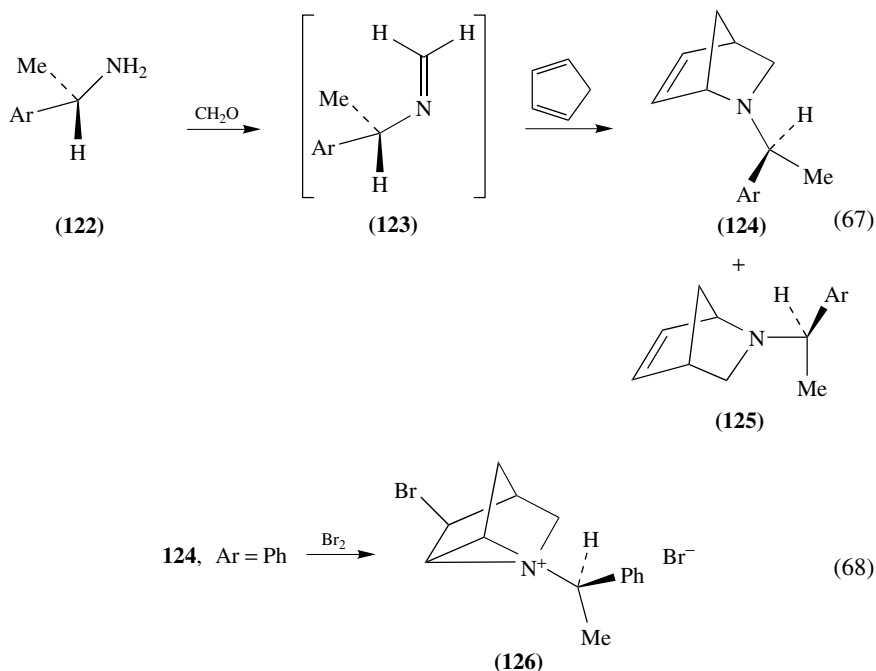
Protonated imines are effective dienophiles. Thus in the reaction of methyl glyoxylate with the hydrochloride **127** of alanine methyl ester in the presence of cyclopentadiene, a mixture of hydrochlorides of the *exo-* and *endo*-adducts **128–131** was formed (equation 69). The diastereomeric ratio of the *exo*-compounds was 83 : 17[61].

The iminium salt **132**, generated from benzylamine hydrochloride and aqueous formaldehyde, reacts with cyclopentadiene during 3 h at room temperature to give, after basification, the cycloadduct **133** in nearly quantitative yield (equation 70). Other examples of this reaction are shown in equations 71–75. The separable diastereomers **134** and **135** are formed in the ratio 4 : 1 from cyclopentadiene, (−)-α-methylbenzylamine hydrochloride and aqueous formaldehyde in a combined yield of 86% (equation 75)[62]. Hydrochlorides **136** of methyl esters of natural amino acids [(S)-valine, (S)-isoleucine] react with cyclopentadiene and formaldehyde in aqueous THF to produce mixtures of the diastereomers **137** and **138**, in which the former predominate (equation 76)[63].

1-Azirines are reactive dienophiles[64]. The cycloadducts to cyclopentadienones spontaneously extrude carbon monoxide and undergo opening of the three-membered ring, followed by a 1,5-shift of hydrogen, to yield 3*H*-azepines (equation 77)[65,66].

Treatment of the azetidinone **139** with zinc chloride generates the highly unstable azetinone **140**, which is trapped as the carbacephem **142** in the presence of the diene

141[67]. The carbacephem was converted into the carbapenam-2-one system (±)-**143** by a multistep sequence (equation 78)[68].

(127)   (128)

(69)

(131)   (130)   (129)

(132)   (133)   (70)

(71)

(72)

(73)

$$\text{(74)}$$

$$\text{(75)}$$

$$\text{(76)}$$
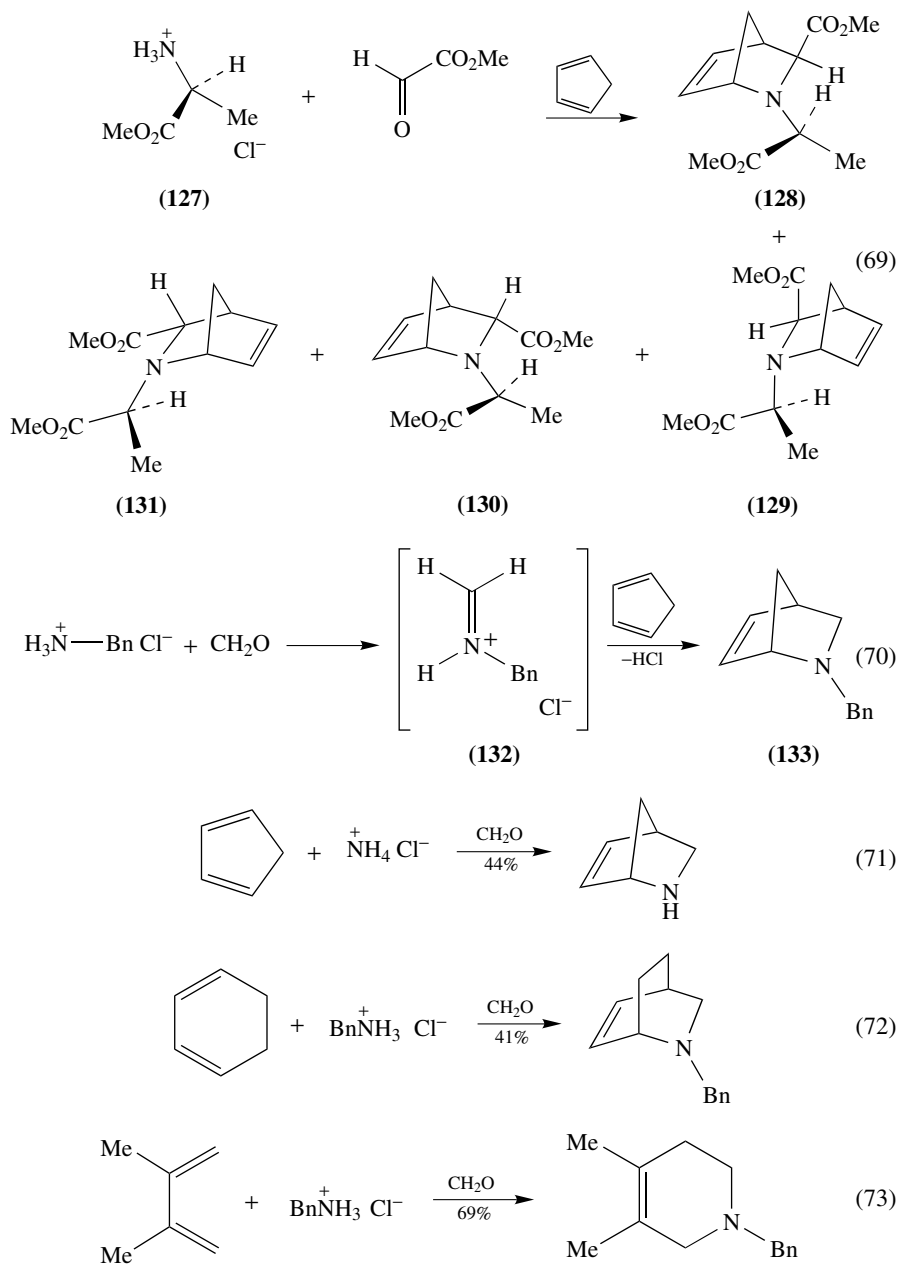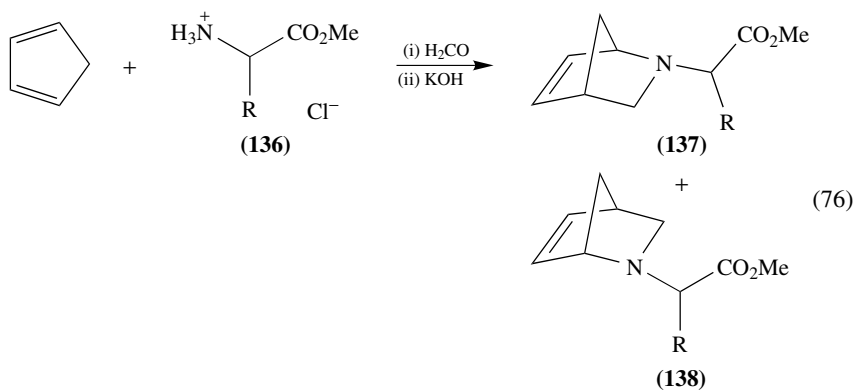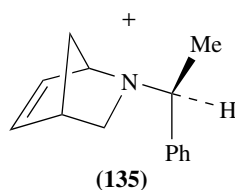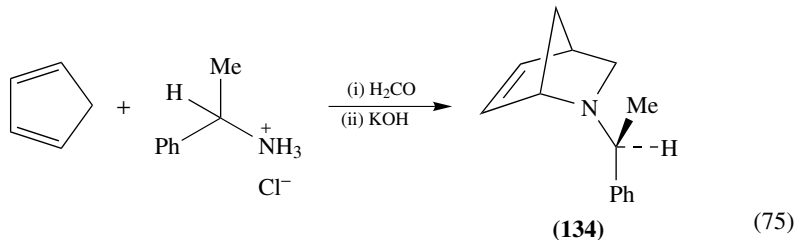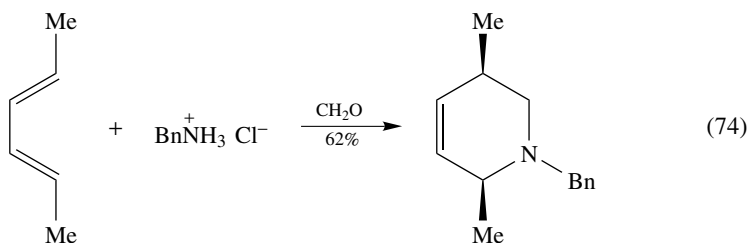
Heating the bis-diazoketone **144** generates the pyrazol-4-one **145**, which was trapped as the bicyclic adduct **146** in the presence of 2,3-dimethylbuta-1,3-diene (equation 79)[69].

Cycloadditions to a cyano group are comparatively rare. The high-temperature reactions of 1,3-dienes, e.g. butadiene, isoprene and 2-chloro-1,3-butadiene, with dicyanogen, propionitrile or benzonitrile result in formation of pyridines (equation 80)[70]. Sulfonyl cyanides **147**, obtained by the action of cyanogen chloride on sodium salts of sulfinic acids, add to dienes to give dihydropyridines **148**, which are transformed into pyridines **149** by oxidation (equation 81)[71].

(77)

−CO

(139)   (140)

t-BuMe₂SiO

(141)

(78)

(143)   (142)

(79)

(80)

(81)

(82)
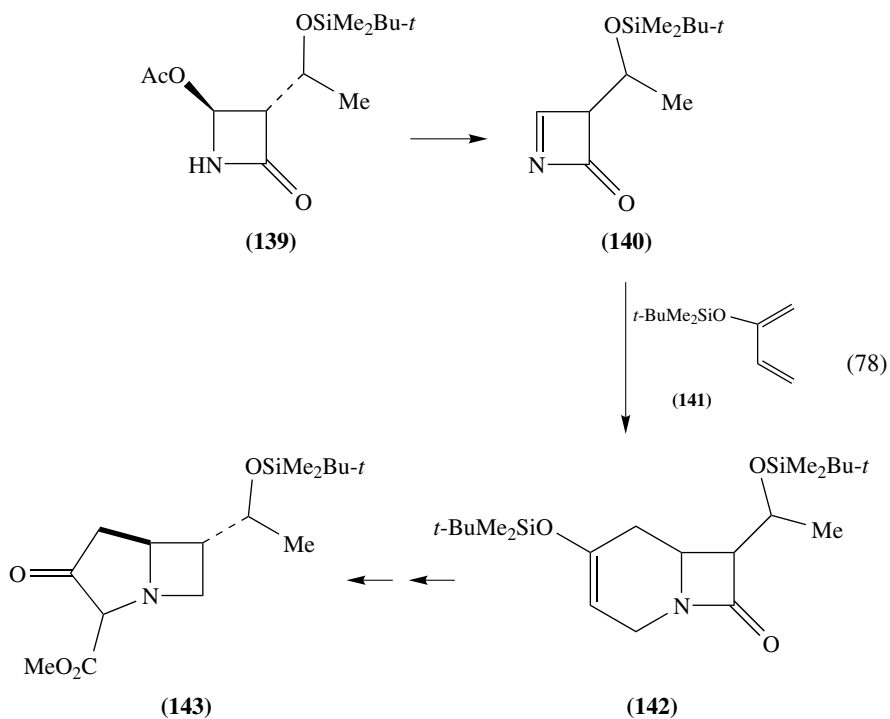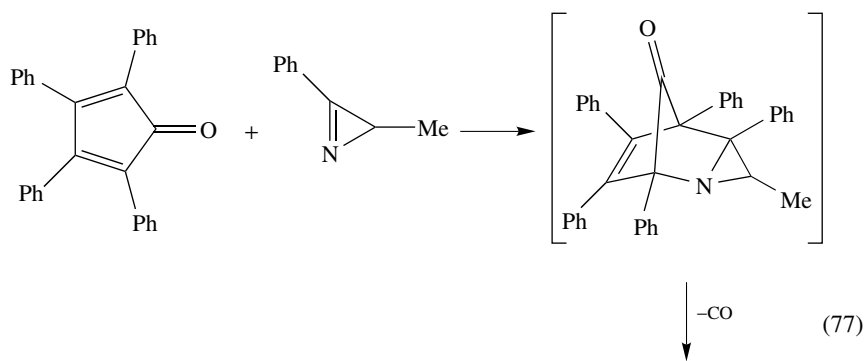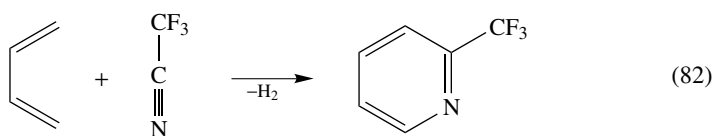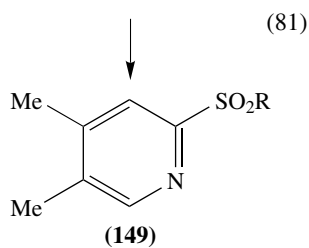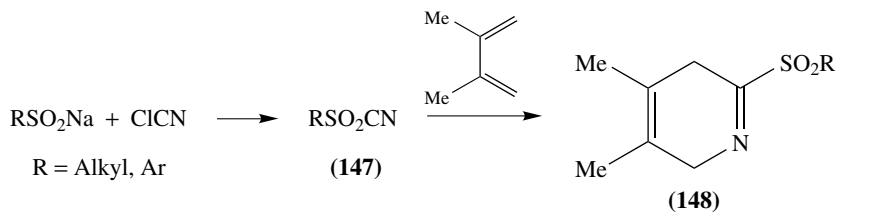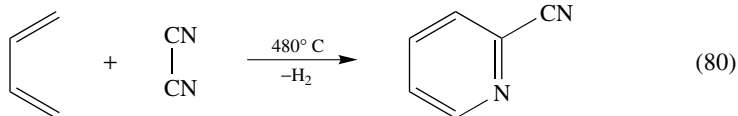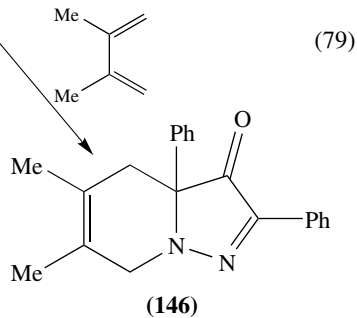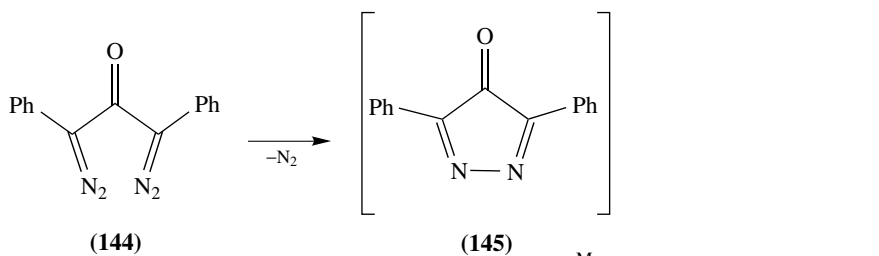
Fluorinated alkyl cyanides, such as trifluoroacetonitrile, pentafluoropropionitrile, per-fluorobutyronitrile and chlorodifluoroacetonitrile, react with butadiene in the gas phase at 350–400 °C to afford pyridines in high yields (equation 82)[72]. The 'push–pull' diene **150** and electron-rich cyanides (acetonitrile or acrylonitrile) furnish pyridines (equation 83)[73].

(83)
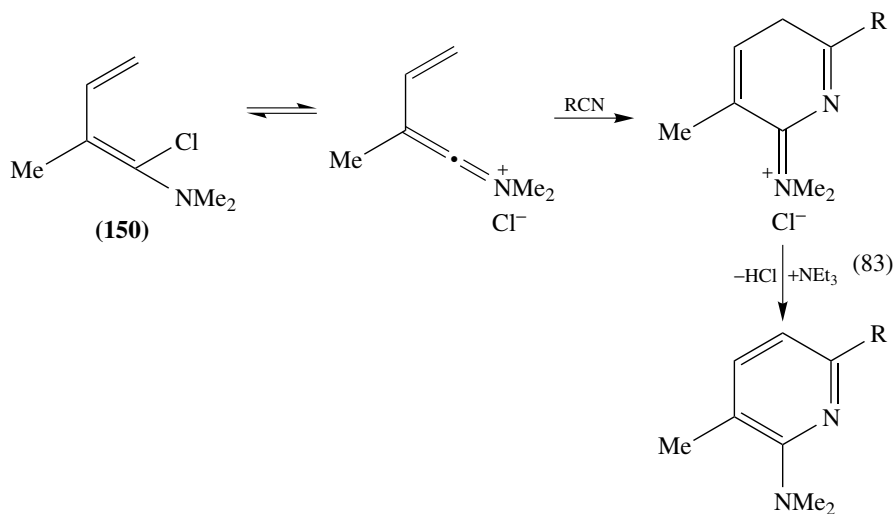
V. ADDITION TO C=P AND C=As COMPOUNDS

Heating the phosphole **151** with 2,3-dimethyl-1,3-butadiene at 170 °C gave the bicyclic phosphorus heterocycle **153**, presumably by way of the rearranged 2*H*-phosphole **152** (equation 84)[74]. The arsole **154** behaved analogously (equation 85)[75].

(84)

(85)
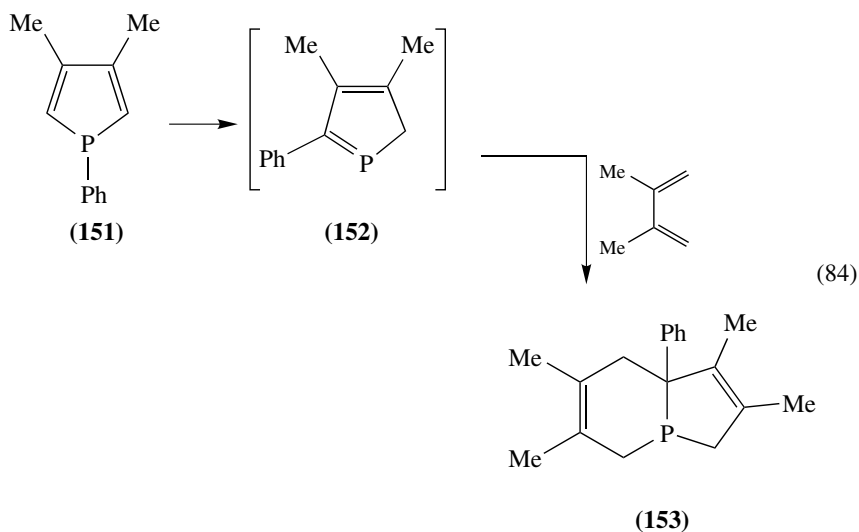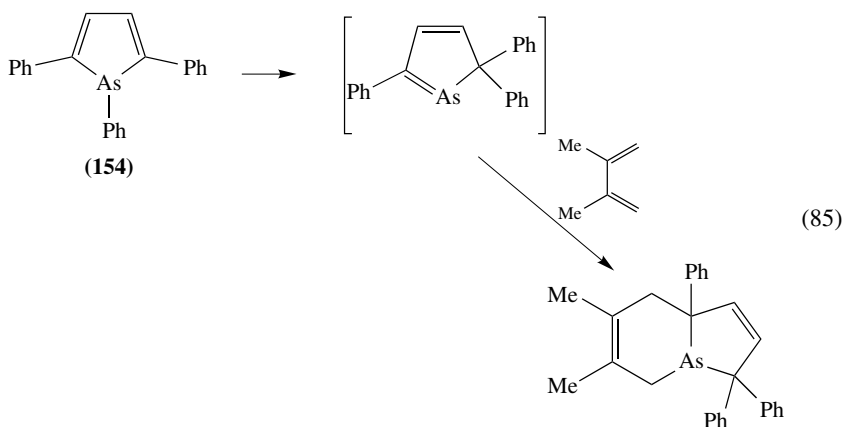
VI. ADDITION TO OXYGEN

The most powerful dienophile is singlet oxygen, produced by the dye-sensitized irradiation of oxygen. Its cycloaddition to dienes to give 'endo-peroxides' (equation 86) has long been known[76].

(86)
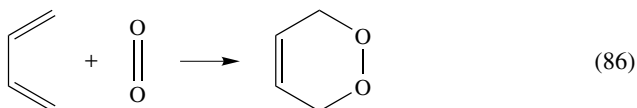
Photooxygenation of α-terpinene 155 in the presence of eosin (equation 87) produces ascaridole 156, a constituent of the essential oil *Chenopodium ambrosioides L.*[77]. The *endo*-peroxide 157 derived from cyclopentadiene is a crystalline solid, stable at $-100\,^\circ C$[78]; above this temperature it rearranges to a mixture of the bis-epoxide 158 and the epoxy-aldehyde 159 (equation 88)[79,80].

(87)
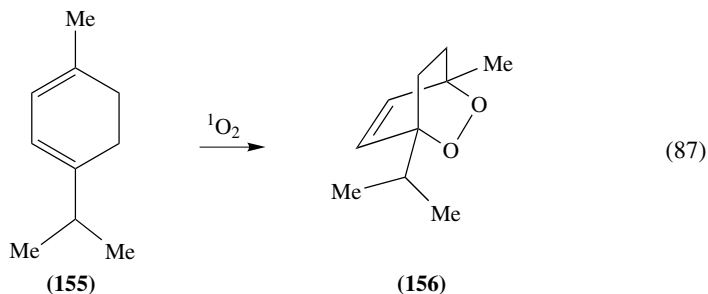
The tetraphenylcyclopentadiene 160 affords the peroxide 161, which rearranges on heating to the bis-epoxide 162 (equation 89)[81]. In the case of the photooxygenation of the fulvene 163, only the rearrangement product 164 could be isolated (equation 90)[81].

(88)

(157) **(158)** **(159)**

(89)

(160) **(161)** **(162)**

(90)

(163) **(164)**
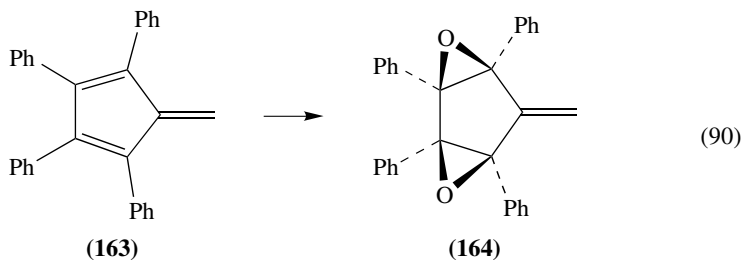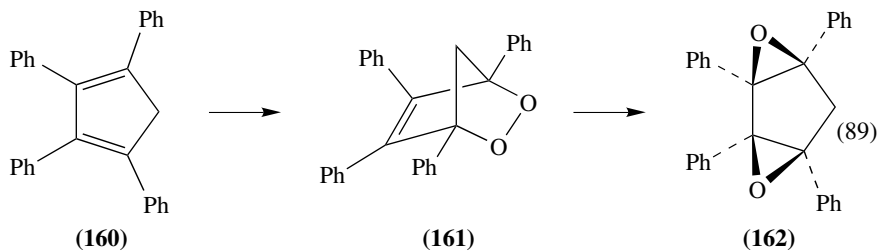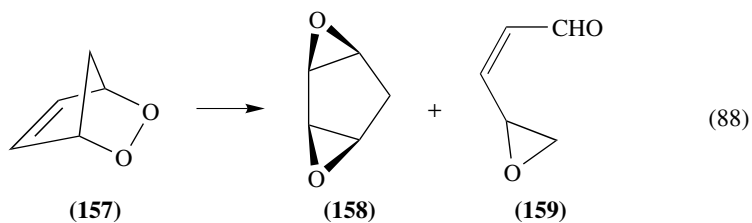
1,2,3,4,5-Pentaphenyl-1,3-cyclohexadiene gives a mixture of the cycloadduct **165**, pen-taphenylbenzene and the bicyclic compound **166** (equation 91)[82]. Photooxygenation of

(91)

(165)

+

(166)
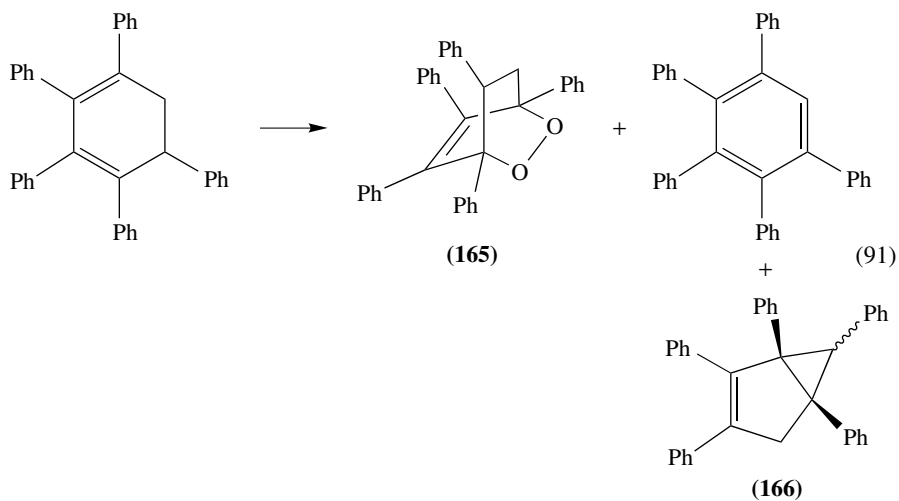
the chiral amide **167** derived from sorbic acid results in the quantitative formation of the diastereomeric cycloadducts **168** and **169** in a ratio of greater than 95 : 5 (equation 92)[83].

(167)

(168)

+ (92)

(169)
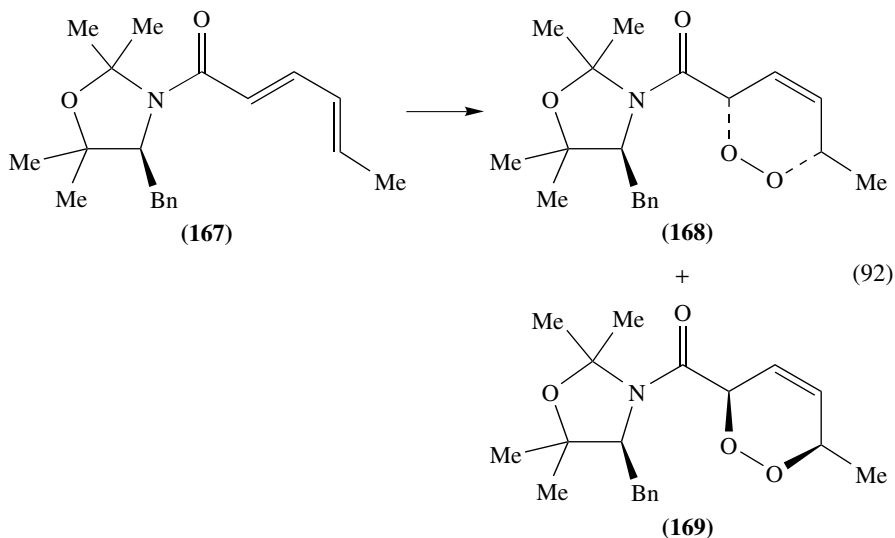
VII. ADDITION TO A S=O COMPOUND

The dioxane−sulfur trioxide complex reacts with 2,3-dimethylbutadiene to give the sultone **170** in low yield (equation 93)[84].

(170) (93)
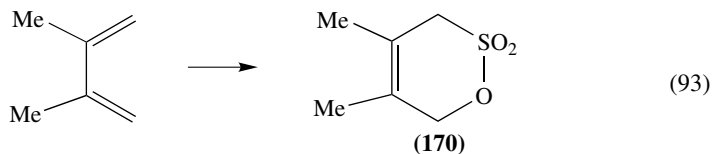
VIII. ADDITION TO NITROSO COMPOUNDS

The first examples of this reaction (which was reviewed several times[85]), i.e. the addition of nitrosoarenes to 2,3-dimethylbutadiene to give 2-aryl-3,6-dihydro-2*H*-1,2-oxazines (equation 94), were reported in 1947[86]. In general, the addition of nitroso compounds to 1,3-dienes to form dihydro-1,2-oxazines is only observed if the nitroso compound is activated by an electron-withdrawing group[87]. Kinetic studies of the reaction of cyclohexa-1,3-diene with *para*-substituted nitrosobenzenes (equation 95) show the accelerating effect of such groups (Hammett constant $\rho = +2.57$)[88].

(94)

$$(95)$$
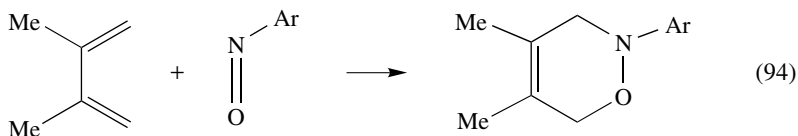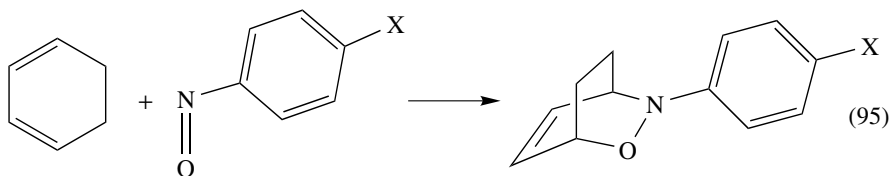
Rate constants in EtOH at $10\,^\circ$C are as follows:

X	OMe	Me	H	Cl	NO_2
10^3 k	0.151	1.30	4.19	12.0	532

However, it was recently reported[89] that all nitrosoarenes (except the 4-nitro compound), when produced by the oxidation of arylamines p-$H_2NC_6H_4R$ (R = MeO, Me, Cl, COMe, $CONH_2$, CF_3) with 2.2 mol hydrogen peroxide in the presence of a catalytic amount of oxoperoxo(2,6-pyridinedicarboxylato-O,N,O') (hexamethylphosphortriamide)-molybdenum(VII) **171**, react with cycohexa-1,3-diene *in situ* to give the bridged dihydrooxazines of equation 95 in 66–81% yields.
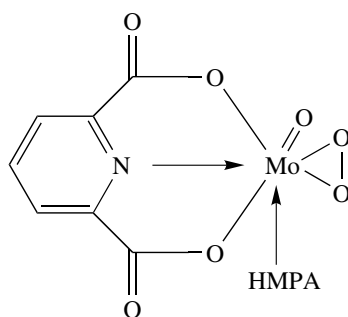
(171)

The regiochemistry of the addition of nitrosoarenes to unsymmetrical dienes has been discussed[90].

The reversible reaction of nitrosoarenes ArNO (Ar = 2, 6-$Cl_2C_6H_3$, 2,4,6-$Cl_3C_6H_2$ or Cl_5C_6) with cyclopentadiene results in unstable adducts **172**, which rearrange at room temperature to mixtures of 'epoxyepimines' **173** and 'epimines' **174** (equation 96)[91]. Similarly, treatment of cyclopentadiene with the vinylnitroso compounds **175** (R = H, Me or Cl) gives the rearranged adducts **176** (equation 97)[92]. In general, the adducts of trichloronitrosoethylene to cyclic dienes with five-, six- or seven-membered rings undergo this epoxyepimine rearrangement, whereas adducts to acyclic dienes do not[93].

Treatment of a mixture of a chloro oxime **177** (R = H, Ph, 4-BrC_6H_4 or 2-furyl) and a diene (cyclopentadiene or 2,3-dimethylbuta-1,3-diene) with solid sodium carbonate results in the formation of a dihydrooxazine, the intermediate nitrosoalkene **178** having reacted as a heterodiene (equation 98)[94]. In contrast, 1,1-dichloro-2-nitrosoethene and cyclopentadiene yield the epoxyepimine **179** (equation 99)[94].

(96)

(172)   (173)   (174)

(97)

(175)   (176)

(98)

(177)   (178)

(99)

(179)
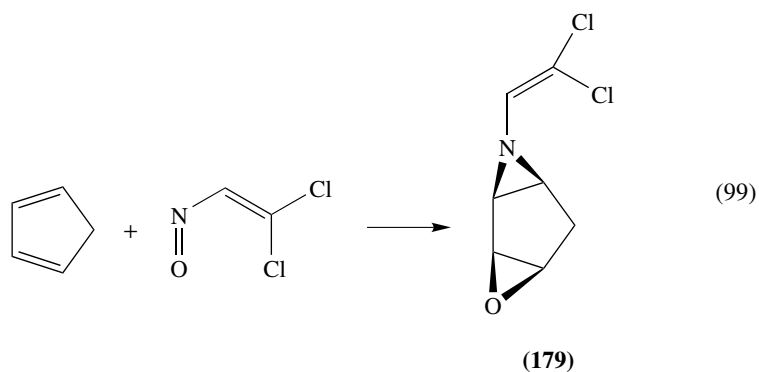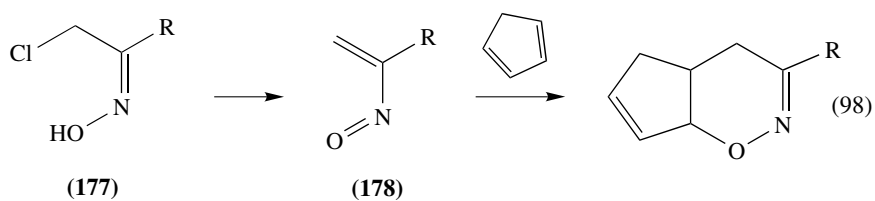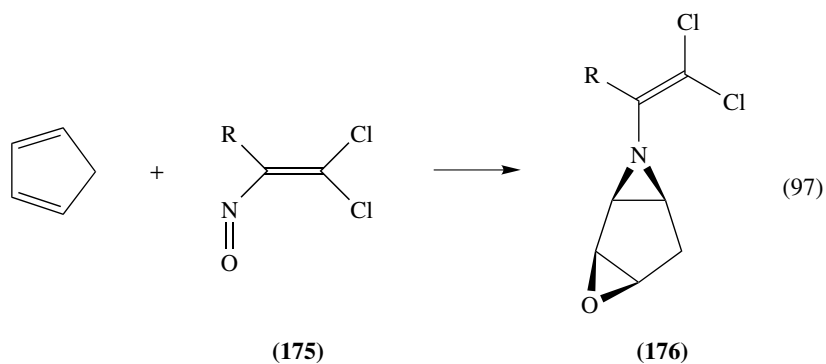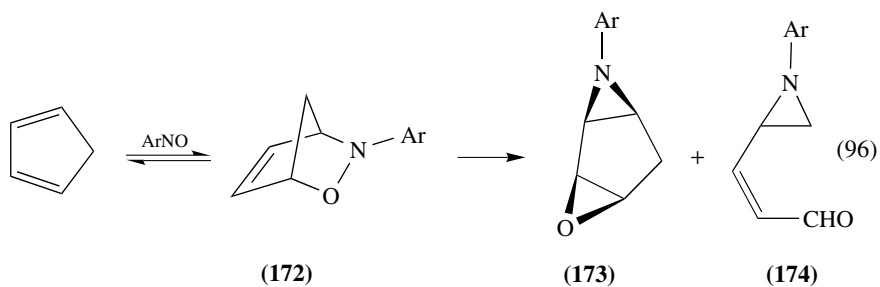
Unlike most tertiary nitrosoalkanes, 1-chloronitrosocyclohexane forms adducts with various 1,3-dienes. Although the reaction is sluggish and reversible, good yields of dihydrooxazines can be obtained if ethanol is present (equation 100)[95].

(100)
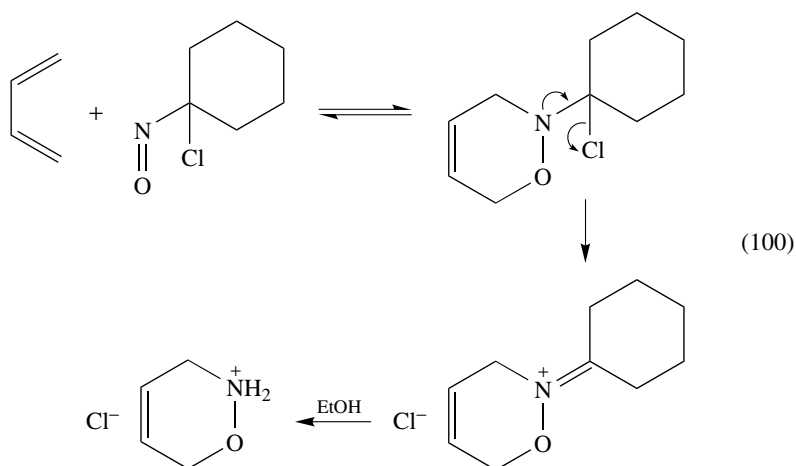
Trifluoronitrosomethane reacts with butadiene at $-78\,^{\circ}$C to give **180** (equation 101). Even perfluorobutadiene, which is unreactive toward conventional dienophiles, reacts with trifluoronitrosomethane to give **181** (equation 102)[96].

(101)

(180)

(102)

(181)
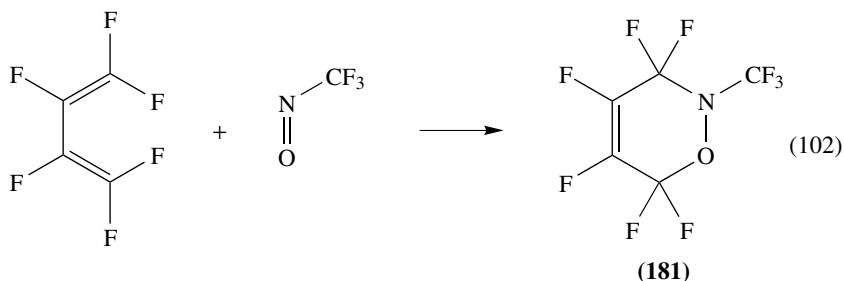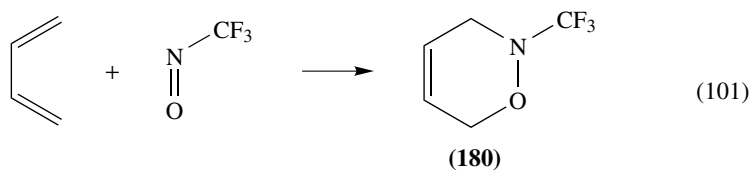
Nitrosyl cyanide, generated from nitrosyl chloride and silver cyanide in chloroform at $-20\,^{\circ}$C, affords unstable products with various dienes, e.g. butadiene and 2,3-dimethyl-1,3-butadiene. With methyl sorbate, compound **182** is produced (equation 103), thebaine **(183)** gives **184** (equation 104)[97] and 9,10-dimethylanthracene yields the stable cycloadduct **185**, which decomposes into its components on heating and consequently can serve as a source of nitrosyl cyanide. Thus heating **185** with 1,4-diphenylbuta-1,3-diene gives the dihydrooxazine **186** and dimethylanthracene (equation 105)[98].

C-Nitrosocarbonyl compounds RCONO (R = Me or Ph), generated from hydroxamic acids and tetraethylammonium periodate, readily react with dienes such as butadiene and

cyclopentadiene. The adducts to 9,10-dimethylanthracene transfer RCONO to thebaine in refluxing benzene (equation 106)[99].

(103)

(182)

(104)

(183)   **(184)**

(105)

(185)   **(186)**

$$\text{(106)}$$
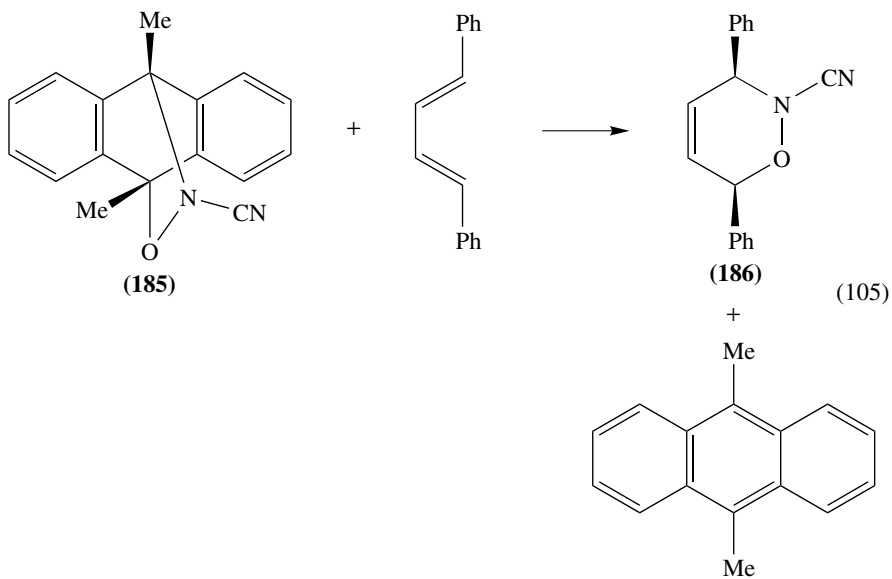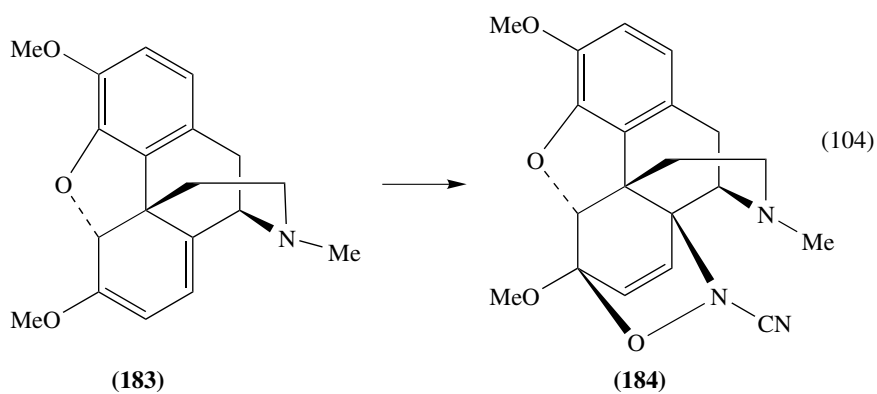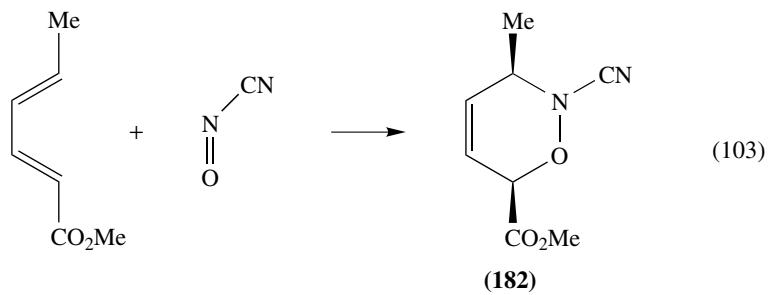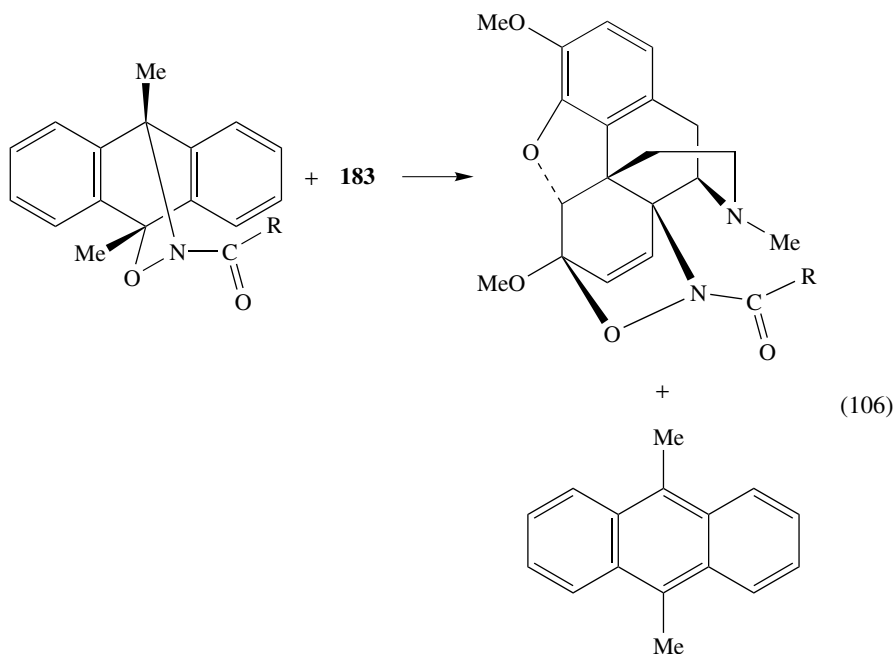
O-Nitrosocarbonyl compounds (nitrosoformates) **187** (R = *t*-Bu or Bn) are obtained from the hydroxylamines ROCONHOH. They can be trapped by reaction with butadiene to give the cycloadducts **188** (equation 107). With 9,10-dimethylanthracene the benzyl

$$\text{(107)}$$

(187)   **(188)**

$$\text{(108)}$$

(189)   **(190)**
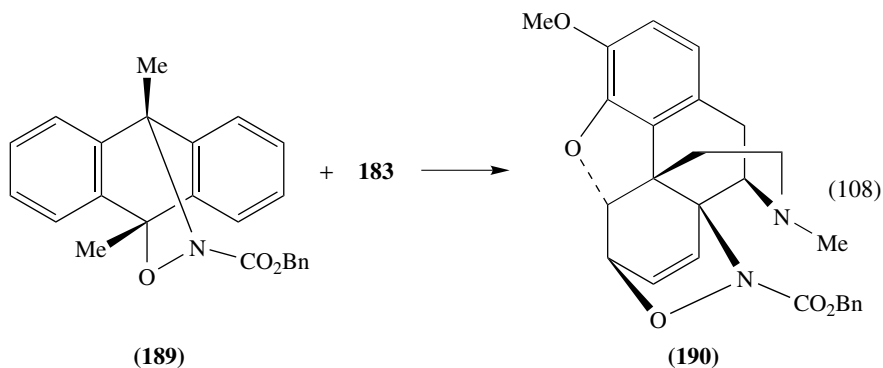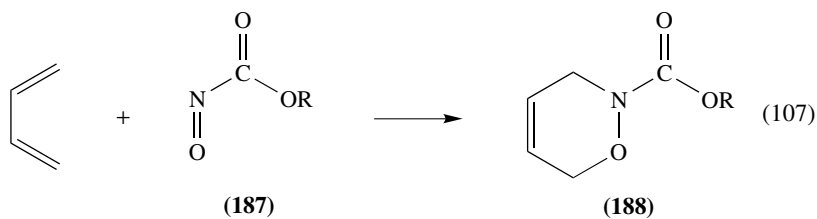
compound forms **189**, which, when treated with thebaine, transfers benzyl nitrosoformate to the latter to give **190** (equation 108)[100]. The *C*-nitrosoformamide PhNHCONO is generated by periodate oxidation of PhNHCONHOH; in the presence of thebaine an analogue of **190** is obtained[100].

The transient *C*-nitrosoimine **193** (Ar = 4-ClC$_6$H$_4$) is formed by the action of ethyl cyanoformate on the sulfimide **191** and also by the oxidation of the amidoxime **192** with lead tetraacetate. In the presence of thebaine, both reactions yield an identical dihydrooxazine[101].
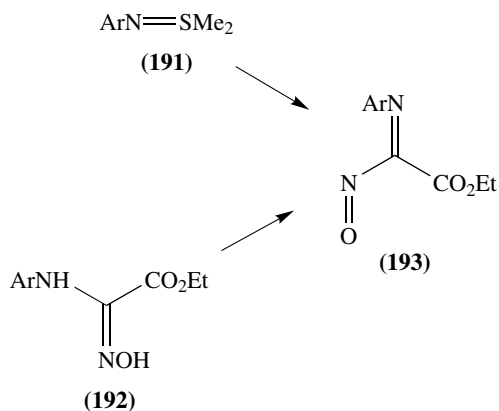
Treatment of alkyl nitrites with arylsulfinic acids **194** generates the unstable nitroso compounds **195**, which, in the presence of dienes, are trapped as cycloadducts **196** (equation 109)[102].

$$(109)$$
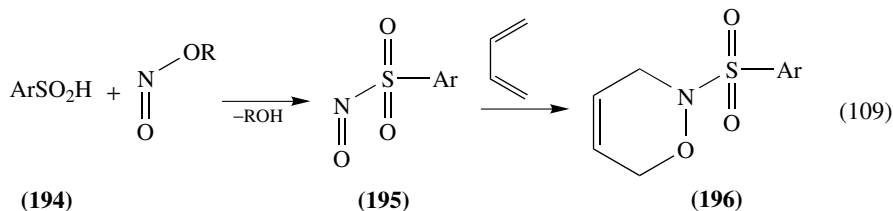
Acylnitroso compounds **197** (R = Me, Ph or Bn) react *in situ* with 1-methoxycarbonyl-1,2-dihydropyridine to yield solely the bridged adducts **198** quantitatively. On the other hand, 1 : 1 mixtures of the regioisomers **199** and **200** were formed from the nitroso-formates **187** (R = Me or Bn) (equation 110)[103]. The chiral acylnitroso compounds **201** and **202**, which are of opposite helicity, add to cyclohexadiene to give optically active dihydrooxazines in greater than 98% diastereomeric excess (equations 111 and 112)[104]. Similarly, periodate oxidation of the optically active hydroxamic acid **203** in the presence of cyclopentadiene, cyclohexa-1,3-diene and cyclohepta-1,3-diene affords chiral products **204** (*n* = 1, 2 and 3, respectively) in 70–88% yields and 87–98% de (equation 113)[105].

The unstable cycloadducts **207**, obtained from the dihydropyridines **205** (R = Me or Bn) and the benzoyl nitroso compound **206**, undergo a hetero-Cope rearrangement in the presence of silicic acid to yield fused dioxazines **208** (equation 114)[106]. Adding the racemic hydroxamic acid **209** (R = *t*-Bu, cyclohexyl or Ph) to a two-phase mixture of
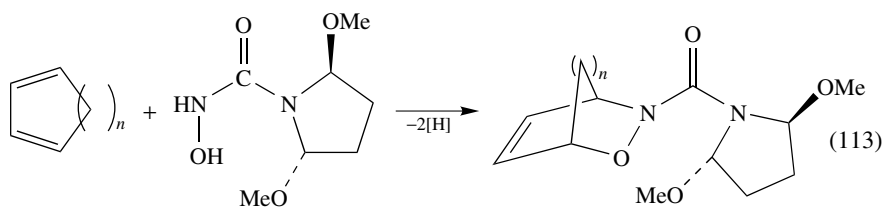
cyclopentadiene or cyclohexadiene and sodium periodate in ethyl acetate/water at 0 °C produced mixtures of diastereomers **210** and **211** in the ratios 3.4–5.1 : 1 and 2.5–4.6 : 1, respectively, indicating a moderate degree of asymmetric induction[107].
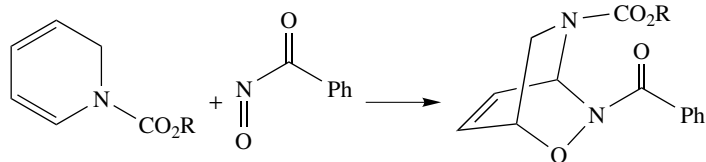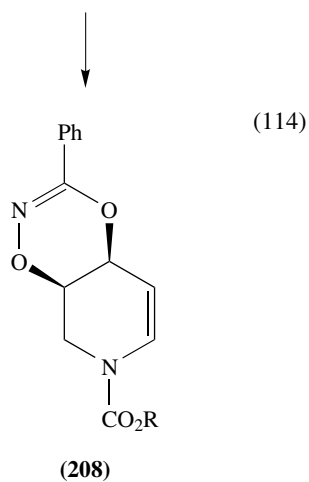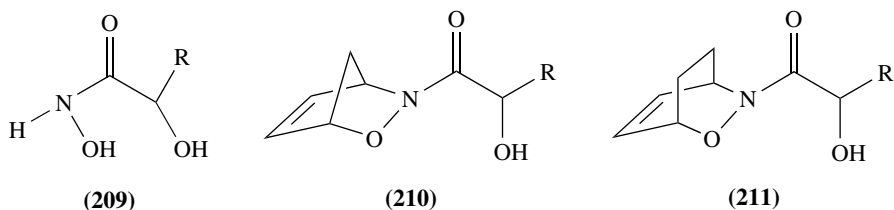
(112)

(202)

(113)

(203)   **(204)**

(205)   **(206)**   **(207)**

(114)

(208)

(209)   **(210)**   **(211)**
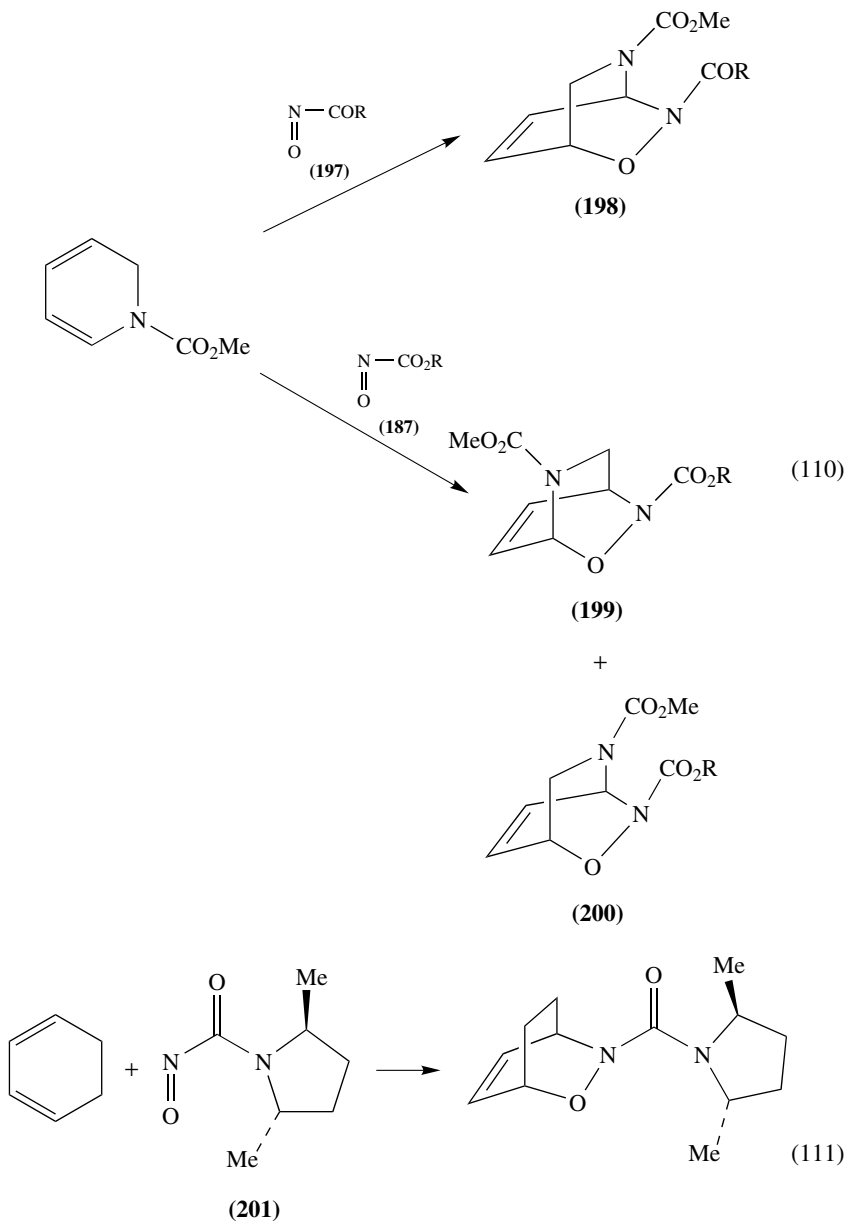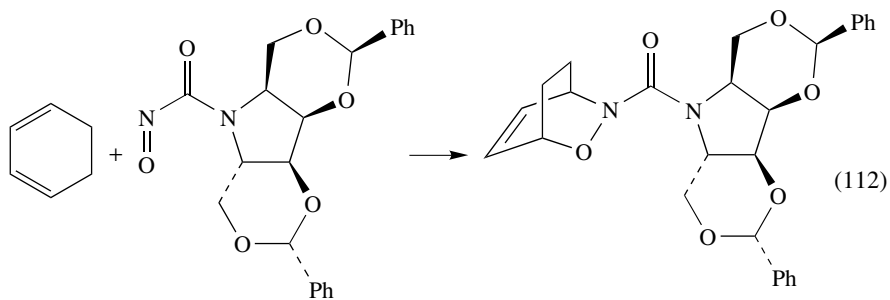
17-Chloro-17-nitroso-3β-hydroxy-5α-androstane **213**, generated from the oxime **212** of epiandrosterone and *t*-butyl hypochlorite, reacts with cyclohexadiene in chloroform/methanol at $-20\,^\circ$C to yield, after two weeks, epiandrosterone and the bridged dihydrooxazine **214** in an enantiomeric excess of better than 95%[108].

(212)

(214)

(213)
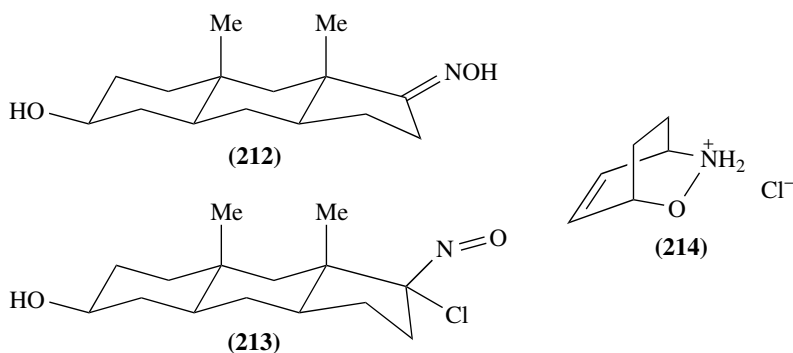
Tetra-*n*-propylammonium periodate oxidation of the hydroxamic acids **215** (R = CH$_2$OH, CH$_2$OMe, CH$_2$NHPh or CO$_2$Me), derived from L-proline, generates nitroso compounds **216**, which, in the presence of cyclohexadiene, give mixtures of diastereomeric cycloadducts **217** in 79–89% yields and 26–68% de values (equation 115)[109].

The chiral nitroso compound **218** derived from camphor (equation 116) adds to various types of dienes to afford adducts **219**–**222** in high yields and excellent de values (equations 117–120)[110].
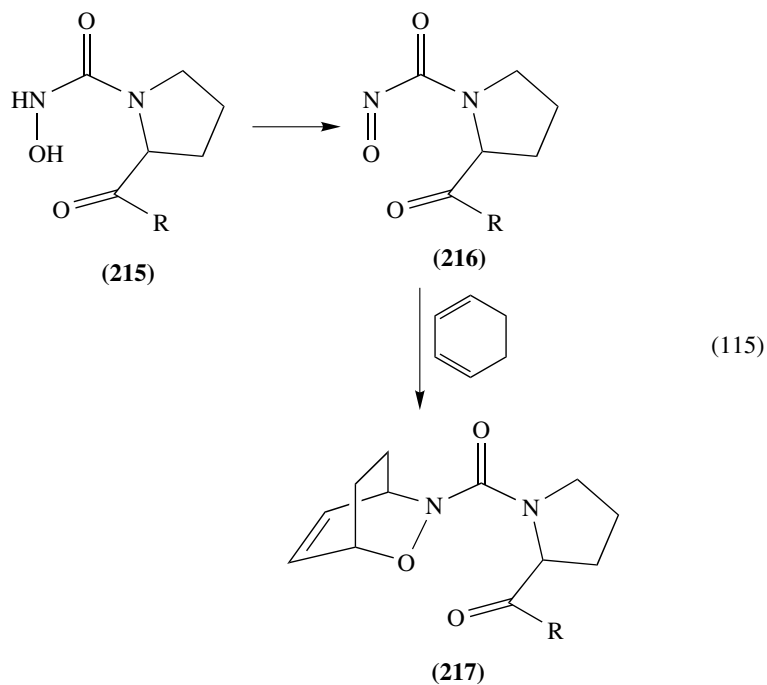
Chiral dienes or chiral dienophiles or chiral Lewis acid catalysts may be involved in cycloaddition reactions. When any two of these are combined 'double asymmetric induction' operates[111]. Thus the chiral diene **223** and the optically active dienophile **224** (from D-mandelic acid) gave **225** in high de values, whereas the same diene and the enantiomeric dienophile **226** (from L-mandelic acid)—a mismatched pair—formed the diastereomeric cycloadduct **227** in only 4% de (equation 121)[112].
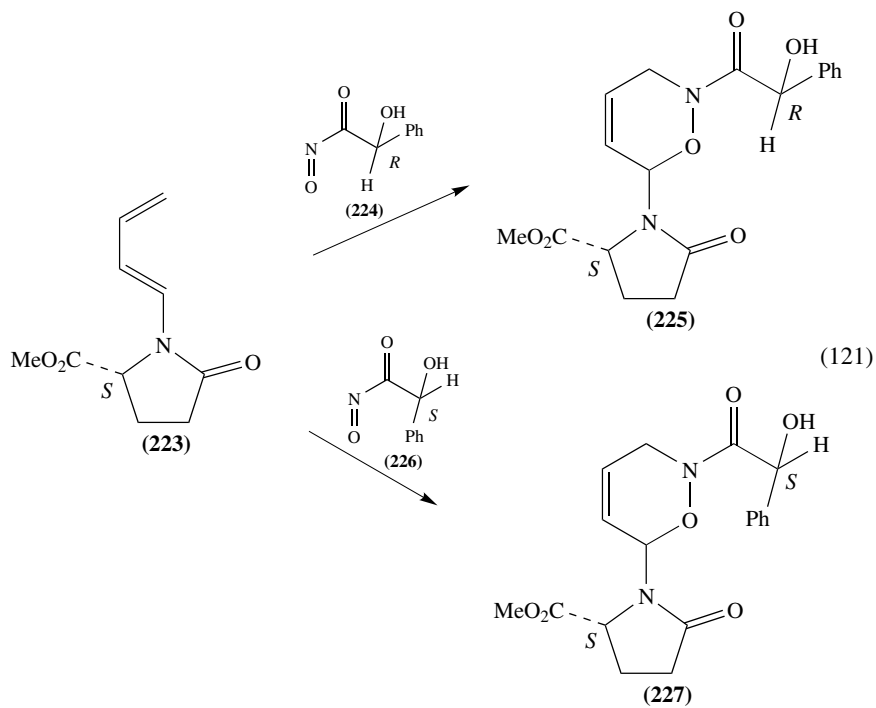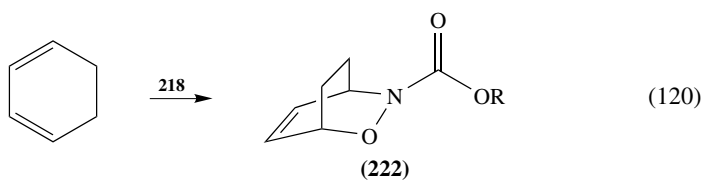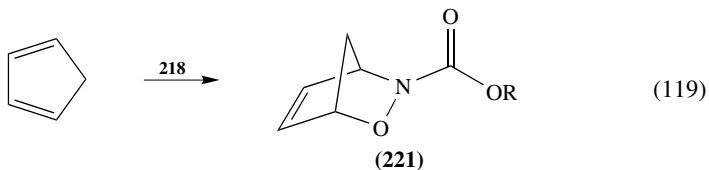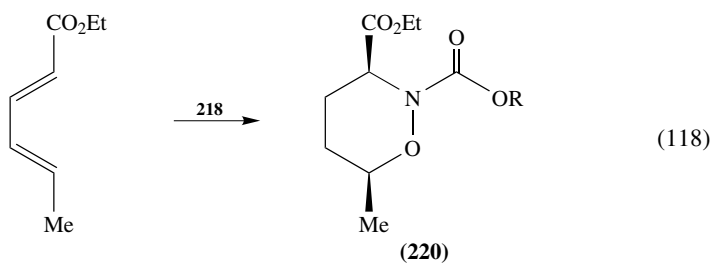
Optically active dihydrooxazines **230** are produced by the reaction of the chiral α-chloronitroso compound **228** derived from D-mannofuranose with a variety of 1,3-dienes in the presence of ethanol at low temperatures via the primary adducts **229** (equation 122). Penta-1,3-diene, for instance, yields a mixture of the regioisomers **231** and **232**[113].
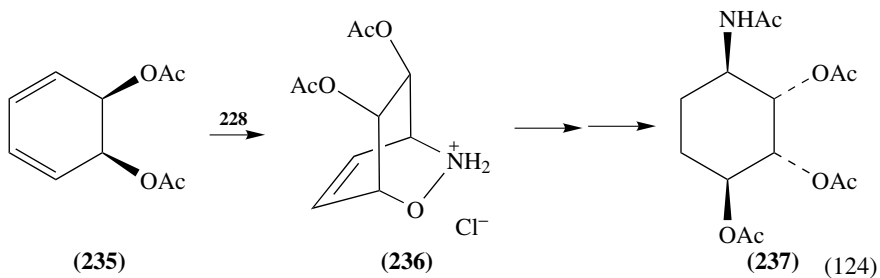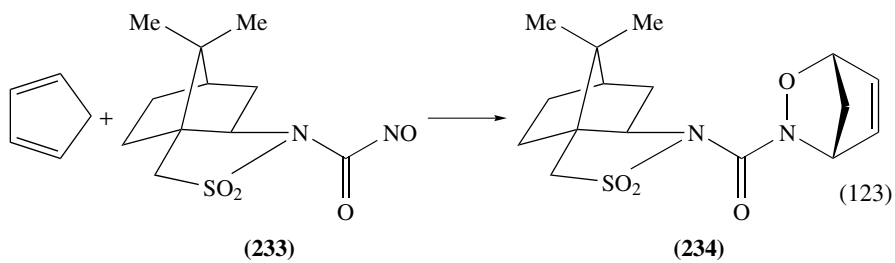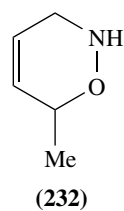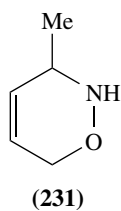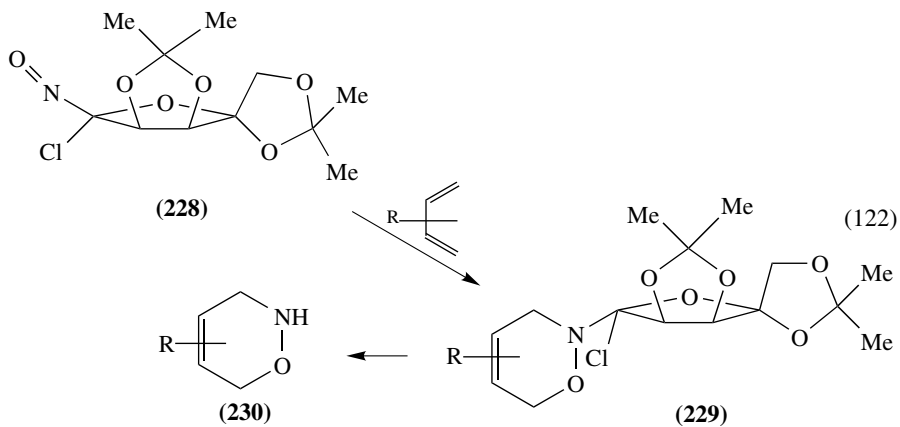
Nitrosocarbonyl-D-bornane-10,2-sultam **233** adds to cyclopentadiene to yield **234** with complete facial selectivity (equation 123)[114].

cis-5,6-Diacetoxy-1,3-cyclohexadiene **235** reacts with the chiral chloronitroso compound **228** in chloroform/ethanol to give 89% of the optically active product **236** in 94% ee, four asymmetric centers having been created (equation 124). The latter was

transformed into tetraacetylconduramine A1 **237** by reduction with zinc/hydrochloric acid, followed by acetylation[115].
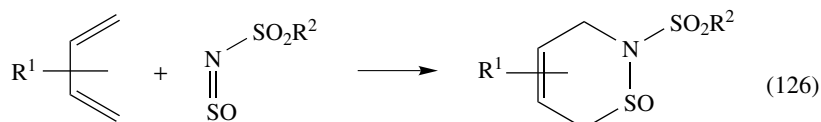

(115)

(116)

(117)

(118)

(220)

(119)

(221)

(120)

(222)

(225)

(121)

(227)

(228)

(122)

(229)

(230)

(231)   **(232)**

(123)

(233)   **(234)**

(124)
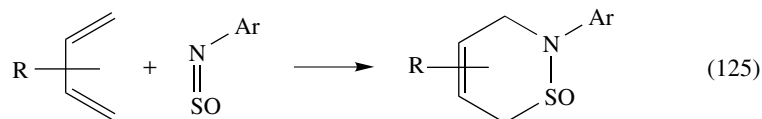
**(235)**   **(236)**   **(237)**
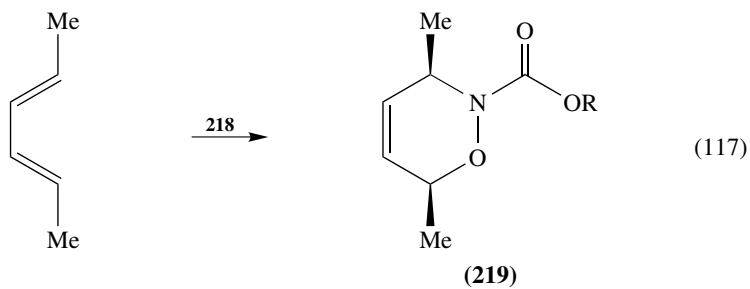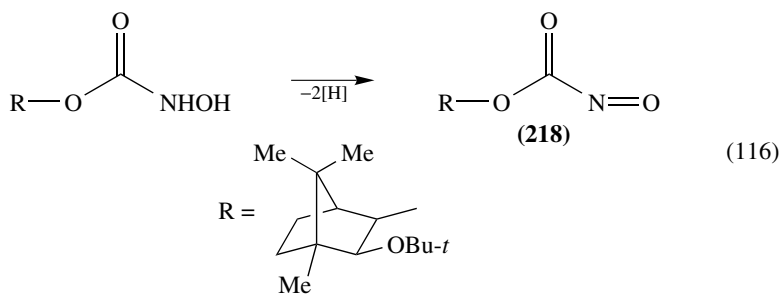
IX. ADDITION TO S=N COMPOUNDS

N-Sulfinylarylamines react sluggishly with dienes (equation 125)[116,117]. *N*-Sulfinylsulfo-namides (from sulfonamides and thionyl chloride) are much more reactive dienophiles

(equation 126)[118]. In some cases, the Diels–Alder reactions of N-sulfinylsulfonamides are reversible; thus the adduct **238** to cyclopentadiene decomposes into its components at room temperature (equation 127)[119] and the products **240** obtained with 1-substituted dienes **239** (R = Me, t-Bu, Ar or CO$_2$Me) at 5 °C rearrange to the isomers **241** at higher temperatures (equation 128). In contrast, 2-substituted dienes **242** (R = Me, Ph or Cl) yield adducts **243** which are thermally stable (equation 129)[120].
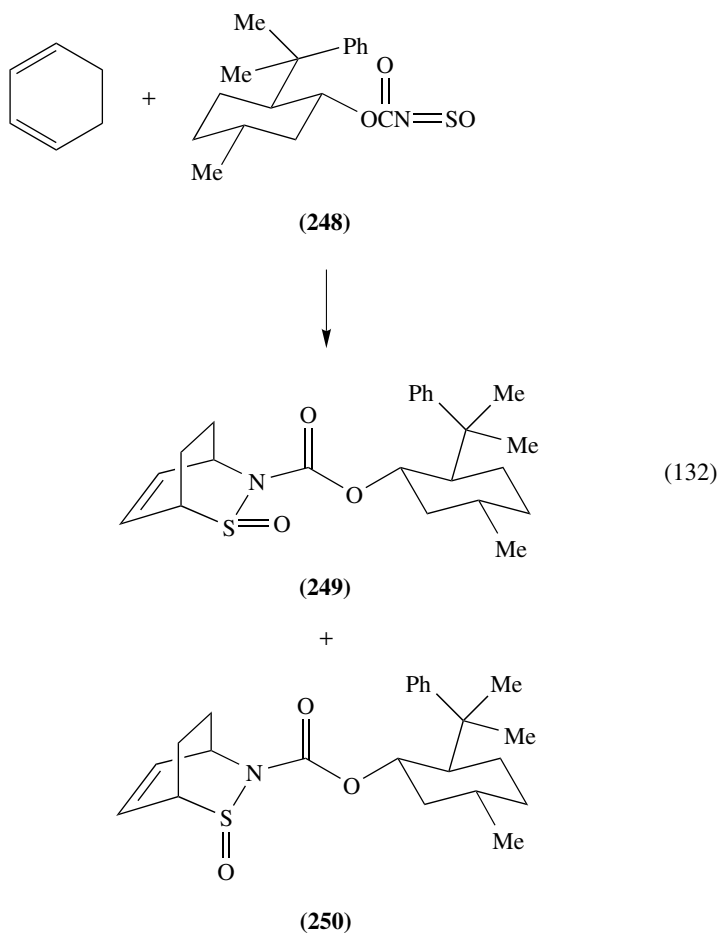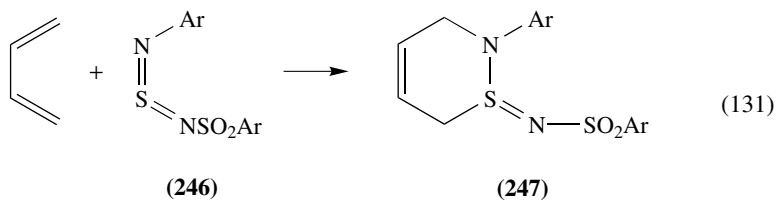
$$(125)$$

$$(126)$$

R^1 = H, Alkyl; R^2 = Alkyl, Ar

$$(127)$$

(238)

$$(128)$$

(239)   **(240)**   **(241)**

$$(129)$$

(242)   **(243)**
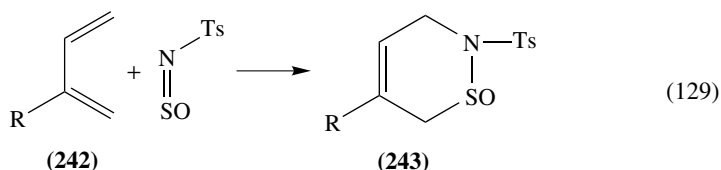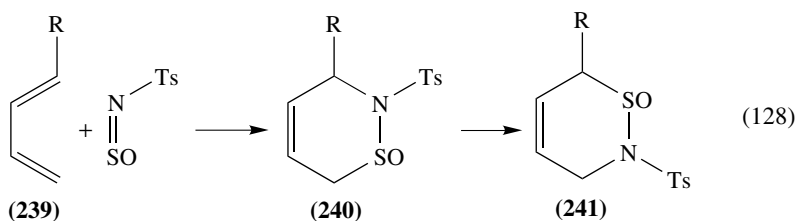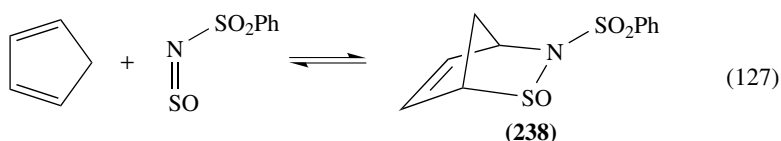
N,N′-Disulfonylsulfodiimides **244** react exothermically with butadiene to give 1-sulfo-nylimino-2-sulfonyl-3,6-dihydro-1,2-thiazines **245** (equation 130)[121,122]. N-Aryl-N′-sul-fonylsulfodiimides **246** are much less reactive as dienophiles. The addition to butadiene to yield **247** takes place in boiling benzene (equation 131)[123]. No cycloaddition reactions of dialkyl- or diarylsulfodiimides are known.

The chiral N-sulfinylcarbamate **248** derived from 8-phenylmenthol formed a mixture of two epimeric cycloadducts **249** and **250** with cyclohexa-1,3-diene (equation 132)[124], whereas the reaction with (E,E)-hexa-2,4-diene in the presence of tin(IV) chloride gave solely the epimer **251** (equation 133)[125].

$$(130)$$

(244)   **(245)**

$$(131)$$

(246)   **(247)**

(248)

$$(132)$$

(249)

+

(250)

$$\mathbf{248} \quad + \qquad \longrightarrow \qquad \tag{133}$$

(251)
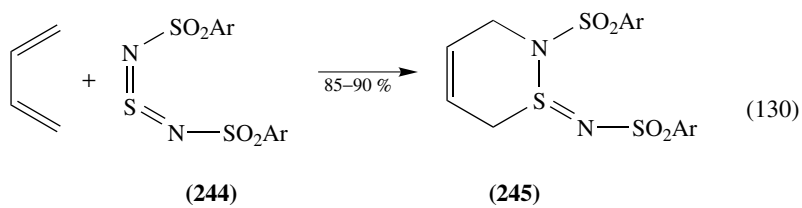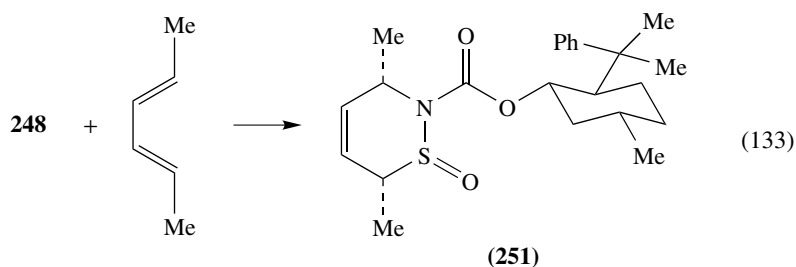
X. ADDITION TO AZO COMPOUNDS[126,127]

Azo compounds are reactive dienophiles. Indeed, one of the very first Diels-Alder reactions was the addition of diethyl azodicarboxylate to cyclopentadiene (equation 134)[128,129]. Other early examples of the reaction are the formation of tetrahydropyridazines from indazolone **252** and phthalazinedione **253** (equations 135 and 136)[130].

$$\tag{134}$$

$$\tag{135}$$

(252)

$$\tag{136}$$

(253)
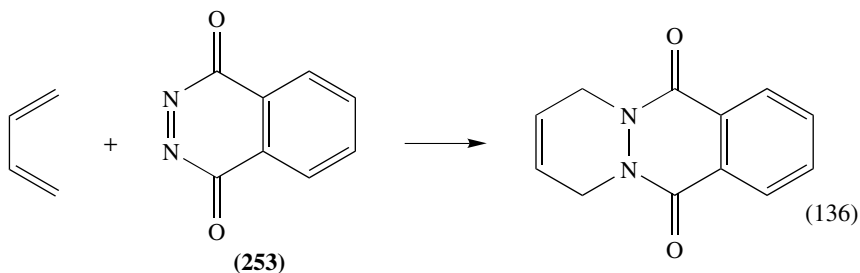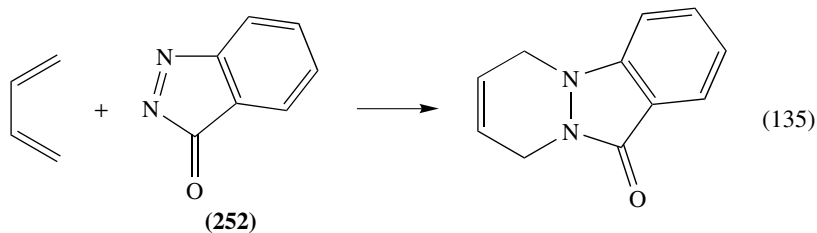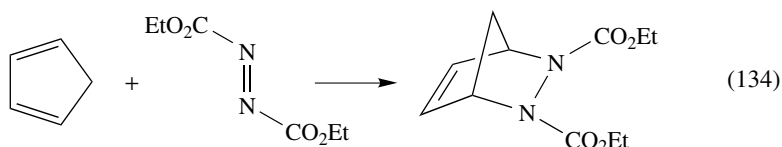
Diethyl azodicarboxylate forms normal adducts with 2,3-dimethylbutadiene and with ethyl sorbate; however, it is not a very good dienophile, presumably because it exists in the *trans*-configuration. The sterically hindered diene **254** adds the ester to give mainly the ene product **255** (equation 137) and even cyclohexa-1,3-diene undergoes an analogous

reaction, yielding **256** (equation 138)[131].

$$\text{(137)}$$

(254)   **(255)**

$$\text{(138)}$$

(256)
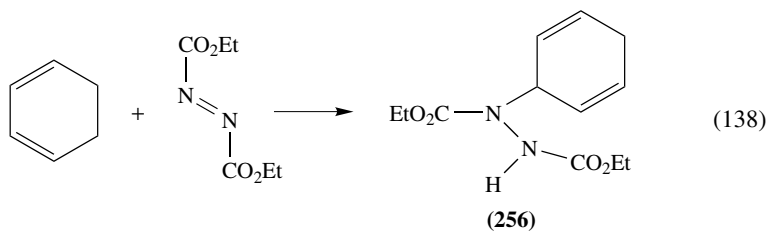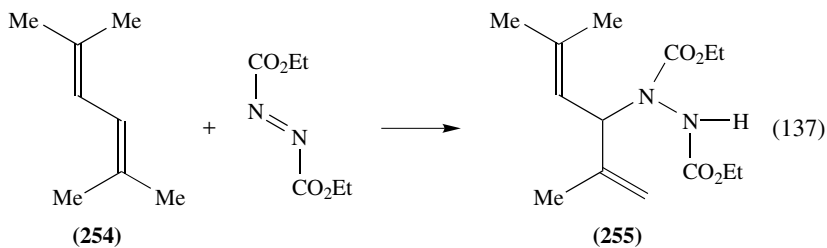
The cycloadducts **257** of esters of azodicarboxylic acid to 2,7-dimethyloxepin undergo a spontaneous Claisen rearrangement to form the dihydrocyclopropapyridazines **258** (equation 139)[132]. Homofulvenes **259** (R^1, R^2 = H or Me) react with dimethyl azodicarboxylate to form rearranged adducts **260** (equation 140)[133].

The action of 2,4,6-trichlorobenzenediazocyanide on cyclopentadiene results in an unstable cycloadduct, which over several days undergoes a 'trisaza-Cope' rearrangement to the fused benzimidazole **261** (equation 141). By contrast, the analogous adduct to cyclohexadiene is stable[134].

(257)

$$\text{(139)}$$

(258)

(140)

(259)   **(260)**

(141)

(261)
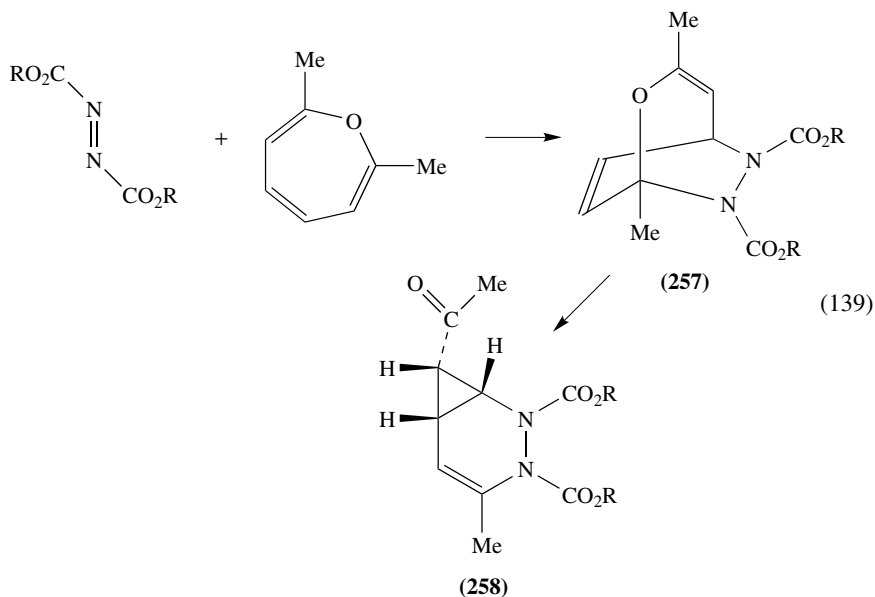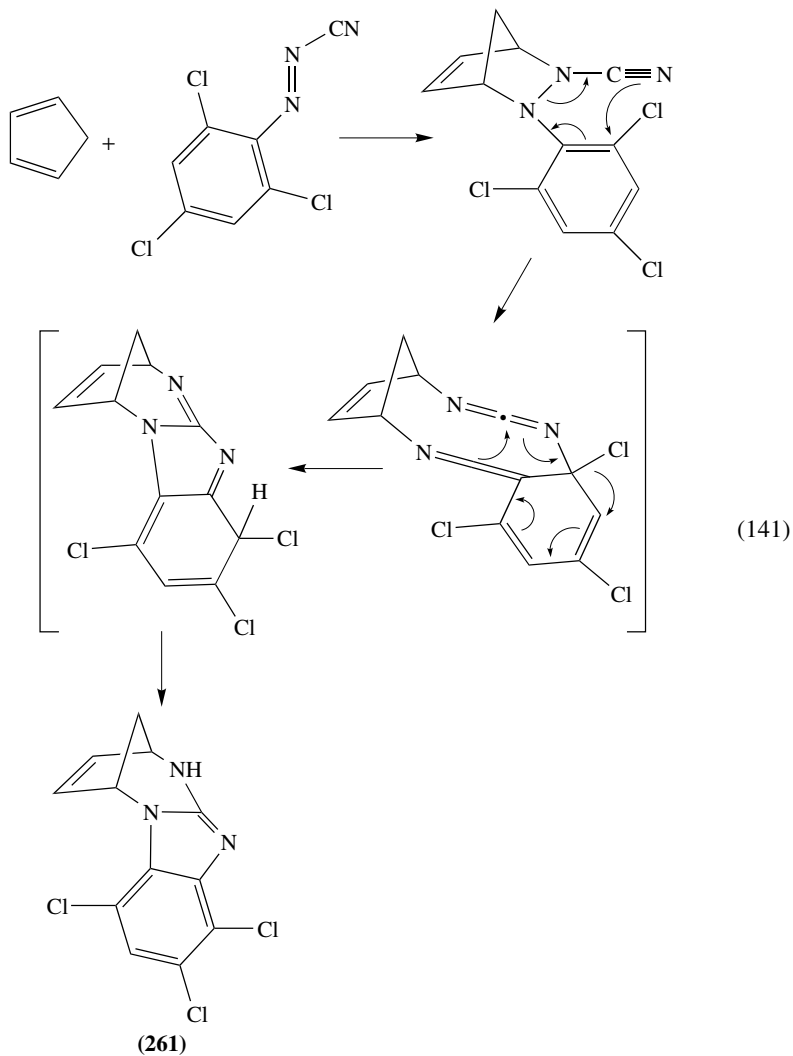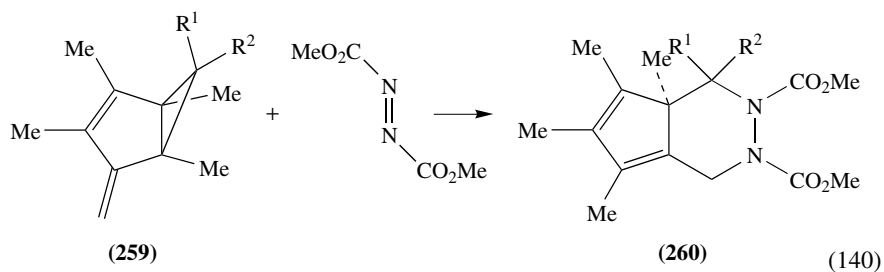
The labile cycloadduct **262** of azodibenzoyl to cyclopentadiene rearranges to the fused oxadiazine **263** on heating. The process involves dissociation of **262** into its components, followed by a Diels–Alder reaction in which the azo compound functions as a hetero diene (equation 142)[135].

The most powerful azo dienophile is the *cisoid* 4-phenyl-1,2,4-triazoline-3,5-dione **264**, which is surpassed in reactivity only by singlet oxygen. The dione adds rapidly to all types of dienes and the process can be followed visually since the bright-red color of the reagent is discharged when the reaction is complete[136].

(142)
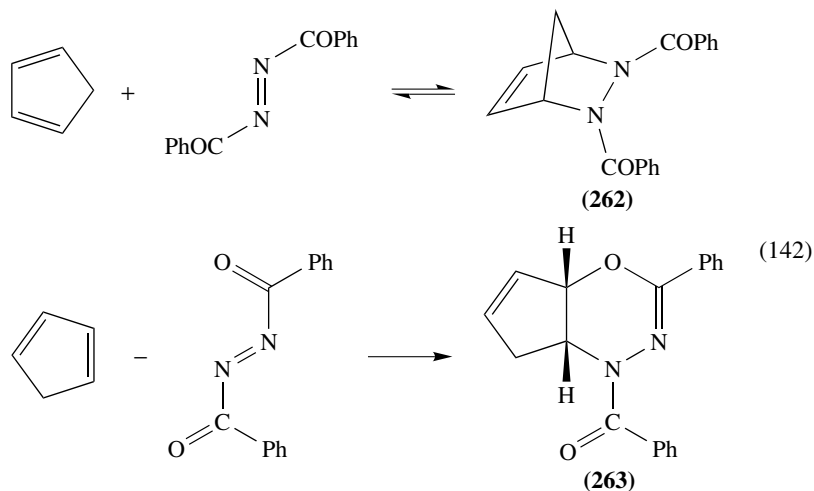
The triazolinedione adds to cycloheptatriene and cyclooctatetraene to yield the valence-isomeric adducts **265** and **266**, respectively (equations 143 and 144)[136].

(143)

$$(144)$$

(266)
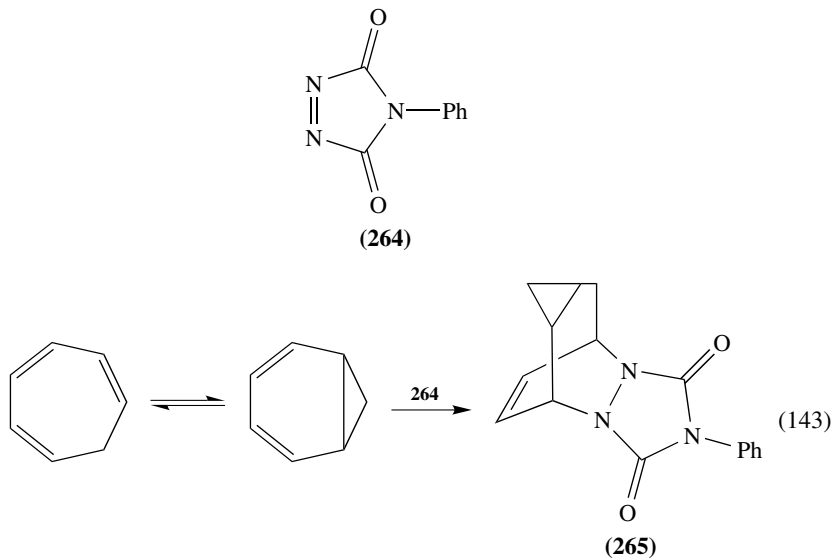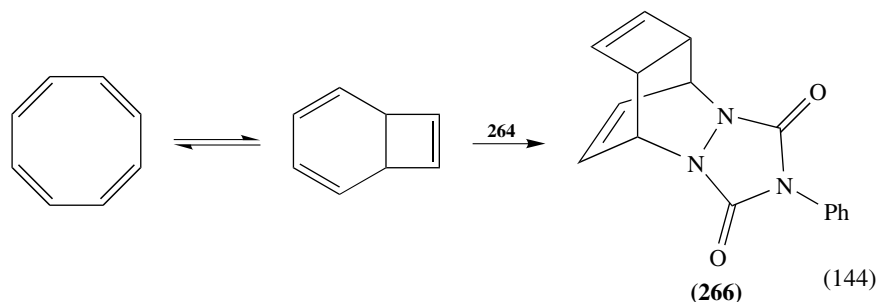
9-Chlorocyclononatetraene **267** rapidly rearranges in liquid sulfur dioxide to 1-chloro-8,9-dihydroindene **268**, which forms the cycloadduct **269** with the triazolinedione **264** (equation 145)[137]. The vinylimidazole **270** affords the purine analogue **271** (equation 146)[138].

(267)   **(268)**   **(269)** $$(145)$$

(270)   **(271)** $$(146)$$
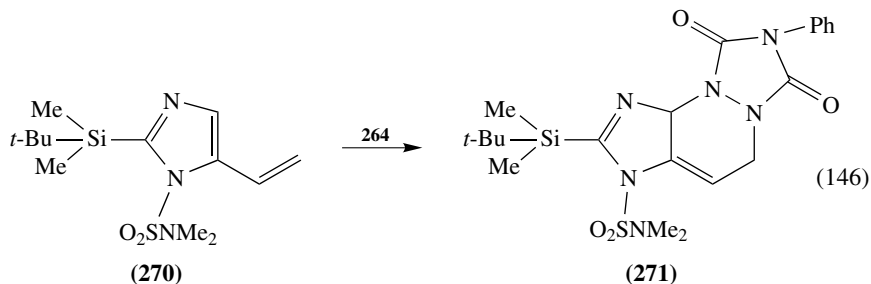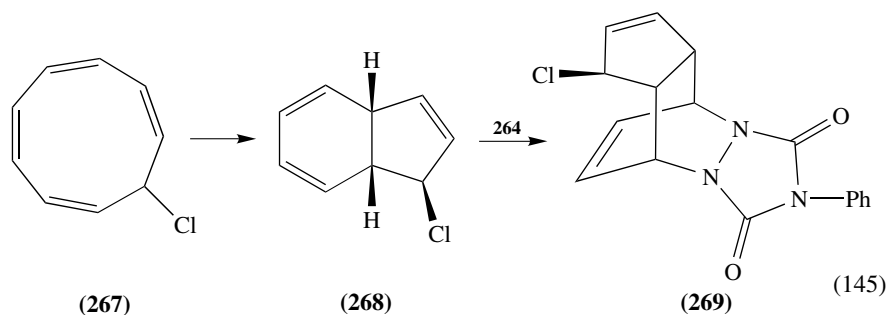
A selection of the many applications of cycloaddition with the triazolinedione **264** follows.

The preparation of an optically active triazolinedione, compound **274**, is shown in equation 147. Commercially available (−)-α-methylbenzylamine hydrochloride is converted into the hydrazine derivative **272** by treatment with phosgene, followed by H$_2$NNHCO$_2$Et. Thermal cyclization gives the urazole **273**, which is dehydrogenated to the product by means of dinitrogen tetroxide. The reagent has been used for the optical resolution of various 1,3-dienes. α-Phellandrene **275**, for instance, forms the cycloadduct **276**, which is separated into its diastereomeric components chromatographically. The chiral diene is then regenerated by alkaline hydrolysis, followed by treatment with manganese

dioxide (equation 148)[139]. *Endo*-Bornylamine has similarly been converted into a chiral derivative of triazolinedione[139].

$$R = \overset{Me}{\underset{Ph}{-\overset{|}{C}-H}}$$

(147)

$$R = \overset{Me}{\underset{Ph}{-\overset{|}{C}-H}}$$

(148)
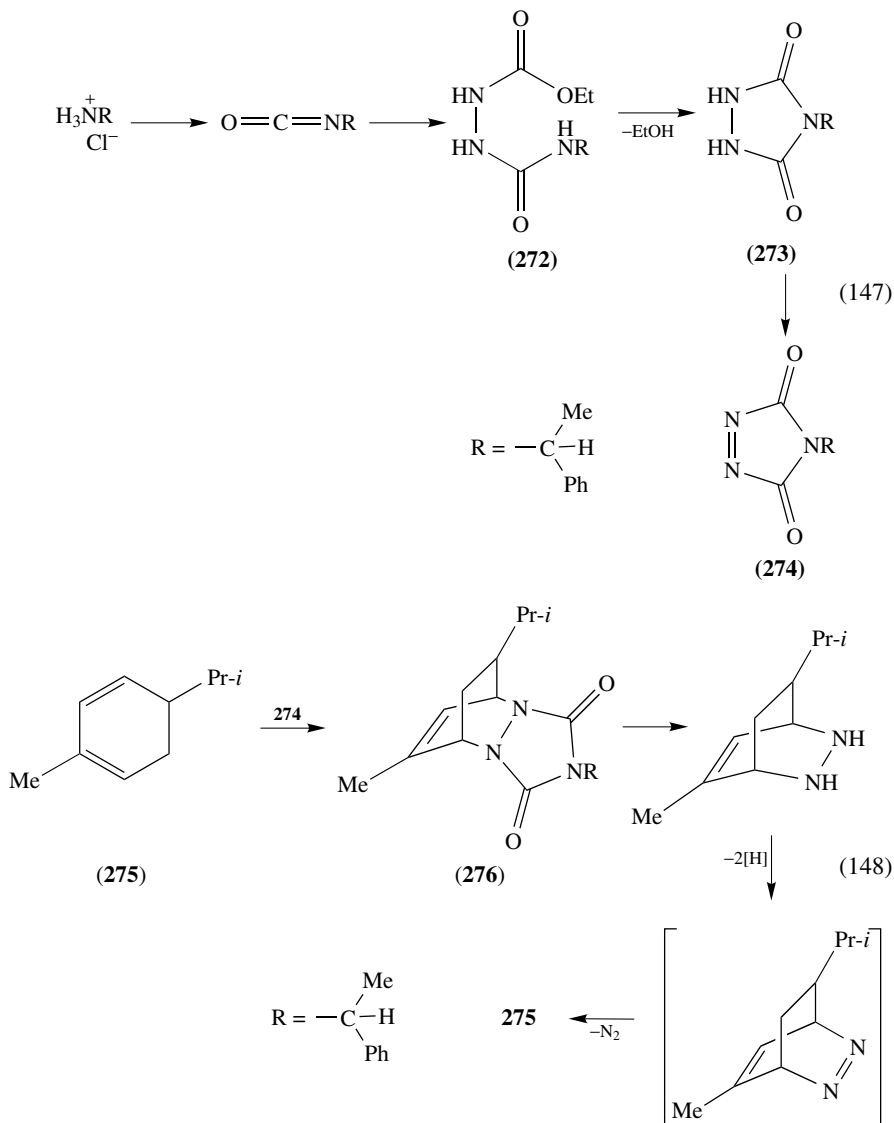
The optical resolution of the rigid racemic 1,2,3-trimethylcyclooctatetraene **277a**, which exists in equilibrium with a small amount of the valence isomer **277b**, was accomplished by means of (−)-*endo*-bornyl-1,2,4-triazoline-3,5-dione **278**. The diastereomeric mixture

of the adducts **279** was separated by fractional crystallization and the chiral cyclooctate-traenes were regenerated as described above (equation 149).[140] 1,2,3,4-Tetramethylcyclo-octatetraene **280** was similarly resolved by way of the (−)-*endo*-bornyltriazolinedione adduct **281** (equation 150)[140], as was the conformationally rigid cyclooctatetraene deriva-tive **282a** ⇌ **282b** via **283** (equation 151)[141].

(277a)   **(277b)**

(149)

(278)

(279)

(150)

(280)   **(281)**

(151)

(282a)   (282b)

(283)
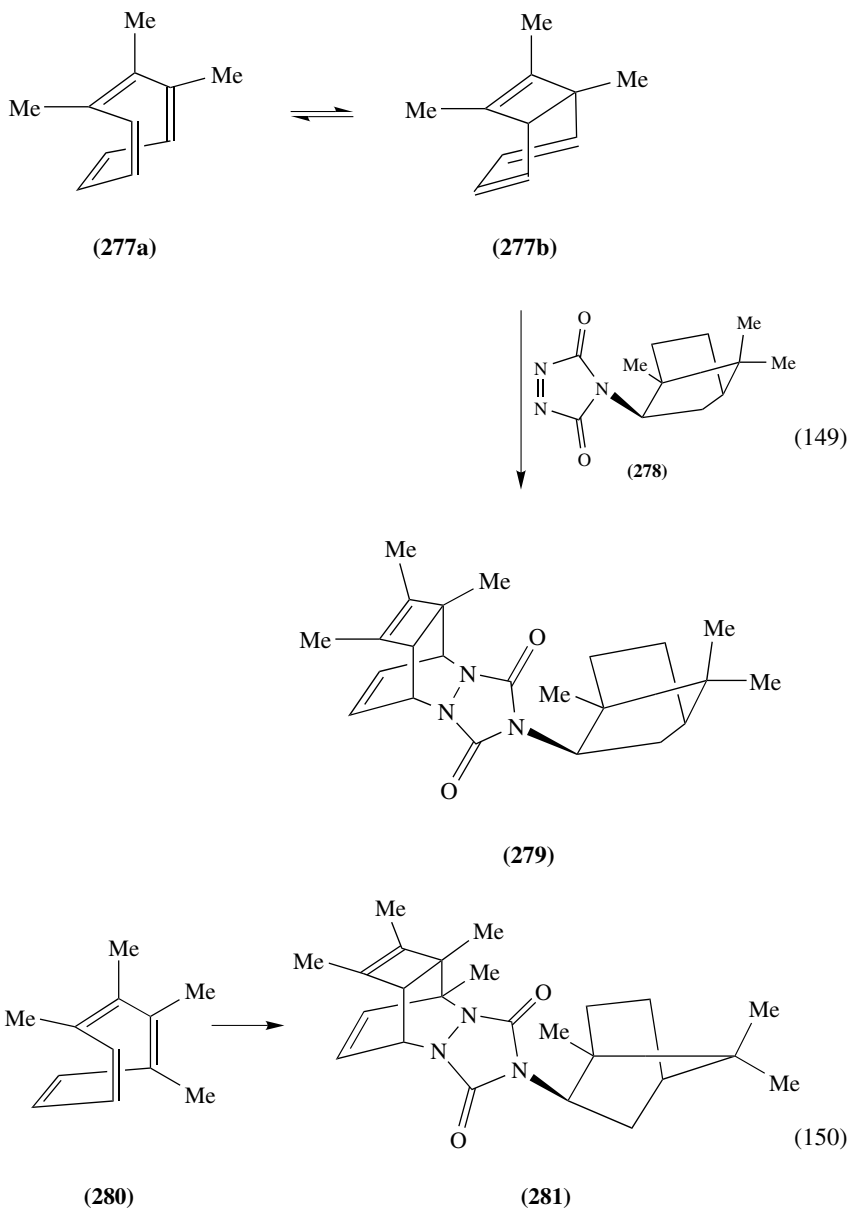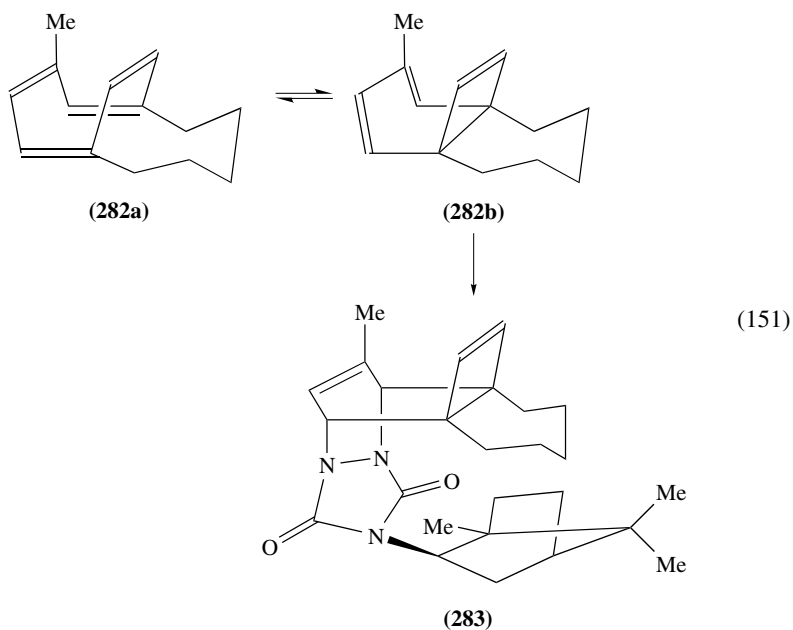
Chiral 2(4)-methylsemibullvalene **288** was prepared from methylcyclooctatetraene **284** as follows. Sensitized irradiation of the (−)-*endo*-bornyltriazolinedione adduct **285** gave **286**, which, in the presence of silver nitrate/silver chloride/potassium nitrate, rearranged to **287**. The latter was resolved by column chromatography and the product **288** was obtained by successive treatment with sodium hydroxide and manganese dioxide (equation 152)[142].

(284)   (285)

(286)

(152)

(287)

(288)

(eq. 152 *continued*)
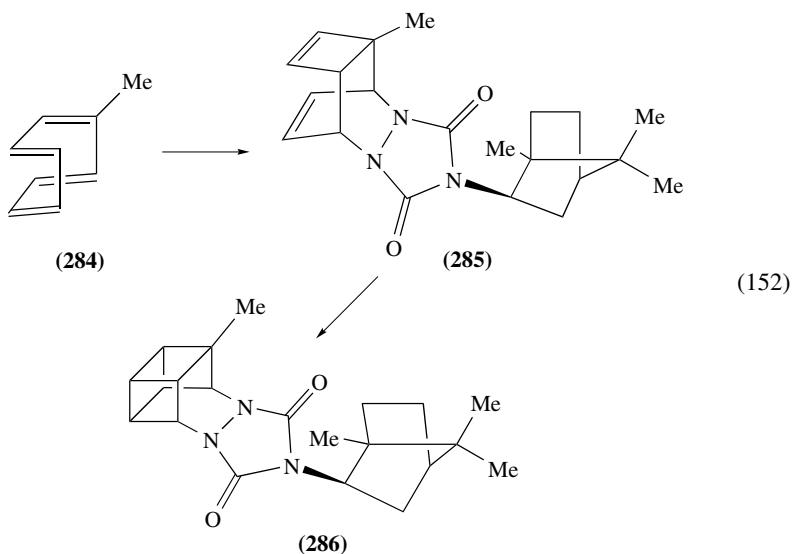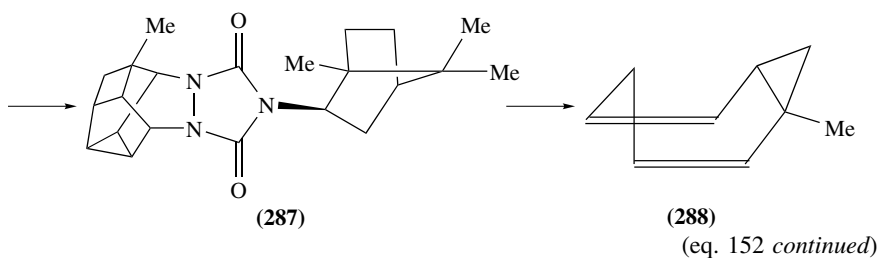
The photochemical cycloaddition of 4-methyl-1,2,4-triazoline-3,5-dione to the dibenzo-cyclooctatetraene **289** yields 3.5% of the cycloadduct **290**, together with 36% of **291**, the product of a di-π-methane rearrangement (equation 153)[143]. Anthrasteroids **293** (R = H, Ac or COPh) are produced in an oxidative rearrangement when the phenyltriazoline-dione adduct of **292** is treated with boron trifluoride etherate[144]. The 5,7-diene system of ergosteryl acetate **294** can be protected by cycloadduct formation, allowing selective hydrogenation of the 22,23-double bond[145].

(289)   **(290)**

+

(153)

(291)

(292)

(293)

(294)
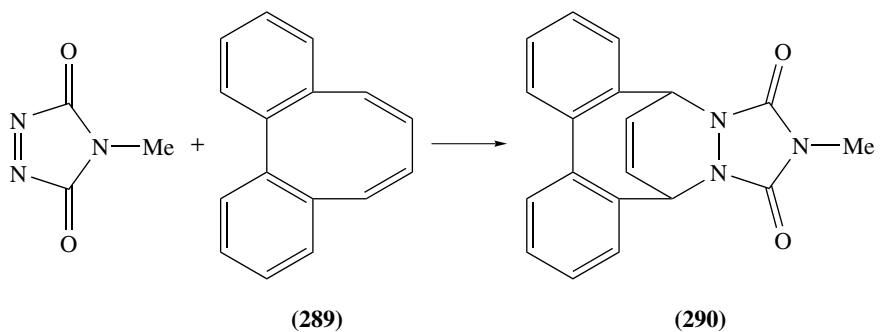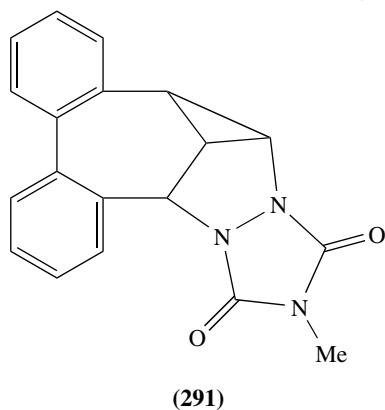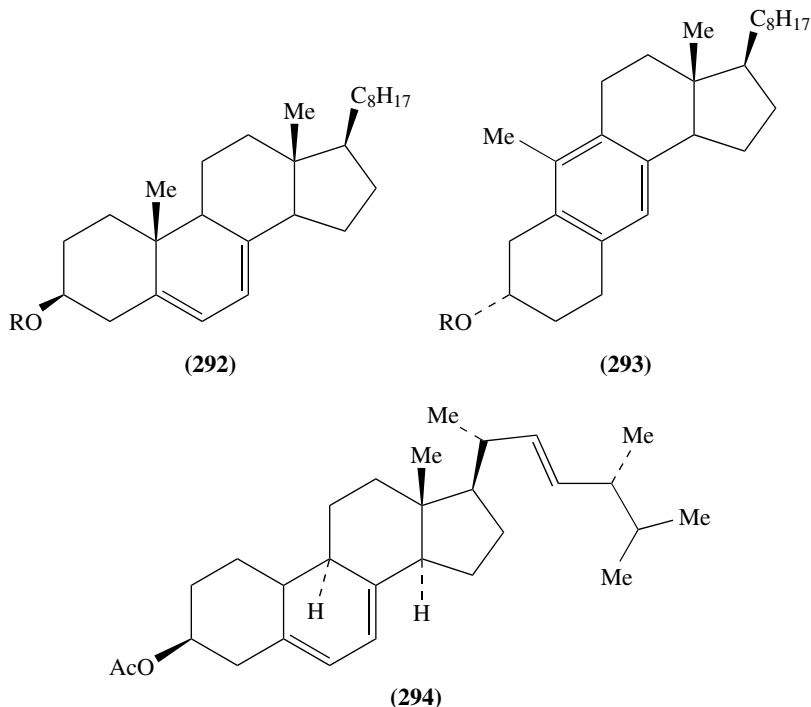
XI. FORMATION OF FIVE-MEMBERED RINGS

The action of methanolic sodium methoxide on hydroxylamine *O*-sulfonic acid generates nitrene NH, which adds to butadiene *in situ* to give a low yield of 1*H*-pyrroline **295** (equation 154)[146].

$$H_2NOSO_3H \xrightarrow[\substack{-Na_2SO_4, \\ -2\,MeOH}]{NaOMe} \;:NH \qquad (154)$$

(295)
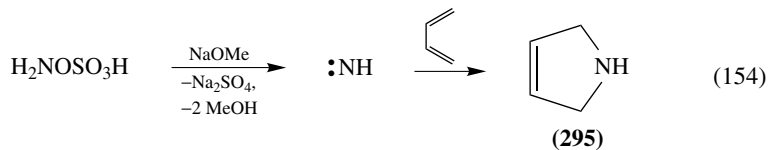
The formation of 1-chlorophospholene chlorides, e.g. **296**, by the action of dichlorophosphines on 1,3-dienes (equation 155) was first reported by McCormack in 1953[147].

$$(155)$$

(296)
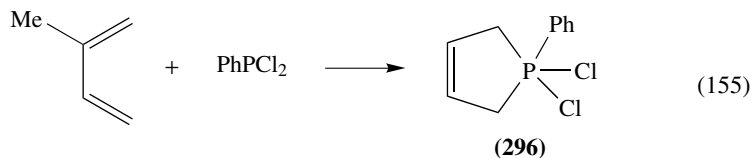
Butadiene, isoprene, chloroprene and 2,3-dimethyl-1,3-butadiene add phosphorus trihalides to form 3-phospholene 1,1,1-dihalides, e.g. **297** from isoprene and phosphorus

trichloride. The products react with methanol or ethanol to afford 1-alkoxy-2-phospholene 1-oxides. For instance, a mixture of **298** and **299** is obtained from **297** (equation 156)[148]. In contrast, the action of methanol on the adduct **300** of phosphorus tribromide to 2,3-dimethylbutadiene results in a mixture of 65% of 1-methoxy-3,4-dimethyl-3-phospholene 1-oxide **301** and 35% of 1-methoxy-3,4-dimethyl-2-phospholene 1-oxide **302** (equation 157)[148]. Halophosphites also react with dienes, e.g. equation 158[149].

(156)

(157)

(158)
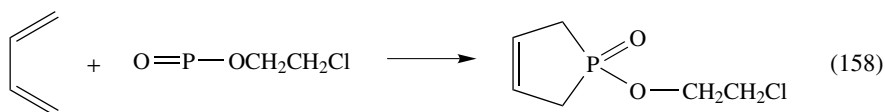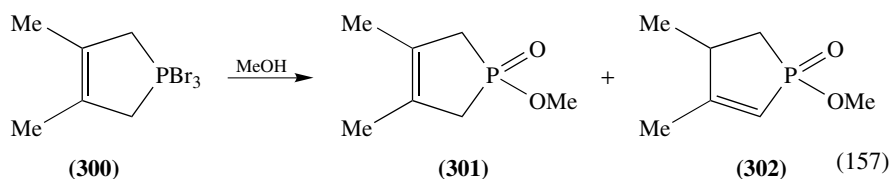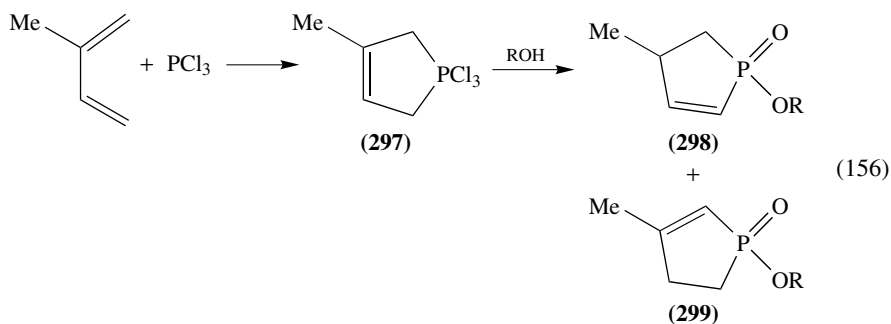
The product **303** from disulfur dichloride and 2,3-dimethylbuta-1,3-diene rearranges spontaneously to the tetrahydrothiophene **304** (equation 159)[150]. The reaction of liquid sulfur dioxide with conjugated dienes **305** (e.g. butadiene, isoprene) results in cyclic sulfones which dissociate into their components on heating (equation 160)[151,152].

(159)

(160)
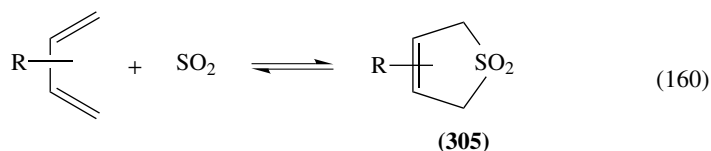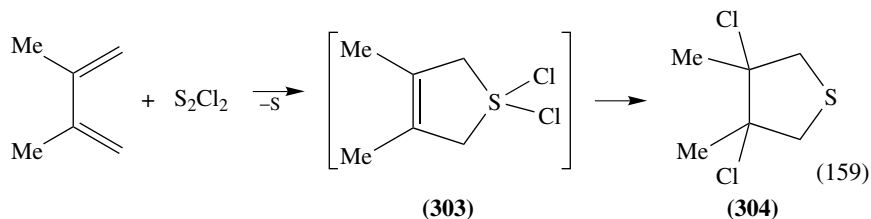
Isoprene, 2,3-dimethylbuta-1,3-diene and other dienes (but not butadiene itself) readily furnish analogous 2,5-dihydroselenophene 1,1-dioxides, e.g. **306**, on treatment with selenious acid in chloroform at room temperature (equation 161)[153].

$$\text{(161)}$$

(306)
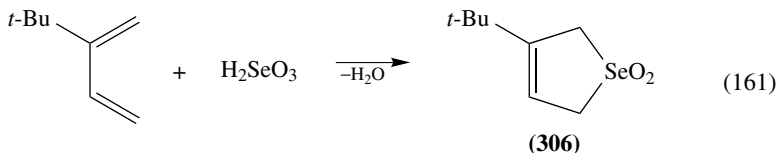
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