Acceleration and Selectivity Enhancement of Diels–Alder Reactions by Special and Catalytic Methods[†]

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Contents

I. Introduction

The Diels–Alder reaction constitutes one of the most frequently employed synthetic methods for pericyclic 6-electron processes resulting in the highly regio-, diastereo-, and enantioselective construction of six-membered and polycyclic ring systems of fundamental interest in organic chemistry.[1] In view of the outstanding importance of the method for the preparation of natural products, and hence also of physiologically active molecules,[1] increasing interest has been placed in recent years on the development of special physical and catalytic methods for the purpose of improving the rate and/or selectivity of [4π + 2π]-cycloadditions. Thus, the present review is intended to provide a survey of those physical and catalytic methods, including special solvent effects, which enhance the rate and/or regio- and stereoselectivity as well as the π-diastereofacial selectivity of Diels–Alder reactions in organic chemistry.

In most cases, these manipulations of the [4 + 2]-cycloaddition procedures enable the reactions to be

carried out under mild conditions and thus considerably extend the scope of cycloaddition reactions with poorly reactive dienophiles. The literature up to the beginning of 1992 is covered.

II. High Pressure

Diels–Alder reactions induced by the application of high pressure have already been reviewed extensively.[2-6] Hence, only a few typical aspects will be discussed here. Intermolecular Diels–Alder reactions have large negative activation volumes (about -25 to -45 cm^3 mol^{-1})[5] as well as large negative volumes of reaction and can accordingly be markedly accelerated by the application of high pressure (typical range is from about 1 to 25 kbar). High-pressure kinetic methods have been widely used to investigate both the structure and the properties of the transition state in Diels–Alder reactions.[2] The use of high-pressure conditions allows cycloaddition reactions of heat-sensitive and/or poorly reactive substrates to be carried out.[3] Thus, for example, the Diels–Alder reaction of 1,4-benzoquinone (1) with methyl 2,4-pentadienoate (2) to furnish 3 proceeds in good yield at room temperature under 15 kbar (reaction time 18 h) (Scheme 1),[7] whereas the yield obtained at atmospheric pressure is significantly lower (24 h at 80 °C; 28%).

Similarly, application of high-pressure conditions to the cycloaddition[8] of (E)-1-methoxy-1,3-butadiene (5) with methyl pyruvate (4) results in an increased yield of 6 (85% with a reaction time of 20 h, as compared to 27% under atmospheric pressure at 160–180 °C, 24 h) (Scheme 2).

New approaches to anthracyclinones via the BCD → ABCD cycloaddition strategy under high pressure were described recently.[9] Thus, the "push–pull" diene 8 underwent smooth addition to the 1,4-anthraquinone 7 under high-pressure conditions (12 kbar) to furnish the expected adduct 9 in 75% yield (Scheme 3). This compound is a potential intermediate for the synthesis of 4-deoxy-ε-rhodomycinone.[9] In the same way, addition of 2-(trimethylsiloxy)-1,3-butadiene (10) to the quinone 7 gave rise to the tetracyclic adduct 11 (Scheme 3), a potential building block for the synthesis of 4-demethoxyfeudomycinone A.[9]

III. Ultrasound (Sonochemistry)

The application of ultrasonic radiation (typical range 20 to 850 kHz) has now been established as a general method to accelerate a variety of chemical reactions.[10-13] Ultrasonic radiation influences chemical processes in solution because the sound waves induce "cavitation",

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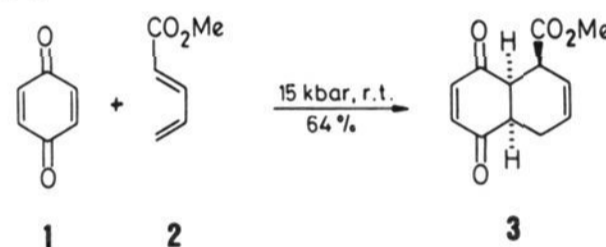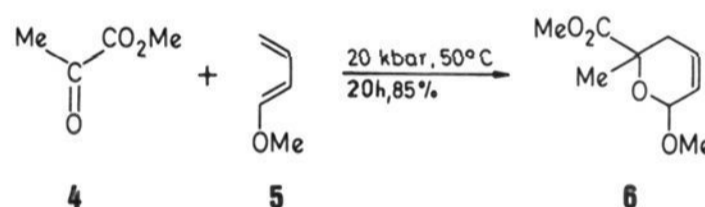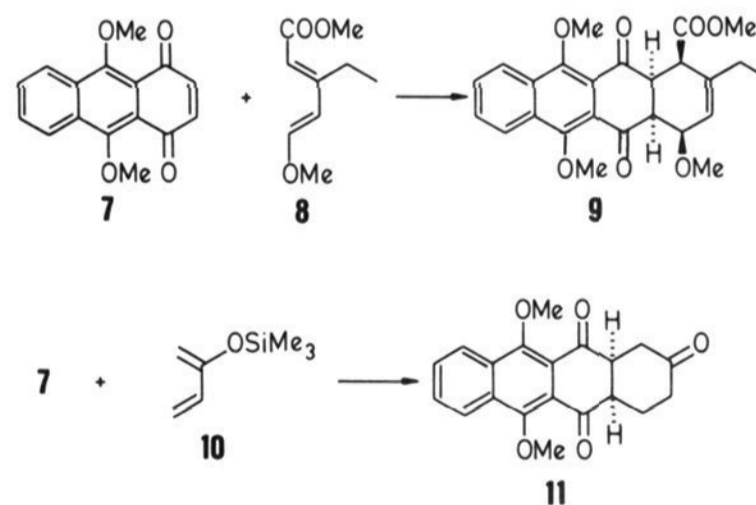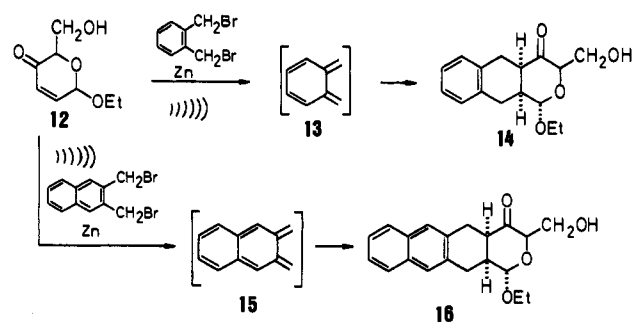
Scheme 1

Scheme 2

Scheme 3

i.e. the rapid growth and sudden collapse of bubbles within the liquid. Surprisingly high pressure, increase of temperature, and electrostatic potential differentials can be achieved in such processes. The following factors have been demonstrated to influence the efficiency of bubble collapse: vapor pressure, temperature, thermal conductivity, surface tension and viscosity, ultrasonic frequency, acoustic intensity, shape of the reaction vessel, and volume of the liquid.[10]

The application of ultrasonic acceleration to Diels–Alder reactions is undergoing continuous expansion. It has been employed in carbohydrate chemistry to prepare optically pure, functionally substituted hexahydroanthracenes and naphthacenes via a Diels–Alder key step.[14] For example, reactions of the carbohydrate enone 12 with the o-xylylenes 13 and 15, generated in situ from the corresponding 1,2-bis(bromomethyl)-arenes by treatment with zinc powder under sonication, afforded the tri- and tetracyclic products 14 and 16 (Scheme 4) which were subsequently converted to anthracene and naphthacene derivatives. These experiments have thus opened new routes to anthracyclinone analogues.[14]

Ultrasound-promoted Diels–Alder reactions were also involved in the synthesis of the o-quinones previously

Scheme 4

isolated from *Salvia miltiorrhiza*.[15] Thus, 3-methyl-4,5-benzofurandione (17) underwent regioselective [4 + 2]-cycloadditions with the dienes 18; subsequent aromatization yielded the tetracyclic products 19 and 20 (Scheme 5). Compound 19c is identical to the naturally occurring comtanshinon IIA; demasking of 19a gave (±)-tanshindiol B (19d). The effect of ultrasound in promoting this cycloaddition parallels that of high pressure and improves the regioselectivity in favor of the natural isomers.

IV. Special Solvent Effects: Solvophobic Effects, Molecular Aggregation

A. Introduction

For a wide range of solvent systems, both the rate constants and the stereoselectivities of Diels–Alder reactions are only moderately sensitive to changes in the nature of the solvent.[16] Nevertheless, the pioneering work of Breslow and co-workers[17] demonstrated the dramatic acceleration of Diels–Alder reactions in aqueous solutions. Other investigations also revealed remarkable rate effects on different types of cycloaddition reactions in water.[18–22]

To obtain an impression of the mechanisms involved, several concepts need to be taken into consideration.
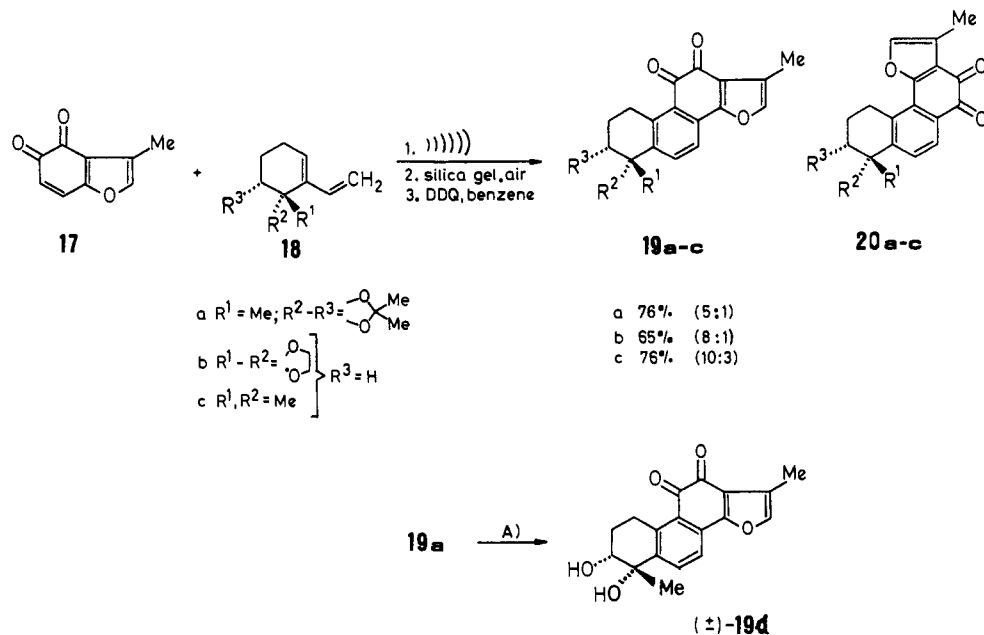
These are the hydrophobic or solvophobic, respectively, packing of diene and dienophile,[17] entropy-driven aggregation processes,[18] and the high internal pressure of water[23,24] and similar solvent systems. In fact, these three terms are equivalent.

The qualitative result of the acceleration can also be described quantitatively by correlating the rate constants to solvent parameters such as $E_T(30)$ values,[21] the polarity parameter,[25] or the solvophobicity parameter S_p.[26] Even the endo:exo ratio of the products shows a correlation with the solvophobicity. It should be noted that the relative influence of solvophobicity on both phenomena seems, in all cases, to depend on the nature of the reagents employed.[28]

The FMO concept offers a completely different approach:[29] the interaction between the solvent, acting as an electrophile, and the dienophile generates a chemical species of the latter with a significantly lowered LUMO energy. More concretely, this can be explained, for example, by hydrogen-bonding interaction between electron lone pairs on the dienophile and acidic hydrogen atoms of the solvent. In other words, the reaction rate is increased as a result of enhanced reactivity of the dienophile. This mechanism can be deduced from the hyperbolic relation between the reaction rates and the acceptor numbers of the solvents.
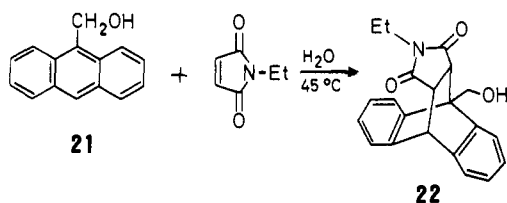
Some other, rather special, phenomena will be discussed only in the context of appropriate reactions.

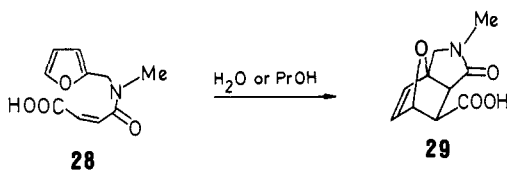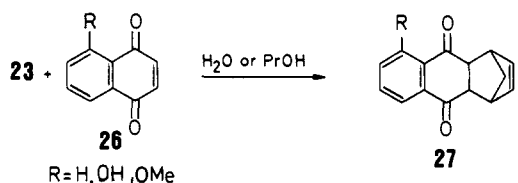### B. Reactions in Aqueous Systems

Some outstanding examples of the acceleration and selectivity enhancement of Diels–Alder reactions in aqueous media or related systems are described below. According to Breslow and co-workers,[17] the rate of the Diels–Alder reaction of 9-(hydroxymethyl)anthracene (21) with N-ethylmaleimide to furnish the bridged anthracene derivative 22 (Scheme 6) was 200 times faster in water than in acetonitrile.

Kinetic measurements on the reactions of cyclopentadiene (23) with the alkyl vinyl ketones 24 and the

Scheme 5

a 76% (5:1)
b 65% (8:1)
c 76% (10:3)

A) Dowex 50(H⁺ form).THF,-70 °C

Scheme 6

Scheme 7

Scheme 8

R	Reaction Conditions	endo/exo Ratio
Et	PhMe, 100 °C, 36h, 97%	0.9
Na	H_2O, r.t., 4.5h, 90%	3

R	Reaction Conditions	Yield
Me	PhMe, r.t., 1 week	Trace
Na	H_2O, r.t., 1h	77%

Scheme 9

36	R
a	Ac
b	H

| 37	R
a	Ac
b	H
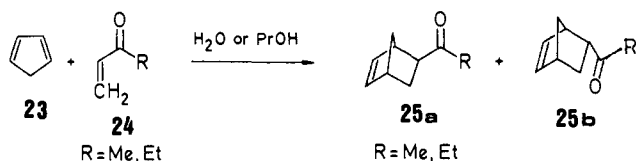
5-substituted 1,4-naphthoquinones **26** as well as the intramolecular Diels–Alder reaction of N-furfuryl-N-methylmaleamic acid (**28**) have been performed in water, in monohydric alcohols, and in highly aqueous solutions containing monohydric alcohols and other organic cosolvents (Scheme 7).[30] Both the inter- and the intramolecular Diels–Alder reactions are characterized by large rate accelerations on changing from an organic solvent to water as the reaction medium.[30] Endo preference is observed, and the inter- and intramolecular reactions are about 200 to 5800 times faster in water than in propanol. These typical, enormous rate enhancements of Diels–Alder reactions in water and in highly aqueous binary mixtures are significantly sensitive to substituent effects.[30] Thus, for example, upon changing the substituent R in **26** from H to OH to OCH₃, an increase of the rate constant in water as the medium is observed. In this case, the acceleration is in harmony with the increasing hydrophobicity of the dienophiles.

Some examples from reports of Grieco and co-workers[18] illustrating how both the reaction rate and the endo:exo diastereoselectivity are significantly influenced by water are given in Scheme 8. It should be noted that, for the reactions in water, the sodium salts of the dienes were used.

Lubineau and co-workers[19,31] have also investigated Diels–Alder reactions in aqueous media. Thus, the novel, water-soluble (E)-butadienyl ethers **36** and **37** were synthesized by using free glucose as the hydrophilic part (Scheme 9).[31] Cycloaddition reactions in aqueous media with a variety of dienophiles revealed rate and selectivity enhancements in comparison with reactions of similar, peracylated dienes in organic solvents (Table 1). In some cases, all four types of stereoisomers, **38a–d**, were formed simultaneously.
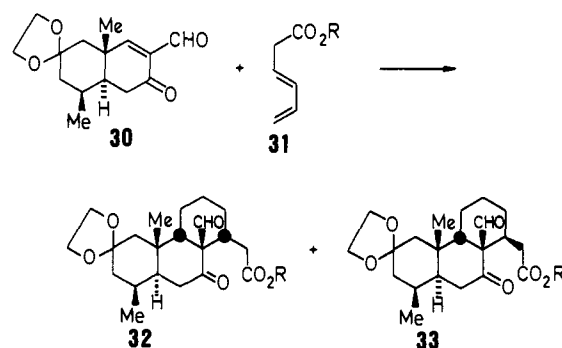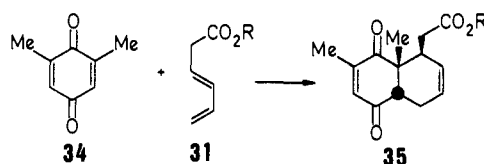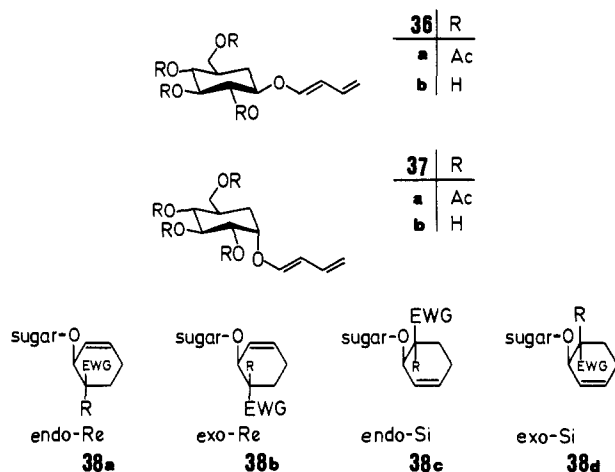
To help rationalize the stereochemistry of cycloadditions using the glycose-substituted substrates, chemical modifications of the glucose moieties in the dienyl glycosides were performed.[32] In this way, several dienyl glycosides possessing a benzyl group at the 2 or 6 position of the sugar ring were obtained. Reactions of these substrates gave rise to the anticipated diastereofacial selectivities.

Thermal Diels–Alder reactions of N-(2-alkenoyl)-(S)-proline esters as chiral dienophiles have been performed in both organic and aqueous reaction media by Waldmann and Dräger.[33] Thus, cyclopentadiene reacts with the benzyl and allyl esters of N-acryloyl-(S)-proline (**39a,b**) in toluene at 0 °C to furnish the bicycloheptenecarboxylic acid amides **40a,b** and **41a,b** with a stereoselection of (2S):(2R) = 81:19 (Scheme 10).

In analogous reactions with the N,N'-fumaroylbis-(proline esters) **42a,b**, the cycloadducts **43a,b** and **44a,b** were formed in high yields and with isomer ratios of up to 97:3 (Scheme 11). In reactions of the acrylamides

Table 1. Cycloadditions of 36 and 37 with the Dienophiles Shown under Various Conditions To Furnish Products 38a–d

EWG = electron withdrawing group

diene	R	EWG	temp (°C)	time (h)	solvent	yield (%)	endo-re (%)	endo-si (%)	exo-re (%)	exo-si (%)	re:si	endo:exo
36b	CH₃	CHO	20	3.5	water	90	60	40			60:40	100:0
36b	H	CHO	20	3	water	92	58	42			58:42	100:0
36b	H	CO₂Me	60	18	water	66	73	27			73:27	100:0
37b	CH₃	CHO	20	6	water	78	34	59	2	5	36:64	93:7
36a	CH₃	CHO	80	168	toluene	80	54	33	8	5	62:38	87:13
37a	CH₃	CHO	80	168	toluene	94	30	54	5	11	35:65	84:16

Scheme 10

a : R = Bzl ; b : R = Allyl
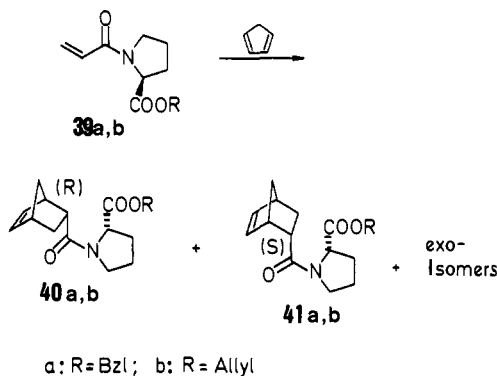
Scheme 11

with cyclopentadiene and of the fumarbisamides with cyclopentadiene, isoprene, and 2,3-dimethylbutadiene (Schemes 10 and 11), the use of water/ethanol mixtures as solvent, in the presence of detergents if necessary, doubled the yields. However, a positive influence of the aqueous medium on the diastereomeric ratio could not be observed.

Hetero-Diels–Alder reactions in aqueous media were first realized by Grieco and co-workers.[18c] For example, the iminium ions, generated in situ from aldehydes and (S)-1-phenylethylamine, reacted with cyclopentadiene to furnish the cycloadducts in a diastereomeric ratio of 4:1.[18c] This methodology was further developed by Waldmann to include the use of amino acid esters as chiral auxiliaries.[34]

Accordingly, the (R)- and (S)-amino acid methyl ester hydrochlorides 51 combined with formaldehyde in THF/water mixtures to furnish the reactive iminium ions 52. The latter species function as electron-deficient dienophiles in hetero-Diels–Alder reactions at 0 °C with cyclopentadiene, cyclohexadiene, and open-chain alkyl-substituted butadienes (diastereomeric ratios up to 93:7, multigram amounts, see Scheme 12 and Table 2).

However, the reactions of alanine, phenylalanine, and leucine with formaldehyde and cyclopentadiene are less diastereoselective. The analogous hetero-Diels–Alder reactions with acyclic 1,3-dienes gave rise to chiral didehydropiperidines with a moderate degree of diastereoselectivity.[34]

In addition to these synthetic investigations, kinetic studies of Diels–Alder reactions in nonaqueous, polar solvents have been performed, and the effects of chaotropic and antichaotropic agents, as well as β-cyclodextrin, were discussed.[17d] Chaotropic agents are compounds (mostly salts) which destroy the ordered structure of liquid water by forming hydrogen bonds;
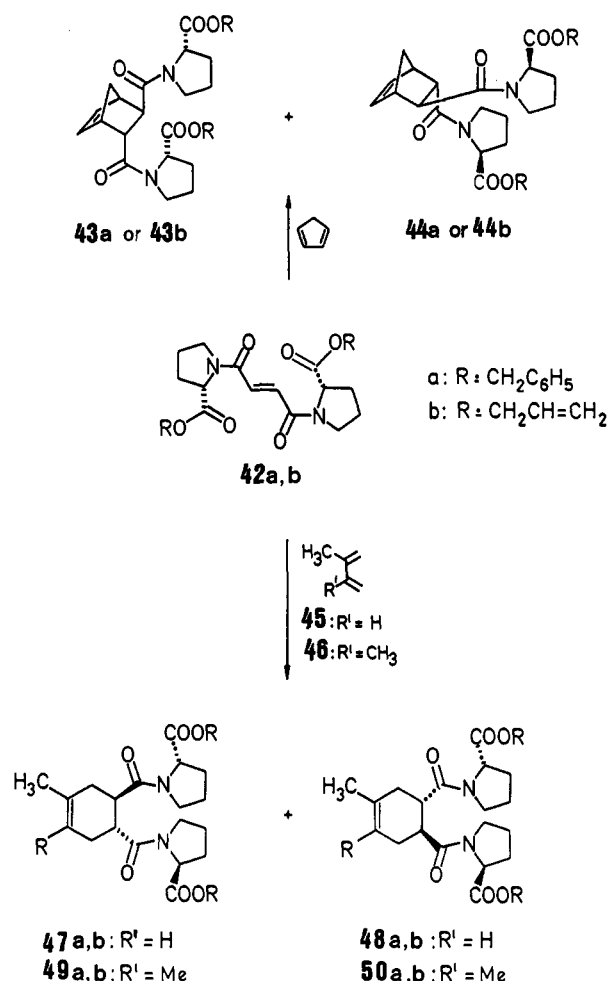
antichaotropic agents are compounds which stabilize the ordered structure of water. Thus, Diels–Alder reactions of nitrosobenzene with 1,3-cyclohexadiene and of methyl vinyl ketone with cyclopentadiene are faster in formamide or ethylene glycol than in other organic solvents, although still not as fast as the reactions in water. Reactions in these solvents are also further accelerated by the presence of β-cyclodextrin. The kinetic results suggest that solvophobic binding of the reactants to each other or into the cyclodextrin cavities occurs in these polar solvents.

From the Diels–Alder reaction of 55 with N-ethyl-maleimide (56) to furnish the cycloadduct 57 (added salts LiCl and guanidinium chloride), it was concluded on the basis of second-order rate constants that hydrophobic packing effects significantly influence the
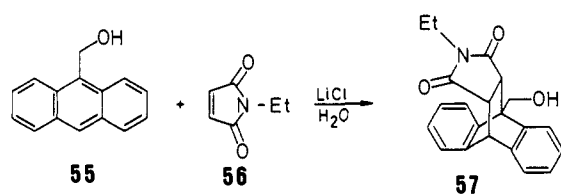
Scheme 12

Scheme 14
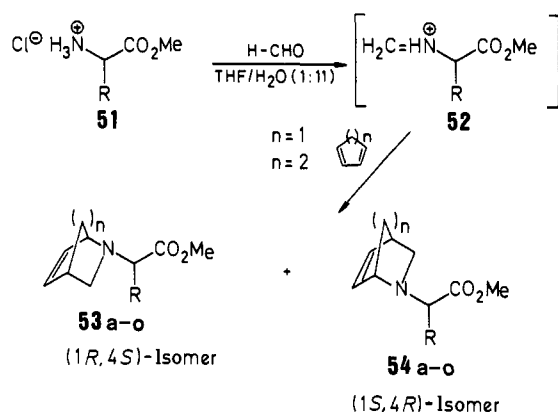
Table 2. Hetero-Diels-Alder Reactions of the Iminium Ions 52 with Cyclopentadiene and 1,3-Cyclohexadiene

product 53/54	amino acid methyl ester	diene[a]	yield (%)	ratio of diastereomers 53:54
a/a	Gly[b]	Cp	77	
b/b	(S)-Ala	Cp	99	73:27
c/c	(S)-Phe	Cp	75	68:32
d/d	(S)-Leu	Cp	85	64:36
e/e	(S)-Val	Cp	74	86:14
f/f	(S)-Ile	Cp	57	93:7
g/g	(S)-Phg	Cp	97	78:22
h/h	(S)-Ser	Cp	63	87:13
i/i	(R)-Val	Cp	69	17:83
j/j	(R)-Phg	Cp	90	20:80
k/k	(R)-Ser	Cp	66	12:88
l/l	(S)-Ile	Ch	35	80:20
m/m	(S)-Phg	Ch	51	54:46
n/n	(R)-Phg	Ch	35	43:57
o/o	(R)-Ser	Ch	40	27:73

[a] Cp = cyclopentadiene; Ch = 1,3-cyclohexadiene. [b] Glycine ethyl ester.

Table 3. Effects of Solvent on the Diels-Alder Reaction of 58 and 59 To Furnish 60

solvent	dielectric constant	relative rate[a]
benzene-d_6	2.3	1.0
acetonitrile-d_3	36.2	1.8
dimethyl sulfoxide-d_6	46.6	3.1
methanol-d_4	32.6	4.1
D_2O	78.0	no reaction
ethylene glycol	37.7	26.1

[a] All reaction rates were determined by NMR spectroscopy.
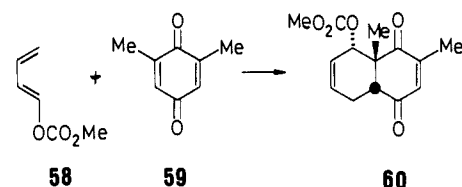
Scheme 13

reaction in the presence of water (Scheme 13).[35] In summary, the action of chaotropic salts can accelerate Diels-Alder reactions considerably.

C. Reactions of Nonaqueous Polar or Water-like Systems

In the context of these investigations on solvent-dependent Diels-Alder reactions, the characteristics of water-free microemulsions were examined.[36] Thus, the use of the Diels-Alder reaction between methyl acrylate and cyclopentadiene as a chemical probe in a water-free formamide microemulsion system has resulted in a conductivity diagram (conductivity versus volumic fraction of formaldehyde), exhibiting two distinct endo:exo-selectivity zones.[36] Even so, good selectivity and high cycloadduct yields can be obtained from Diels-Alder reactions in formamide. Similar to the reactions in water, the use of other solvents with high dielectric constants favors the formation of the

endo isomer; this is probably also due to a "solvophobic" interaction.

The rates of intermolecular Diels-Alder reactions involving, for example, relatively hydrophobic dienes and dienophiles such as 58 and 59 (Scheme 14) are significantly increased when the reactions are carried out in pure ethylene glycol. These rate enhancements are best rationalized in terms of molecular aggregation phenomena.[37] The results of these investigations are listed in Table 3.

It is apparent that performance of the reaction in ethylene glycol results in a substantial increase in the rate relative to benzene (26:1). In retrospect, this result is not so surprising since ethylene glycol possesses, in addition to the facility for extensive hydrogen bonding, the capability for solubilization of hydrophobic dienes and dienophiles. Molecular aggregation should be favored for the π-stacked arrangement of the reactants of type A as compared to the end-on arrangement of type B (Figure 1). In the reagent aggregate A, the volume will be kept to a minimum. The relative concentrations of productive arrangements of diene and dienophile are larger for type A and, as a consequence, the observed reaction rates are higher.

The number of known micellar-induced reactions has increased considerably in recent years.[38] From kinetic studies of the reactions of cyclopentadiene with styrene, cyclopentadiene, acrylonitrile, or acrylates as dienophiles, it was found that the [4 + 2]-cycloadditions are faster in micelles as compared to the reactions in dioxane.[39] Sodium dodecyl sulfate has been used to induce micelle formation; a high endo preference and high acceleration were observed with less water-soluble dienophiles such as n-butyl acrylate. The polarities inside the micelles were estimated from experimental observations (for example, kinetic data, E_T solvent parameters, endo:exo ratios); it could be concluded that the reaction site, that is the inner space of the micelles, has a polar character.

Changes in the stereoselectivity and rate in Diels-Alder processes by hydrophobic solvent effects and by the presence of bovine serum albumin were observed in the reactions of 1,4-naphthoquinone derivatives with various dienes (Scheme 15).[40] The largest increase in reaction rate on changing the solvent from benzene to water was observed for the reaction of 5-methoxy-1,4-
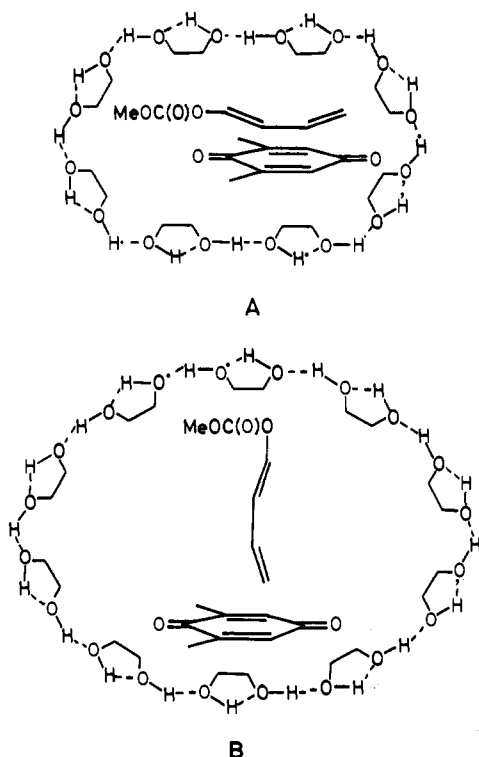
Figure 1. (A) π-Stacked arrangement and (B) end-on arrangement.

Scheme 15
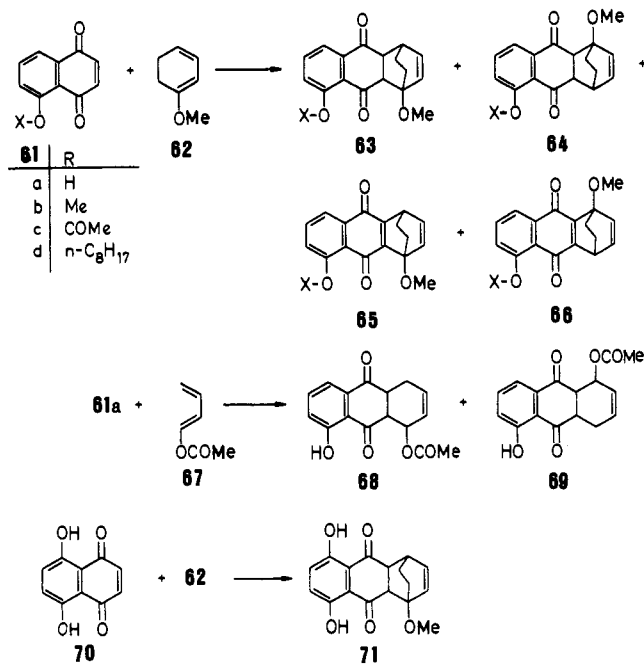
naphthoquinone (61b) with 62; juglone (61a) as well as 5-acetoxy- and 5-(octyloxy)-1,4-naphthoquinones (61c and 61d, respectively) showed intermediate behavior. As expected, the more hydrophilic naphthazarin (70) exhibited a similar reactivity toward 1-methoxycyclo-hexadiene (62) in both water and benzene. However, the regio- and stereoselectivities of these reactions are strongly influenced by the solvent. In the same context, the influence of a catalytic amount of bovine serum albumin on the regio- and stereoselectivity has been investigated in detail.[40] The results indicate that the globular protein did not affect the regioisomer ratio of
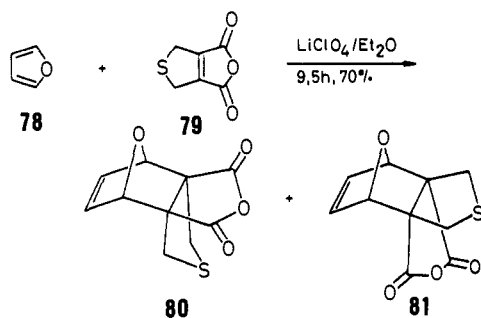
Scheme 16
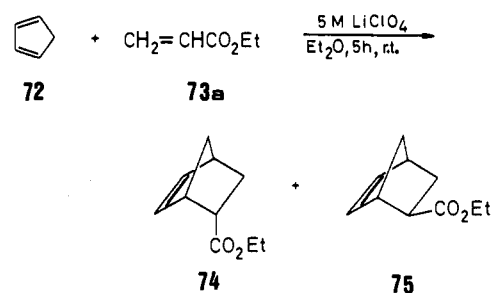
Scheme 17
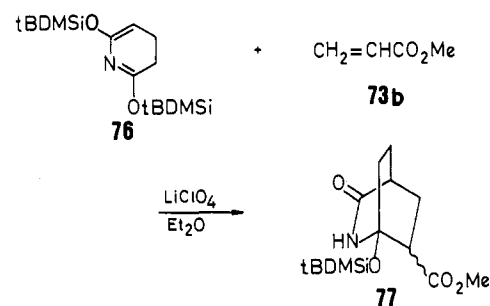
the adducts although some π-diastereofacial selectivity was achieved. The highest enantiomeric excess (38%) was observed in the cycloaddition of juglone (61a) to the diene 62, whereas racemic products were obtained with the n-octyl derivative 61d. Chirality transfer on formation of stable complexes of the quinone chromophore with the (chiral) bovine serum albumin has been discussed on the basis of circular dichroism results.[40]

Sauer and Braun[41] first investigated the influence of LiClO₄ in diethyl ether on the endo:exo ratio of the Diels–Alder reaction of cyclopentadiene with methyl acrylate. This reaction served as a model system for a general survey of the polarity of LiClO₄/diethyl ether solutions. It was found that an increase in the concentration of LiClO₄ in the system was accompanied by increased formation of the endo product. Hence, it was concluded that the presence of this salt should accelerate reactions with polar transition states. On addition of LiClO₄ to diethyl ether, the polarity of the system can be increased by up to about 20 E_T units. In addition to these interesting results, large accelerations of Diels–Alder reactions performed in the presence of a 5 molar solution of lithium perchlorate in diethyl ether have been reported.[18e,42a,b] The reaction of cyclopentadiene (72) with ethyl acrylate (73a) was also studied in detail (Scheme 16).[42b]

A yield of 93% and an endo:exo ratio of 8:1 was obtained for the norbornene derivatives 74 and 75. A further example is the reaction of the azadiene 76 with methyl acrylate (73b) (Scheme 17). After a reaction time of 5 h, the cycloadduct 77 was formed in 80% yield, whereas, for example, the reactants needed to be heated for 72 h at 60 °C in benzene to achieve a yield of 74%. The reaction illustrated in Scheme 18 is also of interest as a pivotal step in the synthesis of cantharidine.

The efficiency of this reaction is surprising since the aromatic furan is known to be one of the less reactive dienes. A direct relation between the reaction rate and the molarity of the LiClO₄ solution was demonstrated.[42b]

Scheme 18

Scheme 19

a, X = CO$_2$Me; b, X = COMe

Scheme 20
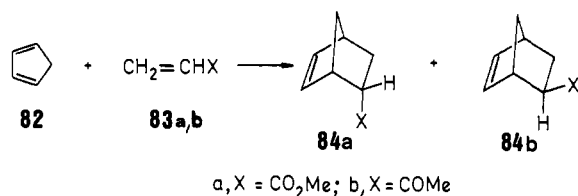
The accelerating effect of the LiClO$_4$–diethyl ether solution can be visualized in analogy to the reaction in water by the creation of an "inner pressure" caused by the change in the solvent structure which induces a "compression" of the reactants.

On the other hand, and in the light of other work,[41] the stabilization of a polarized transition state cannot be discounted because of the relatively high concentration of LiClO$_4$ in the system. As an alternative explanation, Dailey and co-workers[43] presented evidence that the rate accelerations of Diels–Alder reactions in LiClO$_4$–diethyl ether may be due to a Lewis acid catalytic effect by the lithium cation. The second-order rate constants of the Diels–Alder reaction between 9,10-dimethylanthracene and acrylonitrile in diethyl ether were found to depend on the lithium ion concentration. The authors' hypothesis for a "lithium ion-induced effect" was based on the fact that, in general, those Diels–Alder reactions which are susceptible to Lewis acid catalysis can also be accelerated by increasing the concentration of lithium ions.

Recently, ethylammonium nitrate (EAN) was employed as an unusual solvent in Diels–Alder reactions.[44] This salt has a very low melting point (about 12 °C), and it is known that the molten salt has properties similar to those of water. The reactions of cyclopentadiene (82) with methyl acrylate (83a) and methyl vinyl
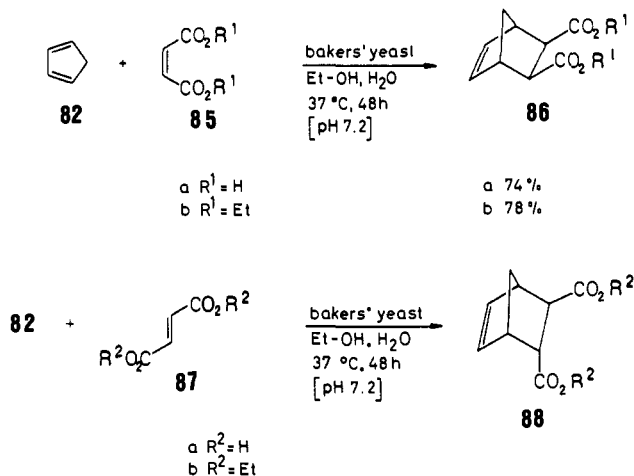
ketone (83b) were investigated (Scheme 19). In comparison to reactions in nonpolar organic solvents, a higher endo selectivity and, in part, also a higher reaction rate were observed (Table 4). However, the application of EAN will probably be limited because of the danger of explosion.

V. Protein, Antibody, and Enzyme Catalysis

The effect of catalytic amounts of bovine serum albumin for controlling the stereoselection of Diels–Alder reactions was already discussed in section IV.[40] In the meantime, bakers' yeast-mediated transformations have now been widely used for numerous types of reactions in organic chemistry.[45] Biocatalysts have also been successfully employed in Diels–Alder reactions. For example, the [4 + 2]-cycloaddition of cyclopentadiene (82) with the unsaturated carboxylic acid derivatives 85 and 87 have been performed in the presence of bakers' yeast (Scheme 20).[46] In contrast to the usual result (endo selectivity), the dienophiles 85a,b now preferentially form the exo cycloadducts 86.
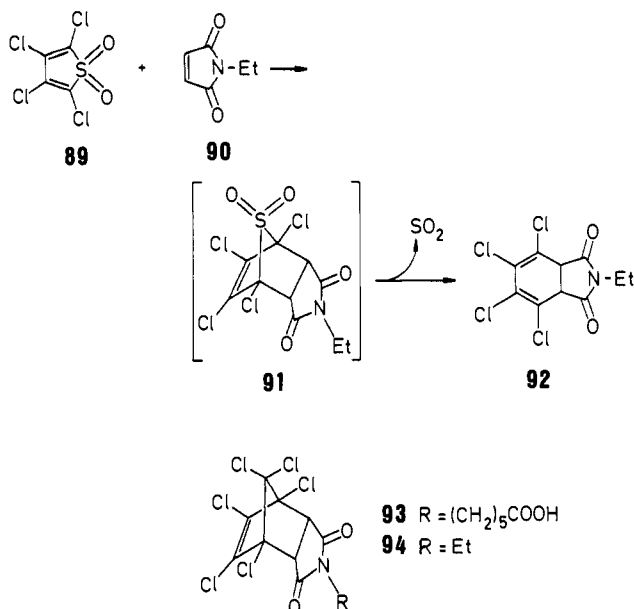
Recent work has been focused on the mammalian immune system as a source of highly specific, tailored catalysts. With transition-state analogues as haptens, it has been possible to elicit antibodies which promote a variety of chemical transformations including ester and amide hydrolysis, photochemical processes, sigmatropic rearrangements, and a β-elimination.[47–49] Antibody catalysis of a Diels–Alder reaction has also

Table 4. Diels–Alder Reactions of Cyclopentadiene (82) with Methyl Acrylate (83a)

solvent	temp (°C)	conc of 82 (M)	conc of 83a (M)	added salt (1.0 M)	ratio of 84a:84b	$10^4 k_2$ M^{-1} sec^{-1}
EAN	25 ± 2	0.20	0.20		6.7	
EAN	20.0 ± 0.2	0.010	0.20		6.7	1.7
EAN	20.0 ± 0.2	0.010	0.20	LiCl	7.2	1.6
EAN	20.0 ± 0.2	0.010	0.20	LiI	7.4	5.4
water	21 ± 1	0.00040	0.012			30
water	25	0.15 (0.30)	0.15 (0.30)		9.3 (5.9)	
water	20	0.15 (0.30)	0.15 (0.30)		7.4 (5.3)	
1-chlorobutane	35					0.53
benzene	35	1.25	1.25		2.8	
ethanol	30				5.2	
methanol	26				7.0	
formamide	20	0.15 (0.30)	0.15 (0.30)		6.7 (6.7)	

Scheme 21

been reported.[49] The transition state of a Diels–Alder cycloaddition is highly ordered, resembling the product more closely than the starting materials. Hence, the reaction shown in Scheme 21 was chosen as a model for antibody-catalyzed cycloadditions. It was reasoned that a stable analogue of the bicyclic adduct should be able to elicit an antibody combining site with the proper shape for promoting the desired reaction. Since the final product **92** does not closely resemble the transition state of the Diels–Alder reaction, product inhibition should be minimized, thus allowing multiple turnovers of the catalyst.

Accordingly, high-affinity, monoclonal antibodies against the hapten **93**, a stable analogue of the bicyclic adduct **91**, were prepared. However, the antibodies had to be modified slightly (reductive methylation) before they could be used in the Diels–Alder reaction. Antibodies of the type 1E9 (secreted by hybridoma 1E9) were found to promote the model reaction with multiple turnovers (>50). The process is first order with respect to immunoglobulin concentration. Thus, on the basis of kinetic measurements, N-ethylmaleimide is a good substrate for the catalyst while maleimide itself is not. Furthermore, the catalyzed reaction is strongly inhibited by compound **94**, a close analogue of the hapten used for immunization. The authors are currently extending this concept to include other [4 + 2]-cycloadditions. Tailored "Diels–Alderase" antibodies as so called "abzymes" should be particularly valuable tools to study proximity effects in catalysis and to achieve regio- and stereoselective transformations in organic synthesis. However, the main problem will generally be the search for an appropriate hapten for the production of the respective antibodies.

VI. Acidic Catalysts

It is well known that numerous Diels–Alder reactions are accelerated by Brönsted or Lewis acids via protonation or complexation of the dienophile.[1,16] According to the frontier molecular orbital (FMO) concept, a significant lowering of the LUMO energy of the dienophile is responsible for the acceleration and

enhanced selectivity usually observed in a HOMO-(diene)–LUMO(dienophile) controlled step (see also Figure 2).[50]

A. Brönsted Acids

The kinetics of Diels–Alder reactions of cyclopentadiene with ethyl acrylate, methyl methacrylate, methyl vinyl ketone, acrylonitrile, acrylic acid N,N-diethylamide, or dimethyl maleinate in the presence of acetic acid, bromoacetic acid, dichloroacetic acid, or trichloroacetic acid have been studied.[51,52] These Brönsted acids generally accelerate the Diels–Alder reactions with trichloroacetic acid usually being the most effective. However, the endo transition state is not specially favored in the reactions of cyclopentadiene with acrylonitrile in the presence of the tested acids.

In general, protic acid-catalyzed [4 + 2]-cycloadditions have received only limited attention although Olah and co-workers[53] had reported that Nafion-H (**95**), a
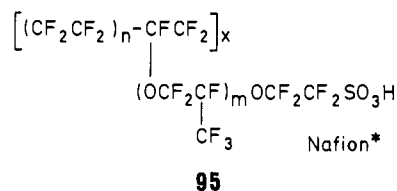
perfluorinated resin–sulfonic acid, is a highly efficient catalyst. For example, 1,4-benzoquinone (**96**) reacts with isoprene (**97**) at room temperature in the presence of Nafion-H to form cycloadduct **98** in high yield (Scheme 22).
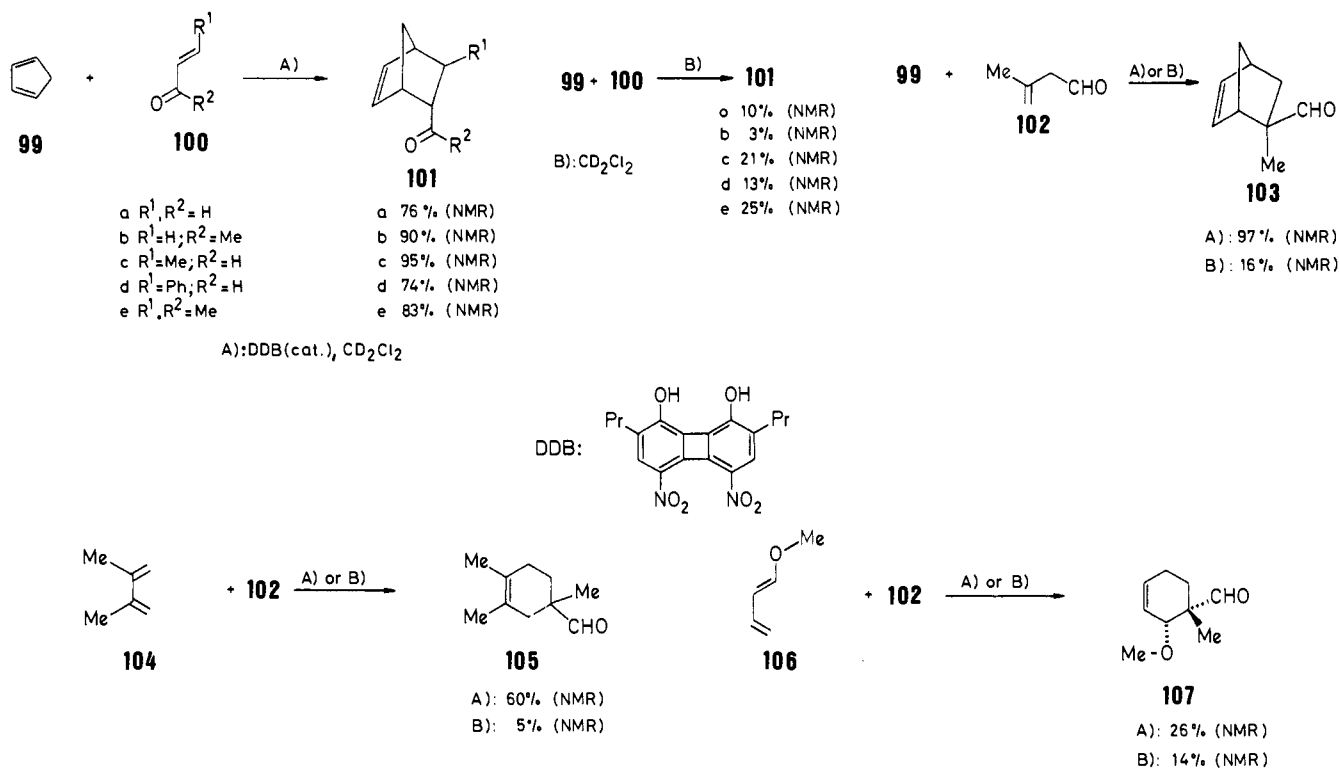
Scheme 22
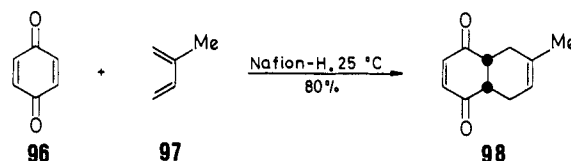
1,8-Dihydroxy-4,5-dinitro-2,7-dipropylbiphenylene (DDB) catalyzes the Diels–Alder reactions of cyclopentadiene (**99**), 2,3-dimethylbutadiene (**104**), and 1-methoxybutadiene (**106**) with the carbonyl group-functionalized dienophiles **100** and **102** (Scheme 23).[54]
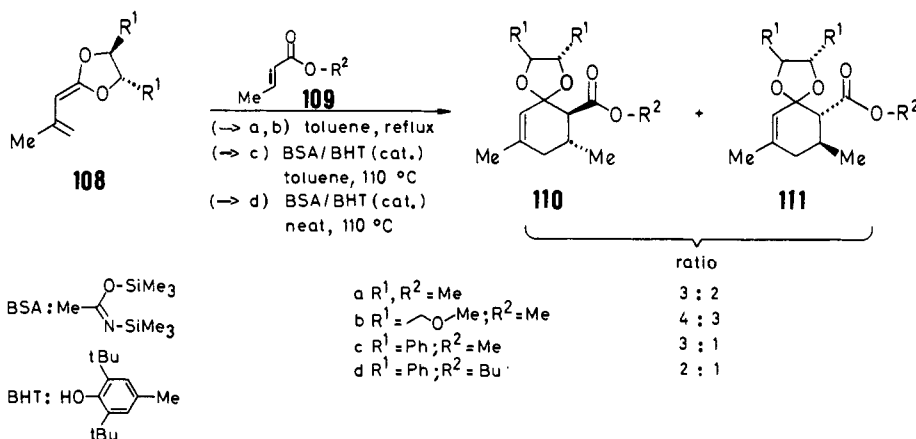
The differences between the yields of the catalyzed and uncatalyzed reactions shown in Scheme 23 are significant. The rate acceleration is due to complexation of the catalyst with the carbonyl groups of the dienophiles **100** and **102**.

A mixture of 3,5-di-tert-butyl-4-hydroxytoluene (BHT) and N,O-bis(trimethylsilyl)acetamide (BSA) catalyzes asymmetric Diels–Alder reactions. For example, enantiomerically pure vinyl ketene acetals such as **108** reacted with dienophiles **109** to furnish the isomeric cycloadducts **110** and **111** (Scheme 24).[55] When the substituents in **108** are small, the facial selectivity of the reaction is modest while the presence of a bulky phenyl group (R^1 = Ph) results in an increased diastereomeric excess. High diastereoselectivity is observed in the reaction of **108c** with N-methylmaleimide. Furthermore, it was shown that the application of high pressure also increased the selectivity in reactions with **108**, whereas variations of the solvent
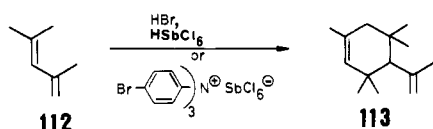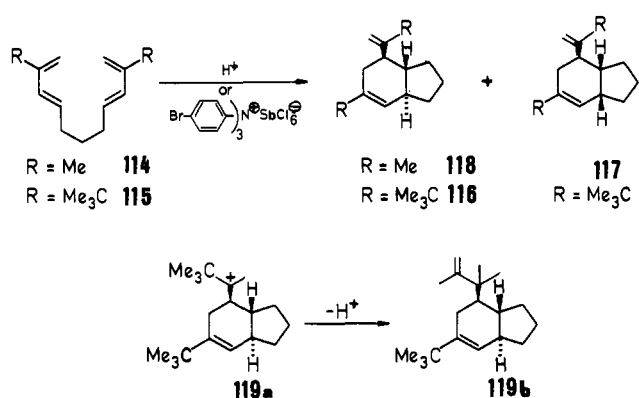
Scheme 23

99   100

101

a R¹,R² = H
b R¹=H;R²=Me
c R¹=Me;R²=H
d R¹=Ph;R²=H
e R¹,R²=Me

a 76 % (NMR)
b 90% (NMR)
c 95% (NMR)
d 74% (NMR)
e 83% (NMR)

A):DDB(cat.), CD₂Cl₂

99 + 100 ──B)──► 101

o 10% (NMR)
b 3% (NMR)
c 21% (NMR)
d 13% (NMR)
e 25% (NMR)

B):CD₂Cl₂

99 + Me ... CHO ──A)or B)──►

102

103

A): 97% (NMR)

B): 16% (NMR)

DDB:

104 + 102 ──A) or B)──► 105   106 + 102 ──A) or B)──► 107

A): 60% (NMR)
B): 5% (NMR)

A): 26% (NMR)
B): 14% (NMR)

Scheme 24

108

109

(→ a,b) toluene, reflux
(→ c) BSA/BHT(cat.)
        toluene, 110 °C
(→ d) BSA/BHT(cat.)
        neat, 110 °C

110   +   111

BSA : Me⟨O-SiMe₃ / N-SiMe₃⟩

BHT: HO⟨tBu / Me / tBu⟩

a R¹,R² = Me
b R¹ = ⌒O⌒Me ;R²=Me
c R¹ =Ph;R² =Me
d R¹ =Ph;R² = Bu·

ratio

3 : 2
4 : 3
3 : 1
2 : 1

Scheme 25

112

HBr,
HSbCl₆
or
Br-⟨⟩-N⊕ SbCl₆⊖
     3

113

polarity and the use of Lewis acid catalysts did not influence the outcome of the reaction.

Further proton-catalyzed, so-called "ionic" Diels–Alder reactions were investigated systematically by Gassman and co-workers via the in situ generation of cationic species from olefinic precursors.[56] In some cases, these results were compared with the corresponding cation radical-induced process (see also section IX). In addition to the aminium cation radical-induced Diels–Alder dimerization of 112 to 113, the use of proton catalysis by, for example, hydrogen bromide and hexachloroantimonic acid, was also successful (yields of 95 and 88%, respectively) (Scheme 25).[56]
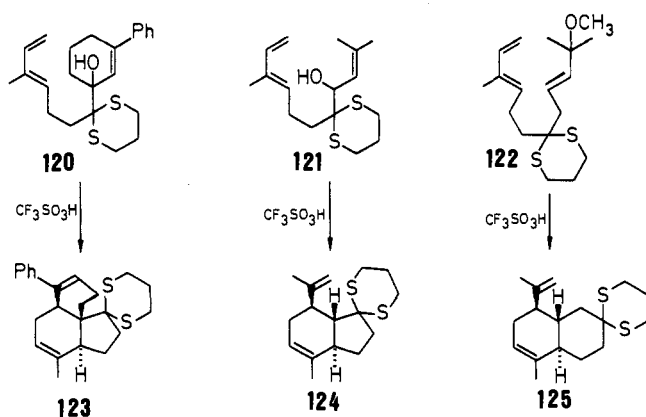
Furthermore, intramolecular, ionic Diels–Alder reactions were performed via in situ generation of allylic cations. These procedures are catalyzed by protic acids and aminium cation radicals. For example, the unreactive tetraenes 114 and 115 reacted in the presence of either tris(p-bromophenyl)ammonium hexachloroantimonate, HSbCl₆, CF₃SO₃H, or p-toluenesulfonic acid to furnish products 116, 117, and 119b (Scheme 26).[57] The formation of 119b is suggestive of a cationic intermediate such as 119a, which, however, would not be expected from a cation radical-catalyzed cyclization. On the other hand, when 114 was treated with CF₃SO₃H at -23 °C, compound 118 was obtained in 88% yield after a reaction time of 6 min. The aminium radical cation seems to act in these cases mainly as an indirect source of protons which are then utilized in an acid-catalyzed Diels–Alder reaction.

Later, the allylic alcohols 120 and 121 as well as an allylic ether 122 were used as precursors of the allylic cation, generated by treatment with CF₃SO₃H in

Scheme 26

R = Me **114**
R = Me$_3$C **115**

R = Me **118**
R = Me$_3$C **116**

117
R = Me$_3$C

119a

119b

Scheme 27

120

121

122

CF$_3$SO$_3$H

CF$_3$SO$_3$H

CF$_3$SO$_3$H

123

124

125

dichloromethane, in an intramolecular, ionic Diels–Alder reaction.[58] Under complete control of the regio- and stereochemistries, the polycyclic products **123–125** were obtained (Scheme 27).

Evidence in support of a stepwise mechanism for a proton-induced, "formal" intramolecular Diels–Alder reaction has been presented.[59] A cation-induced Diels–Alder reaction has also been employed as a chemical probe for the analysis of an unsymmetrical 1,1,3,3-tetramethylallyl cation generated by reaction of a diene system with either CF$_3$SO$_3$H or CF$_3$SO$_3$D.[60]

B. Lewis Acids and Related Catalysts

Lewis acid-catalyzed cycloadditions not only proceed more rapidly than their thermal counterparts but are also generally more regio- and stereoselective. For this reason, such reactions are of additional interest from a theoretical point of view since they appear to represent an exception to the reactivity–selectivity principle. Theoretical interpretations of the apparently anomalous course of these Lewis acid-catalyzed reactions have been proposed by Epiotis and co-workers[61] and by Branchadell and co-workers[62] while the FMO theory was successfully applied to explain the role of the Lewis acid catalyst.[50] Donor–acceptor interactions between the dienophile and the catalyst thus lower the energy of the HOMO and the LUMO of the dienophile. For the case of a [π4s + π2s]-cycloaddition with normal electron demand, this means that the separation between the MO's will decrease and the stabilization of the transition state will increase (Figure 2).

The literature on the acceleration of Diels–Alder reactions by common Lewis acids such as TiCl$_4$, SnCl$_2$,
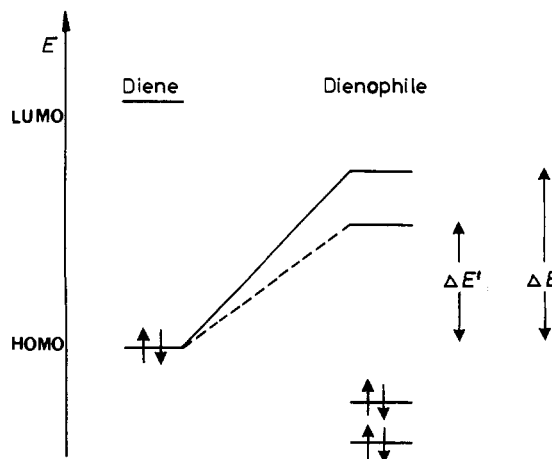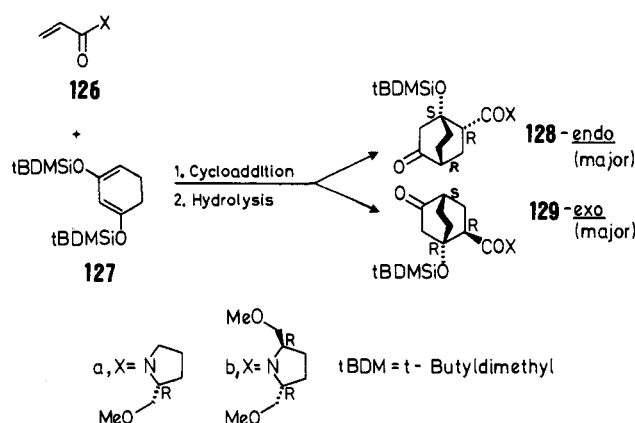
Figure 2. HOMO–LUMO arrangements for Lewis acid-catalyzed (broken line) and uncatalyzed (solid line) Diels–Alder reactions with normal electron demand.

Scheme 28

126

+

127

1. Cycloaddition
2. Hydrolysis

128 - _endo_ (major)

129 - _exo_ (major)

a, X=

b, X=

tBDM = t- Butyldimethyl

ZnCl$_2$ (complexed with ethers), ZnBr$_2$, BF$_3$ (including ether complexes), EtAlCl$_2$, Et$_2$AlCl, SnCl$_4$, achiral and chiral lanthanide complexes [e.g. Eu(III) and Yb(III) complexes] is so extensive that even a mere listing of the relevant citations would be beyond the limits of this review. However, a few special applications of related catalysts will be discussed.

In general, the endo:exo ratio is strictly controlled by the choice of the catalyst. For example, cycloaddition reactions of the 1,3-bis(silyloxy)cyclohexadiene **127** with chiral acrylamides **126**, derived from chiral pyrrolidines, occur with high endo:exo diastereofacial selectivities (Scheme 28).[63a]

The following conclusions can be drawn from an examination of the data given in Table 5. For the case of endo:exo ratios: as previously observed with N,N-dimethylacrylamide, the reactions of **126a** and **126b** with **127** show high endo:exo ratios favoring the endo isomer when tert-butyldimethylsilyl triflate (t-BuMe$_2$-SiOTf) is used as catalyst and the exo isomer when Eu(fod)$_3$ is the catalyst.[63a,b] The thermal reaction (performed at 170 °C) also gave the exo isomer as the major product although the selectivity was lower.

Diels–Alder reactions with the silyloxydiene **130** and the imines **131** occur with high exo selectivity with dependence on the reaction conditions and in the presence of a Lewis acid catalyst such as tert-butyldimethylsilyl triflate, trimethylsilyl triflate, Eu(fod)$_3$, or AlCl$_3$ (Scheme 29).[64] The exo cycloadducts **132a–c** are formed exclusively under kinetic control when tert-

Table 5. Reactions of the Diene 127 with the Acrylamides 126a and 126b

dienophile 126	catalyst (10% molar)	solvent	temp (°C)	time	yield (%)	endo:exo ratio	% de of endo	% de of exo
a	t-BuMe₂SiOTf	CH₂Cl₂	–60	30 min	87	84:16	77	96
a	Eu(fod)₃	toluene	80	24 h	90	0:100		25
b	none	toluene	170ᵃ	64 h	66	23:77	13	74
b	t-BuMe₂SiOTf	toluene	20	40 min	75	70:30	>98	98
b	t-BuMe₂SiOTf	toluene	–60	3 h	60	87:13	>98	>98
b	t-BuMe₂SiOTf	CH₂Cl₂	–60	30 min	96	88:12	>98	>98
b	Eu(fod)₃	toluene	80	66 h	98	0:100		90

ᵃ Reaction performed in a sealed tube.

Scheme 29

a   R = C₆H₅
b   R = 4-CH₃O-C₆H₄
c   R = 2,4,6-(CH₃)₃-C₆H₂

132 exo   133 endo   134
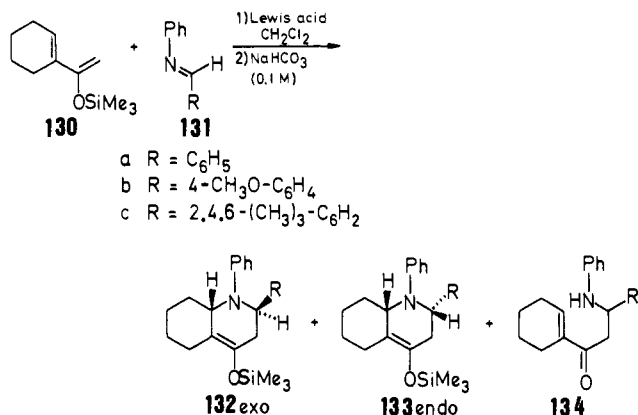
butyldimethylsilyl triflate is used as the catalyst. In the presence of AlCl₃ under thermodynamic control, however, a high endo selectivity has, as yet, only been observed in the case of the imine 131b. In some cases, depending on the type of Lewis acid and the reaction conditions, the α,β-unsaturated ketone 134 is also formed.

Enantiomerically pure α,β-unsaturated sulfoxides, used for example as masked chiral ketene equivalents, are of current interest as dienophiles in asymmetric Diels–Alder reactions.[65] Thus, (+)-(S)-1-(tert-butyl-sulfonyl)-1-(p-tolylsulfinyl)ethene (135) reacts with cyclopentadiene in the presence of catalysts to furnish the norbornene derivatives 136 in high stereoselectivity (Scheme 30).[65] In the absence of catalysts, on the other hand, the reaction is very slow and the selectivity poor while rapid decomposition of the dienophile 135 takes

place in the presence of strong Lewis acids (BF₃·Et₂O, Et₂AlCl, EtAlCl₂). But with moderately acidic catalysts such as ZnBr₂, Eu(fod)₃, or SiO₂ the Diels–Alder reaction proceeds under mild conditions to furnish the product 136 in good yield (Scheme 30). A high stereoselectivity is observed and 136c is the main product of the catalyzed reactions.

Some more recent Lewis acid catalysts such as 2-bromo-1,3,2-benzodioxaborole (137) and the less corrosive (and milder) ferrocenium hexafluorophosphate (138) even accelerate Diels–Alder reactions of cyclic and acyclic carbodienes with dienophiles bearing a carbonyl or ester functional group.[66] However, reactions of acrylonitrile are not influenced by these catalysts.

The aluminum(III) tetraphenylporphyrin chloride (AlTPPCl) has been found to catalyze Diels–Alder reactions of enones and methyl acrylate with cyclopentadiene or isoprene,[67] and the results were compared with those obtained using Et₂AlCl as catalyst. Several competitive cycloaddition reactions were also performed for the purpose of assessing the relative reactivities of the various dienophiles in AlTPPCl-catalyzed reactions. The data reveal that the metalloporphyrin catalyst discriminates essentially on the basis of electronic effects.

Norbornadienes bearing a tether at C-2 containing an alkyne group such as 139 and 141 have been found to undergo cobalt-catalyzed, intramolecular homo-Diels–Alder reactions to furnish the pentacyclic cycloadducts 140 and 142 (Scheme 31, Table 6).[68] These reactions involve Co(II) and Co(III) salts in the presence of 2–4 equiv of diethylaluminum chloride. Thus, it
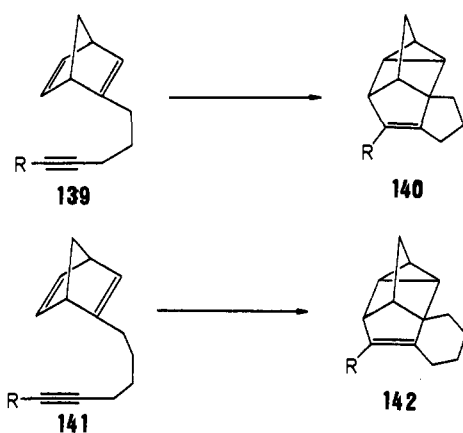
Scheme 30

135   136a,136b,136c,136d

Lewis acid	Time(h)	Yield 136 (%)	ratio 136a:136b:136c:136d	Yield 136c (%)
---	66	36	9 : 23 : 35 : 23	--
ZnBr₂(0.8 eq.)	6	68	12 : -- : 88 : --	58
Eu(fod)₃ (1.0 eq.)	42	70	8 : -- : 92 : --	62
SiO₂ (without solvent)	48	72	10 : -- : 84 : 6	63

136c   137   138

Scheme 31

139 → **140**

141 → **142**

Table 6. Intramolecular Cycloadditions of Dienynes 139 and 141 under Cobalt Catalysis

dienyne no.	R	reaction conditions[a] (% Co)	cycloadduct	yield (%)[b]
139a	H	A	no reaction	
139a	H	B (7%)	140a	78
139a	H	C (7%)	140a	64
139b	Me	B (8%)	140b	69
139c	Me₃Si	B (10%)	140c	63
139d	Ph	B (11%)	140d	70
141a	H	B (5%)	142a	64
141b	Me	B (8%)	142b	43
141c	Me₃Si	B (10%)	142c	48

[a] A = 104–170 °C; B = Co(acac)₃, Ph₂PH, 6 equiv of Et₂AlCl; C = Co(acac)₂, Ph₂PH, 3–4 equiv of Et₂AlCl. [b] Yields of isolated, pure compounds.

could be imagined that the cobalt salts are reduced by the dialkylaluminum species and that low-valent cobalt species may be the actual catalysts. On the other hand, the aluminum reagent may also function as a classical Lewis acid to accelerate the reaction. In these processes, three bonds and the pentacyclic skeleton are created in one step. In the absence of the catalyst, little or no cycloaddition occurs. Important features of this method are the ease of preparation of the substrate dienynes 139 and the efficiency of the construction of the rigid and highly strained polycyclic products.

It is interesting to note that chlorotrimethylsilane is able to catalyze the Diels–Alder reaction of a vinylcarbinol substrate. Accordingly, the cycloaddition reactions of the 1,2,3,4-tetrahydronaphthalene derivative 143 with a series of cyclic and acyclic carbodienophiles in the presence of chlorotrimethylsilane afforded, for example, the corresponding cycloadducts 144 and 145 in high yields by way of diene intermediates (Scheme 32).[69] The yields are reduced (20–60%) when BF₃·Et₂O is used as a catalyst and are even lower or zero in the absence of a catalyst.

All of the traditional Lewis acids such as BX₃, AlX₃, TiX₄, and SnX₄ have a number of undesirable or inconvenient characteristics. Of these, there is firstly their extreme sensitivity to water which is one of the reasons why they are generally employed at high catalytic loadings (usually 20 mol %). Secondly, binding between traditional Lewis acids and the oxygen atoms of the dienophile and of the product is generally thermodynamically strong and, in some cases, exchange may be kinetically slow. For this reason, organometallic Lewis acids and, in particular, organotransition metal

Scheme 32

143 → **144** 84%

143 → **145** 80%

A):Cl-SiMe₃(cat.), Et₂O
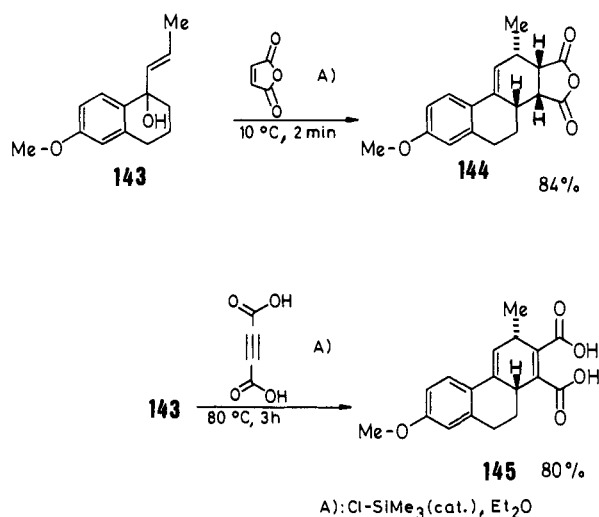
complexes as Lewis acid catalysts have become a subject of intense current interest for the catalysis of numerous chemical reactions.[70] Hersh and co-workers have reported[71] that Diels–Alder reactions between butadiene or cyclopentadiene and α,β-unsaturated enones are catalyzed by as little as 0.1 mol % of the tungsten nitrosyl Lewis acid 146 and that, on the basis of an X-ray crystal structure analysis of a tungsten–acrolein adduct, the mode of catalysis probably involves activation of the α,β-unsaturated enone by simple η¹-carbonyl activation.
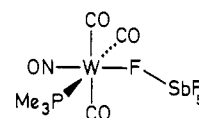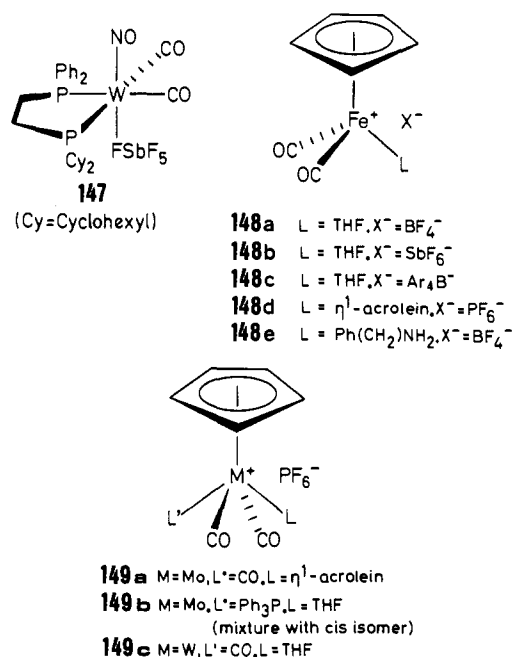

146

In this context, the catalysis of further Diels–Alder reactions by the low oxidation state, transition metal Lewis acids 147–149 was investigated by the same group.[72] The dienes cyclopentadiene, butadiene, isoprene, and piperylene and the dienophiles acrolein, methyl vinyl ketone, and methyl acrylate were investigated in these studies. Enhancements in rates and in regio- and stereoselectivity in comparison to the uncatalyzed (thermal) reactions were observed. The order of apparent catalytic activity is 146 > 147 ≈ 148a > 149a, 149c. The order of Lewis acidity was found to be 146 > 147 > 149a > 148a, which casts some doubt on the role of Cp(CO)₂Fe⁺ in the catalytic process.[72]

A large number of cycloaddition reactions of aliphatic dienes with enones were tested under homogeneous catalysis with [Ti(Cp)₂(H₂O)₂](CF₃SO₃)₂ (Cp = pentamethylcyclopentadienyl anion) in dideuteriodichloromethane at 25 °C and compared with the respective thermal reactions.[73] In most cases, the selectivities of the Diels–Alder reactions were enhanced significantly. It is worthy of note that this catalyst is very insensitive to the presence of water and is stable in the air.

Also, the [Ru(salen)(NO)(H₂O)]⁺ species (salen = N,N'-bis(salicylidene)ethylenediamine dianion ligand; for structure, see formula 150) is an effective homogeneous Lewis acid catalyst for Diels–Alder reactions
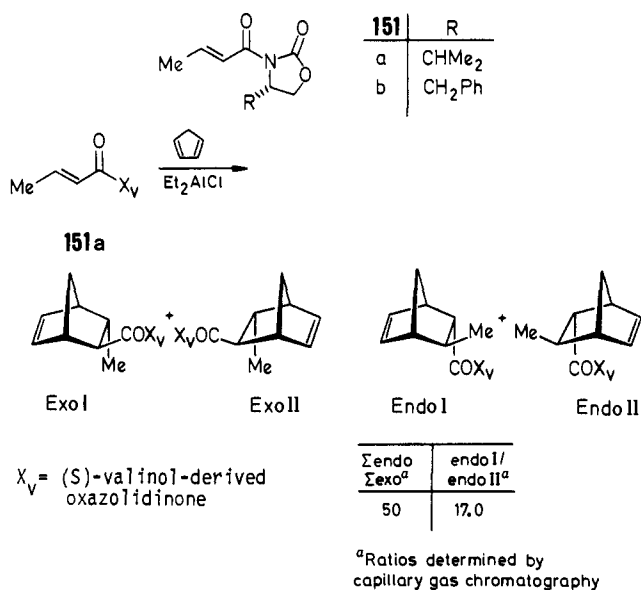
147
(Cy=Cyclohexyl)

148a L = THF.X⁻=BF₄⁻
148b L = THF.X⁻=SbF₆⁻
148c L = THF.X⁻=Ar₄B⁻
148d L = η¹-acrolein.X⁻=PF₆⁻
148e L = Ph(CH₂)NH₂.X⁻=BF₄⁻

149a M=Mo,L'=CO.L =η¹-acrolein
149b M=Mo,L'=Ph₃P.L = THF
        (mixture with cis isomer)
149c M=W,L'=CO.L=THF

at low catalyst loadings of 1–2 mol %.[74] Rate accelerations of more than 10⁵ in comparison to the respective thermal reactions were observed in many cases for the reactions of aldehyde- and ketone-containing dienophiles with aliphatic 1,3-dienes at these low catalyst loadings.[74] The reactivity of an alkoxyzirconocene complex as a catalyst in the Diels–Alder reactions of methyl acrylate with 2-methylbutadiene and cyclopentadiene has been investigated.[75] The respective cycloadducts were isolated in yields of 64 and 72%, respectively, while the conversion degree in each case was 100%.

The application of chiral auxiliaries incorporated in the dienophile has been widely studied, and in some cases, complexation of the chiral dienophile with the appropriate Lewis acid has induced a high π-diastereofacial selectivity (see also section X).[76,96] Evans and co-workers have described the application of chiral α,β-unsaturated N-acyloxazolidinones as dienophiles with a broad synthetic potential.[77] In the presence of the classic Lewis acids dialkylaluminum chlorides, the chiral α,β-unsaturated N-acyloxazolidinones function as highly reactive and highly π-diastereoselective dienophiles in Diels–Alder reactions. In general, a cationic Lewis acid–dienophile complex has been proposed to account for the exceptional reactivities and endo:exo selectivities observed. Thus, for example, the cycloaddition of the crotonyl imide 151a, bearing the (S)-valinol-derived
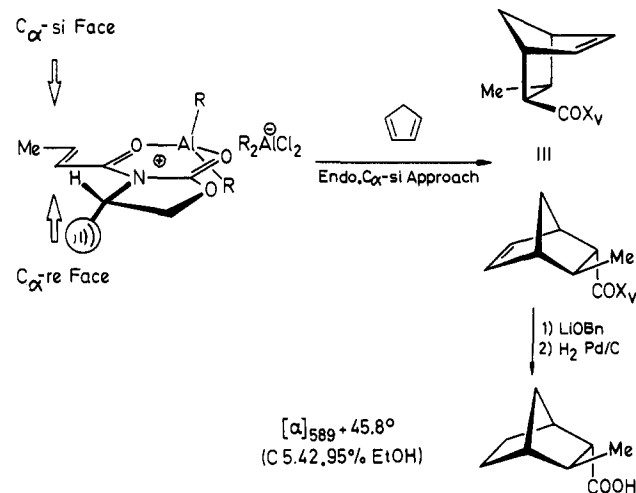

150
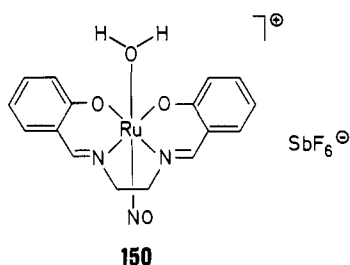
oxazolidinone, with cyclopentadiene in dichloromethane at –78 °C in the presence of diethylaluminum chloride (1.4 equiv) afforded both high levels of endo diaste-

Scheme 33

151	R
a	CHMe₂
b	CH₂Ph

151a

Exo I   Exo II   Endo I   Endo II

X_V = (S)-valinol-derived oxazolidinone

Σendo/Σexo[a]	endo I/endo II[a]
50	17.0

[a]Ratios determined by capillary gas chromatography

Scheme 34. Diastereoface Selection in the Cycloaddition Process

C_α⁻ si Face

C_α⁻re Face

Endo,C_α-si Approach
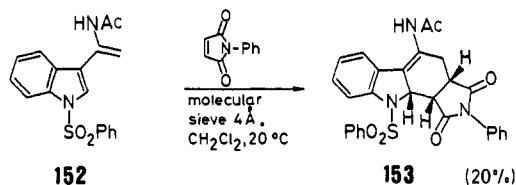
[α]₅₈₉ +45.8°
(C 5.42,95% EtOH)

1) LiOBn
2) H₂ Pd/C

reoselection (17:1) and the highest combined endo:exo ratio (50:1) of all other Lewis acids screened (Scheme 33).[77]

The diastereoface selection in the cycloaddition process is outlined in Scheme 34. The formation of a cationic Lewis acid/base complex is proposed in which the aluminum Lewis acid is simultaneously coordinated to both carbonyl groups of the dienophile, thus accounting for the high selectivity of the process. The enhanced diastereoselectivities observed in Diels–Alder reactions of phenylalaninol-derived dienophiles such as 151b were shown to be the result of electronic interactions involving the phenyl ring (π-stacking interaction model) and not to be of steric origin.

VII. Inorganic Heterogeneous Catalysts

Molecular sieves are synthetic, crystalline zeolites (e.g. zeolite A is sodium aluminum silicate); their crystal lattices have a cagelike structure with numerous cavities normally containing water. When molecular sieves are to be used as catalysts, this water must be removed by heating at 200 °C. To date they have only been

Scheme 35

respectively), sometimes in combination with a cocatalyst, in numerous [4 + 2]-cycloadditions and have found that the conversion and reaction rates are considerably increased (for some outstanding examples, see Scheme 36).

Furthermore, the use of a clay catalyst (ion exchanged with Zn^{2+} or Fe^{3+}) in an asymmetric Diels–Alder reaction was reported just recently (Scheme 37).[84f]
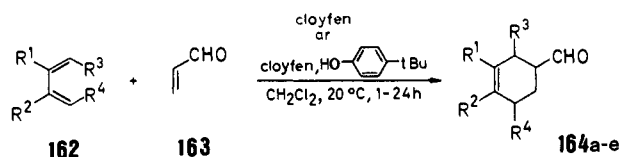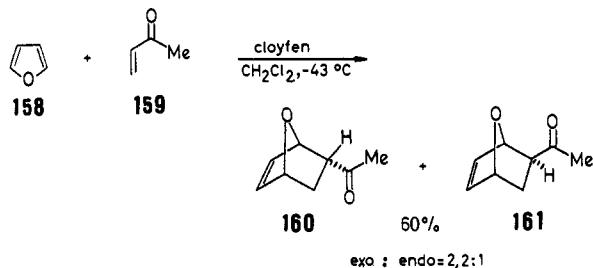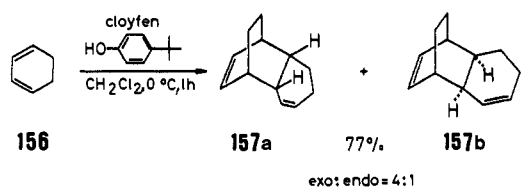
Some results of [4 + 2]-cycloadditions in the presence of chromatographic adsorbents such as SiO_2 or $MgO \cdot SiO_2$ parallel those observed for Diels–Alder reactions in the presence of zeolites or modified clays. Thus, under dry state adsorption conditions (in the absence of any solvent), the rates and regio- or stereoselectivities of the reactions of cyclopentadiene, isoprene, butadiene, 2,3-dimethylbutadiene, 1,3-cyclohexadiene, enones, and furans as dienes with several acyclic carbodienophiles are increased in the presence of SiO_2 or $MgO \cdot SiO_2$, respectively.[85] These observations can be rationalized in terms of the combined action of several effects of "adsorbate–adsorbent interactions". The most obvious effect could be associated with the activation of the reaction partners resulting from multicentered, donor–acceptor interactions on the surfaces of the adsorbent. This methodology was also employed for regio- and stereoselective syntheses of tetrahydrocarbazoles and 2,3-divinylindoles from 2-vinylindoles, as 4π-components, and carbodienophiles.[86] The Diels–Alder reactions of optically active menthyl acrylate or methyl acrylate with cyclopentadiene to furnish norbornene derivatives are catalyzed analogously by γ-alumina.[87] The reactions are selective and yield large endo:exo ratios of the products and large diastereomeric excesses for the endo product; the diastereomeric excess being controlled by the activity of the alumina. Activated γ-alumina has exposed aluminum cations on its surface and these are assumed to catalyze the reactions (the optimum activation temperature for Al_2O_3 is 400 °C). In the course of investigations on the cycloaddition reactions of cyclopentadiene with dimethyl maleate and dimethyl fumarate on γ-alumina, competing mechanisms for the

employed in a few cases as catalysts[78a] for pericyclic reactions such as, for example, the cyclization of 1,3-butadiene.[78b]

Fritz and co-workers[79] employed molecular sieves (pore diameter 4 Å) for the first time as a catalyst in a [4 + 2]-cycloaddition but attributed the results to the ability of the molecular sieves to remove water from the solvent rather than to a direct catalytic effect. Later, comprehensive investigations of similar Diels–Alder systems,[80,81] however, revealed that the reactions were indeed only made possible by the presence of the molecular sieve; one such example is the stereospecific [4 + 2]-cycloaddition of the 3-vinylindole **152** with N-phenylmaleimide to furnish compound **153** (Scheme 35).

Furthermore, the use of activated molecular sieves considerably extends the synthetic potential of Diels–Alder reactions of N-benzoyl-2,3-dihydro-2,3-bis-(methylene)indole (**154**) with carbodienophiles to furnish the functionalized 1,2,3,4-tetrahydrocarbazoles **155** (Table 7).[81]

According to current reasoning,[82,83] only those molecules should be formed on zeolite catalysts for which the transition state is smaller than the diameter of the pores ("transition-state shape selectivity"). In cases of substrate molecules that are larger than the cavity diameter of the zeolite, it is probable that an orientation of partial structures of the molecule on the surface of the zeolite occurs.

The alumina hydrosilicate mineral Montmorillonite consists of acidic lamellar structures containing a number of readily accessible cations. Hence, Laszlo and co-workers[84] have employed Montmorillonite clay doped with Fe^{3+} or Cu^{2+} salts (clayfen and claycop,

Table 7. Diels–Alder Reactions of N-Benzoyl-2,3-dihydro-2,3-bis(methylene)indole (154) with Carbodienophiles to Furnish 1,2,3,4-Tetrahydrocarbazoles 155

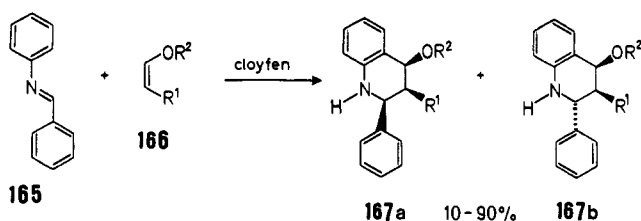| 155	R^1	R^2	R^3	R^4	yield (%)
a	CN	CN	CN	CN	19
b	CN	H	H	CN	13
c	CO_2Et	H	H	CO_2Et	63
d	CN	Cl	H	H	$51^{a,b}$
e	H	H	CN	Cl	
f	SO_2Ph	H	H	H	$10^{a,c}$
g	H	H	SO_2Ph	H	
h	$SO_2CH{=}CH_2$	H	H	H	$14^{a,d}$
i	H	H	$SO_2CH{=}CH_2$	H	
k	CN	H	H	H	$45^{a,e}$
l	H	H	CN	H	
m	COMe	H	H	H	$59^{a,f}$
n	H	H	COMe	H	

^{a} Combined yield of the regioisomers. $^{b-f}$ Ratio of isomers by ^1H NMR: (b) 8:1; (c) 2.3:1; (d) other regioisomer <3%; (e) 4:1; (f) 4:1.
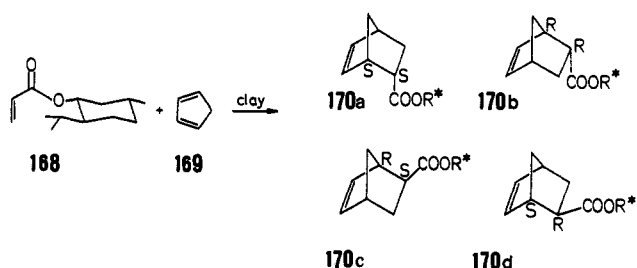
Scheme 36

Table 8. Endo:Exo Ratios for the Reactions of Cyclopentadiene with AC, ACN, and MAC on Activated Neutral Alumina, Cellulose, and Montigel and in an Homogeneous Phase (HP)

dienophile	Al$_2$O$_3$	cellulose	montigel	HP
AC	1.07	2.94	2.5	3
ACN	1.63	1.56	2.6	1.45
MAC	32.3	2.94	13.7	3

Scheme 38
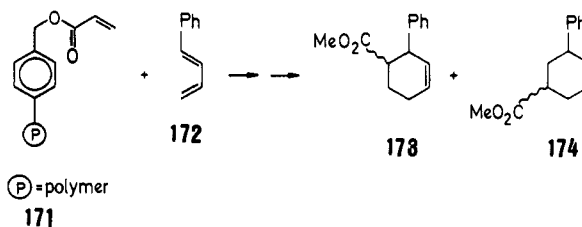
(ACN), and methyl acrylate (MAC)[89] in several solid phases and in a homogeneous phase (HP) is shown in Table 8. The endo:exo ratios are practically independent of the temperature (40–70 °C).

VIII. Reactions of Polymer-Bound Dienophiles

Insoluble polymer supports have also found use in cycloaddition reactions. This methodology is attractive because it should, in principle, allow better control of the selectivity, simplify workup of reaction mixtures, and improve isolation of adducts from excess starting material and byproducts. Thus, polymer-bound benzyl acrylate, prepared from polymer-bound benzyl alcohol and acryloyl chloride, reacted with (E)-1-phenyl-1,3-butadiene to furnish the corresponding polymer-bound adducts. Treatment of the latter with tetra-n-butyl-ammonium hydroxide then afforded the free ortho and meta adducts **173** and **174** in a ratio of 94:6 (Scheme 38).[90]
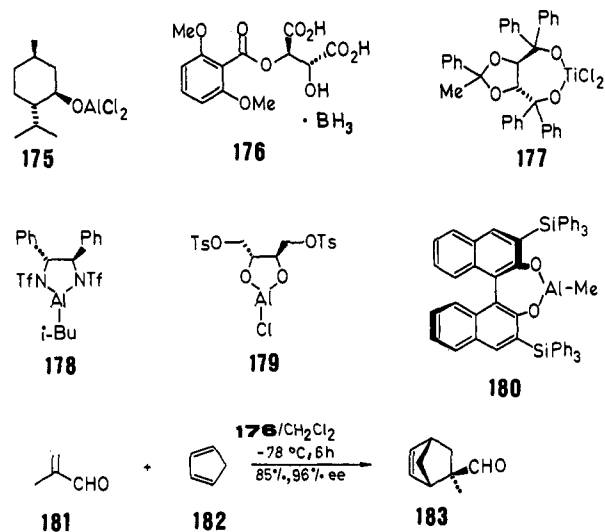
IX. Radical-Enhanced Diels–Alder Reactions

In 1981, Bauld and co-workers discovered the first cation radical-catalyzed Diels–Alder reaction.[91,92] The conversion of neutral or electron-rich dienophiles into the corresponding cation radicals remarkably increases their activity. For example, the dimerization of 1,3-cyclohexadiene under cation radical catalysis occurs under milder conditions (0 °C, 15 min) than the thermal counterpart (200 °C, 20 h). Cation radical-induced cycloaddition is a symmetry-allowed, stereospecific reaction. From a mechanistic point of view, the adduct (A) is formed via either the cation radical of the dienophile (DP) or the cation radical of the diene (D) according to the following sequences (with the triaryl-amine cation radical as a typical initiator):
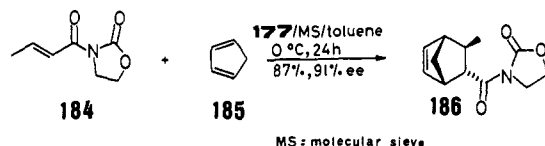
$$DP + Ar_3N^{\ddagger} \rightleftarrows Ar_3N: + DP^{\ddagger}$$

$$DP^{\ddagger} + D \rightleftarrows A^{\ddagger}$$

$$A^{\ddagger} + DP \rightarrow A + DP^{\ddagger}$$
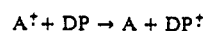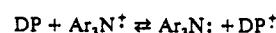
For further applications of triarylaminium cation radical-induced Diels–Alder reactions, see also ref 57.

Scheme 37

exchanged cation in clay	ratios					ratios	
	169:168	clay:169 (g/mol)	solvent	temp (°C)	time (h)	yield (%)	170a,b: 170c,d	170b: 170a
	3		CH$_2$Cl$_2$	20	51	60	79:21	53:47
Zn(II)	3	0.5	CH$_2$Cl$_2$	20	24	40	88:12	63:37
Zn(II)	6	0.5	CH$_2$Cl$_2$	20	48	70	88:12	62:38
Zn(II)	3	0.5	CH$_2$Cl$_2$	20	48	63	92:8	62:38
Zn(II)	6	1.0	CH$_2$Cl$_2$	-25	54	66	96:4	75:25
Zn(II)	7.5	1.5	CH$_2$Cl$_2$	-25	33	75	95:5	72:28
Zn(II)	12	1.5	CH$_2$Cl$_2$	-58	96	33	97:3	79:21
Zn(II)	7.5	1.5	toluene	-20	48	88	96:4	76:24
Fe(III)	7.5	1.5	CH$_2$Cl$_2$	-20	27	20	95:5	76:24

epimerization of the adducts were taken into account.[88]

A comparison of the endo:exo ratios of the reactions of cyclopentadiene with acrolein (AC), acrylonitrile

Scheme 39

Scheme 41

Scheme 40

R	Yield (%)	exo/endo	R/S
H	95	96:4	200:1
CH$_2$OBzl	81	95:5	96:4

Bzl = Benzyl

X. General Acceleration and π-Diastereofacial Selectivity in Asymmetric Diels–Alder Reactions with Chiral Catalysts

Optically active Lewis acids were first used as catalysts for asymmetric Diels–Alder reactions about 14 years ago.[100] Since then, this exceedingly interesting field of reagent-controlled asymmetric processes has been developed further and several comprehensive reviews were published recently.[96–99,121] Thus, only some outstanding results and more recent experimental observations will be discussed here.

The first reported reaction of cyclopentadiene with methacrolein catalyzed by the chiral aluminum compound 175 produced the bicyclo[2.2.1]hept-6-ene product in a reasonable enantiomeric excess (ee) of 72%.[99–101] However, it has since been found that the reaction is best catalyzed by the borate 176 which affords the product in an ee of 96% (Scheme 39).[102,103]

The titanium complex 177[104] and the aluminum complexes 178 and 179[105,106] are examples of catalysts for the reactions of crotonic acid derivatives with cyclopentadiene to afford the respective products under good chiral control with ee's of 91, 95, and 97% (Scheme 40).

A stereochemical model has been proposed for correlating the structure of the ligand 178 with the absolute configuration of the products.[105] Furthermore, a catalytic process using 5–10 mol % of 177 has been developed for the reaction;[107] the key feature of this is the use of molecular sieves (see section VII).

The heterocycloaddition of a diene to an aldehyde to afford the pyran derivative in an excellent ee is also catalyzed by the aluminum reagent 180, derived from 1,1'-binaphthyl-2,2'-diol.[108]

The presence of a sulfonamide unit incorporated in a chiral catalyst has proved to be effective in the promotion of enantioselective [4 + 2]-cycloadditions.
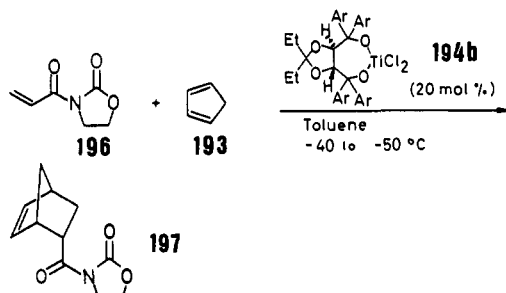
Scheme 42

exo/endo = 95:5 (82% ee)
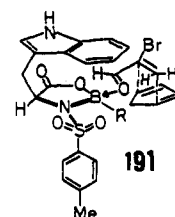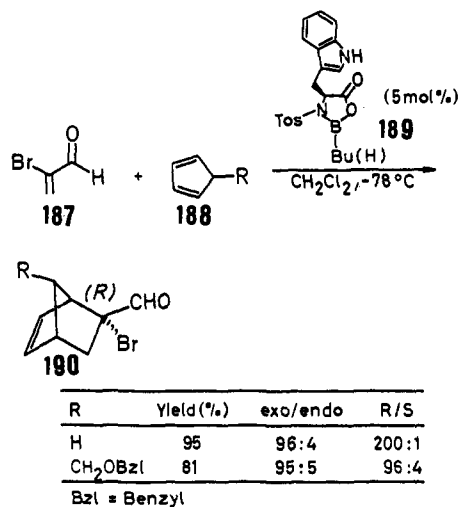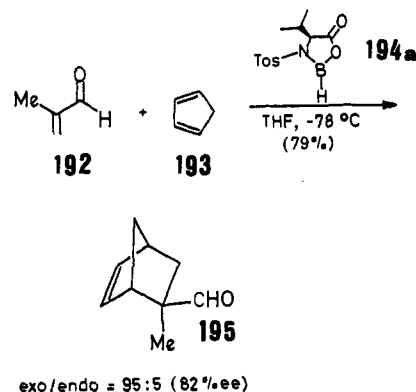
Thus, compound 189, derived from L-tryptophane, catalyzes the cycloadditions of the cyclopentadienes 188 with 2-bromoacrolein (187) (Scheme 41); the exo adducts represent the main products.[109] A transition state with structure 191, stabilized by a donor–acceptor interaction, was proposed.

This interpretation was substantiated by the fact that use of the catalyst 194a, in which such interactions cannot occur, induces the formation of cycloadducts with the opposite configuration (Scheme 42).[110]

Corey and co-workers have demonstrated the utility of π,π-interactions in enantioselective Diels–Alder reactions by a variation of the Narasaka system.[111] Thus, for example, the catalyst 194b (Ar = m-xylyl) induces an enantioselectivity of 94% (endo), whereas the presence of an electron-poor arene group in 194b (Ar = 3,5-dichlorophenyl) results in a decrease to 44% (Scheme 43). A transition state with the structure 198 was proposed.

A catalyst with an electron-rich arene moiety and a large planar surface in combination with a Lewis acid group can also catalyze enantioselective Diels–Alder
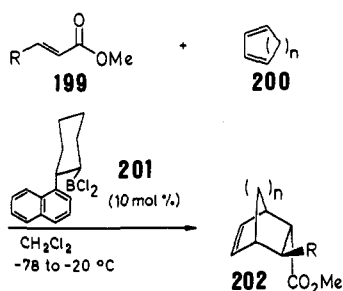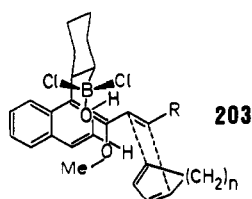
Scheme 43

Ar	endo/exo	%ee(endo)
3,5-dichlor-phenyl	93:7	44
m-xylyl	95:5	94
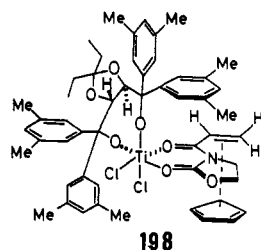
Scheme 44

| R	n	Yield(%)	%ee(endo)
H	1	97	97
Me	1	91	93
H	2	83	86

reactions. Thus, the chiral Lewis acid **201** catalyzes the cycloadditions of methyl acrylate (and methyl crotonate) with cyclic dienes **200**, giving the products in high ee's (Scheme 44).[112] The proposed transition state **203** is also stabilized by π,π-interactions.

Bis(4,5-dihydroxyoxazolyl) derivatives are of synthetic interest as multiple ligand systems for asymmetric catalysis.[113] For example, the Cu(I) complex **204a** (ML$_n$ = Cu+, R = t-Bu) is highly suitable for the cyclopropanation of mono- and 1,1-disubstituted olefins and yields high ee values.[114] On the other hand, it is
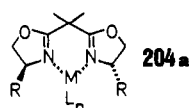
ML· = Cu+ ; catalyst for cyclopropanation
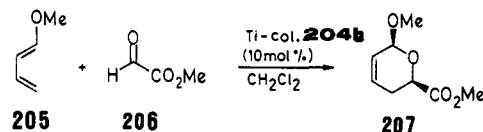
ML· = FeX₂ ; catalyst for Diels-Alder reactions
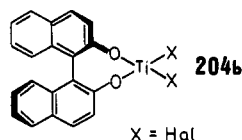
interesting to note that the iron complex **204a** (ML$_n$ = FeX₂, R = Ph) is a good catalyst for Diels-Alder reactions.[115]

The binaphthyldiol–titanium dihalide complex **204b**, prepared in situ, has been used as a catalyst for the asymmetric glyoxolate/ene coupling reaction and for enantioselective Diels–Alder reactions of substituted 1,3-dienes with methyl glyoxolate or methacrolein.[116]

Hetero-Diels–Alder products of the type **207** (Scheme 45), prepared in 97% ee, are also of preparative interest.

Scheme 45

Scheme 46

208a,b R = p-CH₃C₆H₄
209a R = 2,4,6-(CH₃)₃-C₆H₂
210 a,b,c R = CF₃

a ML$_n$ = BH₃·THF
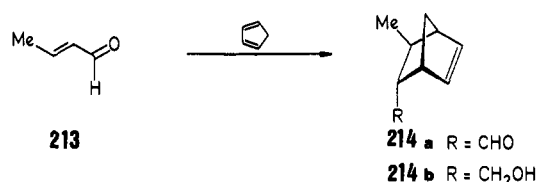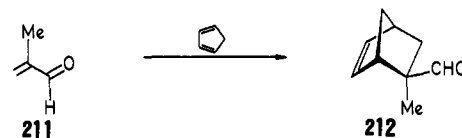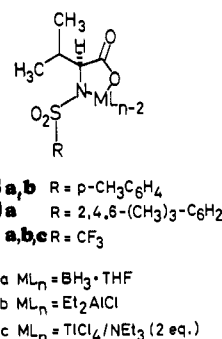b ML$_n$ = Et₂AlCl
c ML$_n$ = TiCl₄/NEt₃ (2 eq.)

Table 9. Enantioselective Diels–Alder Reactions of the α,β-Unsaturated Aldehydes 211 and 213 with Cyclopentadiene in the Presence of the Chiral Lewis Acids 208–210 as Promotors
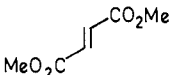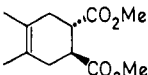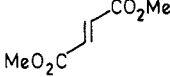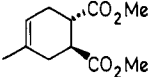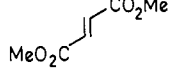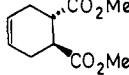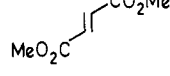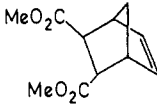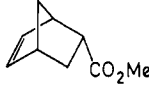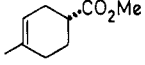
aldehyde	Lewis acid	endo:exo ratio	ee (%)	yield (%)
211	208a	<1:99	64	95
211	208a	6:94	14	71
213	208a	95:5	26	45
213	208a	94:6	35	53
213	209a	97:3	72	58
211	210a	3:97	27	85

This strategy has been employed to prepare anthracyclin and mevinoline derivatives.[116]

The new chiral Lewis acids **208–210** were prepared by reactions of the sulfonamides of (S)-valine with borane and employed in some enantioselective Diels–Alder reactions.[117] Some results of such reactions of cyclopentadiene with methacrolein and (E)-crotonaldehyde (Scheme 46) are summarized in Table 9.

These reactions exhibit a considerable dependence on the reaction conditions. Common features, however,

Table 10. Diels-Alder Reactions Promoted by the Chiral Lewis Acid 217

diene	dienophile	major product	yield (%)[a]	ee (%)
			79	92
			79	88
			78	60
			86	80
			85	36
			91	37

[a] Yield of isolated product.

Scheme 47

are the excellent-to-fair endo:exo ratios, the preferred *si* face attack of the diene at the aldehyde double bond, and the high reaction rates. In this manner, a fairly high degree of enantioselectivity (72% ee) was achieved for the first time with (E)-crotonaldehyde (213) in comparison with the previously obtained ee values of only 2%.[118]

To date, however, the generally less reactive carboxylic ester dienophiles have shown low enantioselectivity under reagent-controlled Diels–Alder conditions.[119] For example, the titanium–Lewis acid complex 217, generated from (R,R)-hydrobenzoin and TiCl₄, has been investigated (Scheme 47),[120] and the results are summarized in Table 10. The enantiomeric excesses are very high in the cases of the Diels–Alder reactions of 2,3-dimethylbutadiene or 2-methylbutadiene with dimethyl fumarate.
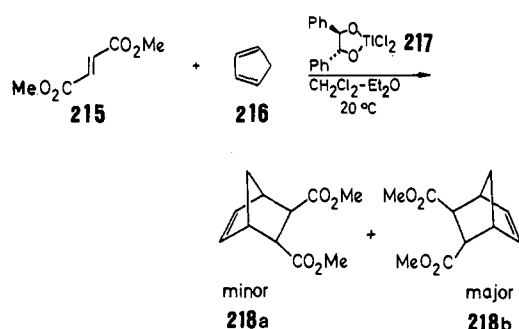
XI. Conclusions

In the last 15 years, the application of special physical methods and special catalysts and solvents has been developed to considerably extend the scope of the Diels–Alder reaction. Thus, the rates and selectivities of Diels–Alder reactions can be enhanced by the appli-

cation of high pressure, ultrasound, hydrophobic packing, or molecular aggregation (in the presence of special solvents or agents for inducing micelle formation), by the addition of proteins (as well as enzymes or antibodies) to the reaction mixture, by the presence of heterogeneous inorganic catalysts, Brönsted acids, or Lewis acids (including chiral representatives), and by performing the reaction in a solid polymer phase. Furthermore, cation radical-catalyzed reactions are also of synthetic interest since the rates of such [4 + 2]-cycloadditions are increased significantly.

In spite of these pioneering developments of the Diels–Alder reaction, future work on the design of new catalysts, especially chiral catalysts, and the use of antibody-catalyzed methodologies will certainly give rise to further interesting synthetic results. As a complement to the purely physical methods, new technological developments in the fields of, above all, ultrasound and perhaps also microwave radiation will provide further possibilities to enlarge the scope and application of the Diels–Alder reaction in synthetic organic chemistry.

XII. Addendum

During the preparation of the present article, a review on the synthetic and mechanistic aspects of catalyzed, asymmetric Diels–Alder reactions was published by Kagan and Riant.[121] In addition to the applications of chiral aluminum catalysts, chiral titanium complexes, chiral boron complexes, chiral lanthanide complexes, and transition metal complexes, base-catalyzed Diels–Alder reactions were also discussed in detail.

XIII. Acknowledgments

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XIV. References

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