Recent Advances in Lewis Acid Catalyzed Diels−Alder Reactions in Aqueous Media

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Recently the aqueous medium has attracted the interest of organic chemists, and many, sometimes surprising, discoveries have been made. Among the organic reactions investigated in aqueous medium, the Diels–Alder cycloaddition has been the most widely studied because of its great importance in the synthetic and theoretical fields. The Diels–Alder reaction is greatly enhanced by Lewis acid catalysis, and this review illustrates recent significant results in this field when the reaction is performed in aqueous medium.

1. Introduction

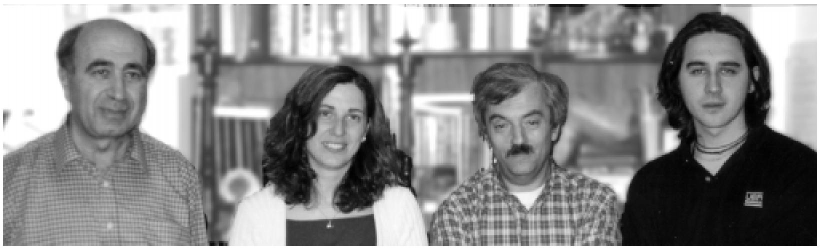
Over a relatively short time (ca. 150 years), organic chemists have determined the structures of thousands of substances and developed highly selective procedures for preparing both simple and complex molecules.

Basic chemical research has generated an imposing chemical industry, which has contributed greatly to the technological development of society.

Today, man is becoming conscious of the importance of environmental issues for life and recognizing that he can change the ecological balance. Environmentally sustainable growth is a common goal of science and industry. This means finding new processes and new techniques, devising new technologies and new procedures. In the field of chemical production, the most important objective is not what to produce but rather how to produce it.

Green chemistry is a branch of chemistry covering all chemical processes that are non-injurious to human health and are environmentally friendly, and its object is to prevent or at least reduce pollution at source.[1]

Four main approaches for synthesising compounds in an environmentally friendly manner have recently been developed. One approach is to use water instead of organic solvent as reaction medium,[2] a second is to use no solvent at all,[3] a third approach is to replace stoichiometric amounts of metal reagents with small amounts of metal



Francesco Fringuelli (left) was born in Perugia in 1936. He received his laurea in Industrial Chemistry from the University of Milano in 1963. He then moved as research associate to the University of Perugia, where he became full professor of Organic Chemistry in 1975. He was a postdoctoral co-worker at the University of La Jolla - California. His current research interests are in the fields of enantioselective synthesis and organic reactions in water.

Oriana Piermatti (second from left) was born in Valtopina (Perugia) in 1968. She received her laurea in Chemistry in 1991 and her Ph.D. in 1996 at the University of Perugia, working with Prof. Fringuelli on the stereoselective synthesis of β-hydroxy acids. She is currently working as a post-doctoral research fellow on the synthesis of new chiral auxiliaries and catalysts and their application in asymmetric synthesis.

Ferdinando Pizzo (second from right) was born in Viterbo in 1951. He received his laurea in 1975. In 1986 he spent a year with E. Wenkert at the University of California at S. Diego working on the metal decomposition of 2-diazoacylfurans. He is now associate professor at the University of Perugia. His current research is the study of reactivity and stereoselectivity of organic reactions in water.

Luigi Vaccaro (right) was born in Cava dei Tirreni (Salerno) in 1972. He studied at the University of Napoli − Federico II where he received his laurea in 1996. In the same year, he joined the group of Prof. Fringuelli at the University of Perugia, where he obtained his Ph.D. in 1999, working on organic reactions in water. He is undertaking postdoctoral research on Lewis acid catalysis in water at the University of Perugia.

MICROREVIEWS: This feature introduces the readers to the authors' research through a concise overview of the selected topic. Reference to important work from others in the field is included.

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catalysts[4] and the fourth is to employ biosynthetic processes.[5]

Water is the most abundant and available resource on the planet and many biochemical processes occur in aqueous medium. Nevertheless, for a long time organic chemists have undervalued water as a reaction medium. The probable reasons for this were: (i) that the low solubility of most organic compounds in water would probably be an obstacle to their reactivity, and (ii) the instability of many intermediates and catalysts in water.

Today, the scene is changed. The aqueous medium has captured the interest of organic chemists[6] and many, sometimes surprising, discoveries have been made.[2] It has been found that pericyclic,[7] condensation,[8,9] oxidation,[10] and reduction[10] reactions can be conducted efficiently in aqueous medium and that, in some cases, water is necessary to increase selectivity and reaction rate. Water-tolerant catalysts that allow organometallic reactions to be carried out in aqueous medium have been prepared.[9,11] Reactions previously thought impossible in water are today a reality.

Among the organic reactions investigated in aqueous medium, the Diels−Alder reaction has been the most widely studied, because of its great importance in the synthetic and theoretical fields.[7a,7b] The Diels−Alder cycloaddition enables stereoselective synthesis of complex polycyclic molecules and it is usually reported that the reaction rate is almost unaffected by solvent.[12a−12d] This is true when the reactants are pure hydrocarbons and the reaction mechanism is concerted and synchronous.[12a] When the diene and dienophile are activated by substituents or contain heteroatoms, a great change in charge separation can occur on going from the initial state to the transition state and the process may be concerted but asynchronous,[12e−12h] or it may proceed along a zwitterionic[12i,12j] or radical[12k,12l] pathway. In these cases, a polar solvent interacts with the heteroatoms of the reactants and the Diels−Alder reaction can be significantly influenced by the reaction medium.[12m−12o]

The rates and stereoselectivities of Diels−Alder reactions are strongly affected by aqueous medium[7a−7c,13] and it was recently reported that the aqueous Diels−Alder reaction between 2-methylfuran and maleic acid in the presence of heavy ions such as Br^-, Cl^-, and Na^+ occurs largely or totally through a radical intermediate.[12p]

The Diels−Alder reaction is also greatly enhanced by Lewis acid catalysis; this review illustrates recent, significant results from this field observed when the reaction is performed in aqueous medium.

2. The Aqueous Medium

Before 1980 very little consideration was given to water as a reaction medium for organic reactions. Then, Breslow observed[14] that some Diels−Alder reactions were strongly accelerated when carried out in water, compared to when performed in organic solvents (Table 1). Some years later, the same author[15a] and others[15b] showed that the use of an aqueous medium also has beneficial effects on the diastereoselectivity of the reaction (Table 2).

Table 1. Relative rates of Diels−Alder reactions performed in water and in organic solvents

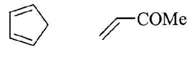
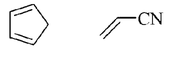
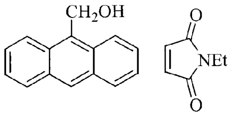
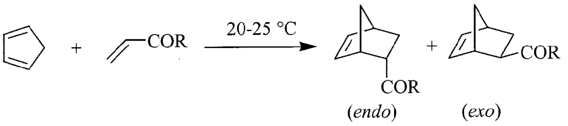
Reactants	T (°C)	Isooctane	Methanol	Water
	20	1	13	740
	30	1	2	31
	45	1	0.43	28

Table 2. *endo*/*exo* Diastereoselectivities of Diels−Alder reactions performed in water and in organic solvents



	endo/exo	
Medium	R = Me	R = OMe
None	3.85	2.9
Isooctane		2.3
Ethanol	8.5	5.2
1-Butanol		5.0
Formamide		6.7
N-Methylacetamide		4.7
Water	21.4	9.3

In truth, Diels−Alder reactions performed in water were not entirely a novelty before 1980. In 1931, Diels and Alder themselves[16a] used water as the reaction medium for the cycloaddition of furan and maleic anhydride. In 1948, Woodward and Baer[16b] employed aqueous maleic acid as a dienophile, and the beneficial effect of an aqueous medium on the reaction was also successfully investigated by Koning[16c] and Carlson[16d] in 1973. In the 1940s, there appeared two patents[17] concerning practical applications of water as a reaction medium for Diels−Alder cycloadditions of simple dienes with activated dienophiles. Breslow's work, however, was the first to show quantitatively the beneficial effects of water on the reactivity and selectivity of an organic reaction, and so stimulated further research in this area. Shortly after, it was discovered that other reactions, besides the Diels−Alder cycloaddition, also benefit when

Table 3. Advantages and disadvantages of aqueous medium

Advantages	Disadvantages
Inflammable and anhydrous solvents are not needed	Not inert
Economical saving	High boiling point
Abundant, cheap, not toxic and environmental friendly	Problems isolating highly water-soluble products
Protection-deprotection of functional groups such as OH, COOH may not be necessary	Carbocarbon acids (p*K*a >17) and water-sensitive reagents cannot be used
Water-soluble compounds can be used directly without derivatization	
Control of pH	
Possibility of using additives such as mineral salts, surfactants, cyclodextrins	
Possibility of isolating products by decanting or filtration	

performed in water. The use of an aqueous medium in organic synthesis is now well recognized by chemists.[2]

The use of aqueous medium affords both advantages and disadvantages, some of which are illustrated in Table 3.

An important advantage, from a chemical point of view, is the possibility of carefully controlling the pH of the reaction medium, and this can dramatically affect both the reactivity and selectivity of the reactions. Recent examples from our laboratory are the epoxidation of allylic[18a,18b] and homoallylic alcohols,[18b] the azidolysis of epoxides[18c,18d] and the reduction of azides.[18e] A practical advantage, greatly appreciated by industry, is the possibility of isolating the reaction products by decanting or by filtration, thereby avoiding the use of organic solvents at all. Some examples are the synthesis of coumarins[19a] and azacoumarins.[19b]

Water can be the sole component of the aqueous medium, or it can be used in a mixture with organic solvents such as THF, MeCN, EtOH, or MeOH. Water is sometimes used as an additive; for example, in the preparation of aquacomplexes[20] or as a catalyst auxiliary ligand.[21] The use of co-solvents and salting-in solutes (guanidinium chloride, $LiClO_4$) enables the reaction to occur in a homogeneous phase, but this may not favour the reactivity of the process.[14] Methanol, for instance, increases the solubility of organic reagents in water, but it disrupts the liquid water structure and, if the process is controlled by hydrophobic interactions, the reaction is decelerated and the selectivity is lower. If a wholly aqueous reaction medium is used, then one or more of the reactants are generally not completely soluble at the usual concentrations used on a preparative scale; the reaction occurs in a heterogeneous phase but excellent results can still be obtained. Salting-out solutes (LiCl, NaCl) assist the course of the reaction under heterogeneous conditions.[14]

Reactions in aqueous medium are generally carried out under conventional conditions of temperature and pressure. The use of water under supercritical or near-supercritical conditions (200−374 °C, 200−220 atm) is a currently active area of research;[22] under these conditions, the dielectric constant and the ionic product of water change dramatically, and water may act as reagent or catalyst, as well as reaction medium.

In Lewis acid-catalyzed Diels−Alder reactions, the aqueous medium influences the coordination of catalysts with the basic site of the reactant molecule both positively and negatively. Generally, the higher the complexation constant, the faster the cycloaddition reaction rate.[13] The polar and protic characteristics of water are an obstacle to complexation by Lewis acid,[23] while the high cohesive energy density favours the coordination of hydrophobic Lewis acid with hydrophobic reactant molecules.[24] Water also has a high electron acceptor capacity[25] and therefore interacts strongly with the basic site of the reactant molecule and with that of the reactant/catalyst complex.

3. Water-Tolerant Lewis Acids

The discovery in 1960 by Yates and Eaton[26] that $AlCl_3$ strongly accelerates the Diels−Alder reaction, relative both to proton catalysis and to thermal conditions, encouraged the development of Diels−Alder cycloadditions of poorly reactive dienophiles[27] and several other carbon−carbon bond-forming reactions.[20] Halides of B^{III}, Fe^{II}, Sn^{IV}, and Ti^{IV} were investigated with notably successful results, as were modified Lewis acids for use in asymmetric synthesis. The main disadvantages of these catalysts are their sensitivities to water and oxygen − necessitating working in aprotic solvents under anhydrous conditions − and their tendency to polymerize the substrate or destroy it. Dry reaction conditions became a mindset for organometallic chemists.

In 1988, Novak and Grubbs[28] were therefore very surprised to observe that, while $RuCl_3$-catalyzed polymerization of 5,6-bis(methoxymethyl)-7-oxanorbornene occurred only in low yield and with a long initiation period when performed in organic solvent under rigorously anhydrous conditions, the reaction proceeded rapidly and quantitatively, with an initiation time of only 30−35 min, when carried out in water alone and under one atmosphere of air. Furthermore, the aqueous ruthenium chloride solution could be used repeatedly and became more active in subsequent polymerizations.

During the last decade, aqueous organometallic chemistry and catalysis have received a lot of attention both in academia[2] and in industry.[11a,29] The prejudice that organometallic reactions must only be carried out under anhydrous conditions has disappeared and many water-tolerant Lewis acids have been prepared.

One strategy is to attach ionic or polar substituents to known ligands of active transition metal catalysts. Sulfonation is the method most widely used for making organic

Table 4. Representative examples of water-soluble ligands and water-tolerant catalysts

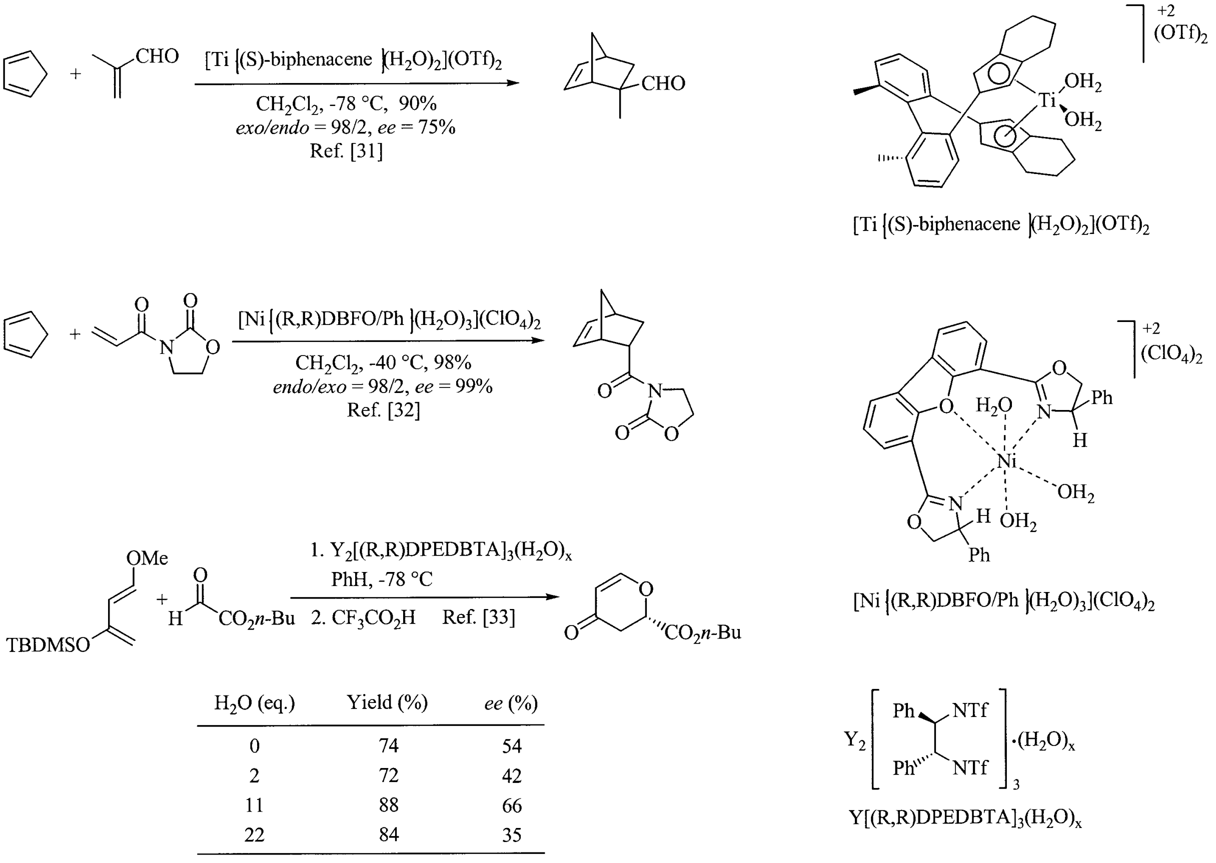
Ligand (abbreviation)	Catalyst	Ref.
(m-$SO_3NaC_6H_4$)Ph_2 (TPPMS)	*trans* IrCl(CO)(TPPMS)$_2$	[30a,30b]
(m-$SO_3NaC_6H_4$)$_3$P (TPPTS)	PdCl(TPPTS)$_3$Cl	[30c]
$Ph_2P(CH_2)_2PO(OX)_2$ X = Et, Na (dppep)	*trans* [PdBr$_2$(dppep)$_2$]	[30d,30e]
$(CH_2)_6N_3P$ (PTA)	RhCl(CO)(PTA)$_2$	[30f]
(2-py)$_2$P(CH_2)$_2$P(2py)$_2$ (d(py)pe)	NiBr$_2$[d(py)pe]	[30g]
$Ph_2P(CH_2)_nPMe_3^+Cl^-$ n = 2, 3, 6, 10, (n-phophos)	Fe(CO)$_4$(n-phophos)	[30h]

ligands water-soluble. Chiral and achiral water-tolerant catalysts have been prepared. A compilation of water-soluble ligands has been reported recently;[2a] Table 4 illustrates some examples. These catalysts have mainly been used in carbonylation, alkylation, coupling, polymerization, oxidation, hydroformylation and hydrogenation reactions.

Metal aquacomplexes − both with chiral ligands and with achiral ones − used in the Diels−Alder reaction show that water as an auxiliary ligand strongly influences the diastereo- and enantioselectivity of the reaction, as well as the chemical yield. Some air-stable and water-tolerant metal aquacomplexes have been isolated and characterized; others are prepared in situ by using two or more equivalents of water. Scheme 1 and Table 5 illustrate typical examples.[20,34] In general, 1−2 mol-% of these catalysts accelerate Diels−Alder cycloadditions by a factor of 10^3−10^5 relative to the corresponding thermal reactions.

These reactions are generally performed in organic solvents (CH_2Cl_2, THF, $MeNO_2$, PhH); the presence of water, at times even in a 100-fold excess over the catalyst concentration, is sometimes necessary to achieve the best selectivity and the highest reaction yield.[33] Because of the acidic characteristic of aqua-ligands, one could hypothesize that the observed catalysis is Brønsted catalysis rather than metal catalysis. The high enantiomeric excesses obtained when using chiral catalysts clearly indicate that the catalytic effect is the result of activation of dienophile by binding to the metal, rather than proton catalysis.

The use of aqua-complexing agents [$Co(NO_3)_2 \cdot 6\,H_2O$, $Ni(NO_3)_2 \cdot 6\,H_2O$, $Cu(NO_3)_2 \cdot 3\,H_2O$, $Zn(NO_3)_2 \cdot 4\,H_2O$], as Lewis acid catalysts for Diels−Alder reactions performed solely in water was investigated in detail in 1995.[13a,13b] The catalysts worked efficiently only if they formed a chelate with the dienophile, and complexation with α-amino acids allowed the first enantioselective Lewis acid-catalyzed Diels−Alder reaction in water to be achieved.[35]



H_2O (eq.)	Yield (%)	*ee* (%)
0	74	54
2	72	42
11	88	66
22	84	35

Scheme 1. Examples of Diels−Alder reactions catalyzed by metal aqua complexes with chiral ligands

Table 5. Diels−Alder reactions catalyzed by transition metal-based Lewis acid aqua complexes. In CD_3NO_2 solution, yields 90%

Dienophile[b]	Diene[b]	$[Ru(salen)(NO)(H_2O)]SbF_6$ t [h]	 isomer ratio	$[TiCp'_2(H_2O)_2](OTf)_2$[a] t [h]	 isomer ratio
IP	AC	5	99:1	6.7	95:5
CHD	AC	4.4	98:2	3.2	94:6
IP	MAC	3	93:7	3.2	91:9
CHD	MAC	48	70:30	76	75:25
IP	MVK	71	91:9	13	94:6
CHD	MVK	22	99:1	2.1	95:5

[a] Cp′ = pentamethylcyclopentadienyl. − [b] AC = acrolein, MAC = methacrolein, MVK = methyl vinyl ketone, IP = isoprene, CHD = 1,3-cyclohexadiene.

Lanthanide triflates (trifluoromethanesulfonates, $Ln(OTf)_3$, Ln = La, Ce, Pr, Nd, Sm, Eu, Gd, Dy, Yb, Lu), together with $Bi(OTf)_3$, $Sc(OTf)_3$, and $Y(OTf)_3$, represent a recent discovery in the area of water-tolerant Lewis acids.[36] They have contributed greatly to the development of aqueous organometallic chemistry in general, and Diels−Alder reactions in particular.

Metal triflates have several unique properties compared with the corresponding metal halides. Metal triflates:

- are air- and water-stable and can be used in wholly aqueous system or in mixtures of water and organic solvents (THF, EtOH, MeCN)
- can be prepared in aqueous medium
- are more soluble in water than in organic solvents such as CH_2Cl_2
- can be recovered from the aqueous mother liquor at the end of the reaction and reused
- are strong Lewis acids because of the electron-withdrawing trifluoromethanesulfonyl group
- have large atomic radii and specific coordination numbers
- have strong affinities to carbonyl oxygen
- hydrolyze slowly,[37] and the small amount of protons produced are not an active catalytic species[38]
- reduce the polymerization of dienes.

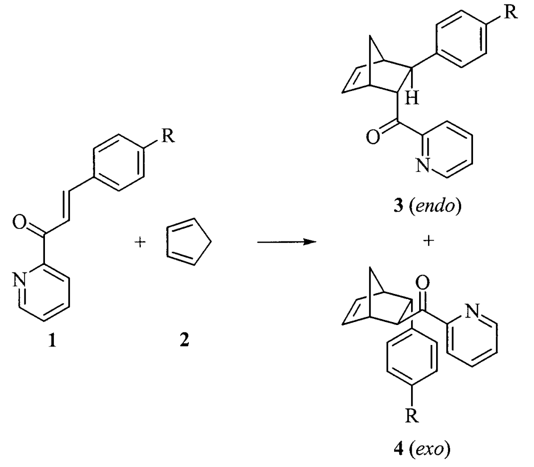
By using metal triflates in aqueous/organic solvent systems (especially in THF/H_2O mixtures), the quantity of water can influence both the yield and the diastereoselectivity of the reaction. There is a THF/H_2O ratio at which the water, rather than THF, preferentially coordinates the metal triflate, thus promoting the dissociation of triflate to form the active metal cation.[6e] Thus, in the $Sc(OTf)_3$-catalyzed Diels−Alder reaction of naphthoquinone with cyclopentadiene, a high yield and high diastereoselectivity were obtained with a 9:1 ratio of THF/H_2O as reaction medium.[39]

Lewis acid/surfactant combined catalysts (LASCs) such as $M(DS)_n$ and $M(DCS)_n$ (M = lanthanides, Sc, Yb, Cu, Zn, Ag, Mn, Co; $n = 1, 2, 3$; DS = dodecylsulfate, DCS = dodecanesulfonate) have recently been prepared and their characteristics and limitations investigated.[13c,40] These catalysts form stable colloidal dispersion systems with organic substrates in water, but reports on their catalytic ability in Diels−Alder reactions are discrepant.[13c,40]

$InCl_3$ and $MeReO_3$ also meet the prerequisite of being water-tolerant Lewis acids, and have been reported to catalyze Diels−Alder cycloadditions and other carbon−carbon bond-forming reactions in water.[41] Indium trichloride is active in water and has a high coordination number and a fast coordination-dissociation equilibrium. Methylrhenium trioxide is soluble in all common organic solvents and in water and is not sensitive to oxygen or acids.

4. Carbo-Diels−Alder Reactions

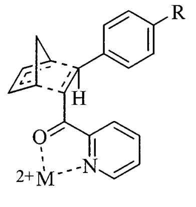
Carbo-Diels−Alder reactions[42] in aqueous media have been extensively investigated by Engberts et al.[6g][6i,13,35] These authors studied the effect of Co^{2+}, Ni^{2+}, Cu^{2+}, and Zn^{2+} ions as Lewis acid catalysts on the rates and *endo*-*exo* diastereoselectivities of Diels−Alder reactions between the bidentate dienophiles **1** and cyclopentadiene (**2**) in water and organic solvents (Scheme 2).[6i][13a][13b]



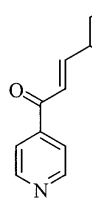
1	a	b	c	d	e	f	g
R	NO_2	Cl	H	Me	OMe	CH_2SO_3Na	$[CH_2NMe_3]Br$

Scheme 2. Diels−Alder reactions of 3-(*p*-substituted-phenyl)-1-(2-pyridyl)-2-propen-1-ones with cyclopentadiene

A bidentate characteristic is required of the dienophile for the success of the metal-catalyzed reaction, which is thought to proceed via an activated complex, illustrated for the *endo* addition with **5**. This is supported by the observation that no catalysis was observed for the cycloadditions of **6** and **7** with **2**; because these compounds cannot form a chelate with the Lewis acid.



5 (M = Co, Ni, Cu, Zn)



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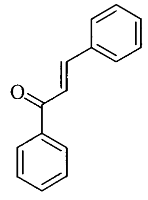

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Focusing attention on the more reactive dienophile **1a**, one observes that water significantly enhances the reaction rate in comparison with MeCN and EtOH (Table 6). 2,2,2-Trifluoroethanol is the reaction medium in which the reaction occurs fastest under uncatalyzed conditions. This acceleration is ascribable to the high Brønsted acidity of the solvent and is supported by the fact that the reaction rate is 19 times faster in 10^{-2} M aqueous HCl than in pure water, due to the higher concentration of protonated dienophile.

Table 6. Relative reaction rates of Diels−Alder reaction of **1a** with **2** at 25 °C in different media and catalytic effect of Cu^{2+} ion

Entry	Medium	k_{rel}	Catalytic effect[a]
1	MeCN	1	
2	EtOH	2.7	
3	H_2O	287	
4	CF_3CH_2OH	482	
5	10^{-2} M HCl in H_2O	5442	19
6	10^{-2} M $Cu(NO_3)_2$ in EtOH	55000	20370
7	10^{-2} M $Cu(NO_3)_2$ in MeCN	158000	158000
8	10^{-2} M $Cu(NO_3)_2$ in H_2O	232000	808

[a] Relative rate between the catalyzed and uncatalyzed reaction in the same solvent.

Complexation of dienophile by Cu^{2+} ion markedly increases the reaction rate. In water and in the presence of 10^{-2} M $Cu(NO_3)_2$, the reaction is accelerated by a factor of 232,000 relative to its uncatalyzed counterpart in MeCN. However, the catalytic effect of Cu^{2+} ion, as quantified by the relative rate between catalyzed and uncatalyzed variants in the same solvent, is less in water than in organic solvents, due to the fact that water does not favour the complexation of dienophile by Lewis acid.

The relative catalytic activities of various metal ions were investigated with regard to the reaction of **1c** with **2**. Cu^{2+} is the best catalyst (Table 7): it is 28 times more active than Ni^{2+} and 55 times more active than Co^{2+} and Zn^{2+}. All these ions form octahedral complexes in aqueous solution.

The higher catalytic activity of Cu^{2+} ion has been attributed to its ability to form square planar complexes as a consequence of the stronger coordination to the equatorial site than to the axial position.[44]

Table 7. Relative catalytic activity of various metal ions with respect to the reaction of **1c** with **2** in water at 25 °C

Catalyst	k_{rel}
$Zn(NO_3)_2 \cdot 4\,H_2O$	1
$Co(NO_3)_2 \cdot 6\,H_2O$	1.05
$Ni(NO_3)_2 \cdot 6\,H_2O$	1.92
$Cu(NO_3)_2 \cdot 3\,H_2O$	55

The substituent effect on the Cu^{2+}-catalyzed reaction between **1** and **2** has been investigated in MeCN, EtOH, H_2O, and CF_3CH_2OH. Excellent linear correlations with Hammet σ^+ constants have been found,[13b] indicating a large charge separation in the activated complex. The ρ-values of the reactions performed in organic solvents are close to unity, while the ρ-values of the reactions carried out in water are significantly smaller; in agreement with the expectation that water interacts more strongly than an organic solvent with the partial charges on the reacting system and substituents.[13b,45]

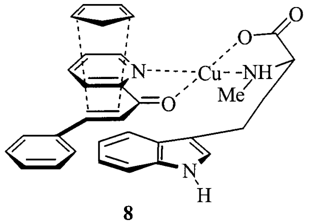
As expected,[12a,46] polar solvents and Lewis acid catalysis favour the *endo* isomer, but the diastereoselectivity of the reaction of **1c** with **2** is not significantly affected either by solvent or by catalyst (Table 8).

Table 8. *endo-exo* Selectivities of Diels−Alder reactions of **1c** with **2** at 25 °C in different media

Medium	*endo* (%)	*exo* (%)
MeCN	67	33
EtOH	77	23
H_2O	84	16
CF_3CH_2OH	87	13
10^{-2} M HCl in H_2O	94	6
10^{-2} M $Co(NO_3)_2$ in H_2O	87	13
10^{-2} M $Ni(NO_3)_2$ in H_2O	86	14
10^{-2} M $Cu(NO_3)_2$ in H_2O	93	7
10^{-2} M $Zn(NO_3)_2$ in H_2O	86	14

Examining Diels−Alder reactions in water between **1c** and **2**, Engberts et al. also investigated[35] the enantioselectivity induced by coordinating chiral, commercially available α-amino acids (AAs) to catalytically active Cu^{2+} ion. This was the first example of enantioselective Lewis acid catalysis of an organic reaction in water. The AA, in its deprotonated form at pH 5−7, coordinates the metal ion, forming a flat five-membered ring.[47] In the presence of 10% Cu^{II}−AA complex, the adduct (*endo*/*exo* = 93:7 ± 2%) is obtained after 48 h at 0 °C, in a yield generally exceeding 90%.

Despite extensive efforts, the authors were unable to establish the absolute configuration of the *endo* adduct. It is probably (*S*,*S*)-*endo* **3**, originating from the *endo* addition of **2** to the less sterically hindered face of ternary Cu^{II}−AA−**1c** complex **8** (the AA is L-abrine).



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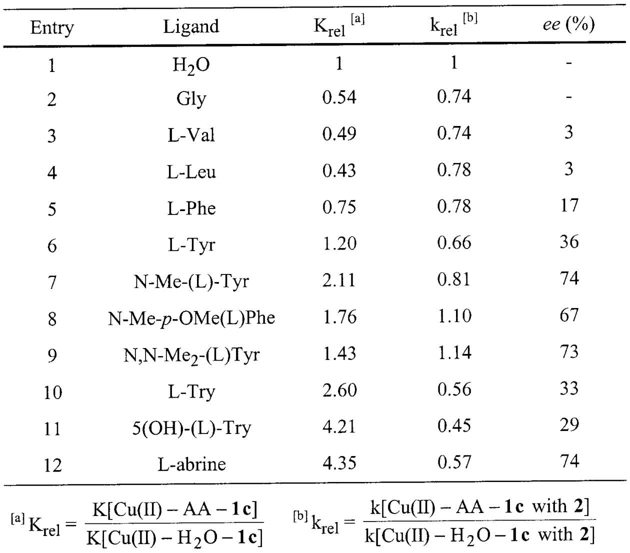
Relative equilibrium constants for the binding of **1c** to Cu^{II}−AA complexes (versus that for the binding of the dienophile to copper aqua ion) and relative reaction rates for cycloadditions of ternary Cu^{II}−AA−**1c** complexes with di-

Table 9. Relative equilibrium constants (K_{rel}) for binding of **1c** to Cu^{II}−AA complexes, relative rate constants (k_{rel}) of Diels−Alder reactions of ternary complexes Cu^{II}−AA−**1c** with **2** and enantiomeric excesses



Entry	Ligand	K_{rel} [a]	k_{rel} [b]	*ee* (%)
1	H_2O	1	1	-
2	Gly	0.54	0.74	-
3	L-Val	0.49	0.74	3
4	L-Leu	0.43	0.78	3
5	L-Phe	0.75	0.78	17
6	L-Tyr	1.20	0.66	36
7	N-Me-(L)-Tyr	2.11	0.81	74
8	N-Me-*p*-OMe(L)Phe	1.76	1.10	67
9	N,N-Me_2-(L)Tyr	1.43	1.14	73
10	L-Try	2.60	0.56	33
11	5(OH)-(L)-Try	4.21	0.45	29
12	L-abrine	4.35	0.57	74

[a] $K_{rel} = \frac{K[Cu(II) - AA - \mathbf{1c}]}{K[Cu(II) - H_2O - \mathbf{1c}]}$ [b] $k_{rel} = \frac{k[Cu(II) - AA - \mathbf{1c} \text{ with } \mathbf{2}]}{k[Cu(II) - H_2O - \mathbf{1c} \text{ with } \mathbf{2}]}$

ene **2** (versus the reaction of $Cu^{II}-H_2O-$**1c** complex with the same diene) are reported in Table 9.

The data show that: (i) the equilibrium constant for the binding of **1c** with a Cu^{II}−aliphatic AA complex is lower than that for the binding of dienophile to the copper aqua ion, while the corresponding equilibrium constant for an aromatic AA is larger; (ii) generally the Diels−Alder reaction is modestly decelerated, (iii) significant *ee*s were obtained for some AAs containing aromatic side chains, and the influence of *N*-methylation on the enantioselectivity is great (entries 6,7 and 9,10). This suggests that the interaction between the aromatic system of an AA ligand and the pyridine ring of **1c** (arene-arene interaction)[48] plays a fundamental role both in the stability of the ternary complex and in differentiating the two faces of the dienophile to the approaching diene.

The authors inferred that the arene-arene interaction, equal to 5.6 KJ/mol, is not governed by hydrophobic interactions or by donor-acceptor interactions, but rather by London dispersion and electrostatic forces.

A comparative study in organic solvents (CF_3CH_2OH, EtOH, MeCN, THF, $CHCl_3$, and CH_2Cl_2) shows that the Diels−Alder reaction, catalyzed by Cu^{II}-(L-abrine), of **1c** with **2** occurs faster and with greater enantioselectivity in water. This can be attributed to a contribution from hydrophobic interactions that enhance, at least partially, the efficiency of arene-arene interactions.

Micelles should have positive effects on Diels−Alder reactions that involve apolar dienes and dienophiles. While a significant influence has been found for surfactants on regio- and diastereoselectivity,[49] that of micellar catalysis on the reaction rate is generally modest.[15a,50] Deceleration has sometimes been observed.[15a,51]

Table 10. Micellar effect on Cu^{II}-catalyzed and uncatalyzed aqueous Diels−Alder reactions of **1a**, **1f** and **1g** with cyclopentadiene **2** at 25 °C

		k_{rel}[a]		
Entry	Catalyst	**1a**	**1f**	**1g**
1	none	1	1	1
2	SDS[b]	0.91	0.83	0.60
3	CTAB[c]	0.90	0.16	0.82
4	$C_{12}E_7$[d]	0.83	0.93	0.84
5	10^{-2} M $Cu(NO_3)_2$	808	793	869
6	CTAB + 10^{-2} M $Cu(NO_3)_2$	—	86	751
7	$C_{12}E_7$ + 10^{-2} M $Cu(NO_3)_2$	—	620	698
8	0.5×10^{-2} M $Cu(DS)_2$	6243	3161	6245

[a] k_{rel} to the reaction performed in sole water. − [b] Sodium dodecyl sulfate. − [c] Cetyltrimetylammonium bromide. − [d] Dodecyl heptaoxyethylene ether.

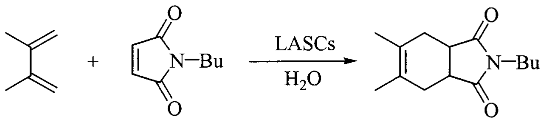
Lewis acid/surfactant combined catalysts (LASCs) are surfactants possessing active metal counterions, and have recently found application in organic synthesis.[52] Engberts[13c] and Kobayashi[40] have investigated the catalytic activity of LASCs towards Diels−Alder reactions in aqueous medium.

Dutch researchers have described[13c] the influence of micelles of CTAB, SDS, and $C_{12}E_7$, as well as that of LASCs possessing transition metal counterions, such as copper and zinc didodecylsulfates [$Cu(DS)_2$ and $Zn(DS)_2$], on the Diels−Alder reactions of non-ionic (**1a−e**), anionic (**1f**), and cationic (**1g**) dienophiles with **2**. Table 10 illustrates some results. In the absence of catalytically active transition metal ions, micelles slow the reaction (entries 2−4), presumably as a result of a decreased diene concentration in the aqueous phase due to its partial solubilization into the micelle, while the cationic dienophile is assumed to reside exclusively in the aqueous phase of the CTAB micellar medium.

Aqueous surfactant solutions containing Cu^{II} ions (entries 6 and 7) accelerate the reaction relative to its pure water counterpart. Relative to conditions purely of Cu^{II} ion catalysis, however (entry 5), the micelles inhibit the cycloaddition. Efficient micellar catalysis was observed in the presence of $Cu(DS)_2$ micelles (entry 8); namely when diene, dienophile and copper ion bind to the micelle simultaneously. Comparing this catalytic effect for the reaction of **1a** with **2** (entry 8; 6243) to its uncatalyzed counterpart in acetonitrile (Table 6; entry 3; 287), in which the slowest reaction rate was observed, the $Cu(DS)_2$ micelles in water accelerate the reaction by a factor of $1.8\cdot10^6$.

Kobayashi investigated[40] the catalytic effect of a number of LASCs on the Diels−Alder reaction between 2,3-dimethylbutadiene (**9**) and *N*-butylmaleimide (**10**) (Scheme 3). No acceleration was observed versus the reaction carried out in pure water.

Assuming that the absence of a catalytic effect is ascribable to the dienophile, which does not have any chelating characteristics and therefore cannot effectively coordinate to the metal cation of the catalyst, thus resulting in the dominance of the uncatalyzed pathway, the author exam-



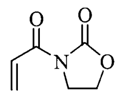
9 **10** **11**

M(DCS)$_n$		M(DS)$_n$	
M	n	M	n
Sc,Yb	3	Sc	3
Mn, Co, Cu, Zn	2	Cu	2
Na, Ag	1		

DCS = dodecane sulfonate

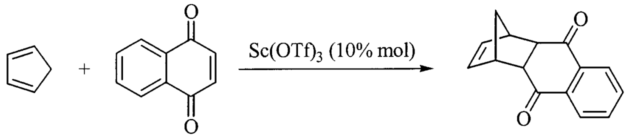
Scheme 3. Diels–Alder reactions of 2,3-dimethylbutadiene with *N*-butylmaleimide in the presence of LASCs

ined the Diels–Alder reaction between the bidentate dienophile **12** and cyclopentadiene. Again, no significant catalytic effect was observed. The LASCs reported in Scheme 3 efficiently catalyzed aldol reactions in water,[40] but did not affect the rate of the Diels–Alder reaction.



12

In contrast, Kobayashi et al.[39,53] found that Sc(OTf)$_3$ is a fairly effective catalyst in the Diels–Alder reaction of naphthoquinone (**13**) with cyclopentadiene (**2**) in THF/H_2O (9:1) at room temperature (Scheme 4).



2 **13** **14**

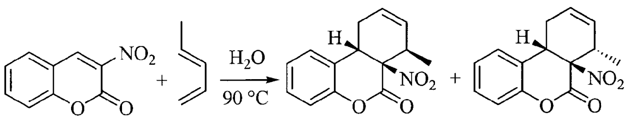
Medium	T (°C)	Yield (%)	*endo/exo*
CH_2Cl_2	0	83	100:0
THF-H_2O (9:1)	r.t.	93	100:0

Scheme 4. Diels–Alder reaction of naphthoquinone with cyclopentadiene in the presence of Sc(OTf)$_3$

This reaction occurs in high yield, and only the *endo* adduct **14** is obtained. Y(OTf)$_3$ and Yb(OTf)$_3$ give only traces of products under the same reaction conditions.[36] The catalyst is easily recovered and can be reused.

Sc(OTf)$_3$ (10% mol) also accelerates the Diels–Alder reaction of 3-nitrocoumarin (**15**) with (*E*)-piperylene (**16**) in wholly aqueous system, but the catalyst does not affect the *exo*/*endo* diastereoselectivity (Scheme 5).[54] Yb(OTf)$_3$ and $InCl_3$ are less effective catalysts.

These reactions (see also below) are the first known Diels–Alder cycloadditions of α,β-unsaturated nitroalkenes carried out in water. Usually, the Diels–Alder reaction in aqueous medium gives mainly the *endo* adduct. The inversion of diastereoselectivity observed in this case can be explained on the basis of NO_2 group secondary orbital interactions, increasing the stabilization of the *exo* transition state.



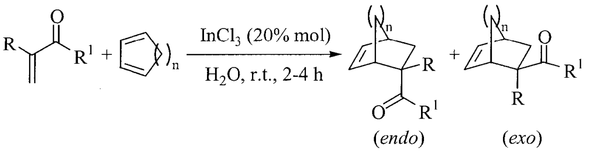
15 **16** **17** (*exo*) **18** (*endo*)

Catalyst	t (h)	*exo/endo*	Yield (%)
none	4	75:25	90
Sc(OTf)$_3$	1	80:20	85
Yb(OTf)$_3$	3	75:25	89
$InCl_3$	2	75:25	88

Scheme 5. Diels–Alder reactions of 3-nitrocoumarin with (*E*)-piperylene in the presence and absence of Lewis-Acid catalysts

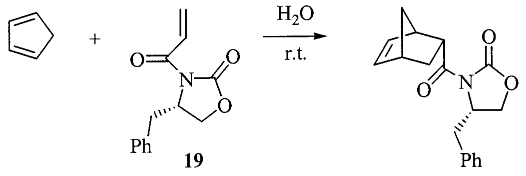
Indium trichloride (20% mol) is reported to catalyze the Diels–Alder reactions in water of methyl acrylate and a variety of acroleins with cyclic and open-chain dienes.[41a] Some results are reported in Table 11. The reactions are clean and occur with excellent yields and diastereoselectivities.

Table 11. $InCl_3$-catalyzed Diels–Alder reactions in water



Entry	R	R^1	n	*endo/exo*	Yield (%)
1	H	H	1	91:9	89
2	Br	H	1	9:91	91
3	Me	H	1	10:90	93
4	H	H	2	90:10	88
5	Me	H	2	4:96	94
6	Br	H	2	5:95	95
7	H	OMe	1	90:10	85
8	H	Me	1	87:13	84
9	H	Me	2	90:10	87

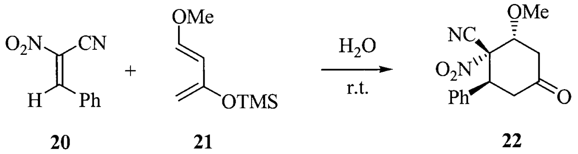
When the cycloadditions of acrolein and methyl acrylate with cyclopentadiene (entries 1 and 7) were carried out in the absence of $InCl_3$, the reaction yields were 40% and 30% lower, respectively, and the *endo*/*exo* ratio was reduced to 75:25. The asymmetric version of the catalyzed reaction was also investigated, using the homochiral dienophile **19** (Scheme 6). The enantioselectivity of the reaction was low (28%); it was increased to 46% by using a great excess of catalyst (120%). The catalyst was recovered at the end of the reaction and reused.



Catalyst	*endo/exo*	*de* (%)	Yield (%)
none	85:15	12	74
InCl$_3$ (20% mol)	95:5	28	94
InCl$_3$ (120% mol)	95:5	46	95

Scheme 6. Asymmetric Diels–Alder reaction of homochiral acrylate **19** with cyclopentadiene in the presence and absence of InCl$_3$

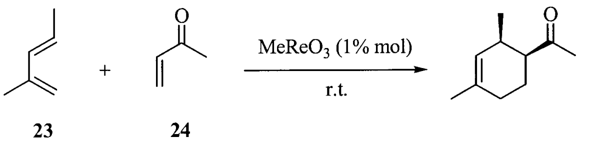
Although Danishesky's diene[55] **21** is known to be water-sensitive, it is converted in excellent yield into the tetrasubstituted cyclohexanone **22** by Diels–Alder reaction with the highly reactive nitroalkene **20** in water at room temperature (Scheme 7).[56] The reaction is completely regio- and stereoselective. InCl$_3$ (20% mol) effectively catalyzes the cycloaddition only in the presence of sodium dodecyl sulfate (SDS), which inhibits the hydrolysis of enol-ether **21**.



Catalyst	t (h)	Conversion (%)
none	7	100
InCl$_3$ (20% mol)	0.25	65
SDS + InCl$_3$ (20% mol)	0.25	100

Scheme 7. Diels–Alder reactions of β-nitro-β-cyano-styrene with Danishesky's diene in the presence and absence of InCl$_3$

Espenson[41b] found that in the presence of methylrhenium trioxide, *trans*-2-methyl-1,3-pentadiene (**23**) reacts with methyl vinyl ketone (**24**) in high yield and with high diastereoselectivity in both organic solvents and water, but the reaction is greatly accelerated in water (Scheme 8).

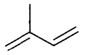
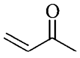
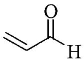
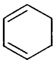
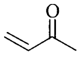
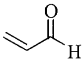
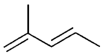
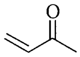
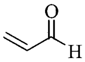


	CHCl$_3$	PhH	Me$_2$CO	MeCN	THF	H$_2$O
t (h)	12	12	12	12	12	4
Yield (%)	94	90	91	91	93	90
endo/exo	98:2					99:1

Scheme 8. Diels–Alder reactions of *trans*-2-methyl-1,3-pentadiene with methyl vinyl ketone in the presence of MeReO$_3$ in various reaction media

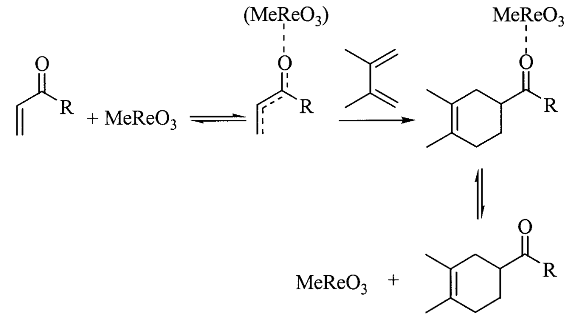
Inspection of the reaction mixture revealed the presence (4–10%) of Diels–Alder adduct originating from the auto-Diels–Alder reaction of diene. Investigations in aqueous medium were extended to other Diels–Alder reactions, and some data are listed in Table 12, including counterparts in CHCl$_3$ for comparison. The selectivities and reaction yields were always high and, compared with uncatalyzed reactions, MeReO$_3$ accelerated the Diels–Alder cycloadditions by a factor of 10^5.

Table 12. MeReO$_3$-catalyzed Diels–Alder reactions in water and chloroform at room temperature

Diene	Dienophile	H$_2$O t (h)	H$_2$O Yield (%)	CHCl$_3$ t (h)	CHCl$_3$ Yield (%)
		2.5	90	18	90
		2.5	91	18	90
		16	91	96	94
		16	90	96	94
		4	90	12	94
		16	90	96	94

The use of water had no beneficial effect with aliphatic β-substituted α,β-unsaturated aldehydes and ketones, nor with some 2-cycloalkenones, nor with α,β-unsaturated esters. In aqueous organic solvents (MeCN/H$_2$O 1:1; Me$_2$CO/H$_2$O 1:1), the solubility of dienes is enhanced but the cycloaddition is decelerated and occurs in lower yield.

After a week in water, MeReO$_3$ decomposed appreciably to give perrhenic acid (HReO$_4$). The catalytic effect of HReO$_4$ was therefore investigated, but the accelerating effect of MeReO$_3$ in water cannot be related to Brønsted acidity. The suggested mechanism (Scheme 9) involves a reversible interaction between the catalyst and the oxygen atom of the dienophile, which lowers the energy of the LUMO and influences the molecular orbital coefficients.

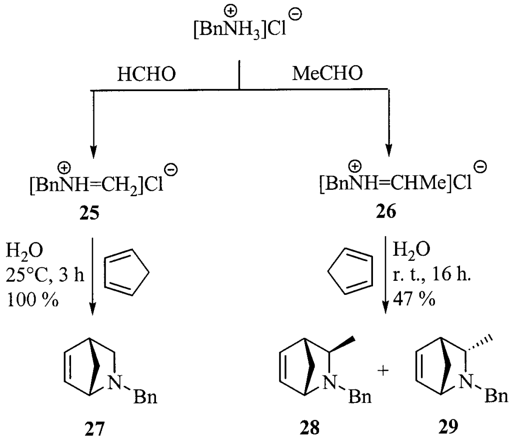


Scheme 9. Mechanism of the Diels–Alder reactions catalyzed by MeReO$_3$

5. Hetero-Diels−Alder Reactions

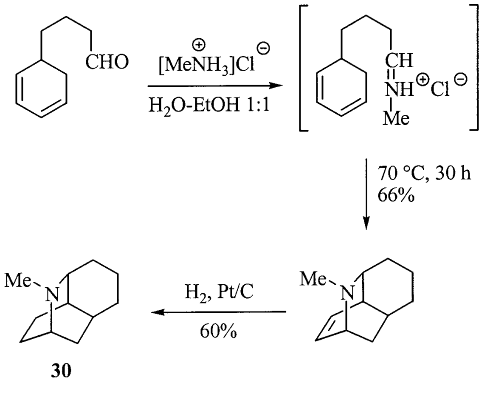
Nitrogen-containing, six-membered heterocycles are present in many naturally occurring compounds and can easily be constructed by Diels−Alder reaction using imines.

Simple imines are poor dienophiles and must be activated by attaching a Lewis acid to the nitrogen atom. When working in aqueous medium, the simplest way is the protonation reaction.[57a] Thus, benzyliminium **25**, generated from an aqueous solution of formaldehyde and benzylamine hydrochloride, reacts with cyclopentadiene to give the bicyclic amine **27** (Scheme 10). Benzyliminium **26**, produced from acetaldehyde, is less reactive and affords a mixture of *exo* and *endo* adducts **28** and **29**, respectively, in low yield.



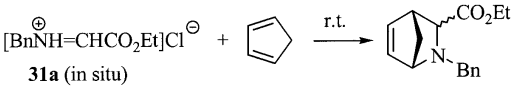
Scheme 10. Intermolecular three-component aza-Diels−Alder reactions

The cycloadditions with iminium ions in aqueous medium are already reversible at room temperature, and therefore the *exo*/*endo* ratio may represent not kinetic but rather thermodynamic diastereoselectivities.[57d][57e][58] The intramolecular version of this three-component (amine, aldehyde, diene) aza-Diels−Alder reaction was used by Grieco[57b] to synthesize dihydrocannivonine **30** (Scheme 11).

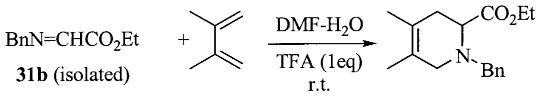


Scheme 11. Intramolecular three-component aza-Diels−Alder reaction and synthesis of dihydrocannivonine

Bailey[59] found that the yield of the reaction of cyclopentadiene with benzyliminium ion **31a**, prepared in situ from benzylamine hydrochloride and ethyl glyoxylate, depended on the solvent (Scheme 12). DMF gave the best result, while no reaction occurred in anhydrous THF.



Solvent	THF	EtOH	H_2O	DMF
Yield (%)	0	17	52	89

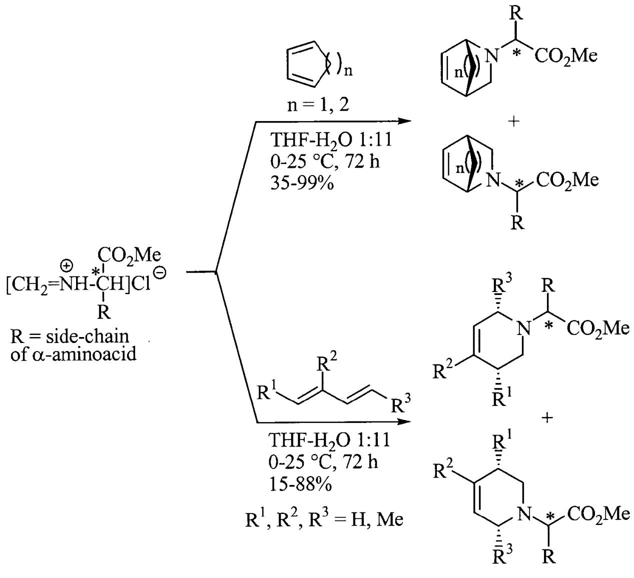


H_2O (mol%)	1	10	100	1000
Yield (%)	94	94	29	9

Scheme 12. Diels−Alder reactions of benzyliminium ion **31a** with cyclopentadiene in various solvents and of imine **31b** with 2,3-dimethyl-1,3-butadiene in the presence of various quantities of water

When using the isolated imine **31b** and treating it with 2,3-dimethyl-1,3-butadiene in the presence of TFA, the reaction only works in the presence of catalytic amounts of water. An excess of water reduces the yield; this is probably because it causes the hydrolysis of imine, but the role of water is not clear. The water probably increases the π-character of the iminium ion by forming a cyclic intermediate by means of two hydrogen bonds.[58b]

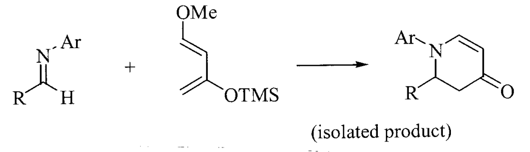
Optically active iminium salts have been used to prepare homochiral azabicyclo derivatives and piperidines.[57−59] Scheme 13 illustrates some examples in which iminium ions derived from (*R*)- and (*S*)-α-amino acid methyl ester hydrochlorides and formaldehyde react with cyclic and open-chain dienes.[57d][58a][58b] Removal of the starting stereogenic centre converts the adducts into the planned products.



Scheme 13. Diels−Alder reactions of homochiral iminium salts with cyclic and open-chain dienes

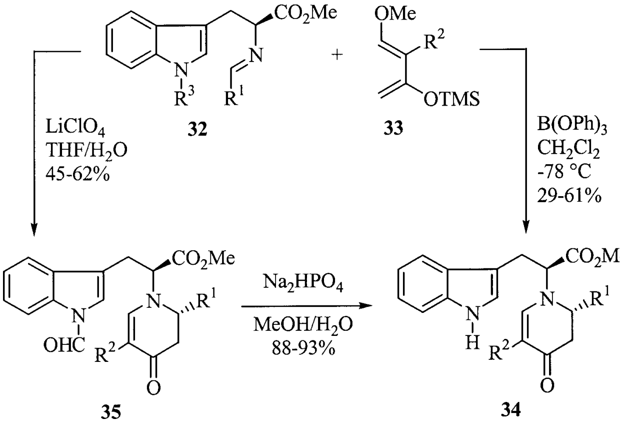
With the highly reactive Danishefsky's diene, the imine Diels−Alder reaction occurs under Brønsted acid catalysis conditions.[60] *p*TsOH, CF_3CO_2H, and HBF_4 (0.1−0.2 equiv.) were screened, HBF_4 giving the best results. Dihydro-4-pyridones were obtained in high yields (Table 13). Water was used either as an additive (10 equiv.) in the reaction performed at − 40 °C in MeCN or MeOH, or as the solvent with the cycloaddition carried out in the presence of SDS.

Table 13. Diels−Alder reactions of aniline imines with Danishefsky's diene, catalyzed by HBF_4



H_2O (10eq.), HBF_4 (0.1eq.), MeOH -40 °C, 0.5 h			H_2O, HBF_4 (0.2eq.), SDS (0.2eq.) r.t., 1 h		
R	Ar	Yield	R	Ar	Yield
Ph	*p*-$OMeC_6H_4$	88	Ph	*p*-$OMeC_6H_4$	88
p-MeC_6H_4	Ph	79	*p*-MeC_6H_4	*p*-$OMeC_6H_4$	86
p-$NO_2C_6H_4$	Ph	65	PhCH=CH	*p*-$OMeC_6H_4$	86
c-C_6H_{11}	Ph	80	*c*-C_6H_{11}	*p*-$OMeC_6H_4$	75

In the course of synthesizing highly functionalized indoloquinolizines, Waldmann and Lock[61] found that imines **32a** react with electron-rich silyloxydienes **33** (R^2 = H, Et) in CH_2Cl_2 and in the presence of chiral and achiral boric acid esters to give cycloadducts **34a** (R^2 = H, Et) with a high diastereoisomeric ratio (Scheme 14). The formaldehyde imine **32c** is unreactive under these reaction conditions. The desired enaminones **34c** (R^2 = H, Et) were obtained by treating the indole-*N*-formyl-protected tryptophan methyl ester **32b** with dienes **33** (R^2 = H, Et) in aqueous THF in the presence of $LiClO_4$ and subsequent deprotection of intermediates **35c** (R^2 = H, Et).

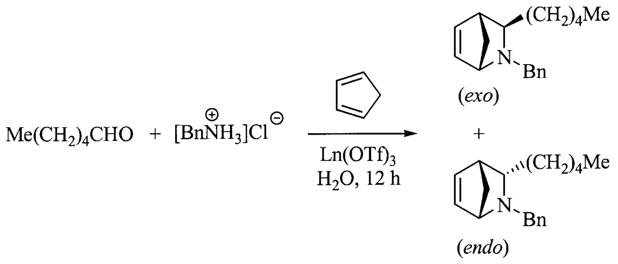


a : R^1 = alkyl, aryl; R^3 = H **b** : R^1 = H, R^3 = CHO **c** : R^1 = R^3 = H

Scheme 14. Diels−Alder reactions of imines **32** with silyloxydienes **33**

A limitation of the Brønsted acid-catalyzed imino Diels−Alder reaction is that it is necessary to use activated reagents (formaldehyde, glyoxylates, cyclopentadiene, Danishefsky's diene) to produce good yields.

Lanthanide triflate greatly accelerates this three-component coupling reaction in aqueous medium, allowing non-activated aldehydes and methyl-1,3-butadienes to be used.[62a][62c] Thus, the uncatalyzed reaction of hexanal and benzylamine hydrochloride with cyclopentadiene afforded only 4% of adduct after 4 h (Scheme 15). When lanthanide triflates (0.2 M; pH 5−7) were used, however, the reaction rate and yield were greatly enhanced. The lanthanide catalyst does not change the *exo*/*endo* ratio (74.7:25.3) relative to that of the uncatalyzed reaction. $Pr(OTf)_3$ and $Yb(OTf)_3$ were the most effective triflates.



Ln	-	Gd	Er	La	Dy	Nd	Yb	Pr
Yield (%)	4	19	46	47	49	57	62	68

Scheme 15. Three-component aza-Diels−Alder reaction catalyzed by lanthanide triflates

It appears that lanthanide triflates act as stable Lewis acids in aqueous medium and a catalytic salt effect[12g] can be discounted, since $MgCl_2$ and LiCl (0.25 M) do not catalyze the reaction. Other examples of $Ln(OTf)_3$-catalyzed imine Diels−Alder reactions are shown in Table 14.[62a] In aqueous medium, benzyliminium ions generated from arylaldehydes and benzylamine are unreactive towards 1,3-cyclohexadiene and 2,3-dimethyl-1,3-butadiene, even in the presence of lanthanide triflates.

The lanthanide-promoted imino Diels−Alder reaction in aqueous medium has been used to synthesize azasugars which inhibit glycoprocessing enzymes (Scheme 16).[62b][62c]

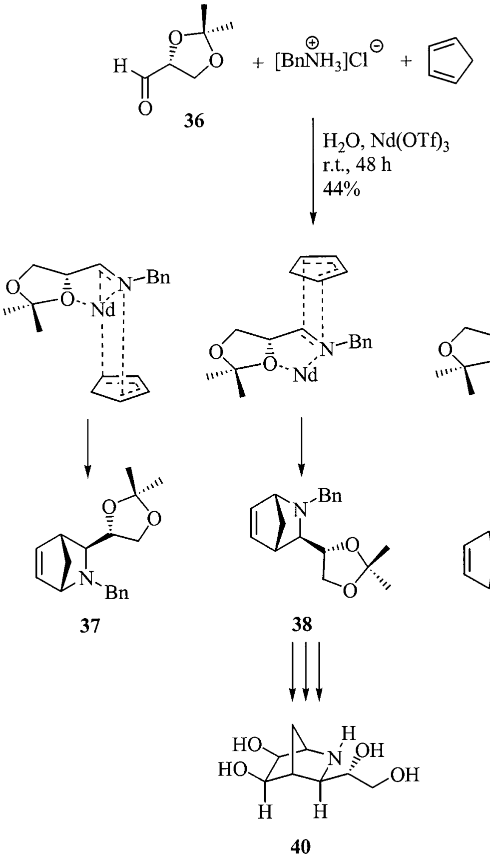
Cycloadditions between optically active glyceraldehyde acetonide **36**, benzylamine hydrochloride and cyclopentadiene in water at room temperature and in the presence of $Nd(OTf)_3$ gave the products **37** (8.3%), **38** (66.7%), and **39** (25%) (Scheme 16). The products **37** and **38** are the result of *exo* addition on the *si* and *re* faces of the aldimine, respectively, the Nd^{III} coordinating the nitrogen atom and adjacent oxygen, while the adduct **39** originates from the *endo-re* attack. The *exo* adduct **38** then successfully underwent a three-step conversion into the azasugar **40**. Similarly, the optically active aldehyde **41**, under the same reaction conditions, exclusively gave the *exo* adduct **42** originating from *si* attack (Scheme 17); this was then converted into the azadisaccharide **43**.

Lanthanide triflates catalyze imino Diels−Alder reactions of imines generated from anilines and aldehydes, with

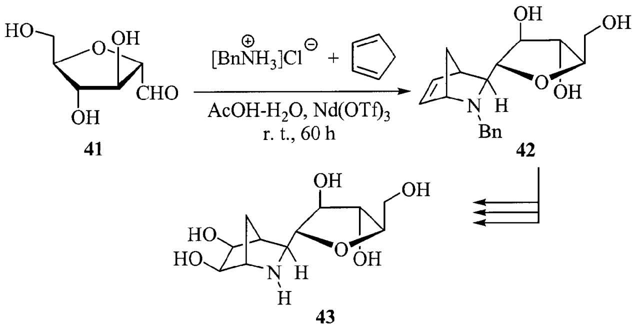
Table 14. Imine Diels−Alder reactions in aqueous medium, catalyzed by lanthanide triflates

RCHO (R)	Diene[a]	$[R^1NH_3]^+Cl^-$ (R^1)	$Ln(OTf)_3$ (Ln)	*exo*/*endo*	Yield (%) Catalyzed	Yield (%) Uncatalyzed
Et	CP	Bn	La	71.5:28.5	64	4
Bn	CP	Bn	Yb	80:20	72	3
H	2,3-DMB	Bn	Nd		93	23
H	2,5-DMB	Bn	Yb		92	54
H	CHD	L-PAME[b]	Nd	75:25	84	27
H	2,3-DMB	L-PAME	Nd		98	58
H	IP	L-PAME	Nd		96	37

[a] CP = cyclopentadiene, DMB = dimethylbutadiene, CHD = 1,3-cyclohexadiene, IP = isoprene. − [b] L-PAME = L-phenylalanine methyl ester.

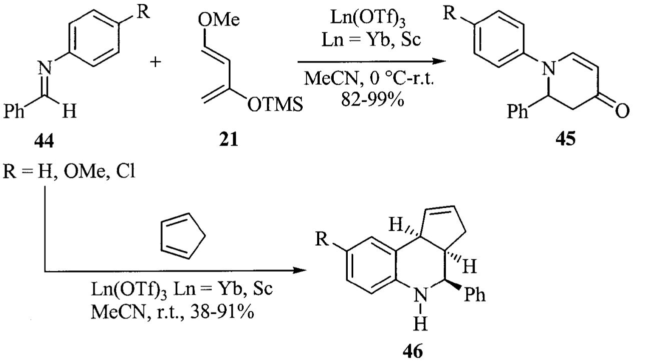


Scheme 16. Synthesis of azasugar **40** by $Nd(OTf)_3$-promoted imino Diels−Alder reaction

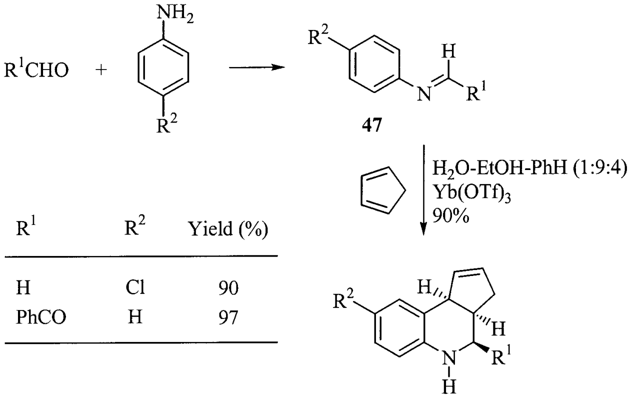


Scheme 17. Synthesis of azadisaccharide **43** by $Nd(OTf)_3$-promoted imino Diels−Alder reaction

both dienes and alkenes.[63] *N*-Benzylideneanilines **44** and Danishefsky's diene **21** (Scheme 18) react in organic solvents in the presence of $Yb(OTf)_3$ or $Sc(OTf)_3$ to give quantitatively the dihydro-4-pyridones **45**. The reaction pathway of **44** with cyclopentadiene is different: the imine acts as an aza-diene towards one of the double bonds of cyclopentadiene acting as dienophile, and tetrahydroquinoline derivatives **46** are obtained. $Yb(OTf)_3$ also catalyzes the reaction in water, so commercial aqueous formaldehyde solution can be used directly. In aqueous medium, the *N*-benzylideneanilines **47**, generated by treatment of formaldehyde and phenylglyoxal with aniline and *p*-chloroaniline, behaved analogously in the cycloaddition with cyclopentadiene (Scheme 19).



Scheme 18. Cycloadditions of *N*-benzylideneanilines with Danishefsky's diene and cyclopentadiene in the presence of $Yb(OTf)_3$ and $Sc(OTf)_3$



R^1	R^2	Yield (%)
H	Cl	90
PhCO	H	97

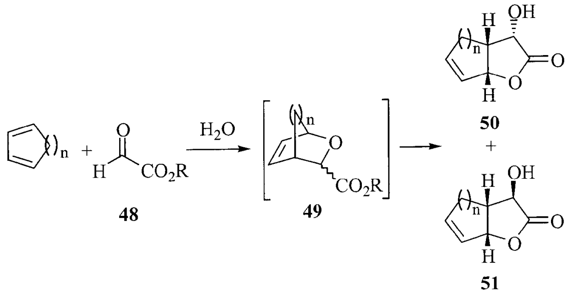
Scheme 19. *N*-Benzylideneanilines as azadienes in the $Yb(OTf)_3$-catalyzed Diels−Alder reaction with cyclopentadiene

Hetero-Diels−Alder reactions that use carbonyl compounds as dienophiles permit the preparation of dihydropyran derivatives; useful intermediates for the synthesis of many natural compounds. The cycloaddition is usually carried out using glyoxylates and mesoxalates in organic solvents under high pressure, at high temperatures and in the presence of Lewis acids.[64]

Lubineau found[65a,65b] that aqueous solutions of glyoxylic acid, pyruvaldehyde, pyruvic acid and glyoxal easily underwent hetero-Diels−Alder reactions with cyclic and open-chain dienes. This result is particularly significant because these dienophiles are mostly in the hydrate form in water, and so the cycloaddition should in principle be compromised, because of the very low concentration of the reactive species.

An aqueous solution of glyoxylic acid (**48** R = H) reacted with cyclopentadiene (Table 15, *n* = 1) and 1,3-cyclohexadiene (*n* = 2) to give a mixture of α-hydroxy-γ-lactones **50** and **51**. The best results were achieved under strongly acidic conditions. The cycloadduct **49** was not isolated. By performing the cycloaddition of *n*-butylglyoxylate (**48** R = *n*Bu) with cyclohexadiene in a sealed tube at 120 °C for 21 h, the cycloadduct **49** (*n* = 2, R = *n*Bu, *endo*/*exo* = 9:1) was isolated in a 57% yield. After hydrolysis, the acid **49** (*n* = 2, R = H) was obtained and, in water and at room temperature, rearranged spontaneously into **50** and **51** (*n* = 2). The rearrangement occurs at 150 °C in the absence of solvent. The cycloaddition reactions in water of glyoxylic acid with cyclopentadiene and 1,3-cyclohexadiene have also been investigated in the presence of Cu^{II} [65c] and Bi^{III} salts.[36b]

Table 15. Diels−Alder reactions of glyoxylic acid **48** (R = H) with cyclopentadiene and 1,3-cyclohexadiene in water

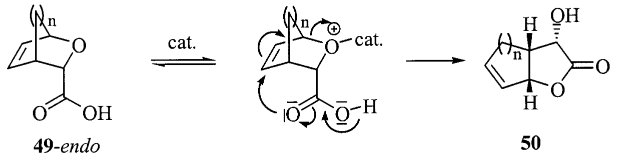


pH	n	T (°C)	t (h)	50/51	Yield (%)
6	1	60	24	60:40	16
2.5	1	60	7.5	60:40	72
0.9 [a]	1	40	1.5	73:27	83
1	2	90	48	60:40	85

[a] 2.25 M Solution of glyoxylic acid in water.

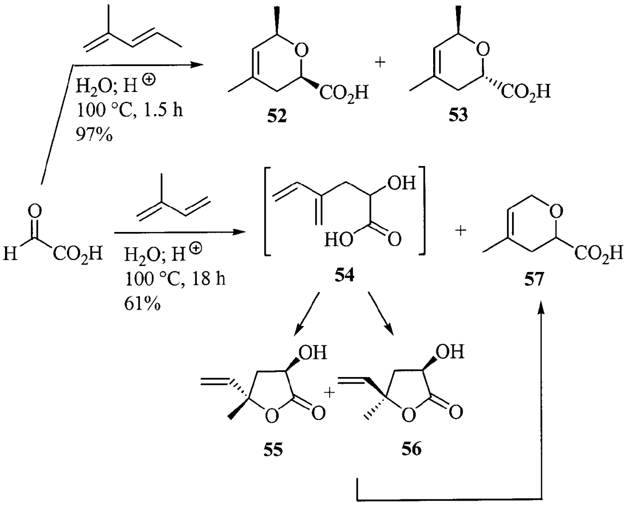
$CuCl_2$, $CuSO_4$, and $Cu(NO_3)_2$ accelerate the cycloaddition in water of glyoxylic acid (**48** R = H) with cyclopentadiene (*n* = 1; 3 h at 60 °C; **50/51** = 65:35; yield 63%),[65c] while $Bi(OTf)_3$ efficiently catalyzes the cycloaddition in water of **48** (R = H) with either cyclopentadiene (*n* = 1; 2 h at 40 °C; **50/51** = 82:18; yield 86%) or 1,3-cyclohexadiene (*n* = 2; 2 h at 80 °C; **50/51** = 50:50; yield 88%).[36b]

The lactones **50** and **51** are obtained from the intermolecular rearrangement of *endo* and *exo* intermediates, as depicted in Scheme 20 for the major *endo* adduct **49**. The formation of **50** from a competitive *ene* reaction cannot be ruled out.[36b]



Scheme 20. Rearrangement of *endo* adduct **49** to bicyclic lactone **50** in the presence of Lewis acids

Glyoxylic acid reacts with *trans*-2-methyl-1,3-pentadiene under strongly acidic conditions (9 M glyoxylic acid in water) at 100 °C to give the adducts **52** and **53** in 97% yield after 1.5 h (Scheme 21).[65a,65b] At 60 °C, the yield is only 55% after 12 h, but addition of 0.1 equiv. of $Yb(OTf)_3$ or $Nd(OTf)_3$ results in quantitative cycloaddition under the same conditions.



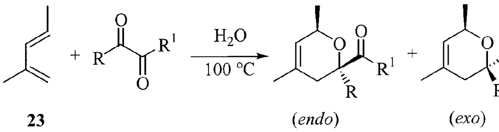
Scheme 21. Diels−Alder reactions of glyoxylic acid with *trans*-2-methyl-1,3-pentadiene and isoprene

Glyoxylic acid also reacts with isoprene at low pH values (5.4 M aqueous solution of glyoxylic acid) at 100 °C, but under these conditions, the lactones **55** and **56** were obtained, along with the adduct **57**, in 33%, 21%, and 46% yield, respectively (Scheme 21). The lactones **55** and **56** arise from the *ene*-product **54**. Lateral experiments show that the adduct **57** is partially derived from each lactone **55** and **56**, so it is impossible to discern what proportion of **57** originates from the Diels−Alder reaction and what from the *ene* reaction via **55** and **56**, with subsequent rearrangement.

The cycloadditions of glyoxylic acid (**48** R = H) with 1,3-butadienes (butadiene, isoprene, (*E*)-piperylene) are greatly accelerated by $Bi(OTf)_3$, but the Lewis acid favours the formation of α-hydroxy-γ-lactone-types **55** and **56**, relative to the cycloadduct-type **57**.[36b]

The French authors[65a,65b] studied the Diels−Alder reaction of *trans*-2-methyl-1,3-pentadiene (**23**) with aqueous so-

Table 16. Diels–Alder reactions in water of *trans*-2-methyl-1,3-pentadiene with pyruvaldehyde (R = H, R^1 = Me), glyoxal (R = R^1 = H) and pyruvic acid (R = Me, R^1 = OH)



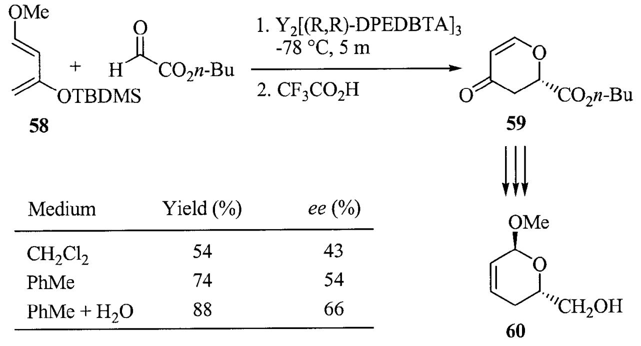
R	R^1	t (h)	*endo/exo*	Yield (%)
H	Me	48	53:47	96
H	H	60	50:50 [a]	36
Me	OH	48	33:67	74

[a] After $NaBH_4$ reduction and acetylation.

lutions of pyruvaldehyde, glyoxal and pyruvic acid. The results are summarized in Table 16. The cycloaddition of pyruvic acid occurred under conditions of thermodynamic control in water and under conditions of kinetic control in toluene or in solvent-free systems (100 °C, 48 h, *endo*/*exo* = 67:33).

These results have been used to prepare key compounds in the synthesis of 3-deoxy-D-manno-2-octulosonic acid (KDO), an essential constituent of the outer lipopolysaccharide membrane of all gram-negative bacteria,[66a] of ketodeoxyheptulosonic acid derivatives,[66b] and of racemic sesbanimide A and B, which are potent natural antitumour compounds.[66c]

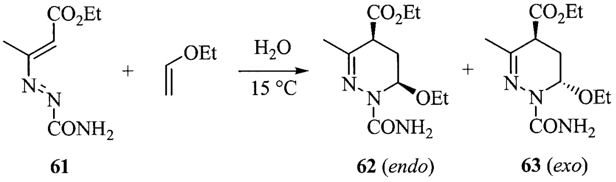
Mikami[33] found that the yield and enantioselectivity of the reaction of butyl glyoxylate with Danishefsky-type diene **58**, catalyzed by an (*R*,*R*)-1,2-diphenylethylenediamine-derived bis(triflamide) of yttrium and carried out in organic solvent, are increased by using water as additive (11 equiv. relative to the catalyst) (Scheme 22). The dihydropyrone ester **59** was converted into (hydroxymethyl)dihydropyran **60**, which is an intermediate for the synthesis of monosaccharides and other natural products, such as mevinolin and compactin.[67]



Medium	Yield (%)	*ee* (%)
CH_2Cl_2	54	43
PhMe	74	54
PhMe + H_2O	88	66

Scheme 22. Diels–Alder reaction of butyl glyoxylate with Danishefsky-type diene **58**

Hetero-Diels–Alder reactions with inverse electron demand are rare in aqueous media.[7a,68] A recent example is the cycloaddition of 1,2-azadiene **61** with ethylvinyl ether (Scheme 23).[69]



Catalyst	t (h)	*endo/exo*	Yield (%)
-	16	94:6	80
$Yb(OTf)_3$	8	95:5	83

Scheme 23. Diels–Alder reactions of 1,2-azadiene **61** with ethyl vinyl ether

The reaction occurs at room temperature in high yield, and the *endo* adduct is greatly favoured. $Yb(OTf)_3$ significantly accelerates the cycloaddition, but does not affect the diastereoselectivity.

6. The Role of Water and Catalyst

Among solvents, water occupies a very special place because of its very particular properties.

Water has a very small molecular volume, is highly polar, has a low value of internal pressure and a very high value of cohesive energy density (also called cohesive pressure). The surface tension of water is very high and its heat capacity, neat fusion, and heat vaporisation are high.[12c] These properties are the result of intermolecular forces between closed-shell molecules.

The molecular structure of water is well known, but the fine inner structure of liquid water is complex, and none of the proposed models completely describes its physical-chemical properties.[12c,70] An inspection of liquid water at the molecular level reveals ordered bound molecules which form chains and rings, random bound molecules, free or trapped molecules in structured cages, holes and vacancies.[12c]

Many studies have been carried out in an effort to understand the reasons for the beneficial effect of water on reaction rates and selectivities, but to date the underlying reasons are still not well known.

In his pioneering work of 1980, Breslow[14] suggested that the acceleration and selectivity of Diels–Alder reactions is ascribable to hydrophobic interaction: the aggregation of apolar molecules or apolar groups of large molecules in water, minimizing their exposure to the water. This hypothesis was based on kinetic data, activation parameters, and by the fact that the reaction is accelerated by addition of salting-out salts or cyclodextrins to the reaction mixture and is retarded by addition of salting-in salts. The hydrophobic packing of the reactants in aqueous medium[12c–12h,46a,71a–71c] however, cannot be considered responsible for the rate enhancement of aqueous Diels–Alder reactions, because intramolecular

Diels–Alder cycloadditions and Claisen rearrangements, in which the reactants are already *packed*, are considerably faster in water than in organic solvents.[71d]

Micellar catalysis has also been suggested, and when certain amphiphilic reactants are used it cannot be ruled out,[71e–71i] but it has also been shown that micellar effects sometimes lead to a deceleration of reactions versus their pure water counterparts.[15a,51b]

The Diels–Alder reaction is assisted by high pressure.[71j] On this basis, the importance of internal pressure[12c,12d] (a measure of the energy necessary to change the distance of water-water molecules by an infinitesimal amount) has been invoked,[71k–71m] but its value is very low[12c] and therefore its effect should be minimal. The effect of cohesive energy density[12c,12d] (a measure of energy required to create a cavity in the water to accommodate the solute) could be an important factor for enhancing the reaction rate in water. This parameter has been used to describe the solvophobicity (*Sp*) in a multiparameter equation.[71n] The *Sp* parameter correlates Diels–Alder reaction rates and selectivities but these correlations are not observed in a broad series of solvents.[46b,71o]

Hydrogen bonding has also been reported to play an important role,[71p,71q] as shown in the relationship between the acceptor number (AN) of the solvent and the Diels–Alder reaction rates.[12m,12o]

Recent experimental studies[6g,6i,13,35] and computer simulations[71r,71s] indicate that there are two main effects responsible for the rate enhancement of aqueous Diels–Alder reactions: enforced hydrophobic interactions and hydrogen-bonding interactions. The term "enforced" has been used to emphasize that the rate enhancement is not the result of hydrophobic packing of reactants but rather "to stress that hydrophobic interactions occur simply because they are an integral part of the activation process".[71t] Hydrogen bonding of the water molecules to reactants and activated complex act in the same way as Lewis acid catalysis, and stabilize the transition state that, in water, seems to have a more polar character than in other solvents.[13]

Hydrophobic interactions, polarity of water and hydrogen-bonding interactions favour *endo* addition[13] as well as the diastereofacial selectivity[12d,71u] and regioselectivity[12d,71v] of the aqueous Diels–Alder reaction.

The first mechanistic study on the benefits of a combination of Lewis-acid catalysis and water as solvent for the Diels–Alder reaction appeared in 1995[13a,13b] and an overview of this field was published the following year.[6i] The fundamental steps of the catalytic cycle are illustrated in the example shown in Scheme 9. The first step is the coordination of the Lewis acid to key sites in the starting material (generally the dienophile). The complex of Lewis acid and starting material then undergoes cycloaddition with the other starting material (diene) (second step), and finally the complex of Lewis acid and adduct dissociates, making the catalyst available for another cycle.

Generally, efficient coordination between Lewis acid and starting material ensures efficient catalysis, provided that the coordination of adduct to the catalyst is not very strong. Polar and protic solvents, such as water, hamper the complexation because they are hard solvents and interfere with the interactions between a hard Lewis acid and hard key sites of starting material. The result is that the catalytic effect may be more marked in organic than in aqueous media (see Table 6). The coordination of Lewis acid to a bidentate starting material in water is two or three orders of magnitude greater than that for monodentate binding and therefore a bidentate starting material seems to be essential in order to obtain efficient catalysis.[13a,13b]

The Diels–Alder reaction can be strongly accelerated by combining the aqueous medium and the Lewis acid catalyst; however, it seems that it is the water (enforced hydrophobic interactions and hydrogen-bonding interactions) that makes the greatest contribution to the marked rate enhancement observed.

Water is a unique and extraordinary reaction medium and chemists have only recently begun to discover its benefits. The exploration of Lewis acid catalysts in water is an intriguing challenge for the near future in terms of mechanistic considerations and synthetic applications.

Acknowledgments

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