

Lewis-Acid Catalysis¹

Many Diels-Alder reactions can be catalysed efficiently by Lewis acids in organic solvents. It is also known that the use of water as a solvent has a favourable effect on rate and selectivity of these reactions. A detailed investigation of the possibilities of combining both effects has hitherto not been reported and forms the goal of this chapter. It will be demonstrated that Lewis-acid catalysis of a Diels-Alder reaction in aqueous media is feasible and can actually lead to astonishing increases in the rate of the reaction. A detailed study of the kinetics of this process will be presented, alongside with results of investigations of the complexation behaviour of the Diels-Alder reagents to a number of different Lewis acids in aqueous solution. Also the effects of Lewis acids on the endo-exo selectivity in water will be described and compared to the corresponding effects in organic solvents.

2.1 Introduction

The Diels-Alder reaction is often quoted as an example of a reaction that is little influenced by the solvent. However, this is not fully justified, since particularly water can have a pronounced effect on the rate of this reaction. This was first noticed by Eggelte et al.² in 1973 and rediscovered in 1980 by Breslow³. In the years that followed this intriguing discovery, it turned out that acceleration of Diels-Alder reactions by water is a general phenomenon that can ultimately result in up to 12,800 fold accelerations⁴. Synthetic applications followed rapidly⁵.

Mechanistic studies have tried to unravel the origin of the special effect of water. Some authors erroneously have held aggregation phenomena responsible for the observed acceleration⁶, whereas others have hinted at effects due to the internal pressure⁷. However, detailed studies have identified two other effects that govern the rate of Diels-Alder reactions in water.

In the first place *enforced hydrophobic interactions* are important⁸. The initial state of the Diels-Alder reaction is significantly destabilised in water relative to organic solvents, due to the relatively unfavourable solvation of the apolar moieties in aqueous solution. During the activation process the apolar character of the groups near the reaction centre is largely lost⁹. Consequently, the transition state is hardly destabilised by water and, hence, the reaction is accelerated. The term “enforced” has been introduced to stress the fact that it is the occurrence of the organic reaction that gives rise to the hydrophobic interaction, whereas the hydrophobic interaction is, in itself, not strong enough to bring the reactants together.

Hydrogen bonding of water to the activating group of (for normal-electron demand Diels-Alder reactions) the dienophile constitutes the second important effect^{4,10}. Hydrogen bonds strengthen the electron-withdrawing capacity of this functionality and thereby decrease the HOMO-LUMO gap

between diene and dienophile.

The relative extents to which enforced hydrophobic interactions and hydrogen bonding influence the rate of the Diels-Alder reaction depends on the particular reaction under study¹¹.

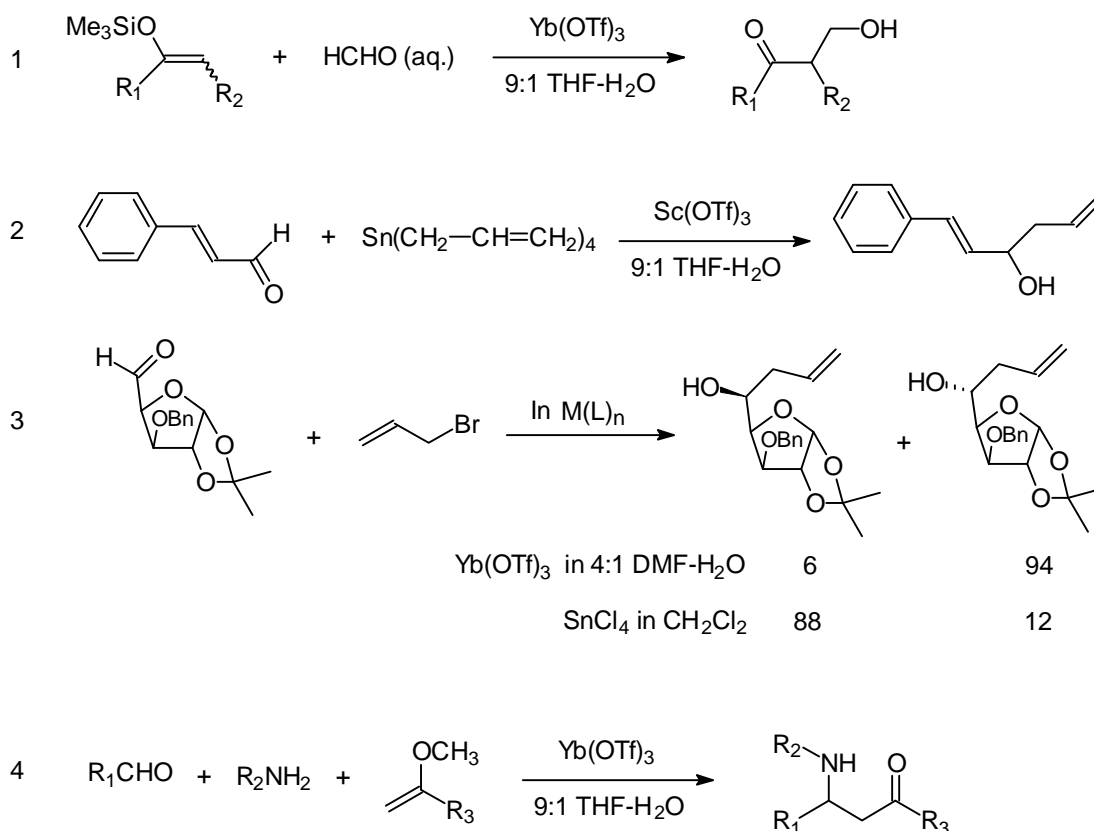
The appreciable rate effects in water are generally overshadowed by the large accelerations that can be induced in organic solvents by coordinating a Lewis-acid catalyst to the activating group of (for normal electron demand Diels-Alder reactions) the dienophile¹². Analogous to the hydrogen bonding effect, Lewis acids can decrease the HOMO-LUMO gap between diene and dienophile and thereby induce an increase of the rate of the reaction.

Appreciating the beneficial influences of water and Lewis acids on the Diels-Alder reaction and understanding their origin, one may ask what would be the result of a combination of these two effects. If they would be additive, huge accelerations can be envisaged. But may one really expect this? How does water influence the Lewis-acid catalysed reaction, and what is the influence of the Lewis acid on the enforced hydrophobic interaction and the hydrogen bonding effect? These are the questions that are addressed in this chapter.

In order to be able to provide answers to these questions, a Diels-Alder reaction is required that is subject to Lewis-acid catalysis in aqueous media. Finding such a reaction was not an easy task. Fortunately the literature on other Lewis-acid catalysed organic reactions in water was helpful to some extent.

*2.1.1 Lewis-acid catalysis of organic reactions in aqueous solutions*¹³

The demand for environmentally friendly chemistry has made the use of water as a solvent for organic transformations increasingly popular^{5,14}. However, this trend does not seem to extend to Lewis-acid catalysis, at least not when pure water is considered. Mixtures of organic solvents and water (typically 9:1 mixtures of THF and water), on the other hand, are now commonly employed media for a number of organic transformations¹⁵. One example is the Lewis-acid catalysed *aldol reaction*, commonly known as the Mukaiyama aldol reaction, of silyl enol ethers, which was first reported in the early seventies¹⁶. With titanium tetrachloride as catalyst this reaction proceeds in a regioselective manner, giving high yields. These transformations were traditionally carried out under strictly non-aqueous conditions to prevent decomposition of the catalyst and hydrolysis of the silyl enol ethers used in the reaction. The same reaction in the absence of catalyst was previously studied by Lubineau, who observed that water had a beneficial influence on this process¹⁷. However, the scope and yields were not satisfactory. In 1991, Kobayashi reported the first Lewis-acid catalysed cross aldol reaction in an aqueous mixture¹⁸. He examined the effects of lanthanide triflates on the reaction of several silyl enol ethers with a commercial formaldehyde solution (entry 1 in Scheme 2.1). The reactions were most effectively carried out in a 1:9 commercial aqueous formaldehyde-THF mixture under the influence of 5-10 mole percent of Yb(OTf)₃, which can be reused after completion of the reaction¹⁹. Various aldehydes could be used²⁰. The amount of water in the reaction mixture is crucial. The best results were obtained when the organic solvent contained 10-20% (v/v) of water. When the amount of water was increased, the yield of aldol product decreased. This



Scheme 2.1. Lewis-acid catalysed organic reactions that are promoted by small amounts of water in organic solvents.

fall in yield was attributed to the competitive hydrolysis of the silyl enol ether.

The use of indium in aqueous solution has been reported by Li and co-workers as a new tool in organometallic chemistry²¹. Recently Loh reported catalysis of the Mukaiyama-aldol reaction by indium trichloride in aqueous solution²². He attributed the beneficial effect of water to aggregation phenomena in connection with the high internal pressure of this solvent²³. This work has been severely criticised by Kobayashi²⁴.

Lewis-acid catalysed *allylation reactions* also benefit from the presence of water as a cosolvent. The synthesis of homoallylic alcohols via a Lewis-acid catalysed reaction of organometallic reagents with a carbonyl compound in organic media has been frequently reported²⁵. The first example of such a Lewis-acid catalysed allylation reaction in aqueous medium was again reported by Kobayashi²⁶. In a smooth reaction under the influence of 5 mole percent of Sc(OTf)₃, tetraallyltin was allowed to react with several ketones and aldehydes (an example is given in entry 2 in Scheme 2.1). The reactions were carried out in water-THF, water-ethanol or water-acetonitrile mixtures (1:9) providing high yields of the corresponding homoallylic alcohol. The much cheaper Yb(OTf)₃ is also effective in this reaction and the Lewis acid can be reused without loss of activity¹⁹. Loh has demonstrated that indium can be used to promote the allylation of aldehydes and ketones in water at room temperature without the need of an inert atmosphere²⁷. The use of a Lewis-acid promotor in this reaction can have a large effect on the stereoselectivity²⁸. Furthermore the

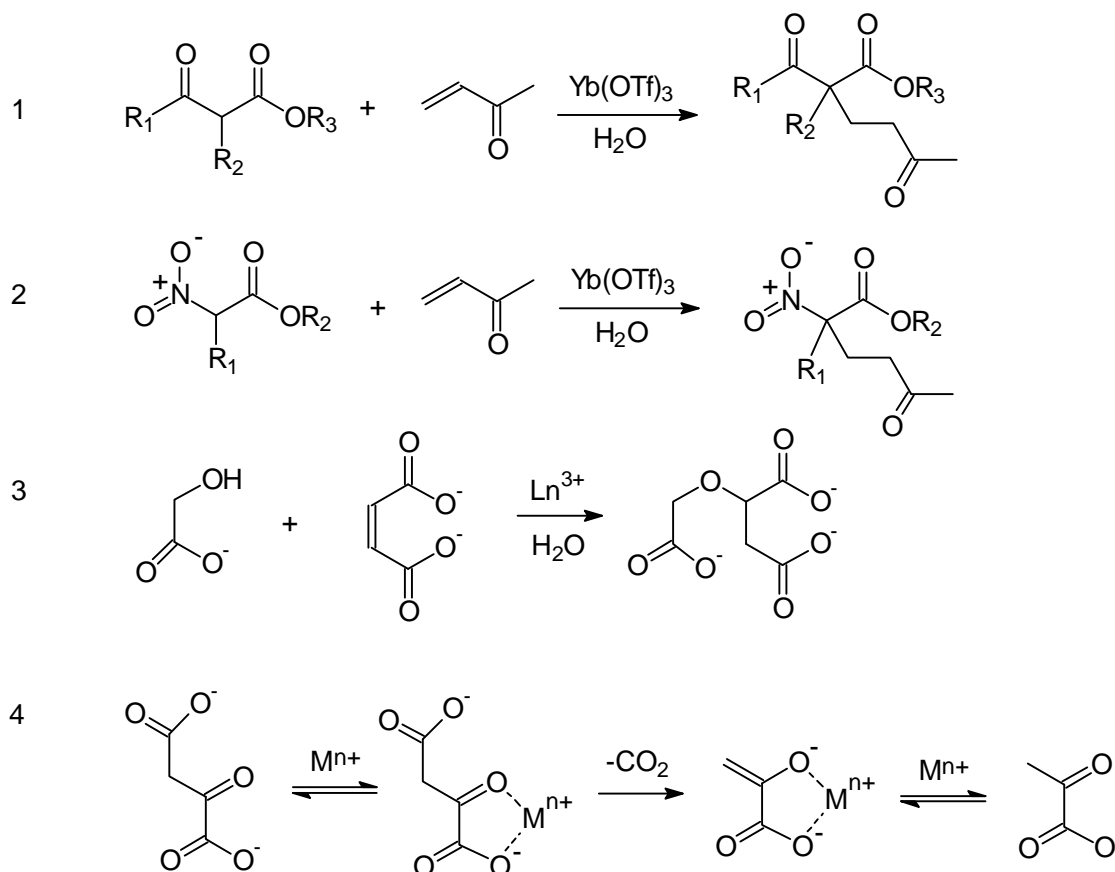
reaction time was significantly reduced. Compared to the reaction under aprotic conditions, in which case allylsilane was used instead of allylbromide/indium, almost complete reversal of diastereoselectivity was found (entry 3 in Scheme 2.1). Recently it has been demonstrated that pure water and particularly saturated ammonium chloride solutions promote the Lewis-acid catalysed allylation efficiently²⁹.

Finally, Lewis-acid catalysed *Mannich reactions* can be carried out conveniently in a mixture of organic solvent and water. An aldehyde, an amine and a vinyl ether have react in THF-water (9:1) mixtures, in the presence of 10 mole percent of Yb(OTf)₃, to give the β-amino ketone in 55-100 % yield (entry 4 in Scheme 2.1)³⁰. The exact role of the Lewis acid in this reaction has not been clarified. Recently, Loh reported an indium trichloride catalysed Mannich-type reaction in water³¹.

Relatively few examples of organic transformations are known that are catalysed efficiently by Lewis acids in water in the absence of an organic (co)solvent. One such example is the lanthanide-ion catalysed *Michael addition*. The use of water as a solvent in the uncatalysed Michael addition of 1,3-diketones had already been reported occasionally³². The corresponding reaction of β-ketoesters did not give satisfactory results³³. However, Keller et al. demonstrated that upon introduction of a catalytic amount of Yb(OTf)₃ a large range of β-ketoesters react efficiently with various β-unsubstituted enones (entry 1 in Scheme 2.2)³⁴. Likewise, α-nitroesters smoothly undergo Lewis-acid catalysed Michael additions in water (entry 2 in Scheme 2.2)³⁵. Van Bekkum and co-workers studied a lanthanide-ion catalysed Michael-like addition of glycolate to maleate (entry 3 in Scheme 2.2)³⁶. Extensive mechanistic studies demonstrated that this reaction proceeds through a ternary complex, wherein attack of coordinated and double deprotonated glycolate on the coordinated maleate dianion is rate limiting.

Perhaps the most extensively studied catalytic reaction in aqueous solutions is the metal-ion catalysed *hydrolysis* of carboxylate esters³⁷, phosphate esters³⁸, phosphate diesters³⁹, amides^{36b,37f,40} and nitriles⁴¹. Inspired by hydrolytic metalloenzymes, a multitude of different metal-ion complexes have been prepared and analysed with respect to their hydrolytic activity. Unfortunately, the exact mechanism by which these complexes operate is not completely clarified⁴². The most important role of the catalyst is coordination of a hydroxide ion that is acting as a nucleophile. The extent of activation of the substrate through coordination to the Lewis-acidic metal centre is still unclear and probably varies from one substrate to another. For monodentate substrates this interaction is not very efficient. Only a few quantitative studies have been published. Chin et al. reported an equilibrium constant for coordination of the amide carbonyl group of formylmorpholine to a cobalt(III) catalyst of $0.4 \pm 0.1 \text{ M}^{-1}$ ⁴³. The same catalyst coordinates acetonitrile in water with an equilibrium constant^{41d} of 2.5 M^{-1} .

Examples of metal-ion catalysed organic reactions in water where the catalyst acts exclusively as Lewis acid are the *bromination* of diketones⁴⁴ and the *decarboxylation* of oxaloacetate. The latter reaction has been studied in detail. In 1941 it was demonstrated that magnesium(II) ions catalyse this reaction⁴⁵. Later also catalysis by other multivalent metal ions, such as Zn(II), Mn(II), Cu(II), Cd(II), Fe(II), Pb(II), Fe(III) and Al(III) was reported⁴⁶. Likewise, trivalent lanthanide ions were found to promote the decarboxylation⁴⁷. A large number of mechanistic studies have established the mechanism of the catalysed reactions, which is



Scheme 2.2. Lewis-acid catalysed reactions in pure water.

outlined in entry 4 in Scheme 2.2⁴⁸. Similarly, acetonedicarboxylic acid has been observed to undergo Lewis-acid catalysed decarboxylation⁴⁹. Later studies have focused on the effects of ligands on the efficiency of the catalysed reaction⁵⁰. This topic will be discussed extensively in Chapter 3.

In summary, only for a limited number of Lewis-acid catalysed reactions mechanistic studies have been published. Invariably, these studies involve bidentate substrates⁵¹. In the majority of reports on Lewis-acid catalysed transformations in (heterogeneous) aqueous media little attention is paid to the mechanism underlying these reactions. A large number of these studies make use of lanthanide ions. In some cases monodentate substrates are used and coordination of the lanthanide ion to a carbonyl group is assumed. However, Richardson stated that: “In aqueous solutions, donor groups containing neutral oxygen or nitrogen atoms generally bind (or occupy Ln^{3+} coordination sites) *only* when present in multidentate ligands that contain at least one or two other donor groups having negatively charged oxygens.”⁵² Hence, instead of Lewis-acid catalysis, the beneficial effect of the presence of Lewis-acids on the efficiency of these reactions might well be indirect. For instance, Brønsted-acid or base catalysis can be expected to be operative. Solutions of Lewis-acid ions in water are modestly acidic, which indicates the simultaneous presence of lanthanide-ion coordinated hydroxide ion as well as free protons. Clearly, detailed mechanistic studies are required to identify the exact mechanism through which the presence of Lewis acids affects these reactions.

2.1.2 Lewis-acid catalysis of Diels-Alder reactions in aqueous solutions

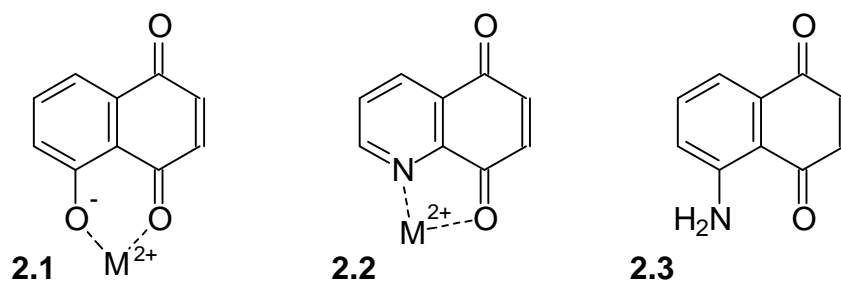
There is a growing number of examples of Lewis-acid catalysed Diels-Alder reactions that tolerate the presence of small amounts of water⁵³ or even benefit from it⁵⁴. Going one step further, Kobayashi has reported catalysis of the Diels-Alder reaction between naphthoquinone and cyclopentadiene by scandium triflate in a 90:10 THF - water mixture⁵⁵. Unfortunately, no comparison was made with the reaction in the absence of the catalyst, which is known to proceed rapidly at ambient temperature. The first example of a Lewis-acid catalysed Diels-Alder reaction in pure water can be found in a paragraph in an article on aqueous hetero Diels-Alder chemistry by Lubineau⁵⁶. He observed a quantitative reaction of glyoxylate with 2-methyl-1-3-pentadiene in the presence of lanthanide triflates after 12 hours at 60 °C. In the absence of catalyst the reaction gave 55% yield under the same conditions. Very recently, Wang and co-workers observed catalysis of an aza-Diels-Alder reaction by lanthanide(III)triflates in water⁵⁷. In this process in situ formation of the hetero dienophile is followed by the actual Diels-Alder reaction. The role of the catalyst is still unclear. Interestingly Grieco et al. have studied the reversal of this process, and observed catalysis by copper(II)sulfate⁵⁸. Loh et al. claim catalysis of an extensive number of Diels-Alder reactions by indium trichloride in water⁵⁹. However, this work has been criticised by Kobayashi⁶⁰. Likewise, kinetic experiments by the author of this thesis have failed to demonstrate any catalytic effect of indium trichloride on the prototypical Diels-Alder reaction of methyl vinyl ketone with cyclopentadiene under homogeneous conditions. Zhu and Espenson have studied the effect of methylrhenium trioxide on a number of Diels-Alder reactions under heterogeneous conditions in aqueous solution⁶¹. These authors also report a kinetic study on the effect of their catalyst on the Diels-Alder reaction of methyl vinyl ketone with cyclopentadiene under homogeneous conditions. Unfortunately, these kinetic experiments could not be reproduced in our hands.

2.2 Results and discussion

Searching for a suitable system for studying Lewis-acid catalysis of Diels-Alder reactions in water, several points have to be considered.

First, the use of water limits the choice of Lewis-acid catalysts. The most active Lewis acids such as BF_3 , TiCl_4 and AlCl_3 react violently with water and cannot be used. However, bivalent transition metal ions and trivalent lanthanide ions have proven to be active catalysts in aqueous solution for other organic reactions and are anticipated to be good candidates for the catalysis of aqueous Diels-Alder reactions.

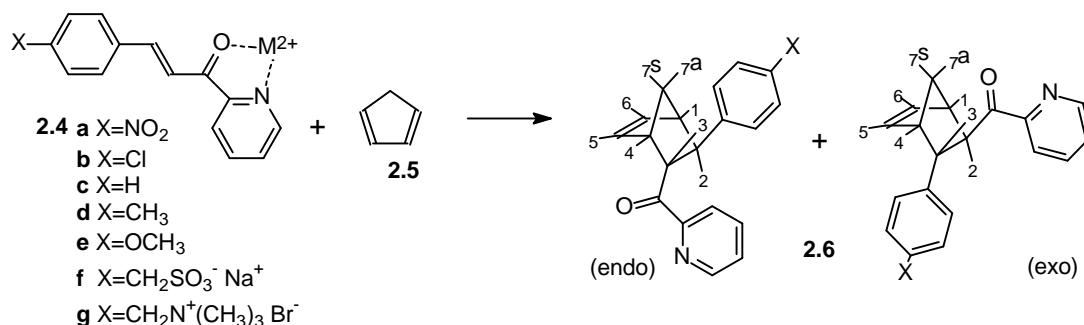
Furthermore, the number of diene - dienophile combinations that can be expected to undergo a Lewis-acid catalysed Diels-Alder reaction is limited. Studies by Wijnen leave little doubt that the rate of typical Diels-Alder reactions, where the dienophile is activated by one or more carbonyl functionalities, does not respond to the presence of Lewis acids in aqueous solution^{11d}, at least not beyond the extent that is expected for non-specific interactions (salt effects). No coordination of the Lewis acid to the dienophile was observed in these cases, which is perhaps not surprising. Water is



Scheme 2.3. Unsuccessful attempts⁶³ to catalyze Diels-Alder reactions in water. $M = \text{Zn}^{2+}$ or Cu^{2+} .

about the worst solvent one can imagine with respect to hard Lewis acid - Lewis base interactions, since water itself interacts extremely efficiently with the Lewis acid as well as the Lewis base (see section 1.5.2). Interestingly, as far as we know, all the examples of organic reactions where proof exists that true Lewis-acid catalysis takes place involve *bidentate* substrates⁶². Apparently interaction of monodentate compounds with Lewis acids in water is not strong enough to allow efficient catalysis. But even when bidentate coordination is achieved, success is not guaranteed, as is demonstrated by the examples in Scheme 2.3⁶³. Juglone (**2.1**) binds efficiently to bivalent zinc and copper ions but is deactivated upon coordination due to the deprotonation of the hydroxyl moiety. Alternatively, **2.2** is activated, but more towards undesired reactions (among them the Michael addition of water) than towards the Diels-Alder addition. Catalysis of the reaction of **2.3** was not successful either, since this compound showed little to no tendency to coordinate to hard metal ions in aqueous solution.

Fortunately, azachalcone derivatives (**2.4a-g**, Scheme 2.4) turned out to be extremely suitable dienophiles for Lewis-acid catalysed Diels-Alder reactions with cyclopentadiene (**2.5**). This reaction is outlined in Scheme 2.4 and a large part of this thesis will be devoted to the mechanistic details of this process. The presence of a chromophore in **2.4** allows kinetic studies as well as complexation studies by means of UV-vis spectroscopy. Furthermore, the reactivity of **2.4** is such that also the



Scheme 2.4.

uncatalysed reaction can be followed, allowing quantitative comparison with the catalysed reaction.

2.2.1 Synthesis

The synthesis of 3-phenyl-1-(2-pyridyl)-2-propen-1-one (**2.4c**) via an aldol reaction of 2-acetylpyridine with benzaldehyde has been described in the literature⁶⁴. Compound **2.4a-e** have been prepared in high yields, using slightly modified versions of these literature procedures.

The highly water-soluble dienophiles **2.4f** and **2.4g** have been synthesised as outlined in Scheme 2.5. Both compounds were prepared from p-(bromomethyl)benzaldehyde (**2.8**) which was synthesised by reducing p-(bromomethyl)benzotrile (**2.7**) with diisobutylaluminium hydride following a literature procedure⁶⁵. **2.4f** was obtained in two steps by conversion of **2.8** to the corresponding sodium sulfonate (**2.9**), followed by an aldol reaction with 2-acetylpyridine. In the preparation of **2.4g** the sequence of steps had to be reversed. Here, the aldol condensation of **2.8** with 2-acetylpyridine was followed by nucleophilic substitution of the bromide of **2.10** by trimethylamine. Attempts to prepare **2.4f** from **2.10** by treatment with sodium sulfite failed, due to decomposition of **2.10** under the conditions required for the substitution by sulfite anion.

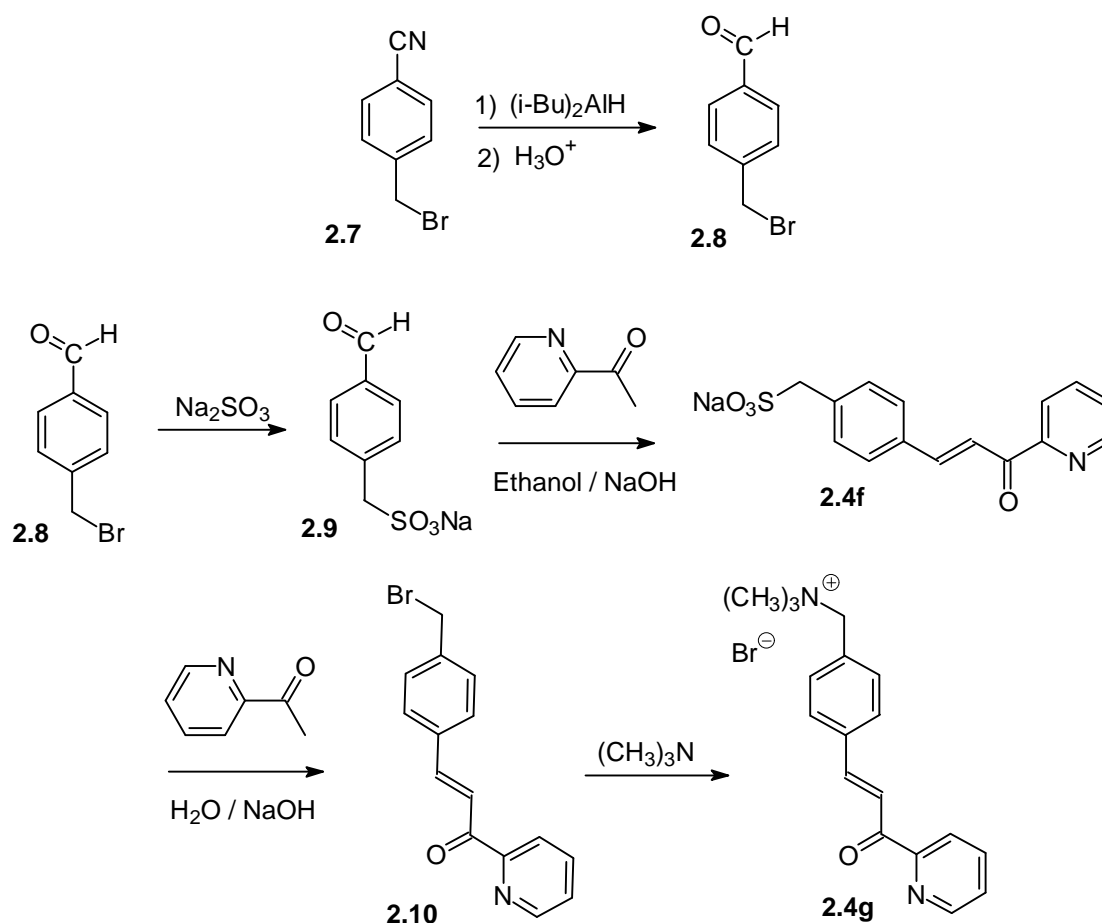
Table 2.1. Second-order rate constants (k_2) for the uncatalysed Diels-Alder reaction of **2.4a** and **2.4g** with **2.5** in different solvents at 25°C.

solvent	2.4a		2.4g
	k_2 (M ⁻¹ s ⁻¹)	k_{rel} ^a	k_2 (M ⁻¹ s ⁻¹)
acetonitrile	$1.40 \cdot 10^{-5}$	1	
ethanol	$3.83 \cdot 10^{-5}$	2.7	$2.22 \cdot 10^{-5}$
water	$4.02 \cdot 10^{-3}$	287	$2.45 \cdot 10^{-3}$
2,2,2-trifluoroethanol	$6.75 \cdot 10^{-3}$	482	

^a Rate constant relative to the reaction in acetonitrile.

2.2.2 Effect of the solvent on the rate of the uncatalysed reaction.

Before elaborating on the effect of Lewis acids on the Diels-Alder reaction of **2.4** with **2.5**, some

**Scheme 2.5.** Synthesis of the ionic dienophiles **2.4f** and **2.4g**.

features of the uncatalysed reaction will be discussed. The kinetics of the Diels-Alder reaction of **2.4**

with **2.5** can be studied by following the disappearance of the absorbance of the dienophile using UV-vis spectroscopy⁶⁶. In the absence of catalysts, the rate of the reaction is low, so that initial rate methods are required in order to obtain reliable rate constants. Of the dienophiles, **2.4a** is the most reactive, as is expected for a normal electron demand Diels-Alder reaction on the basis of FMO considerations (see Section 1.2.2). **2.4b-e** are increasingly less reactive and unfortunately, the Diels-Alder reaction of these compounds cannot compete with spontaneous decomposition. Both ionic dienophiles turned out to be sufficiently stable. The second-order rate constants of the reaction of **4.2a** and **4.2g** have been determined in water and three organic solvents. The results are shown in Table 2.1.

The solvents listed in Table 2.1 were chosen to cover a broad range in solvent properties. In fact hexane was initially also among them, but unfortunately the rate of the reaction in this solvent is extremely low. It turned out that in this solvent spontaneous decomposition of **2.4a** competes with the Diels-Alder reaction.

It is obvious that the reaction is accelerated markedly by water. However, for the first time, the Diels-Alder reaction is not fastest in water, but in 2,2,2-trifluoroethanol (TFE). This might well be a result of the high Brønsted acidity of this solvent. Indirect evidence comes from the pH-dependence of the rate of reaction in water (Figure 2.1). Protonation of the pyridyl nitrogen obviously accelerates the reaction.

Comparison of the water-induced acceleration of the reaction of **2.4a** with the corresponding effect on **2.4g** is interesting, since **2.4g** contains an ionic group remote from the reaction centre. The question arises whether this group has an influence on the acceleration of the Diels-Alder reaction by water. Comparison of the data in Table 2.1 demonstrates that this is not the case. The acceleration upon going from ethanol to water amounts a factor 105 (± 10) for **2.4a** versus 110 (± 11) for **2.4g**. Apparently, the introduction of a hydrophilic group remote from the reaction centre has no effect on the aqueous acceleration of the Diels-Alder reaction.

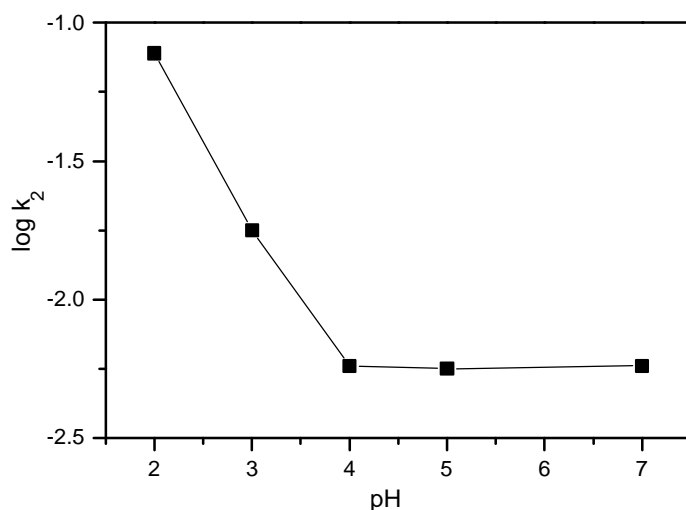


Figure 2.1. pH Dependence of the rate of the Diels-Alder reaction between **2.4a** and **2.5** in water at 25 °C.

2.2.3 Solvent and substituent effects on the Cu²⁺-catalysed reaction

The rate of the uncatalysed reaction in all four solvents is rather slow. (The half-life at [2.5] = 1.00 mM is at least 28 hours). However, upon complexation of Cu²⁺ ion to **2.4a-g** the rate of the Diels-Alder reaction between these compounds and **2.5** increases dramatically. Figure 2.2 shows the apparent rate of the Diels-Alder reaction of **2.4a** with **2.5** in water as a function of the concentration of copper(II)nitrate. At higher catalyst concentrations the rate of the reaction clearly levels off, most likely due to complete binding of the dienophile to the catalyst. Note that in the kinetic experiments

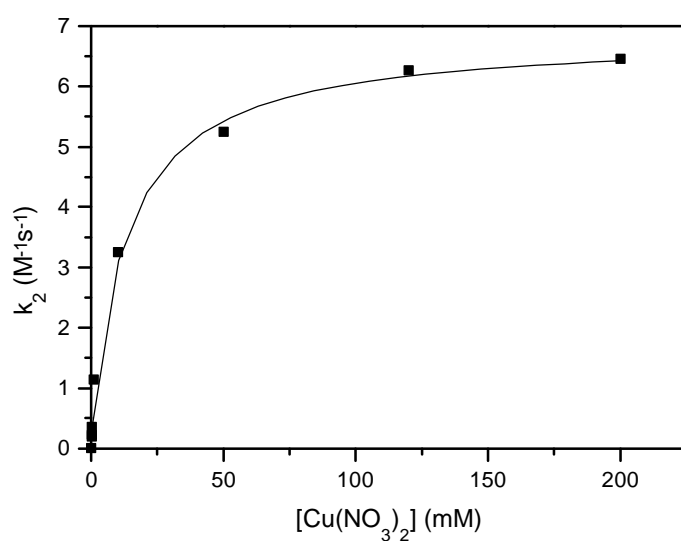


Figure 2.2. Second-order rate constant for the Diels-Alder reaction of **2.4a** with **2.5** in aqueous solution as a function of the concentrations of copper(II)nitrate.

Table 2.2. Apparent second-order rate constants (k_{app}) for the Cu^{2+} -ion catalysed reaction of **2.4a** and **2.4g** with **2.5** and ratios of the rate constants for the catalysed and uncatalysed reaction in different solvents at 25 °C.

solvent	$[\text{Cu}^{2+}]$ (mM)	2.4a		2.4g
		k_{app} ($\text{M}^{-1}\text{s}^{-1}$)	$k_{app} / k_{uncat.}$	k_{app} ($\text{M}^{-1}\text{s}^{-1}$)
acetonitrile	10	2.21	$1.58 \cdot 10^6$	0.497
ethanol	10	0.769	$2.01 \cdot 10^4$	0.543
water	10	3.25	$8.08 \cdot 10^2$	2.13
2,2,2-trifluoroethanol	0.10	15.6	$2.31 \cdot 10^3$	

the concentration of the catalyst is orders of magnitude higher than the concentration of dienophile. Use of an excess of catalyst is inevitable when using UV-vis techniques and therefore very low concentrations of **2.4**.

In organic solvents Lewis-acid catalysis also leads to large accelerations of the Diels-Alder reaction. Table 2.2 shows the rate constants for the Cu^{2+} -catalysed Diels-Alder reaction between **2.4a** and **2.5** in different solvents.

Relative to the uncatalysed reaction in acetonitrile, the presence of Lewis acids leads to accelerations in the order of 10^6 - 10^7 . The relatively large solvent effect of water observed in the uncatalysed reaction (Table 2.1) is strongly diminished for the catalysed reaction. This trend can be rationalised as follows. For the Lewis-acid catalysed reactions the hydrogen bonding part of the acceleration will be largely taken over by the Lewis-acid, so it is likely that only the hydrophobic effect will remain. This contribution will not be unaffected by the catalyst either, since the catalyst will partly destroy the hydrophobic character of the hydration shell of the dienophile in the initial state. This will result in a significantly smaller aqueous solvent effect on the catalysed reaction. Note that the effect of the catalyst in acetonitrile, quantified by the ratio of the rate constants for the catalysed reaction and the uncatalysed counterpart, is larger than in any of the protic solvents. This trend further underlines the observation that the activation of Diels-Alder reactions by hydrogen-bonding and by Lewis-acid catalysis are not additive.

Surprisingly, the highest catalytic activity is observed in TFE. One might envisage this to be a result of the poor interaction between TFE and the copper(II) cation, so that the cation will retain most of its Lewis-acidity. In the other solvents the interaction between their electron-rich hetero atoms and the cation is likely to be stronger, thus diminishing the efficiency of the Lewis-acid catalysis. The observation that $\text{Cu}(\text{NO}_3)_2$ is only poorly soluble in TFE and much better in the other solvents used, is in line with this reasoning.

Rate constants for the Diels-Alder reaction of **2.4b-e** have also been determined. The results are shown in Table 2.3. These data allow an analysis of the influence of substituents on the Lewis-acid catalysed Diels-Alder reaction. This is interesting, since there are indications for a relatively large

Table 2.3. Apparent second-order rate constants ($M^{-1}s^{-1}$) of the Cu^{2+} -catalysed Diels-Alder reaction of **2.4b-e** with **2.5** in different solvents at 25°C.

solvent	2.4b	2.4c	2.4d	2.4e	2.4g
acetonitrile	0.594	0.472	0.240	0.0689	0.497
ethanol	0.382	0.309	0.162	0.0510	0.543
water	1.23	1.11	0.654	0.262	2.13
2,2,2-trifluoroethanol	3.31	3.22	1.52	0.549	

charge separation in the activated complex of the catalysed reaction compared to the uncatalysed one in organic solvents⁶⁷. This charge separation might induce a larger effect of substituents on the rate of the catalysed reaction. The data of Table 2.3 have been analysed in terms of the Hammett equation⁶⁸:

$$\log\left(\frac{k_x}{k_0}\right) = \rho \cdot \sigma_x \quad (2.1)$$

Herein k_x is the rate constant for a dienophile with substituent x ; k_0 is the corresponding rate constant for unsubstituted **2.4c**; σ_x is the substituent constant for substituent x and ρ is the reaction constant, defined as the slope of the plot of $\log(k_x/k_0)$ versus σ_x . The parameter ρ is a measure of the sensitivity of the reactions towards introduction of substituents. Figure 2.3 and Table 2.4 show the results of correlating the kinetic data for the reaction of **2.4a-e** with **2.5** with σ^+ .

The fact that good correlations are observed with σ^+ rather than with σ , is indicative of a strong influence of the substituent through a direct resonance interaction with a positive charge in the reacting system. The ρ -values are positive, which is expected for substituted dienophiles in a normal electron demand Diels-Alder reaction. Furthermore, the ρ -values do not exceed unity and are not significantly different from literature values reported for the uncatalysed reaction⁶⁹. It is tempting to

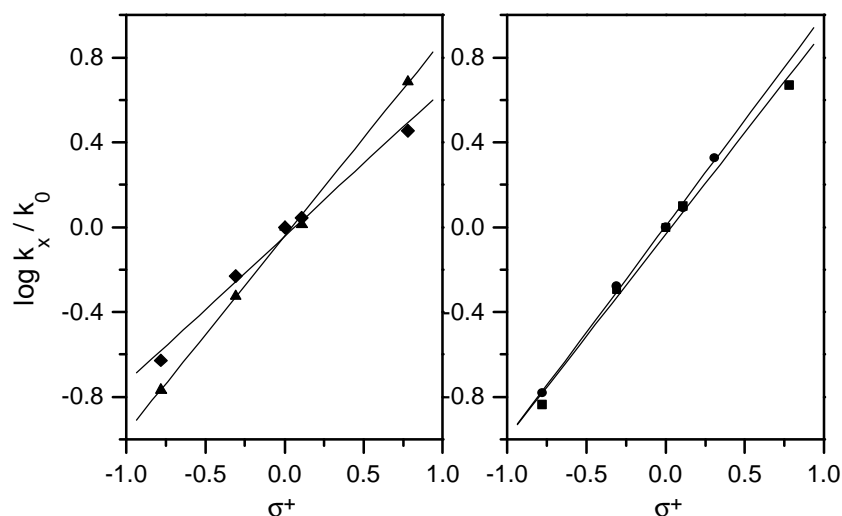


Figure 2.3. Hammett plots for the Diels-Alder reaction of **2.4a-e** with **2.5** in water (◆); 1,1,1-trifluoroethanol (▲); ethanol(●) and acetonitrile (■).

Table 2.4. Solvent effect on the Hammett ρ -values for the Diels-Alder reaction of **2.4** with **2.5** catalysed by $\text{Cu}(\text{NO}_3)_2$ at 25°C.

solvent	$[\text{Cu}^{2+}]$ (mM)	ρ	r
acetonitrile	10	0.96	0.997
ethanol ^a	10	1.00	0.999
water	10	0.69	0.997
2,2,2-trifluoroethanol	0.10	0.90	0.990

^a For unknown reasons the point for **2.4a** in the Hammett plot for ethanol strongly deviates from the otherwise good correlation. The data for **2.4a** in ethanol have therefore not been used in the calculation of ρ . Instead the data for another compound **2.4** with $\text{X} = \text{CO}_2\text{CH}_3$ ($k_2 = 0.655 \text{ M}^{-1}\text{s}^{-1}$) were used in the correlation.

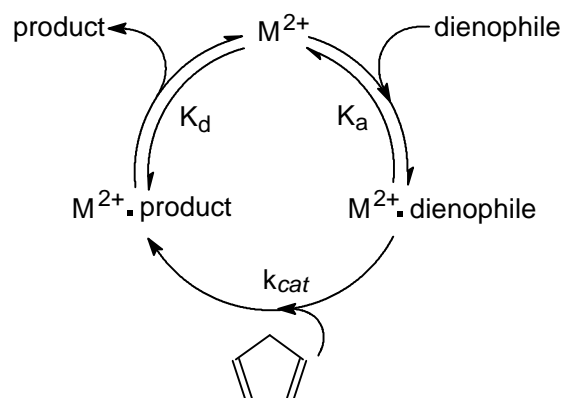
conclude that the charge separation in the activated complex of the catalysed reactions is also not significantly different from that in the uncatalysed reaction. However this conclusion is not valid. Since it is reasonable to assume that the initial state of the catalysed reaction (the dienophile - Lewis-acid complex) is more polarised than the initial state of the uncatalysed reaction, it is not justified to make a direct comparison between the activated complexes of the rate-limiting step for the uncatalysed and catalysed reactions simply on the basis of ρ -values. Moreover, the ρ -values are likely to reflect, to a small extent, the substituent effect on the complexation step.

Among the different solvents, water occupies a special position with a relatively small ρ -value. This is anticipated, since water is the solvent with the strongest interactions with the partial charges of the reacting system and the substituents. Substituent effects are usually larger in solvents that only weakly interact with these partial charges⁷⁰ and, hence, have maximal values in vacuum⁷¹. The ρ -values are of comparable magnitude in the different solvents, which makes it unlikely that there is a significant change in the extent of charge separation during the Diels-Alder reaction upon changing the solvent⁷².

The rate constants for the catalysed Diels-Alder reaction of **2.4g** with **2.5** (Table 2.3) demonstrate that the presence of the ionic group in the dienophile does not diminish the accelerating effect of water on the catalysed reaction. Comparison of these rate constants with those for the nonionic dienophiles even seems to indicate a modest extra aqueous rate enhancement of the reaction of **2.4g**. It is important to note here that no detailed information has been obtained about the exact structure of the catalytically active species in the organic solvents. For example, ion pairing is likely to occur in the organic solvents.

2.2.4 Variation of the catalyst

In the previous section efficient catalysis of the Diels-Alder reaction by copper(II)nitrate was encountered. Likewise, other bivalent metal ions that share the same row in the periodic system show catalytic activity. The effects of cobalt(II)nitrate, nickel(II)nitrate, copper(II)nitrate and zinc(II)nitrate



Scheme 2.6. Catalytic cycle for a Lewis-acid catalysed Diels-Alder reaction.

will be described in this section. Of the lanthanides, LaCl_3 , $\text{Yb}(\text{OTf})_3$ and $\text{Eu}(\text{NO}_3)_3$ have been tested, but these salts failed to reveal any catalytic activity with respect to the Diels-Alder reaction of **2.4**. Also Kobayashi's $\text{Sc}(\text{OTf})_3$ did not significantly promote this reaction. Likewise, salts of soft metals, PdCl_2 and $\text{Hg}(\text{NO}_3)_2$, have been tested, but these salts catalysed the hydration and oligomerisation of the diene rather than the desired Diels-Alder reaction.

The mechanism by which Lewis-acids can be expected to affect the rate of the Diels-Alder reaction in water is depicted in Scheme 2.6. The first step in the cycle comprises rapid and reversible coordination of the Lewis-acid to the dienophile, leading to a complex in which the dienophile is activated for reaction with the diene. After the irreversible Diels-Alder reaction, the product has to dissociate from the Lewis-acid in order to make the catalyst available for another cycle. The overall

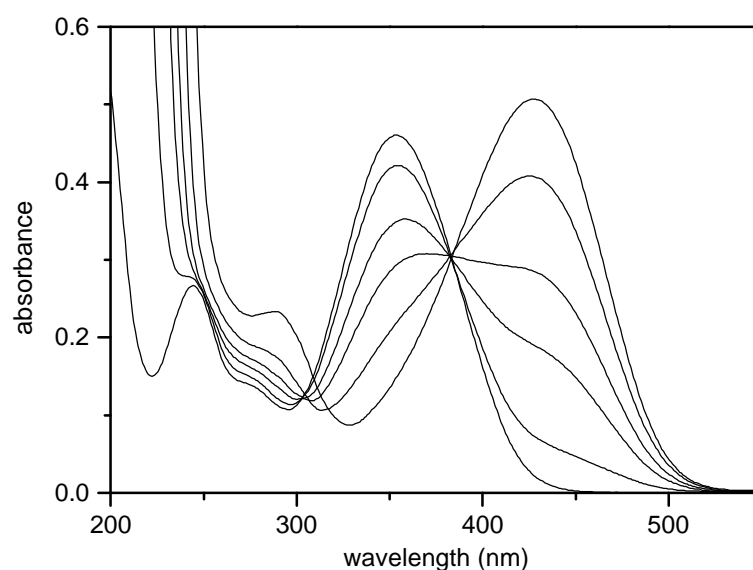


Figure 2.4. UV-vis absorption spectrum of **2.4e** in water at concentrations of copper(II)nitrate varying between 0 and 10 mM.

Table 2.5. Apparent second-order rate constants (k_{app}) for the catalysed Diels-Alder reaction between **1c** and **2**, equilibrium constants for complexation of **2.4c** to different Lewis-acids (K_a) and second-order rate constants for the reaction of these complexes with **2.5** (k_{cat}) in water at 2M ionic strength at 25°C.

Lewis-acid	k_{app} ($M^{-1}s^{-1}$) ^a	K_a (M^{-1})	k_{cat} ($M^{-1}s^{-1}$)
Co ²⁺	$4.53 \cdot 10^{-2}$	$1.17 \cdot 10^2$	$8.40 \cdot 10^{-2}$
Ni ²⁺	$8.26 \cdot 10^{-2}$	$6.86 \cdot 10^2$	$9.46 \cdot 10^{-2}$
Cu ²⁺	2.36	$1.16 \cdot 10^3$	2.56
Zn ²⁺	$4.29 \cdot 10^{-2}$	$7.28 \cdot 10^1$	$1.18 \cdot 10^{-1}$

^a For $[M^{2+}] = 10$ mM.

rate of the reaction is determined by K_a , k_{cat} , and K_d .

In the kinetic runs always a large excess of catalyst was used. Under these conditions K_d does not influence the apparent rate of the Diels-Alder reaction. Kinetic studies by UV-vis spectroscopy require a low concentration of the dienophile ($\sim 10^{-5}$ M). The use of only a catalytic amount of Lewis-acid will seriously hamper complexation of the dienophile because of the very low concentrations of *both* reaction partners under these conditions. The contributions of K_a and k_{cat} to the observed apparent rate constant have been determined by measuring k_{app} and K_a separately⁷³.

In determining the values of K_a use is made of the pronounced shift of the UV-vis absorption spectrum of **2.4** upon coordination to the catalytically active ions as is illustrated in Figure 2.4⁷⁴. The occurrence of an isosbestic point can be regarded as an indication that there are only two species in solution that contribute to the absorption spectrum: free and coordinated dienophile. The exact method of determination of the equilibrium constants is described extensively in reference 75 and is summarised in the experimental section. Since equilibrium constants and rate constants depend on the ionic strength, from this point onward, all measurements have been performed at constant ionic strength of 2.00 M using potassium nitrate as background electrolyte⁷⁶.

The equilibrium constants obtained using the metal-ion induced shift in the UV-vis absorption spectrum are in excellent agreement with the results of the Lineweaver-Burke analysis⁷⁷ of the rate constants at different catalyst concentrations. For the copper(II)ion catalysed reaction of **2.4a** with **2.5** the latter method gives a value for K_a of 432 versus 425 using the spectroscopic method.

From the equilibrium constant and the apparent rate constant, the rate constant for reaction of the metal-ion (M^{n+}) coordinated dienophile (k_{cat}) can be calculated using equation 2.2 (derived in Appendix 2.1).

$$k_{app} = \frac{K_a \cdot [M^{n+}]_t}{K_a \cdot [M^{n+}]_t + 1} k_{cat}$$

Equilibrium constants and second-order rate constants for Co²⁺, Ni²⁺, Cu²⁺ and Zn²⁺ catalysed of the reaction of **2.4c** with **2.5** in water at constant ionic strength (2.00 M KNO₃) are shown in Table 2.5.

Clearly, Cu²⁺ is the best catalyst with respect to both complexation and rate of reaction with **2.5**. The

trend observed in rate and equilibrium constants follows the empirical Irving-Williams order⁷⁸ $\text{Co}^{2+} < \text{Ni}^{2+} < \text{Cu}^{2+} > \text{Zn}^{2+}$. This order is usually observed for equilibrium constants of binding processes and catalytic activities of these metal ions. This order can be accounted for using ligand field theory⁷⁹. The presence of a ligand in an octahedral arrangement around a metal ion causes a splitting in the energy level of the d-electrons of the metal into two new levels: t_{2g} and e_g (Figure 2.5). Depending on the occupation of the d-orbitals, this ligand field splitting results in a stabilisation of the complex. The extent of splitting is dependent on the ligand and follows the spectrochemical series. In general, bidentate ligands increase the splitting when compared to water. Hence, in the metal-**2.4** complexes ligand field splitting gives rise to an extra stabilisation as compared to the aquo complex. On the basis of these observations and considering the occupation of the t_{2g} and e_g levels for the different ions, ranging from d^7 to d^{10} , one would expect the order $\text{Co}^{2+} < \text{Ni}^{2+} > \text{Cu}^{2+} > \text{Zn}^{2+}$ with respect to the magnitude of K_a . However, copper(II) occupies a special position, which is a result of the Jahn-Teller effect. Of the three electrons in the e_g level, two are present in the d_{z^2} orbital and only one in the $d_{x^2-y^2}$ orbital. Consequently, those ligands that occupy the four equatorial sites experience repulsion due to only one d-electron and are bound more strongly than those that occupy the two axial positions, where they experience the two electrons of the d_{z^2} orbital. When combining the Jahn-Teller effect with ligand field theory, one arrives at the Irving-Williams series.

A quantitative correlation between rate and equilibrium constants for the different metal ions is absent. The observed rate enhancements are a result of catalysis by the metal ions and are clearly not a result of protonation of the pyridyl group, since the pH's of all solutions were within the region where the rate constant is independent of the pH (Figure 2.1).

Catalysis by the four metal ions was also compared with respect to their sensitivity towards substituents in the dienophile. To this end the equilibrium constants for complexation of **2.4a-g** to the four different ions were determined. The results are shown in Table 2.6.

Good to excellent Hammett plots were obtained using σ^+ substituent constants (see Figure 2.6). Surprisingly, literature examples of good Hammett correlations of stability constants are rare⁸⁰. The ρ -values are shown in Table 2.7.

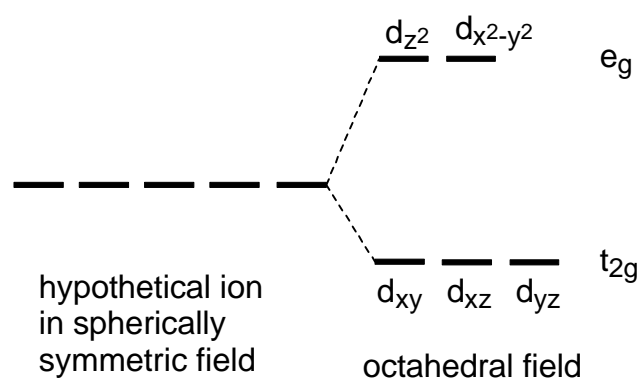


Figure 2.5. Splitting of the d energy level in an octahedral complex.

Table 2.6. Equilibrium constants from complexation of **2.4a**, **2.4b**, and **2.4d-g** to different metal ions (K_a) and second-order rate constants for the Diels-Alder reaction of these complexes with **2** (k_{cat}) in water at 2.00 M ionic strength and 25°C.

	Co^{2+}		Ni^{2+}		Cu^{2+}		Zn^{2+}	
	K_a	k_{cat}	K_a	k_{cat}	K_a	k_{cat}	K_a	k_{cat}
2.4a	86.9	$2.84 \cdot 10^{-1}$	$3.18 \cdot 10^2$	$5.69 \cdot 10^{-1}$	$4.25 \cdot 10^2$	11.1	34.5	$5.03 \cdot 10^{-1}$
2.4b	112	$1.02 \cdot 10^{-1}$	$5.79 \cdot 10^2$	$1.18 \cdot 10^{-1}$	$1.06 \cdot 10^3$	2.82	57.3	$1.22 \cdot 10^{-1}$
2.4d	127	$4.67 \cdot 10^{-2}$	$9.47 \cdot 10^2$	$4.61 \cdot 10^{-2}$	$1.55 \cdot 10^3$	1.36	88.1	$5.81 \cdot 10^{-2}$
2.4e	178	$2.11 \cdot 10^{-2}$	$1.50 \cdot 10^3$	$1.91 \cdot 10^{-2}$	$2.76 \cdot 10^3$	0.518	161	$2.48 \cdot 10^{-2}$
2.4f					$1.32 \cdot 10^3$	2.59		
2.4g	77	$1.64 \cdot 10^{-1}$	$5.04 \cdot 10^2$	$1.57 \cdot 10^{-1}$	$8.86 \cdot 10^2$	5.72	50.3	$2.17 \cdot 10^{-1}$

As anticipated, the complexation is characterised by negative ρ -values, indicating that the binding process is favoured by electron donating substituents. The order of the ρ -values for complexation of the different Lewis-acids again follows the Irving-Williams series.

The effect of substituents on the rate of the reaction catalysed by different metal ions has also been studied. Correlation with σ^+ resulted in perfectly linear Hammett plots. Now the ρ -values for the four Lewis-acids are of comparable magnitude and do not follow the Irving-Williams order. Note that the substituents have opposing effects on complexation, which is favoured by electron donating substituents, and reactivity, which is increased by electron withdrawing substituents. The effect on the reactivity is clearly more pronounced than the effect on the complexation equilibrium.

So far the four metal ions have been compared with respect to their effect on (1) the equilibrium constant for complexation to **2.4c**, (2) the rate constant of the Diels-Alder reaction of the complexes with **2.5** and (3) the substituent effect on processes (1) and (2). We have tried to correlate these data with some physical parameters of the respective metal-ions. The second ionisation potential of the metal should, in principle, reflect its Lewis acidity. Furthermore the values for k_{cat} might be strongly influenced by the Lewis-acidity of the metal. A quantitative correlation between these two parameters

Table 2.7. Hammett ρ -values for complexation of **2.4a-e** to different Lewis-acids and for rate constants (k_{cat}) of the Diels-Alder reaction of **2.4a-e** with **2.5** catalysed by different Lewis-acids in water at 2.00 M ionic strength at 25°C.

Lewis-acid	complexation		rate constants	
	ρ	r	ρ	r
Co^{2+}	-0.19	0.981	0.72	0.999
Ni^{2+}	-0.44	0.999	0.94	0.999
Cu^{2+}	-0.51	0.997	0.85	0.999
Zn^{2+}	-0.42	0.991	0.84	0.998

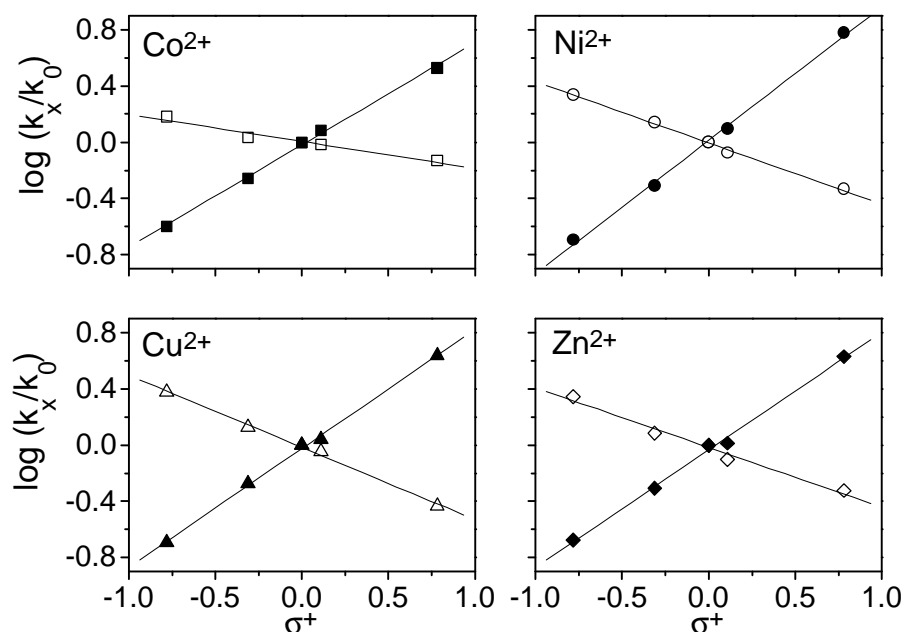


Figure 2.6. Hammett plots for the equilibrium constant K_a of binding of **2.4** to Co^{2+} , Ni^{2+} , Cu^{2+} and Zn^{2+} (open symbols), and for the rate constants of reaction of the metal-ion - **2.4** complex with **2.5** (solid symbols).

is, however, not observed. Alternatively, the acidity of the hexaquo metal cation can be taken as a measure of Lewis-acidity but this parameter did not exhibit a satisfactory correlation with the above data either.

2.2.5 Endo-exo selectivity

The reaction between **2.4** and **2.5** yields four products: two enantiomeric endo products and two enantiomeric exo products. In this section the effect of the solvent, the Lewis-acid and the substituents on the endo-exo selectivity are described. Chapter 3 will mainly focus on aspects dealing with the enantioselectivity of the reaction.

The endo and the exo isomer (Scheme 2.4) give rise to two different NMR-spectra with several peaks that are well separated. From the integration of those signals the endo-exo ratio can be determined. Measurement of the endo-exo ratio by GC was not successful, most likely because the adducts are subject to a retro-Diels-Alder reaction at elevated temperatures. Assignment of the signals to the different isomers was based on COSY and NOESY spectra. Interpretation of the spectra starts with the identification of the long-range coupling between $\text{H}7^s$ and $\text{H}2$, characteristic for norbornene systems⁸¹. The chemical shifts of the other protons can now easily be deduced. Discrimination between endo and exo adduct was subsequently based upon the following considerations. A NOE signal between $\text{H}3$ and a proton on the phenyl ring and a long-range coupling between $\text{H}2$ and a proton of the phenyl ring are both characteristic for the endo-isomer. Furthermore, the downfield shift

Table 2.8. Solvent effect on the endo-exo selectivity (% endo - % exo) of the uncatalysed and Cu²⁺-ion catalysed Diels-Alder reaction between **2.4c** and **2.5** at 25°C.

solvent	uncatalysed	10 mM Cu ²⁺
acetonitrile	67-33	94-6
ethanol	77-23	96-4
water	84-16	93-7
2,2,2-trifluoroethanol	87-13	

of H3 is larger in the endo isomer, where it experiences the influence of the nearby carbonyl-pyridyl group, than in the endo adduct, where H3 is situated next to the phenyl group. Comparison of the NMR data with literature data reported for the Diels-Alder adducts of cyclopentadiene and substituted cinnamic acids⁸¹ further supports the assignments.

The effects of the solvent on the endo-exo selectivity of the uncatalysed and Cu²⁺-catalysed reaction are shown in Table 2.8. For the uncatalysed reaction the endo isomer is preferred over the exo isomer. This tendency becomes even more pronounced in more polar and protic solvents, which is in good agreement with previous studies of the solvent effect on the selectivity of Diels-Alder reactions (see Section 1.2.3). For the Cu²⁺-catalysed reaction the differences between the selectivities in the four solvents are much smaller. Obviously, water does not induce a higher selectivity in this case and there appears to be no indication for enforced hydrophobic interactions favouring the endo activated complex. Possibly, this effect is overwhelmed by differences in efficiency of activation by the Lewis acid in the different solvents. It should be noted that the energy differences underlying the aqueous enhancement of endo-exo selectivity are in the range of 4 kJ/mole. In contrast, water lowers the activation energy for the Diels-Alder reaction of **2.4a** and **2.5** by 14 kJ/mol.

Table 2.9 shows the endo-exo selectivities for the Diels-Alder reaction between **2.4c** and **2.5** catalysed by Brønsted-acid and four different metal ions in water.

Copper is clearly the most selective metal-ion catalyst. Interestingly, proton catalysis also leads to high selectivities. This is a strong indication that selectivity in this catalysed Diels-Alder reaction does not result from steric interactions.

Table 2.9. Effect of different catalysts on the selectivity of the Diels-Alder reaction between **2.4c** and **2.5** in water at 25°C.

catalyst	% endo - % exo
10 mM Co(NO ₃) ₂	87-13
10 mM Ni(NO ₃) ₂	86-14
10 mM Cu(NO ₃) ₂	93-7
10 mM Zn(NO ₃) ₂	86-14
10 mM HCl	94-6

Table 2.10. Substituent effect on the selectivity of the Cu²⁺-catalysed reaction of **2.4** with **2.5** in water at 25°C.

dienophile	% endo - % exo
1a	88-12 ^a
1b	92-8 ^a
1c	93-7
1d	93-7
1e	93-7

^a The dienophile was not completely dissolved.

Table 2.10 shows the effect of substituents on the endo-exo ratio. Under homogeneous conditions there is hardly any substituent effect on the selectivity. Consequently the substituents must have equal effects on the Gibbs energies of the endo and the exo activated complex.

In summary, the effects of a number of important parameters on the catalysed reaction between **2.4** and **2.5** have been examined, representing the first detailed study of Lewis-acid catalysis of a Diels-Alder reaction in water. Crucial for the success of Lewis-acid catalysis of this reaction is the bidentate character of **2.4**. In Chapter 4 attempts to extend the scope of Lewis-acid catalysis of Diels-Alder reactions in water beyond the restriction to bidentate substrates will be presented.

2.3 Conclusions

The data presented in this chapter have clearly demonstrated that Lewis-acid catalysis of a Diels-Alder reaction in water is feasible. Relative to the reaction in acetonitrile, million-fold accelerations can be achieved by combining the beneficial effects of water and Lewis-acid catalysis. Unfortunately, these effects are not completely additive. The rate enhancing influence of water on the catalysed reaction is less pronounced than on the uncatalysed reaction. Most likely, this is a result of a reduced influence of hydrogen bonding in the aqueous rate enhancement of the catalysed reaction. In general, the solvent effect on the catalysed reaction is remarkably modest. Investigation of the substituent effects resulted in good Hammett correlations. The ρ -values obtained for the catalysed reactions are similar to those normally obtained for uncatalysed Diels-Alder reactions. This implies that the changes in charge separation during the activation process of the catalysed reaction are not significantly larger than the corresponding changes for the uncatalysed reaction. Of the different Lewis-acid catalysts that have been tested, the bivalent cobalt, nickel, copper and zinc ions showed the highest activity. The catalytic efficiency of these Lewis-acids followed the empirical Irving-Williams order: $\text{Co}^{2+} < \text{Ni}^{2+} < \text{Cu}^{2+} \gg \text{Zn}^{2+}$. Study of the solvent effect on the endo-exo ratio of the uncatalysed reaction revealed the commonly observed increased selectivity for endo adduct in aqueous media. In contrast, the endo-exo selectivity of the Lewis-acid catalysed Diels-Alder reaction is not enhanced by water. Endo-exo ratios of the catalysed reaction were only moderately sensitive to

the solvent and to substituents in the dienophile.

Studies of the Diels-Alder reaction of the ionic dienophile **2.4g** have demonstrated that the aqueous acceleration of the uncatalysed reaction as well as the catalysed reaction is not significantly affected by the presence of the ionic group at a site remote from the reaction centre.

2.4 Experimental section

Materials

Cyclopentadiene (**2.5**) was prepared from its dimer (Merck-Schuchardt) immediately before use. Dimineralised water was distilled twice in a quartz distillation unit. Ethanol (Merck) was of the highest purity available. Acetonitrile (Janssen) was run over basic aluminium oxide prior to use. 2,2,2-Trifluoroethanol (Acros) was purified by distillation (bp 79°C). Co(NO₃)₂·6H₂O, Ni(NO₃)₂·6H₂O, Cu(NO₃)₂·3H₂O, Zn(NO₃)₂·4H₂O and KNO₃ were of the highest purity available. Substituted 3-phenyl-1-(2-pyridyl)-2-propene-ones (**2.4a-e**) were prepared by an aldol condensation of the corresponding substituted benzaldehyde with 2-acetylpyridine, following either of two modified literature procedures⁶⁴.

2.4a and 2.4b

To a stirred solution of 0.5 ml of 10% aqueous sodium hydroxide and 8.25 mmol of the appropriate aldehyde in 10 ml of ethanol, 8.25 mmol of 2-acetylpyridine was added dropwise during 2-3 hours. The temperature was kept at 0°C. After stirring for another 2 hours the reaction mixture was filtered, yielding almost pure solid **2.4a** (7.26 mmol, 88%) or **2.4b** (7.76 mmol, 94 %). After crystallisation from ethanol the melting points were recorded and the compounds were characterised by ¹H-NMR and mass spectroscopy. **2.4a**: mp 158.2-158.5°C (lit. 156°C⁸²; 154-5°C⁸³), ¹H NMR (200 MHz, CDCl₃) δ 7.55 (m,1H), 7.86 (d,2H), 7.91 (m,2H), 8.22 (m,1H), 8.27 (d,2H), 8.45 (d,1H), 8.77 (d,2H). Exact mass: calcd 254.069; found: 254.069. **2.4b**: mp 102.2-102.5°C (lit. 104°C⁸²; 91-92°C⁸³), ¹H NMR (200 MHz, CDCl₃) δ 7.39 (d,2H), 7.50 (m,1H), 7.67 (d,2H), 7.88 (m,2H), 8.19 (m,1H), 8.29 (d,1H), 8.75 (m,1H).

2.4c, 2.4d and 2.4e

17 mmol of 2-acetylpyridine and 16.5 mmol of the appropriate benzaldehyde were introduced into 100 ml of water at 0-5 °C. The mixture was shaken thoroughly in order to obtain a finely dispersed emulsion. 10 ml of a 10% sodium hydroxide solution was added. The mixture was again shaken and left overnight undisturbed at 4°C. The solution should not be stirred since this results in a phase separation and lower yields due to transport limitations. The product separated as an oil that solidified upon shaking. Filtration and washing with water gave the almost pure product in

satisfactory yields: **2.4c**: 95%, **2.4d**: 84%, **2.4e**: 96%. After crystallisation from ethanol the melting points were recorded and the compounds were characterised by ¹H-NMR. **2.4c**: mp 74.5-75.3 (lit. 74 °C⁸²; 71°C⁸³), ¹H NMR (200 MHz, CDCl₃) δ 7.46 (m,4H), 7.74 (m,2H), 7.86 (m,1H), 7.95 (d,1H), 8.20 (m,1H), 8.32 (d,1H), 8.75 (m,1H). **2.4d**: mp 84.8-85.3 (lit. 83°C⁸²), ¹H NMR (200 MHz, CDCl₃) δ 2.40 (s,3H), 7.23 (d,2H), 7.49 (m,1H), 7.64 (d,2H), 7.87 (m,1H), 7.93 (d,1H), 8.19 (m,1H), 8.27 (d,1H), 8.74 (m,1H). **2.4e**: mp 84.6-85.2 (lit. 84-85°C⁸²; 84°C⁸³), ¹H NMR (200 MHz, CDCl₃) δ 3.85 (s,3H), 6.93 (d,2H), 7.47 (m,1H), 7.69 (d,2H), 7.86 (m,1H), 7.92 (d,1H), 8.19 (d,1H), 8.19 (m,1H), 8.73 (m,1H).

2.4f and 2.4g

2.4f and **2.4g** have been prepared as outlined in Scheme 2.5. Yields were not optimised. p-(Bromomethyl)benzaldehyde (**2.8**) has been prepared by reaction of p-(bromomethyl)benzotrile (**2.7**, Acros) with diisobutylaluminium hydride following a literature procedure⁶⁵.

Sodium (p-oxomethylphenyl)methylsulfonate (2.9)

A suspension of 3.90 g (19.6 mmol) of p-(bromomethyl)benzaldehyde (**2.8**) and 4.00 g (31.7 mmol) of sodium sulfite in 40 ml of water was refluxed for two hours, after which a clear solution was obtained. The reaction mixture was cooled on an ice bath resulting in precipitation of some sodium sulfite. After filtration, the solvent was evaporated. Ethanol was added to the remaining solid and the suspension was refluxed for 10 minutes. After filtering the hot solution, the filtrate was allowed to cool down slowly to -18 °C whereupon sodium (p-oxomethylphenyl)methylsulfonate (**2.9**) separated as colourless crystals. The extraction procedure was repeated two more times, affording 2.29 g (10.3 mmol, 53%) of the desired product. ¹H-NMR (200 MHz, D₂O) δ(ppm) = 4.10 (s,2H); 7.44 (d,2H); 7.76 (d,2H); 9.75 (s,1H).

Sodium (4-(3-oxo-3-(2-pyridyl)-1-propenyl)phenyl)methylsulfonate (2.4f)

A solution of 75 ml of ethanol and 3.75 ml of a 10% solution of sodium hydroxide in water was cooled to 0 °C and 2.13 g (9.57 mmol) of sodium (p-oxomethylphenyl)methylsulfonate (**2.9**) and 1.28 g (10.6 mmol) of 2-acetylpyridine were added. The solution was stirred for 16 hours at 0°C and filtered affording 2.47 g (7.66 mmol, 80%) of crude **2.4f**. Crystallisation from methanol yielded 1.08 g (35%) of the desired product, mp 220 °C (decomposition). ¹H-NMR (200 MHz, D₂O) δ(ppm) = 4.00 (s,2H); 7.36 (d,2H); 7.55 (m,1H); 7.58 (d,2H); 7.61 (m,2H); 7.81 (m,2H); 8.43 (d,1H) Anal. Calcd for C₁₅H₁₂NO₄SNa : C, 55.4; H, 3.72; N, 4.31; S, 9.84; Na, 7.07. Found: C, 54.7; H, 3.74; N, 4.19; S, 9.41; Na, 6.97.

3-(p-(Bromomethyl)-phenyl)-1-(2-pyridyl)-2-propen-1-one (2.10)

A solution of 10 g of sodium hydroxide in 1.0 L of water was cooled to 0-5 °C. 5.95 g (49.2 mmol)

of 2-acetylpyridine and a solution of 7.25 g (36.4 mmol) p-(bromomethyl)benzaldehyde (**2.8**) dissolved in a minimal amount of ethanol were added. The resulting suspension was stirred for 48 hours at 0-5 °C. The product was filtered and washed extensively with water until the smell of the 2-acetylpyridine had disappeared. After drying at 50 °C under vacuum, 10.5 g (34.8 mmol, 96%) of 3-(p-(bromomethyl)phenyl)-1-(2-pyridyl)-2-propen-1-one (**2.10**) was obtained. ¹H NMR (200 Mhz, CDCl₃) δ(ppm) = 4.50 (s,2H); 7.42 (d,2H); 7.44 (m,1H); 7.70 (d,2H); 7.85 (m,1H); 7.91 (d,1H); 8.20 (d,1H); 8.31 (d,1H); 8.75 (d,1H).

(4-(3-Oxo-3-(2-pyridyl)-1-propenyl)phenyl)methyltrimethylammonium bromide (2.4g)

5.00 g (16.6 mmol) of 3-(p-(bromomethyl)phenyl)-1-(2-pyridyl)-2-propen-1-one (**2.10**) was suspended in 350 ml of dry ether under a nitrogen atmosphere. 20 ml of a 4.2 M solution of trimethylamine in ethanol (Fluka) was added. The reaction mixture was stirred for 24 hours at room temperature under a nitrogen atmosphere. Evaporation of the solvents and excess of trimethylamine afforded crude **2.4g** in quantitative yield. The very hygroscopic product can be crystallized from anhydrous 1-propanol. Removal of this solvent from the crystals is not possible by conventional methods. However, dissolving the product in water, filtration and subsequent freeze drying afforded 3.10 g (8.59 mmol, 52%) of **2.4g**, mp 212.5 °C (decomposition). ¹H-NMR (200 MHz, CDCl₃) δ(ppm) = 3.44 (s,9H); 5.16 (s,2H); 7.50 (m,1H); 7.75 (s,4H); 7.84 (d,1H); 7.85 (m,1H); 8.01 (d,1H); 8.31 (d,1H); 8.72 (d,1H). Anal. Calcd for C₁₈H₂₁N₂BrO: C, 60.0; H, 5.88; N, 7.78; Br, 21.92. Found: C, 59.8; H, 5.97; N, 7.58; Br, 21.77.

Kinetic measurements

All kinetic measurements were performed using UV-Vis spectroscopy (Perkin Elmer λ2, λ5 or λ12) monitoring the disappearance of the absorption of the dienophile at 25 ± 0.1 °C in the presence of a known excess of diene. Measurements were performed in cuvettes of 1 cm path length, initially containing only a solution of the dienophile. After equilibration, a 10-25 μl of a stock solution of cyclopentadiene in 1-propanol was added and the absorption was monitored. Two different methods were used to determine the second-order rate constants. The rates of the faster reactions (half-lives not more than a few hours) were determined by following the reaction during at least four half-lives. From the absorbance data, pseudo-first-order rate constants were obtained using a fitting-program. The rate constants of the slower reactions in organic solvents and the reactions with cyclopentadiene in water with half-lives of more than 15 minutes were determined using initial rate kinetics⁸⁴. Using a known excess of cyclopentadiene, the following expression was used to calculate the second-order rate constants:

$$k_2 = \frac{d(A_{2.4})}{dt} \cdot \frac{1}{d \cdot (e_{2.4} - e_{2.6}) \cdot [2.4]_0 \cdot [2.5]_0}$$

Herein d(A_{2.4})/dt is the slope of the plot of the absorption of the dienophile versus time during the first

five percent of the reaction and d is the pathlength of the cuvette. The extinction coefficients of the dienophile and the product were determined separately under the same conditions as used in the kinetic runs. This method has been successfully tested by comparing the results with rate constants obtained by traditional pseudo-first-order kinetics. Typical concentrations were: [dienophile] = $1 \cdot 10^{-5}$ M, [cyclopentadiene] = $1 \cdot 10^{-3}$ M and [catalyst] = $1 \cdot 10^{-2}$ M. All rate constants were measured at least three times. Those obtained by the traditional method were reproducible to within 3%, whereas the initial rate method gave a reproducibility of 5%.

Equilibrium constants

Measurements were performed employing a Perkin Elmer $\lambda 2$, 5 or 12 UV-Vis spectrophotometer at $25 \pm 0.1^\circ\text{C}$. Equilibrium constants were determined by measuring the extinction coefficient at a suitable wavelength of the partially complexed dienophile (ϵ_{obs}) as a function of the concentration of metal ion. The following expression can be derived⁸⁵:

$$\frac{[\text{M}^{n+}]}{\epsilon_{2.4} - \epsilon_{\text{obs}}} = \frac{1}{(\epsilon_{2.4} - \epsilon_{\text{compl}}) \cdot K_a} + \frac{[\text{M}^{n+}]}{\epsilon_{2.4} - \epsilon_{\text{compl}}}$$

After determining the extinction coefficient of the uncomplexed dienophile ($\epsilon_{2.4}$), $[\text{M}^{n+}]/(\epsilon_{2.4} - \epsilon_{\text{obs}})$ was plotted versus $[\text{M}^{n+}]$ yielding a straight line. The equilibrium constant now equals the ratio of the slope and the intercept of this line. Very accurate measurements of the extinction coefficients are a prerequisite for obtaining reliable equilibrium constants. Crucial in this respect were the choice of the wavelength and the choice of the appropriate metal-ion concentrations. The most accurate results were obtained at the wavelength of maximal difference between the extinction coefficients of uncomplexed and complexed dienophile. The metal-ion concentrations were chosen so as to cover the largest possible change in ϵ_{obs} with the smallest possible change in $[\text{M}^{2+}]$. Solutions of different $[\text{M}^{2+}]$ with total ionic strength of 2.00 M were prepared. KNO_3 was used as the background electrolyte. Extinction coefficients were determined by filling the cuvet with an accurately known volume of this solution and measuring the absorption after injection of 3-10 μl of a stock solution of the dienophile in 1-propanol. Typical concentration ranges were: [dienophile] = $6 \cdot 10^{-6}$ - $2 \cdot 10^{-5}$ M and $[\text{M}^{2+}]$ = $5 \cdot 10^{-3}$ - $2 \cdot 10^{-5}$ M. The reproducibility of the equilibrium constants varied between 5-10%.

Product analysis

Endo-exo product mixtures were isolated using the following procedure. A solution of cyclopentadiene (concentration $2 \cdot 10^{-3}$ M in water and 0.4 M in organic solvents) and the dienophile (concentration 1-5 mM) in the appropriate solvent, eventually containing a 0.01 M concentration of catalyst, was stirred at 25°C until the UV-absorption of the dienophile had disappeared. The reaction mixture (diluted with water in the case of the organic solvents) was extracted with ether. The ether layer was washed with water and dried over sodium sulfate. After the evaporation of the ether the

adducts were obtained in quantitative yields and almost invariably as oils. Only the reaction of **2.4c** and **2.5** in water with 10 mM HCl gave a white precipitate. The product mixtures were analysed with respect to their endo-exo ratio by $^1\text{H-NMR}$ spectroscopy. By repeating the extraction-drying procedure it was confirmed that the work-up procedure did not influence the endo-exo ratio of the isolated product mixture.

We have purified only the products of **2.4a** and **2.4c** by crystallisation from 1-propanol and ethanol, respectively. The purified products were still a mixture of endo and exo isomers. Elemental analyses of these compounds are given below. The Diels-Alder adducts of **2.4b**, **2.4d-g** were characterised by comparison of their NMR spectra with those of **2.4a** and **2.4c**. We will report here only the NMR data for the endo isomer, since the signals of the minor (7-12%) exo isomer partly coincide with the larger signals of the endo isomer and no attempts were made to separate the two. **2.6a**: Anal. ($\text{C}_{19}\text{H}_{16}\text{N}_2\text{O}_3$) calcd. C: 71.22, H: 5.04, N: 8.75; found C: 70.82, H: 4.93, N: 8.66. $^1\text{H NMR}$ (300 MHz, CDCl_3) δ 1.65 (dd,1H), 1.99 (d,1H), 3.11 (d,1H), 3.52 (d,1H), 3.59 (s,1H), 4.46 (dd,1H), 5.85 (dd,1H), 6.47 (dd,1H), 7.21 (m,3H), 8.0 (m,5H), 8.6 (d,1H). **2.6b**: $^1\text{H NMR}$ (300 MHz, CDCl_3) δ 1.61 (dd,1H), 2.00 (d,1H), 3.04 (d,1H), 3.40 (dd,1H), 3.54 (s,1H), 4.45 (dd,1H), 5.82 (dd,1H), 6.47 (dd,1H), 7.21 (m,5H), 7.45 (m,1H), 7.82 (m,1H), 7.99 (d,1H), 8.66 (d,1H). **2.6c**: Anal. ($\text{C}_{19}\text{H}_{17}\text{NO}$) calcd. C: 82.87, H: 6.23, N: 5.09; found C: 82.28, H: 6.24, N: 5.21. $^1\text{H NMR}$ (300 MHz, CDCl_3) δ 1.61 (dd,1H), 2.05 (d,1H), 3.07 (d,1H), 3.43 (dd,1H), 3.53 (s,1H), 4.51 (dd,1H), 5.81 (dd,1H), 6.47 (dd,1H), 7.21 (m,5H), 7.41 (m,1H), 7.80 (m,1H), 7.99 (m,1H), 8.65 (m,1H). **2.6d**: $^1\text{H NMR}$ (300 MHz, CDCl_3) δ 1.60 (dd,1H), 2.07 (d,1H), 3.06 (d,1H), 3.42 (d,1H), 3.54 (s,1H), 4.53 (dd,1H), 5.83 (dd,1H), 6.49 (dd,1H), 7.09 (d,2H), 7.22 (d,2H), 7.43 (m,1H), 7.80 (m,1H), 8.00 (d,1H), 8.67 (d,1H). **2.6e**: $^1\text{H NMR}$ (300 MHz, CDCl_3) δ 1.59 (dd,1H), 2.05 (d,1H), 3.02 (d,1H), 3.39 (d,1H), 3.52 (s,1H), 4.49 (dd,1H), 5.81 (dd,1H), 6.48 (dd,1H), 6.82 (d,2H), 7.23 (d,2H), 7.43 (m,1H), 7.79 (m,1H), 7.99 (d,1H), 8.67 (d,1H). **2.6f**: $^1\text{H NMR}$ (300 MHz, D_2O) δ 1.49 (dd,1H), 1.90 (d,1H), 2.98 (d,1H), 3.15 (d,1H), 3.27 (s,1H), 4.07 (s,2H), 4.25 (m,1H), 5.75 (m,1H), 6.44 (m,1H), 7.26 (s,4H), 7.55 (m,1H), 7.87 (m,2H), 8.52 (d,1H). **2.6g**: $^1\text{H NMR}$ (300 MHz, CDCl_3) δ 1.62 (dd,1H), 1.98 (d,1H), 3.07 (d,1H), 3.36 (s,9H), 3.43 (d,1H), 3.55 (2,1H), 4.45 (m,1H), 4.92 (s,2H), 5.82 (m,1H), 6.47 (m,1H), 7.36 (d,2H), 7.46 (m,1H), 7.52 (d,2H), 7.83 (dt,1H), 7.99 (d,1H), 8.66 (d,1H).

Appendix 2.1

In the presence of excess catalysts (M^{n+}) the rate of the Diels-Alder reaction of **2.4** with **2.5** is given by:

$$\frac{d[\mathbf{2.4}]_t}{dt} = k_0[\mathbf{2.4}]_f[\mathbf{2.5}] + k_{cat}[\mathbf{2.4} \cdot \text{M}^{n+}][\mathbf{2.5}] \quad (A1)$$

Herein k_0 is the second-order rate constant for the uncatalysed reaction and k_{cat} is the second-order rate constant for the reaction of the **2.4**-catalyst complex. $[\mathbf{2.4}]_f$ is the concentration of free dienophile

and $[2.4]_t$ is the total concentration of **2.4**.

An expression for the concentration of coordinated **2.4** (A4) can be obtained by combining the expression for the equilibrium constant K_a (A2) with the mass balance for **2.4** (A3).

$$K_a = \frac{[2.4 \cdot M^{n+}]}{[2.4]_f [M^{n+}]_f} \quad (A2)$$

$$[2.4]_t = [2.4]_f + [2.4 \cdot M^{n+}] \quad (A3)$$

$$[2.4 \cdot M^{n+}] = \frac{K_a \cdot [M^{n+}]_f}{K_a \cdot [M^{n+}]_f + 1} [2.4]_t \quad (A4)$$

Substitution of A4 in A1 gives:

$$\frac{d[2.4]_t}{dt} = k_0 [2.4]_f [2.5] + \frac{K_a \cdot [M^{n+}]_f}{K_a \cdot [M^{n+}]_f + 1} [2.4]_t [2.5] k_{cat} \quad (A5)$$

Under pseudo first-order conditions (excess **2.5**) k_{app} is given by:

$$k_{app} = \frac{1}{[2.5]} \cdot \frac{d[2.4]_t}{dt} \cdot \frac{1}{[2.4]_t} \quad (A6)$$

Substitution of A5 in A6 yields:

$$k_{app} = \frac{k_0 [2.4]_f}{[2.4]_t} + \frac{K_a \cdot [M^{n+}]_f}{K_a \cdot [M^{n+}]_f + 1} k_{cat} \quad (A7)$$

Since for the kinetic measurements a large excess of catalyst is used, the concentration of free catalyst $[M^{n+}]_f$ essentially equals the total concentration of catalyst. Moreover, since $k_0 \ll k_{cat}$ and under the conditions of the measurements the concentration of free **2.4** is small, the contribution of the uncatalysed reaction can be neglected and equation A7 simplifies to:

$$k_{app} = \frac{K_a \cdot [M^{n+}]_t}{K_a \cdot [M^{n+}]_t + 1} k_{cat} \quad (A8)$$

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