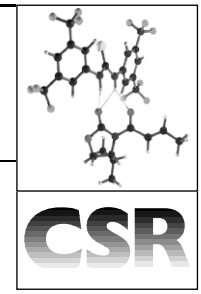
# Metal-free organocatalysis through explicit hydrogen bonding interactions



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**The metal (ion)-free catalysis of organic reactions is a contemporary challenge that is just being taken up by chemists. Hence, this field is in its infancy and is briefly reviewed here, along with some rough guidelines and concepts for further catalyst development. Catalysis through explicit hydrogen bonding interactions offers attractive alternatives to metal (ion)-catalyzed reactions by combining supramolecular recognition with chemical transformations in an environmentally benign fashion. Although the catalytic rate accelerations relative to uncatalyzed reactions are often considerably less than for the metal (ion)-catalyzed variants, this need not be a disadvantage. Also, owing to weaker enthalpic binding interactions, product inhibition is rarely a problem and hydrogen bond additives are truly catalytic, even in water.**

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## 1 Introduction

Metal (ion) catalysis undoubtedly has been the most vibrant area of research in synthetic organic chemistry over the past two decades. Highly selective, metal (ion)-promoted reactions are milestone achievements of modern chemistry and one confidently expects much more to come. For the sake of the focus of this article it is sensible to differentiate between metal-specific reactions and those where the metal acts as a Lewis acid. Metal-specific transformations involve only one or very few metals (not at the same time) in a well-defined oxidation state that is capable of catalyzing a particular reaction (*e.g.*, Pd-catalyzed couplings). The other class, Lewis acids, is characterized by electron-deficient metal sites that interact with excess electron densities (Lewis bases) typically available at heteroatoms (O, N, S, Hal) or multiple bonds. Many metals act as Lewis acids (even the ones that may belong to the first class but in a different function) and the literature on these is vast. Lewis acid catalysts (*e.g.*, $Al_2Cl_6$, $FeBr_3$, $BF_3$, $TiCl_4$ and many others) are being used ubiquitously in Friedel–Crafts, Diels–Alder as well as many other reactions. One should be reminded, however, that these types of reactions very often require over stoichiometric amounts of the "catalyst" because the product still contains a basic moiety that binds the Lewis acid.[1] Hence, very often there is no "catalytic turnover," that is, the catalyst only helps one molecule of starting material to be converted to one molecule of product. This so-called "product inhibition" is a very common problem and derives from the fact that many of the simpler Lewis acids mentioned above bind basic sites too strongly, limiting the usability of Lewis acids in aqueous or other environmentally benign media. However, much progress has been made in this direction by using much weaker Lewis acids[2] such as the lanthanides that retain activity even in water;[3] note that Brønsted catalysis in these systems can not yet be ruled out.

Nature typically does not use strong Lewis acids. Quite the contrary, Nature's catalytic systems (enzymes, ribonucleases, antibodies as well as others), are far more sophisticated (Figure 1) and apparently do not need strong enthalpic binding that would automatically come with the use of a highly electron-deficient metal center; even when a metal is used (*e.g.*, copper or zinc), it is often considered "soft" in the Pearson HSAB sense and is well embedded in a larger highly polarizable structure.[4,5] Owing to the much smaller Gibbs energy changes associated with the "recognition" (binding) of the starting material (the substrate), enzymes, for instance, can be far more selective and are, by means of a very long period of evolution, far more

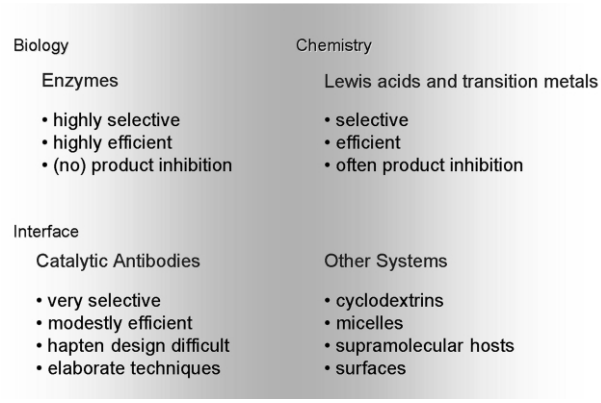



**Fig. 1** Comparison of catalysis in Nature and in chemistry. This is a simplified picture that is meant to contrast the hugely different approaches and the necessity for seeking common grounds.

efficient than catalytic chemical systems; product inhibition is generally not a problem. From a different point of view, Nature strikes a much better balance in terms of using metal-catalyzed and metal-free reactions. Stereoselective chemical transformations perhaps have over emphasized the virtue of metal catalysis but this picture is changing rapidly; fast developing metal-free catalysis with small organic molecules has been described as utilizing "artificial enzymes" or being "enzyme mimetics."[6,7]

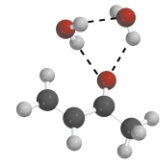
Chemists have learned much from Nature and, for instance, have recently very successfully been using the catalytic antibody approach including evolutionary improvement.[8,9] It is clear that the recognition process in such systems relies on hydrogen bonding and hydrophobic interactions.[9,10] Although many of these are well understood when enzyme as well as enzyme-inhibitor structures are available, or from computational studies, we are far from fully rationalizing enzymatic selectivity and activity. Nevertheless, the "tool box" is beginning to take shape and designing metal-free catalysts building on these interactions is timely.

Since metal catalysis is – despite some of the perhaps less important limitations mentioned above – reasonably well developed and since Nature is much superior to chemical catalysis, one may ask: why worry about the title topic in the present brief review? First of all, many metals are poisonous, which often presents a real challenge in terms of the production process in the chemical and pharmaceutical industry.[11] In particular, if water is used as the solvent (and this would obviously be preferred in "green chemistry" and environmentally benign approaches), great care must be taken with regards to waste water cleanup. It is often rather difficult to immobilize traditional Lewis acids on polymers or other stationary phases for easier catalyst removal and flow processes without washout.[12] Metal-free reactions can also be run under aerobic conditions. Secondly, what can be learnt from Nature from a physical-organic point of view? Why and how does Nature accomplish formidable transformations such as the Diels–Alder reaction apparently *without* using a metal although chemists cannot circumvent the use of metals for the activation of, for instance, unreactive dienophiles?

Metal-free organocatalysis has been around for over a century,[13] but was left largely unacknowledged.[14,15] Only recently has the activity in this field increased considerably because of the many opportunities organocatalytic systems may offer in terms of catalyst design. Enantioselective organocatalysis has been excellently reviewed by Dalko and Moisan[7] who emphasize practical synthetic aspects. These authors present a useful classification into four different organocatalytic mechanisms: a) activation of a reaction by means of the nucleophilic/electrophilic properties of the catalysts; this is comparable to conventional Lewis acid/base activation; b) catalysts forming covalently bound reactive intermediates; c) phase-transfer catalysis where an organic ion helps transport components between multiple phases, and d) reactions in molecular cavities. The present paper focuses more on the nature of the hydrogen bonding interactions in a subset of these reactions and aims at identifying the components of successful catalytic systems, as in a) above. While many organocatalytic systems essentially evolved from the ligand chemistry of organometallic reactions, we will focus on ureas and related compounds as a class of catalysts that is not commonly used as organometallic ligands. We will in part focus on the Diels–Alder reaction of carbonyl-containing dienophiles as a platform for catalyst development.

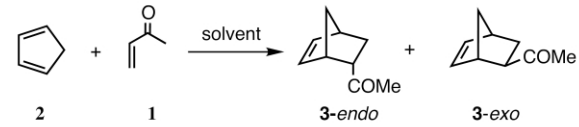
## 2 Catalysts and reactions

There are several key experimental and computational findings that provide a rational basis for the design of a metal-free, hydrogen-bonding based catalytic system that is applicable to the Diels–Alder reaction of a diene with an electron deficient α,β-unsaturated carbonyl compound. First of all, water itself does have a significant effect on many reactions, in particular, the Diels–Alder reaction (Scheme 1);[16] there are several vividly



**1**•$(H_2O)_2$

| solvent | rel. rate | *endo*/*exo* |
|---|---|---|
| isooctane | 1 | 4 |
| methanol | 13 | 9 |
| water | 741 | 23 |



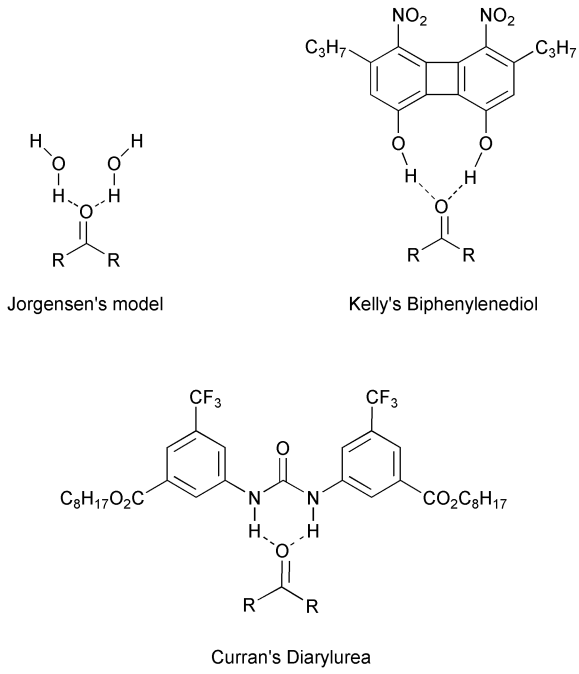

**2** **1** **3**-*endo* **3**-*exo*

**Scheme 1** Models of explicit water hydrogen bonding interactions in the Diels–Alder reaction of **1**: two waters "clamp" the carbonyl group, leading to a significant aqueous solvent effect.[49]

debated reasons for this acceleration (solvent polarity, hydrophobicity, internal pressure (note that this effect is often misunderstood and apparently mixed up with cohesive energy density) *etc*.),[17,18] but we will focus on the *explicit* interactions to derive a hydrogen-bonding catalyst motif. Jorgensen *et al*. showed for the Diels–Alder[19,20] and other pericyclic reactions that two water molecules coordinate to the carbonyl function, leading to a preferential stabilization of the transition states and to rate enhancements. Such coordination is confirmed by X-ray structural studies.[21]

The bidentate nature of the binding interaction is particularly attractive because it removes some conformational degrees of freedom. To avoid entropic loss upon coordination, this also means that the hydrogen-bond donor must be relatively rigid.[22] Kelly apparently was the first to utilize this approach (Scheme 2) for the catalysis (at catalyst loadings of 40–50 mol%) of a variety of Diels–Alder reactions; the rate enhancements were in the range of 0–30).[23] Curran introduced urea derivatives for altering the stereochemistry of allylation reactions of cyclic α-sulfinyl radicals, observing very small rate accelerations but improved *cis*/*trans* selectivities in the presence of 20–100 mol% additive.[24] These types of catalysts (including their thiourea derivatives) were also employed for the catalytic (20–50 mol%) one- to fourfold rate acceleration of some Claisen rearrangements at 80–100 °C; 100 mol% gave relative rate enhancements of up to 22.[25] The notorious insolubility of ureas made the fatty acid groups necessary for these derivatives. One drawback is that this also introduces a binding site that may compete with the substrate molecules.

Our own group took these ideas together and settled for using thioureas because they are a) more soluble in a variety of




**Scheme 2** Model interactions of explicit water molecules with a carbonyl function and two hydrogen bonding additives capable of catalysis.

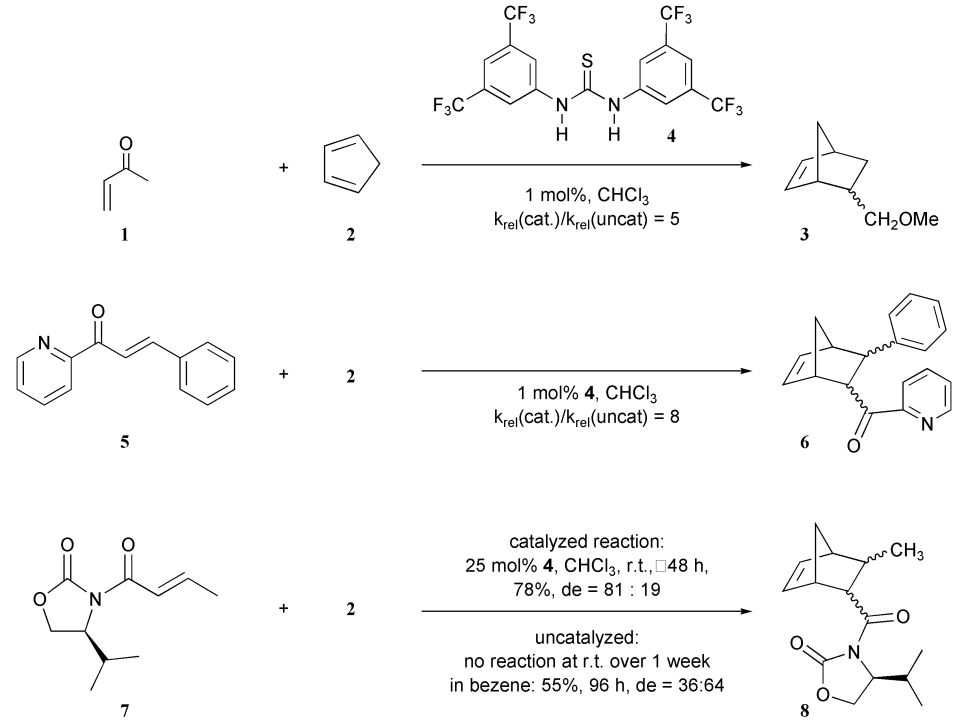
solvents, b) easier to prepare (thiophosgene is much easier to handle than phosgene) c) the thiocarbonyl group is a much weaker hydrogen-bond acceptor.[22,26,27] As expected, the introduction of electron-withdrawing groups in the *meta*-position that are not capable of much hydrogen bonding themselves, increases the catalytic efficiency;[22] this observation is also in line with the fact that co-crystals are of higher quality when trifluoromethyl groups are present in the thiourea derivative.[28]

In a systematic study we identified several catalytically active (at catalyst loadings of 1 mol%) thiourea derivatives; *N*,*N*′-bis[3,5-bis(trifluoromethyl) phenyl] thiourea (**4**) is most active (Scheme 3).[22] The rate accelerations can be amplified (up to a factor of about 1000, based on relative yields at a given temperature for the catalyzed *vs.* uncatalyzed reaction) by cooperative hydrogen bonding in the case of unsaturated 1,3-diketones as dienophiles.[26] Remarkably, no product inhibition is observed apparently due to the weak enthalpic and favorable differential binding of the catalyst to the carbonyl function of the dienophile and the transition structure (*vide infra*). That is, these catalytic systems do show turnover, in marked contrast to many traditional Lewis-acid catalyzed reactions. Enantioselective Diels–Alder reactions can also be accomplished utilizing chiral, enantiomerically pure thiourea derivatives. However, the enantiomeric excess observed to date is far from satisfactory (0–30% ee based on $^1$H-NMR analyses with chiral shift reagents for the reaction of bromacrolein with cyclopentadiene); further catalyst development is required.[29] It is particularly noteworthy that these catalysts are most effective in water.

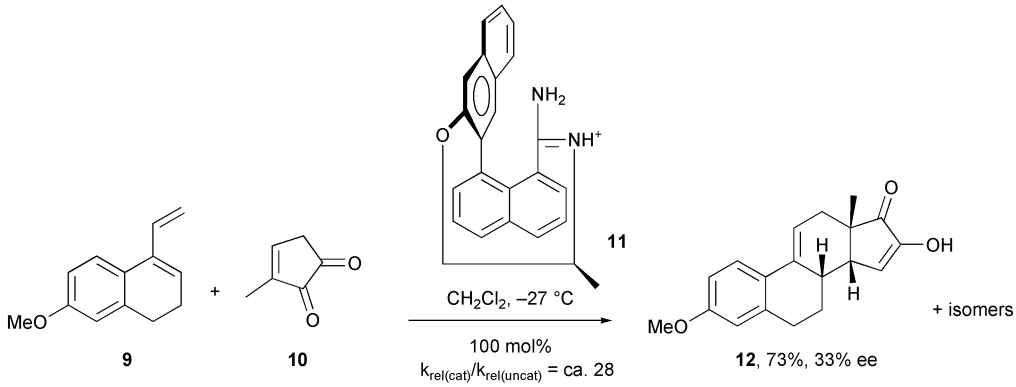
Amidinium and guanidinium ions are also capable of catalysis comparable to that of very mild Lewis acids,[30,31] mostly due to an increased interaction of the highly polarized N–H bonds in the cations. Remarkably, enantioselectivity can also be induced (up to 50% ee) using axially chiral amidinium ions (**11**) in reactions of unsaturated diketones with dienes (Scheme 4).[32] However, questions regarding facile protonation/deprotonation equilibra have yet to be answered.

Diversity and hence generality for these types of catalysts was introduced by Jacobsen *et al.* who showed that urea and thiourea derivatives act as catalysts in the enantioselective Strecker[33–36] and Mannich[37] reactions (Scheme 5). The emphasis of these studies was placed on the remarkably high enantioselectivities observed in the presence of enantiopure catalysts.

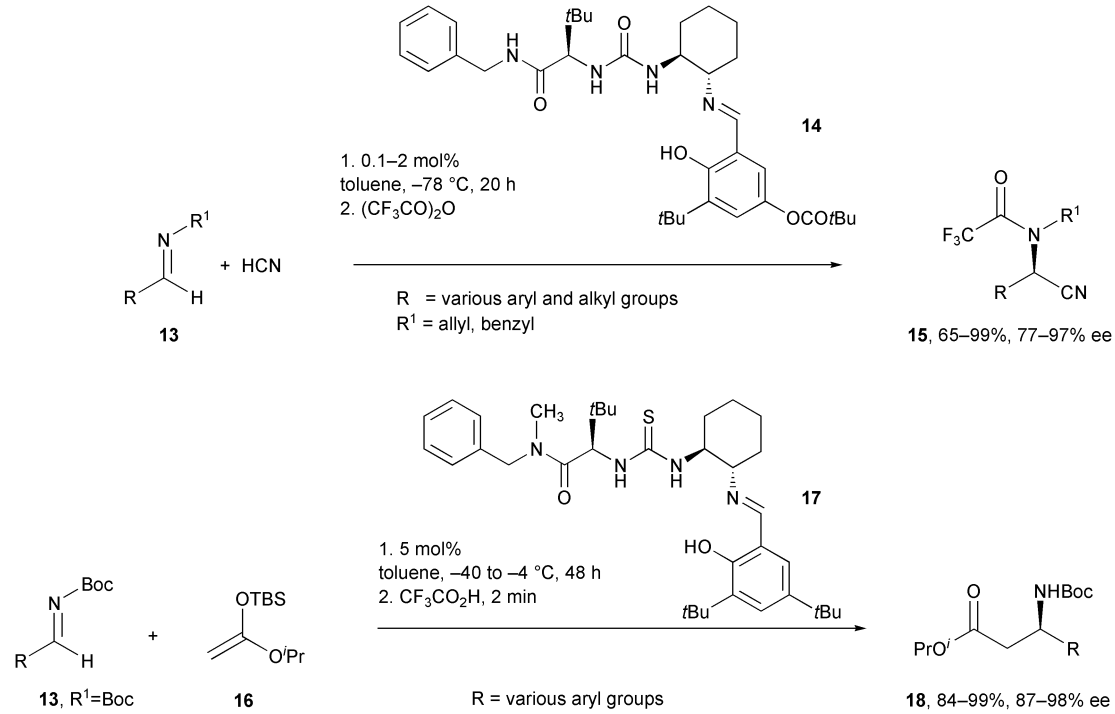
These asymmetric Strecker reactions partially build on one of the oldest organocatalytic reactions, the hydrocyanation of carbonyl compounds utilizing optically active alkaloids.[13,15] The initially unsatisfactory enantiomeric excesses were considerably improved when small cyclic peptides incorporating a guanine motif were used (Scheme 6).[38–40] Note that the original Strecker reaction of 1850 *was* carried out in water. Some structurally related guanines are efficient in catalyzing the



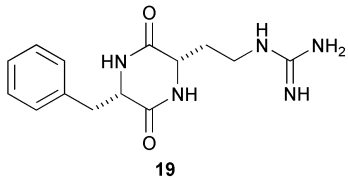

**Scheme 3** Catalysis of Diels–Alder reactions with electron-deficient thiourea derivative **4**.

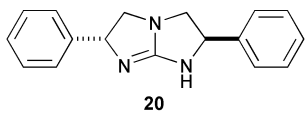



**Scheme 4** Enantioselective catalysis of a Diels–Alder reaction by an amidinium ion.




**Scheme 5** Enantioselective addition of HCN to ketoimines and enantioselective Mannich reactions catalyzed by (thio)urea derivatives.




**Scheme 6** Organocatalysts with guanine moieties used for the effective enantioselective addition of HCN to Schiff bases.

addition of HCN to Schiff bases, further identifying the hydrogen-bonding "clamp" motif as essential for asymmetric induction.[41]

While rate accelerations were not reported in Jacobsen's studies, the authors note that these reactions follow Michaelis–Menten kinetics that is consistent with reversible binding of the imine followed by the rate-determining addition of HCN.[36] Jacobsen *et al*. optimized the structures of the catalysts by screening catalyst libraries using enantioselectivities as a measure for activity in a set of reference reactions. These optimized catalysts are impressively broad in their applicability to a wide variety of imines in the asymmetric Strecker reaction. Remarkably, the catalysts show virtually the same activity when bound to a polystyrene resin, and this emphasizes the point made in the introduction, namely that the immobilization and library optimization of non-covalent organocatalysts is straightforward.

## 3 Binding and structural studies

While it is very probable that the interactions of the organocatalytic systems reviewed here are dominated by bidentate hydrogen bonding of urea, thiourea, guanine (guanidinium), and amidinium moieties with carbonyl as well as imino functions, little is known about the binding energies and structural consequences. Astonishingly, this partially also applies to traditional Lewis acid interactions with basic sites. Although the excellent results speak for themselves, improvements can only be made through an understanding of the controlling elements of catalysis. The following section briefly highlights structural and binding studies on some of the above catalysts and compares those to traditional Lewis acids. Since the working hypothesis is that hydrogen bonding catalysts behave like weak Lewis acids, similarities should be apparent.

In his ground-breaking work on chiral *N*-acyloxazolidinones as auxiliaries in asymmetric, Lewis acid catalyzed reactions, Evans introduced the notion of bidentate binding of the 1,3-diketone (such as **7**) to the Lewis acid (specifically $Et_2AlCl$).[42] This model was necessary to understand the high selectivities observed. Castellino and Dwight could finally confirm this mechanistic proposal based on NMR studies of the complexes of $Et_2AlCl$ with **7** (Scheme 7).[43] Note that the *anti* form of **7** is the ground state so that the effect of the Lewis acid is, by means of the bidentate nature of **7**, to stabilize the less preferred *syn* conformation, which is a requirement imposed by the observed stereoselectivities in Diels–Alder reactions with these complexes. These kinds of complexes apparently only form when more than one equivalent of $Et_2AlCl$ is used.

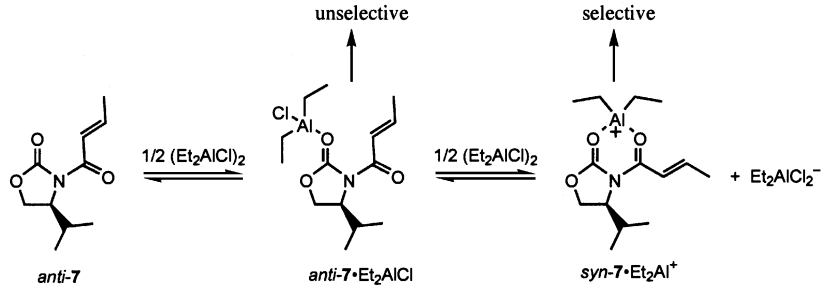
Are these observations transferable to hydrogen bonding catalyzed Diels–Alder reactions? The first question concerns the ground state conformation of, for instance, thiourea **4** that has shown to be effective in catalytic Diels–Alder test reactions. A crystal structure confirms our model that the thiourea moiety displays the desired *syn*-orientation of the N–H bonds and is therefore set up for binding a basic site in its center by means of a bidentate hydrogen bond (Figure 2);[44] this is further supported by a plot of the electrostatic potential (at B3LYP/6-31G*) of minimum **4**. Unfortunately, co-crystals with carbonyl compounds are not yet available. The interactions of electron-deficient thiourea derivatives such as **4** and its disubstituted derivative with **7** were analyzed by a combination of low-temperature infrared (IR) spectroscopy and quantum mechanical computations on reduced model systems.[26] Although $^1$H NMR spectroscopy is usually the method of choice for analyzing intermolecular hydrogen-bonding interactions by monitoring changes in the proton absorptions, we took the complementary route by analyzing the fate of the highly IR-active carbonyl absorptions upon binding. Indeed, we found that **4** and others bind to **7** in a fashion depicted on the right in Figure 2. The similarities to the binding of $Et_2AlCl$ are apparent and the stereochemical outcome as well as the observed rate accelerations by lowering the LUMO of the dienophile through electron-deficient complexation completely agree with this analysis: hydrogen bonding additives act as weak Lewis acids.[26] Similar structural binding features were found in NMR studies for the complexes of **14** with imines.[35]

In order to put this qualitative structural analysis on a semi-quantitative footing,[45] combined semi-empirical/DFT computations were also carried out. As the systems under consideration are quite large, semi-empirical theory (AM1) was utilized for geometry optimizations, frequency calculations, and self-consistent reaction field (SCRF) solvent simulations in combination with higher-quality relative energies at the DFT level using B3LYP/6-31+G**.

The dissociation energies ($D_e$) of the complexes of the thiourea derivatives with **1** show little dependence on the substituents. This is apparent from a comparison of the complexes with the catalytically active **4** and the respective phenyl (**21**) and cyclohexyl (**22**) derivatives (Figure 3). All three association energies are around 5–6 kcal mol$^{-1}$ in reasonable agreement with experiment.[26] As expected, the H-bonded structures confirm Jorgensen's two-point complexation motif. In all three cases the H-bond distances are comparable (*ca*. 2.2 Å); some additional secondary (hydrophobic) interactions between the hydrogen atoms of the phenyl groups and those of the substrate can also be identified. The small differences in the complexation energies found for the three catalysts do not reflect the observed experimental rate accelerations. As the interaction energies are small, entropy becomes increasingly important: The more rigid the free catalyst, the more stable the complex, minimizing the entropy loss.

The key effect of a catalyst in a chemical reaction is to reduce the reaction barrier. If the catalyst is able to interact with the starting material, the transition structure (TS) and the products, it is necessary that the relative stabilization of the TS is the largest. Increased stabilization of the TS in the reactions examined here has two components. First, the TSs are more polarized than the starting materials or the product (see NBO charges on the carbonyl oxygen, in italics, Figure 4) leading to stronger H-bonds with the catalyst. Second, there are secondary (hydrophobic) attractive interactions between both substrates and the catalyst assisting the approach of the reactants and decreasing the barrier.

To validate the efficiency of the catalyst in the non-coordinating solvent cyclohexane we compared the gas-phase results of the reaction of **1** with **2** catalyzed by **4** with the uncatalyzed reaction (Figure 4). While the starting materials are stabilized by about 6 kcal mol$^{-1}$ the "dissociation energy" of the TS and the product amounts to about 8 kcal mol$^{-1}$. The 2 kcal mol$^{-1}$ reduction of the barrier is somewhat larger but still in the right ball park to explain the observed 8.8-fold rate acceleration by **4**.[46]




**Scheme 7** Complexation of an aluminium containing Lewis acid to an *N*-acyloxazolidinone.

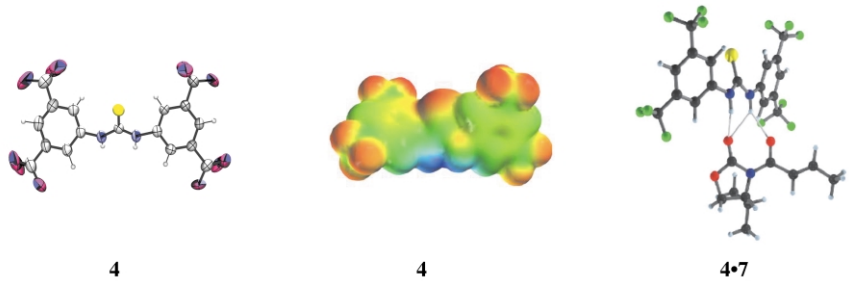



**Fig. 2** Crystal structure (left) of **4**, its electrostatic potential map (middle, HF/6-31G*), and the complex **4·7** derived from combined IR and computational studies.

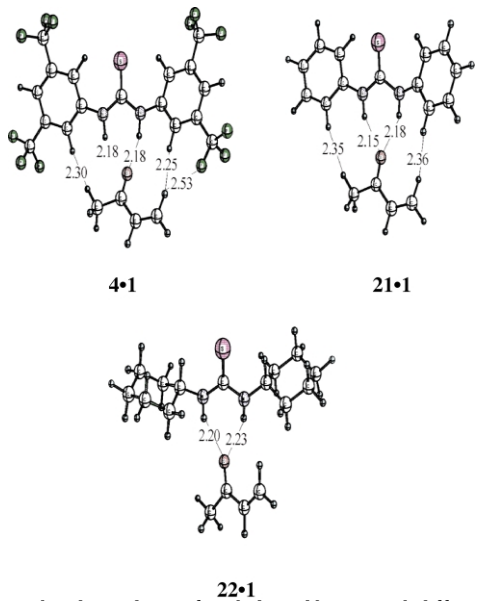



**Fig. 3** The H-bond complexes of methyl vinyl ketone with different thiourea derivatives.

To validate the observed effectiveness of the thiourea catalyst in water, aqueous solutions were also included (Figure 4 and 5, values in parentheses). Although the presence of water, simulated by an external field, reduces the relative catalytic activity (the barrier-decrease changes from 2.0 to 1.7 kcal mol$^{-1}$), the thiourea has a rate enhancing effect even in water. To determine if the catalytic effect by H-bonds, observed in the thiourea reaction, can also be caused by aqueous H-bonds we included two explicit water molecules bound to the carbonyl function on the parent reaction (Figure 5).[47] Comparison of the complex containing two water molecules with the **4·1** complex emphasizes that the thiourea is the better H-bond donor (while the binding energy of the two explicit water molecules with the dienophile **1** is only 3.7 kcal mol$^{-1}$ thiourea **4** stabilizes the starting compound by 6.4 kcal mol$^{-1}$). Hence, the catalyst can effectively *compete* with water: two explicit water molecules reduce the barrier by only 0.5 kcal mol$^{-1}$ while **4** reduces the barrier by 2 kcal mol$^{-1}$.

The effect of two explicit water molecules on the Diels–Alder reaction is approximately reproduced when an external reaction field is applied. Here, the starting compound is stabilized by 8.6 kcal mol$^{-1}$ and the barrier is lowered by 0.8 kcal mol$^{-1}$ compared to the gas phase reaction. The combination of two explicit water molecules with the reaction field gives nearly the same barrier lowering by 0.9 kcal mol$^{-1}$. This implies that the accelerating effect of water in Diels–Alder reactions is mainly due to electrostatic stabilization of the polarized transition state through explicit hydrogen bonding.

## 4 Conclusions and outlook

The development of catalysts that bind to a substrate through explicit hydrogen bonds offers attractive alternatives to metal-catalyzed reactions. Hence, this approach combines supramolecular recognition with chemical change in terms of catalysis. Although the catalytic rate accelerations relative to uncatalyzed reactions are often considerably less than for the metal-catalyzed variants, this need not be a disadvantage, for instance, in the case of labile substrates. Also, owing to weaker binding interactions, product inhibition is rarely a problem and hydrogen bond additives are truly catalytic.

To the best of my knowledge, this is the first review devoted to this field and this emphasizes that we are very much in the state of infancy. Many catalyst motifs are available from metal ligand design, even more through following other, less well-trodden alleys. Several aspects should perhaps be kept in mind when developing other hydrogen bonding catalyst:

a) The bi- or multidentate nature of catalyst-substrate binding amplifies the catalytic effectiveness and restricts the degrees of freedom. This also necessitates that the catalysts should be

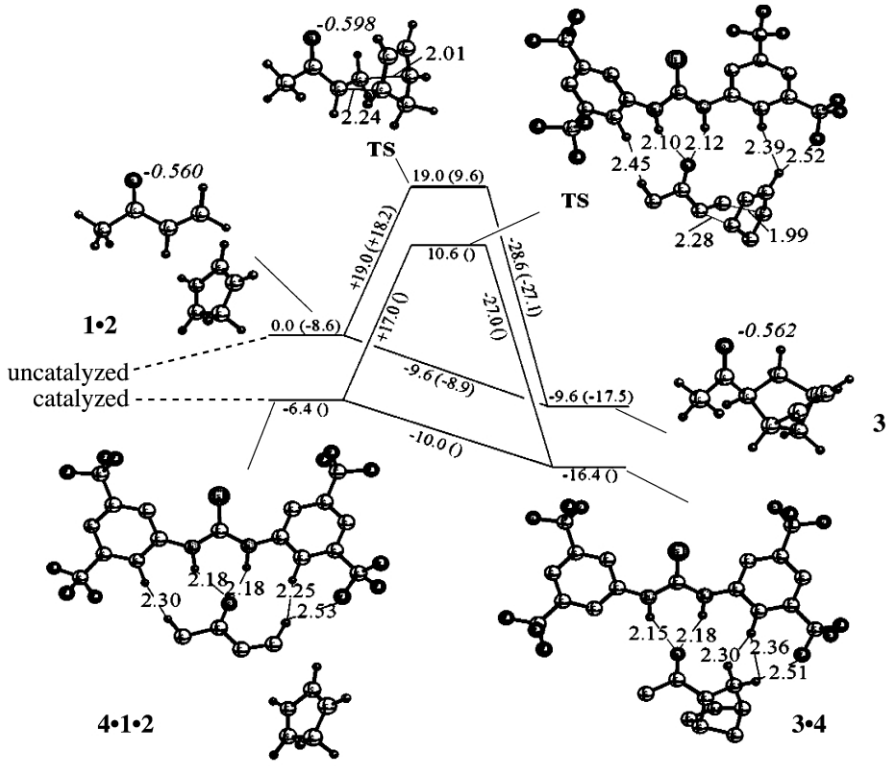



**Fig. 4** The Diels–Alder reaction of methyl vinyl ketone (**1**) and cyclopentadiene (**2**) uncatalyzed and catalyzed by *N*,*N*′-bis[3,5-bis(trifluoromethyl) phenyl] thiourea (**4**). The energies at the B3LYP/6-31+G**//AM1 level relative to the starting materials are given in kcal mol$^{-1}$ (the SCRF-energies are in parentheses, NBO-charges in italics). Some of the hydrogens were removed for clarity.

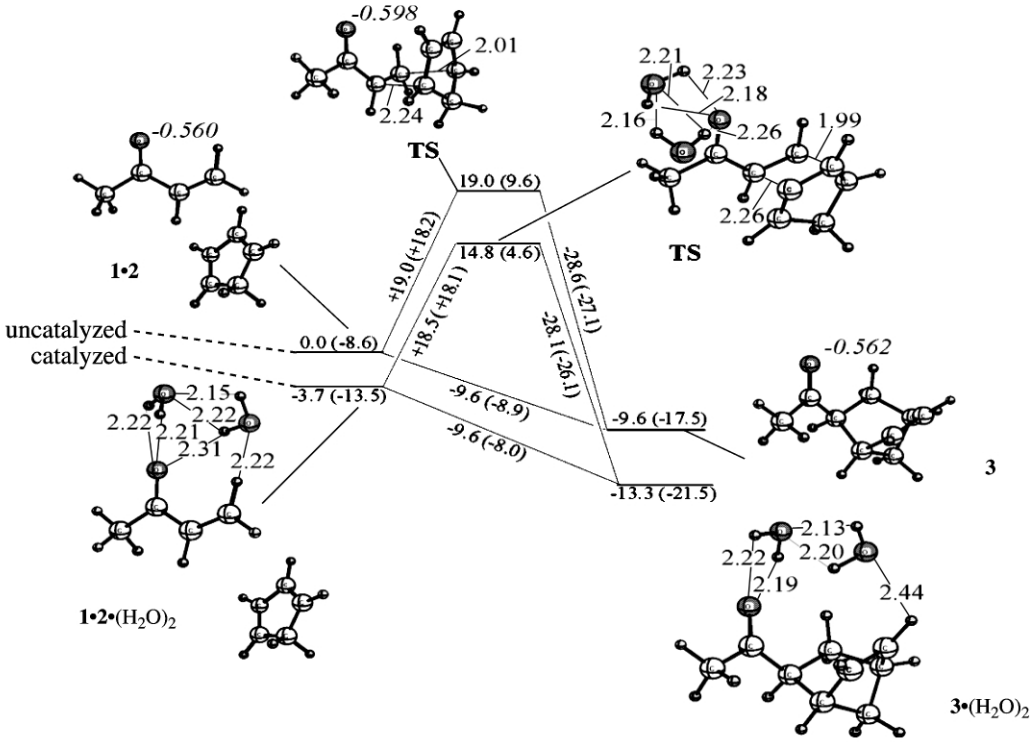



**Fig. 5** The Diels–Alder reaction of **1** and **2** catalyzed by water. The energies at the B3LYP/6-31+G**//AM1 level relative to the starting materials are given in kcal mol$^{-1}$ (the SCRF energies are in parenthesis). Some of the hydrogens were removed for clarity.

*somewhat* rigid, with an emphasis on *somewhat* because this aspect apparently has been overemphasized in the past.[48]

b) The binding interactions must not be excessively large as is the case for traditional Lewis acids because this will inevitably lead to product inhibition.

c) Finally, the catalysts should be water-compatible or even catalytically active in water; we should be reminded that many of these types of reactions, and also Nature's enzymatic arsenal are most active in water.[10]

Utilizing hydrogen bonds and hydrophobic interactions in the design of new catalyst types is not only rewarding from a synthetic as well as environmental point of view, it is an excellent way to understand biocatalysis at the molecular level.

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