Metal-Free, Noncovalent Catalysis of Diels–Alder Reactions by *Neutral* Hydrogen Bond Donors in Organic Solvents and in Water

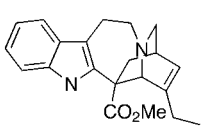
Alexander Wittkopp[a] and Peter R. Schreiner*[a, b]

Abstract: We examined the catalytic activity of substituted thioureas in a series of Diels–Alder reactions and 1,3-dipolar cycloadditions. The kinetic data reveal that the observed accelerations in the relative rates are more dependent on the thiourea substituents than on the reactants or solvent. Although the catalytic effectiveness is the strongest in noncoordinating, nonpolar solvents, such as cyclohexane, it is also present in highly coordinating polar solvents, such as water. In 1,3-dipolar cycloadditions, the thiourea catalysts demonstrate only very moderate selectivity for reactions with inverse electron demand. Our experiments emphasize that both hydrophobic and polar interactions can co-exist, making these catalysts active, even in highly coordinating solvents. This class of catalysts increases the reaction rates and *endo*-selectivities of Diels–Alder reactions, in a similar manner to weak Lewis acids, without concomitant product inhibition.

Keywords: catalysis · Diels–Alder reaction · hydrogen bonds · hydrophobicity

Introduction

Although there are many natural products, for example catharanthine **1** and tabersonine **2**,[1, 2] that may formally



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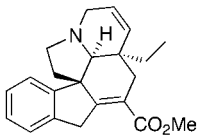

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derive from intramolecular [4+2]-cycloadditions (there are naturally occurring proteins which catalyze Diels–Alder reactions[3, 4]), there is no definitive proof that these reactions actually take place in biosynthesis.[5] Notwithstanding, there are many examples of catalytic Diels–Alder reactions under conditions reminiscent of biological systems, such as RNA-based mixtures of metals,[6, 7] catalytic antibodies,[8–14] encapsulating polysaccharoids,[15–17] and selfassembling molecular capsules.[18–20] While the catalytic activity is usually ascribed to hydrogen bonding, hydrophobicity, and other effects or combinations thereof, the exact type of interaction often remains uncertain. We will demonstrate herein that catalytic activity can be achieved quite simply by means of properly designed hydrogen-bond donors that activate the unsaturated carbonyl moiety of, for instance, Michael-type dienophiles.

Lewis acids, such as $AlCl_3$ and $TiCl_4$ accelerate Diels–Alder reactions dramatically,[21–24] making them progress at reasonable rates, even at low temperatures, while reducing the amount of side products.[25–27] The rate enhancements can be readily understood in terms of FMO theory. Upon coordination to a lone pair located on the Lewis-basic center of the dienophile, the catalytically active Lewis acid withdraws electron density and lowers the LUMO energy of the entire (conjugated) system. This improves the $HOMO_{Diene}$–$LUMO_{Dienophile}$ interaction.[28–31] More modern approaches that combine experiment and theory show that Lewis acids strongly affect the geometries of the transition structures, that is, making them more asynchronous; these reactions are nevertheless considered to be concerted.[32, 33] A comparison of computed and experimental H/D and $^{13}C/^{12}C$ kinetic isotope effects is a particularly effective tool to probe the nature of the experimental transition structure of the parent[34] and catalyzed Diels–Alder reactions.[35–39]

While the effects of hydrogen bonding in protic solvents or active sites may be rationalized similarly, the binding energies are expected to be much smaller. This is not undesirable because strong binding of the starting materials or products does not necessarily lead to rate accelerations. Quite the contrary, binding of the product often leads to *product inhibition* that is often observed in simple Lewis acid catalyst reactions (vide infra);[40] exceptions are known.[41–44] Hence, an ideal binding situation consists of a variety of interactions

[a] Prof. Dr. P. R. Schreiner, A. Wittkopp
Institut für Organische Chemie, Georg-August-Universität Göttingen
Tammannstrasse 2, 37077 Göttingen (Germany)
E-mail: prs@org.chemie.uni-giessen.de

[b] Prof. Dr. P. R. Schreiner
New address: Institute of Organic Chemistry, Justus-Liebig-University,
Heinrich-Buff-Ring 58
35392 Giessen (Germany)

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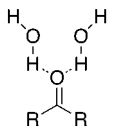
(hydrogen bonding plus hydrophobic effects[45, 46]) which all are relatively small, but complementary if the overall fit to the transition state is to be maximized relative to reactants and products.[8]

Besides the classic monodentate Lewis acids there are also polydentate Lewis acids which often doubly coordinate carbonyl functionalities; one of many examples is the complex of bidentate 1,2-phenylenedimercury derivatives with the carbonyl group of dimethylformamide.[47] Not surprisingly, a similar coordination pattern is found for the complexation of carbonyl compounds with small hydrogen-bond donors, such as water itself. Jorgensen's theoretical rationalization of the experimentally observed acceleration of the Claisen rearrangement in water also suggests that carbonyl groups accept two H bonds (**3**).[48, 49] Experimental confirmation of this theoretical prediction is available through the X-ray structures of the adduct of the biphenylenediol (**4**) with 2,6-dimethylpyran-4-one[50, 51] and the complexes of a *m*-nitrodiaryl urea with several Lewis bases.[52]



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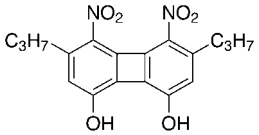

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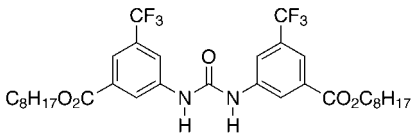
The similarity between Lewis acids and hydrogen-bond donors is also apparent from their ability to accelerate and stereochemically alter organic transformations.[53] Hence, some well-chosen bidentate hydrogen-bond donors increase the reaction rates and change the stereochemical course of some reactions. For instance, 40 mol% of **4** increases the yields of Diels–Alder reactions of α,β-unsaturated carbonyl compounds with cyclopentadiene by a factor of 12.[54] An equimolar amount of the substituted diphenylurea **5** causes up to fivefold rate enhancement in Claisen rearrangements.[55] The same reagent (20 mol%) increases the *endo*/*exo* selectivity in allylations of α-sulfinyl radicals by a factor of 1.5.[56] The catalytic activity of the amidinium ion **6** is comparable to that of mild Lewis acids accelerating some Diels–Alder reactions by a factor of 1.7–450;[57] this is largely attributed to an increased interaction of the highly polarized N–H bonds in the cation.

In a similar manner to these designed bidentate reagents, protic solvents, such as water, also accelerate pericyclic reactions.[58] Although organic and organometallic additives are still active in protic and polar



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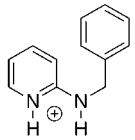

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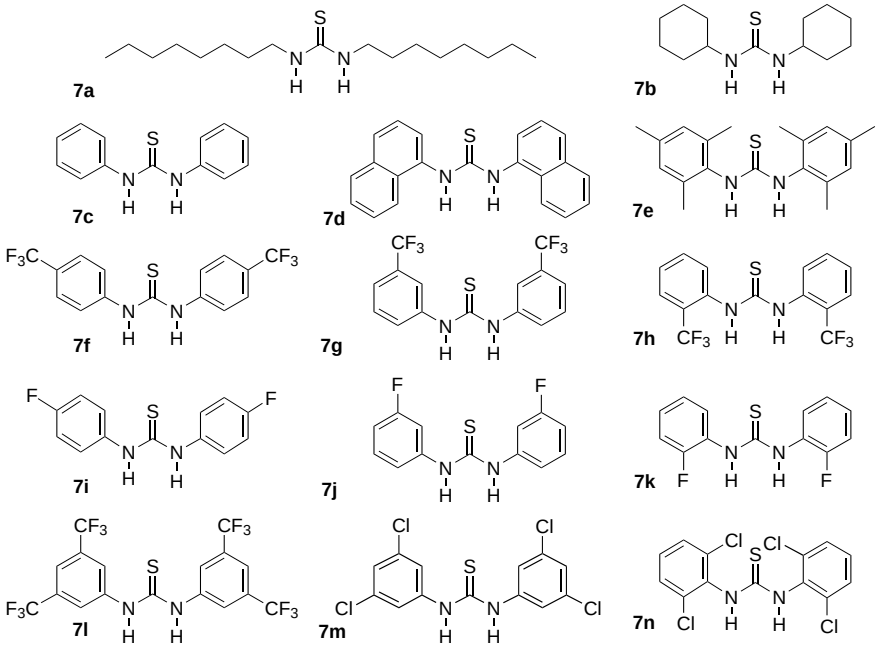
solvents,[59] very often they are not even needed.[60] Again, the primary factors for the frequently remarkable changes in increased reaction rates, stereochemistry, and chemoselectivities in these hydrogen-bonding environments are assigned to hydrogen bonding and hydrophobic effects.[46, 61–64]

We demonstrate in the following that bidentate hydrogen-bond donors, like certain substituted thioureas, catalyze Diels–Alder reactions with a catalytic loading of 1 mol%. As thiourea derivatives are generally more soluble in a wide range of solvents, long alkyl chains as in **5** are dispensable.[55] The hydrogen-bond donor ability of thiourea derivatives to carbonyl groups is expected from the enhanced differences in acidities {pK_a thiourea = 21.0; pK_a urea = 26.9}.[65] Furthermore, the lower electronegativity of sulfur makes self-association (interaction of the N–H group of one molecule with the carbonyl or thiocarbonyl group of another) less favorable. As these model catalysts are easy to synthesize, we investigated the catalytic effectiveness of a series of symmetrically substituted thioureas **7a–n** (Scheme 1). Several 1,3-disubstituted alkyl, cycloalkyl, and phenyl thioureas were tested to screen their catalytic abilities. Since different substituents with possibly opposing effects would unnecessarily cloud our analysis, we only utilized symmetrical thioureas. We also prepared two alkyl derivatives with *n*-octyl (**7a**) and cyclohexyl groups (**7b**) for comparison.

To be systematic, we examined aniline derivatives with electron-donating and electron-withdrawing groups in various



Scheme 1. The symmetrically substituted thioureas used in the present work.

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ring positions. Our expectation was that noncoordinating electron-withdrawing groups (e.g., CF_3) in the *meta* positions of the ring would enhance the hydrogen bonding ability of the N–H bonds. Such electron-withdrawing substituents are the trifluoromethyl group (monosubstituted in *para*, *meta*, and *ortho* positions; **7f–h**) and the fluoro group (also monosubstituted in *para*, *meta*, and *ortho* positions; **7i–k**). To determine the effect of double substitutions on the catalyst quality we also examined thioureas derived from the respective aniline derivatives (**7l–n**). It is noteworthy that the hydrogen-bonding properties of ureas play an important role in their functions as herbicides, solubilizers, inclusion compounds, nonlinear optical materials,[66] and as HIV-protease inhibitors.[67]

Results and Discussion

Catalyst evaluation: To screen catalyst efficiencies, we carried out a series of Diels–Alder reactions of cyclopentadiene with several α,β-unsaturated carbonyl compounds catalyzed by thiourea derivatives (**7a–n**, 1 mol% in all experiments) and without an additive in deuterated chloroform. Although chloroform is an hydrogen-bond donor and is known to accelerate Diels–Alder reactions[68] (compared to reactions in nonpolar, non-coordinating solvents, vide infra) we utilized it in our reactions because it dissolves a wide range of organic compounds. Furthermore, its hydrogen-bond donor abilities are rather poor so that its rate-accelerating effects should easily be overcome by those of the catalyst. We also carried out reactions in cyclohexane and water to unveil solvent effects and to separate them from the effectiveness of the catalyst. With a 10-fold excess of cyclopentadiene, all reactions were strictly pseudo-first-order and the relative rate constants k_{rel} were determined by least-error square fits of the kinetic data. While k_{rel} strongly depends on the choice of catalyst, the reaction order is nearly constant over time (Figure 1), indicating the absence of product inhibition.

Most thioureas under investigation show catalytic behavior and increase the rate of product formation significantly, even at a catalytic loading of only 1 mol%. For instance, adding 1 mol% of catalyst **7g** increases the reaction rate by a factor

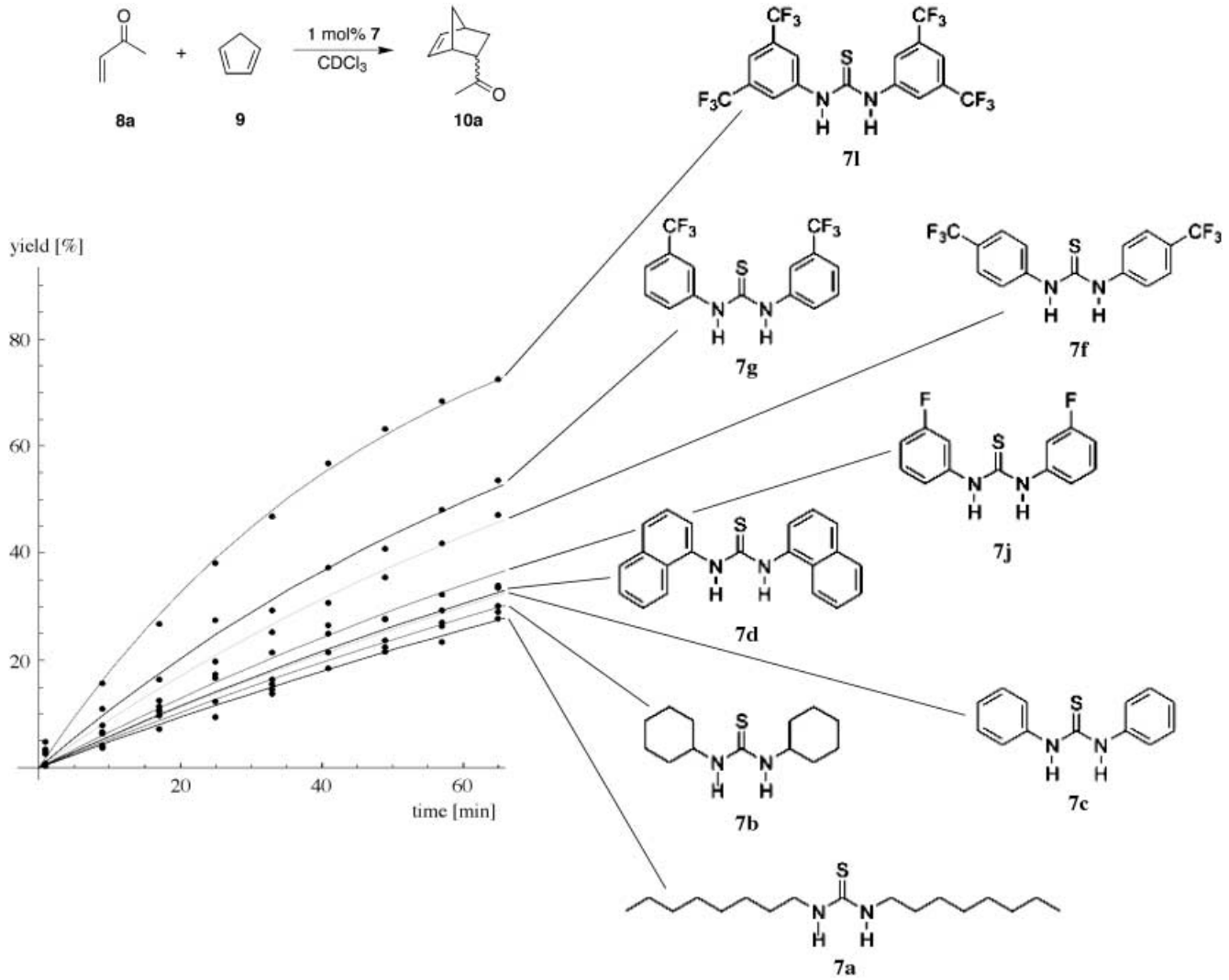

Figure 1. Kinetic data of the Diels–Alder reaction of methyl vinyl ketone and cyclopentadiene catalyzed by the thiourea derivatives **7**. The curves result from fits of least-error square fits.

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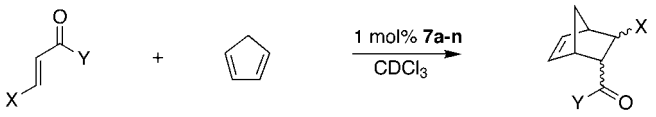
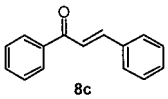
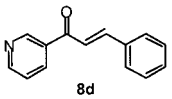
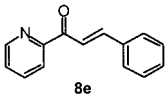
Table 1. Relative rate constants k_{rel} of the reaction of cyclopentadiene (**9**, 10-fold excess) with the dienophiles **8a–e**.



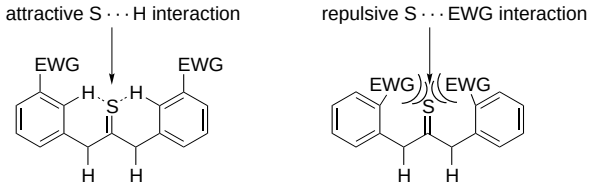
8a–e **9** **10a–e**

Entry	Dienophile	7													
		a	**b**	**c**	**d**	**e**	**f**	**g**	**h**	**i**	**j**	**k**	**l**	**m**	**n**
1	 **8a**	1.0	1.2	1.4	1.4	1.3	2.4	2.5	1.1	2.9	1.4	1.2	4.8	3.3	1.0
2	 **8b**	1.2	1.0	1.1	1.3	1.1	1.2	2.4	1.3	1.7	1.6	1.1	4.3	2.7	1.1
3	 **8c**	0.9	1.1	1.1	1.2	1.2	1.3	3.1	1.2	3.1	3.3	1.0	5.1	2.7	1.0
4	 **8d**	1.0	1.3	1.3	1.5	1.2	1.6	2.2	1.3	1.9	2.0	1.4	5.3	2.1	1.1
5	 **8e**	1.1	1.2	1.5	1.4	1.2	1.9	5.9	1.1	5.2	4.1	1.7	**8.2**	3.5	4.0

of ≈6 (Table 1, entry 5). Furthermore, product inhibition seems to be very minor because the activity is still present even after 80% conversion. The highly dynamic interactions between the catalysts, starting materials, and products apparently make the catalysts less susceptible to product inhibition.

As expected, the choice of catalyst is crucial. While the alkyl-substituted thioureas (**7a** and **7b**) and 1,3-diphenylthiourea (**7c**) only cause minimal rate accelerations, the accelerating effects of the fluorophenyl-substituted thiourea (**7j**) and especially the trifluoro-substituted (**7f–l**) thioureas are appreciable.

Since the complexation between thioureas and carbonyl compounds is modestly strong (≈7 kcal mol^{-1} at room temperature in dichloromethane)[53, 69] the complexation constants are likely to be dominated by entropic effects that may surpass the binding exothermicities. This also implies that the strength of the interaction depends on the rigidity of the catalyst. Thus, the poor performance of **7a** and **7b** is entropically unfavorable since the floppy alkyl substituents of the free thiourea derivatives have to be ordered for proper interaction of the catalyst with the dienophile. A similar argument applies to the rotation of the aryl groups in **7c** and **7d**. In uncomplexed **7c** or **7d**, the rotational barrier is small (according to B3LYP/6-31G* computations the barrier of **7c** is only 1.5 kcal mol^{-1}, while the barrier of rotation in **7l** is 3.4 kcal mol^{-1})[70] resulting in entropy loss upon binding and hence leading to a negligible catalytic effectiveness. For the same reason, all *ortho*-substituted phenylthioureas **7e**, **h**, **k**, **n** are also less active. In the case of the thioureas derived from *meta*- and *para*-substituted anilines, **7f**, **g**, **i**, **j**, **l**, **m**, the hydrogen atoms in the *ortho* position are more positively polarized because of the electron-withdrawing groups (EWGs). The small hydrogen-bond donor ability of these C–H bonds leads to internal interactions between the Lewis-basic sulfur and the *ortho* hydrogen atoms which hinder the rotation of the phenyl groups (Scheme 2).[70]



Scheme 2. The interactions influencing the rotation of the phenyl groups.

In summary, thiourea derivatives with rigid electron-withdrawing aromatic substituents are the most effective H-bonding catalysts for Diels–Alder reactions considered in the present study. The electron-withdrawing substituents in *meta*- or *para*- positions aid in reducing the flexibility of the catalyst, thus minimizing the entropic penalty upon complexation. The accelerating effect can even be magnified by disubstituted electron-poor phenyl groups, making **7l** and **7m** some of the more efficient catalysts in this series.

These new types of catalysts are also active for other Diels–Alder reactions with α,β-unsaturated carbonyl compounds (Table 1). The relative effectiveness does not depend on the reaction, that is, the relative catalyst efficiencies are the same in different reactions: **7g**, **7l**, and **7m** are consistently the best catalysts as they increase the relative rates by factors of 3–8;

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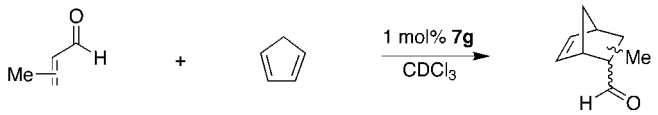
dienophile **8e** may be considered to be special case as it could form a doubly hydrogen-bonded complex.[71]

In a separate series of experiments we examined the changes of the *exo*/*endo* selectivities in reactions of two α,β-unsaturated compounds with cyclopentadiene (Table 2). Metallic Lewis acids generally increase the selectivity of Diels–Alder reactions mostly in favor of the *endo* product.[72] For instance, $AlCl_3 \cdot OEt_2$ improves the *endo* selectivity of the reaction of cyclopentadiene and methyl acrylate from 82% to 98%.[73] Since the analysis of the *endo*/*exo* ratio by ^{1}H NMR techniques is simplified when aldehydes instead of ketones are used, we chose crotonaldehyde (**8f**; *endo* selectivity, entry 1, Table 2) and methacrolein (**8g**; *exo* selectivity, entry 2, Table 2) as the dienophiles.

In this set of reactions, thiourea **7g** also reveals its similarity with mild Lewis acids.[53] In the case of crotonaldehyde, the yield obtained after 20 h is increased by a factor of 1.5 and the *endo* selectivity increases from 65% to 77%. For methacrolein we found a 2.1-fold yield increase (also after 20 h) of the uncatalyzed reaction while the *exo* selectivity changed from 82% to 92%.

Table 2. Yields and selectivities (after 20 h) of Diels–Alder reactions between cyclopentadiene (**9**, 10-fold excess, 40 °C) and α,β-unsaturated aldehydes with and without 20 mol% **7g**. Values in parentheses are from references [74, 75].



8f,g **9** **10f,g**

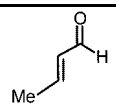
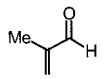
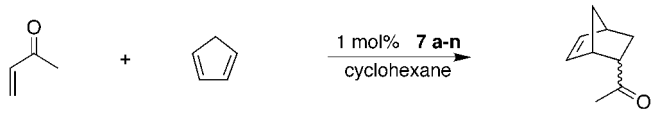
Entry	Dienophile	Yield without cat. [%]	Yield with cat. [%]	*endo*:*exo* without cat.	*endo*:*exo* with cat.
1	 **8f**	16	24	65:35 (62:38)	77:23
2	 **8g**	31	66	18:82 (17:83)	8:92

Table 3. Relative rate constants k_{rel} of the reaction of cyclopentadiene (**9**) with **8a**.



8a **9** **10a**

	7												
a	**b**	**c**	**d**	**e**	**f**	**g**	**h**	**i**	**j**	**k**	**l**	**m**	**n**
1.1	1.8	1.9	2.0	1.8	3.7	3.9	1.3	3.3	2.0	1.4	**8.8**	5.1	1.5

Effect of solvent: As chloroform itself is a weak hydrogen-bond donor capable of accelerating [4+2] cycloadditions to some degree, we carried out a selected set of Diels–Alder reactions of methyl vinyl ketone and cyclopentadiene with **7a–n** in cyclohexane. This solvent is expected to have negligible interactions with the solutes, allowing direct observation of the rate enhancements by the respective catalyst (Table 3). As a consequence, the catalysts show the same order of activity while the increases in the reaction rates are even higher (with k_{rel} up to 9, for **7l**).

While strong Lewis acids often cannot be used in protic or highly polar solvents because of hydrolysis or strong solvation that completely deactivates the catalysts (again, exceptions are known[71, 76, 77]),[78–83] and while only rather mild Lewis acids with metal centers, such as $[Yb(OTf)_3]$, are active in such solvents,[83–86] the much lowered acceptor strength of **7** should make these catalysts less sensitive to competitive aqueous solvation. This was confirmed by the reaction of cyclopentadiene (**9**) and methyl vinyl ketone (**8a**) in cyclohexane, chloroform, and *water* (Figure 2, Table 4). This reaction is particularly suitable since it is easily monitored by NMR spectroscopy (the product ^{1}H NMR resonance signals are well separated from those of the starting materials)

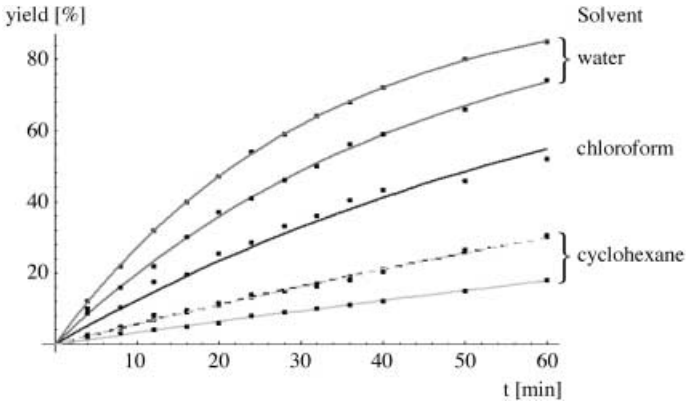


Figure 2. Product formation over time ([%], ^{1}H NMR) in the reaction of **8a** with **9** in three solvents without and with 1 mol% catalyst **7g**. The steeper slopes refer to the catalyzed reaction. The data are fitted on the basis of a first-order reaction (see the Experimental Section).

Table 4. Product yields in three solvents with and without catalyst **7g** in the reaction of **8a** with **9**.

Solvent	Catalyst [mol%]	Yield after 1 h [%][a]
cyclohexane	–	18
	1	42
chloroform	–	31
	1	52
	40	65
water (incl. 10 vol% *t*BuOH)	–	74
	1	85

[a] ±1%, determined by ^{1}H NMR spectroscopy.

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and because of its reaction rate, which is fast enough to obtain the data within a reasonable timeframe and slow enough to be observable on the NMR time scale.

Figure 2 demonstrates that in cyclohexane, chloroform, and water (with 10% *tert*-butyl alcohol to solubilize all reactants[87]) the reaction orders were constant and of pseudo-first order. While catalyst **7g** is active in all chosen solvents, it is particularly striking that acceleration is also observed in *water*, even in catalyst concentrations as low as 1 mol%! Protic solvents, for example alcohols, generally accelerate Diels–Alder reactions[88] by H-bonding and by reducing the HOMO–LUMO gap of the reactants. In water, however, not only the polarity of the solvent but also the *hydrophobicities* of the solutes are important.[87–91] This rather complex property is governed by the limited ability of water to dissolve nonpolar molecules and is considered to be important in enzyme–substrate interactions,[10] the aggregation of amphiphilic molecules into supramolecular structures (e.g., micelles and vesicles),[92] molecular recognition phenomena, and surface forces.[93] It causes nonpolar molecules or parts thereof to agglomerate to small capsules in aqueous media.[63]

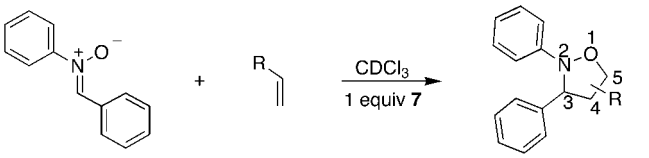
Metallic Lewis acids, on the other hand, are rather polar and, if not hydrolyzed, are often highly solvated in aqueous media leading to a reduction of their catalytic effectiveness. Hence, a possible explanation for our findings is that the hydrophobic organic molecules are forced together in water that interacts better with itself than with the solute. This effect is cumulative to the TS-stabilizing polar interactions of water with the transition state. These conclusions compare well with a very recent computational study of the solvent effects on the Diels–Alder reaction of butadiene with acrolein.[46]

The authors found that the microsolvation effect of explicit water molecules induces a polarization and hence energy lowering of the transition structure. In the spirit of the Jorgensen model (vide supra), our catalysts take the place of the 2–3 required water molecules. The aforementioned computational study also showed that this hydrogen-bonding microsolvation accounts for approximately one-half of the observed catalytic effect. The other half stems from increased hydrophobic interactions which are maximized in water as the solvent around both the reactants and the catalysts in our case. The explicit hydrogen bonding is necessary to induce charge polarization of the transition structure and to allow enforced hydrophobic interactions. The *endo*/*exo* selectivity is equally influenced by both hydrogen bonding and bulk phase effects.[46] The present study, therefore, is a welcome confirmation of the computational analysis and emphasizes the possibility that both effects, polarization and hydrophobicity, can indeed be complementary rather than competitive.

1,3-Dipolar cycloadditions with normal and inverse electron demand: To verify the hypothesis that the interaction between the thiourea and the carbonyl groups causes the observed accelerations, we examined the catalytic activity of **7f–l** in 1,3-dipolar cycloadditions of *N*-benzylideneaniline *N*-oxide (nitrone **11**) with dipolarophiles. In 1,3-dipolar cycloadditions with normal electron demand (e.g., between a nitrone and α,β-unsaturated carbonyl compounds), the most important FMO interaction is the overlap of the $HOMO_{nitrone}$ with the $LUMO_{dipolarophile}$.[94] Complexation of the most Lewis-basic site, the nitrone oxygen, would lower the energy of the $HOMO_{nitrone}$ and hence *decelerate* the reaction. On the other hand, complexation of the nitrone in a 1,3-dipolar cycloaddition with *inverse* electron demand (e.g., between a nitrone and a α,β-unsaturated ether where the $LUMO_{nitrone}$ is interacting with the $HOMO_{dipolarophile}$) would reduce the HOMO–LUMO gap and thus *accelerate* the reaction. Hence, if our assumption that hydrogen-donor complexation is mainly responsible for the observed thiourea catalysis is correct, 1,3-dipolar cycloadditions with *inverse* electron demand should be accelerated. To test this hypothesis, we examined the reactions of **11** with **8a** and with isopropyl vinyl ether (**12**).

While addition of an equimolar amount of any of our thiourea derivatives does not have an accelerating effect on the 1,3-DC with normal electron demand (**8a**, Table 5) or may even be considered decelerating, the catalysts are very modestly effective in the reaction with inverse electron demand (**12**, Table 5). Again, thiourea **7l** is one of the more efficient additives; after 10 h, the yield is nearly doubled compared to the uncatalyzed reaction.

Table 5. The yield ratio of the catalyzed and the uncatalyzed 1,3-dipolar cycloadditions of above reactants; $t = 20$ h, $T = 60\,^{\circ}C$, 1 equiv catalyst, 10 equiv dipolarophile.



11 **8a** : R = C(O)CH$_3$, **12** : R = O*i*Pr → **13a** : R = 4-C(O)CH$_3$, **13b** : R = 5-O*i*Pr

Dipolarophile	7						
	f	**g**	**h**	**i**	**j**	**k**	**l**
8a	1.0	0.9	0.9	1.0	1.0	1.1	**0.8**
12	1.6	1.5	1.0	1.2	1.4	1.0	**1.8**

The observation that our catalysts do accelerate the 1,3-dipolar cycloaddition with *inverse* but not the one with normal electron demand, supports our proposition that the catalysts operate by hydrogen-bonding to the most Lewis-basic groups and reducing the HOMO–LUMO gap in analogy to mild Lewis acids.

Finally, we also probed catalysts with only one N–H bond donor (the *N*-monomethylated forms of **7g** and **7l** and found them virtually ineffective. This is supported by the clamplike binding motif (i.e., Jorgensen's water model) found for these types of catalysts when interacting with carbonyl groups.[53]

Conclusion

Simple, neutral hydrogen-bond donors, such as substituted thioureas, are able to catalyze Diels–Alder reactions and 1,3-dipolar cycloadditions, increasing the reaction rates and stereoselectivities. The relative effectiveness of these catalysts depends more on their substituents than on the reactants or

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solvent. Generally, highly flexible hydrogen-bond donors suffer from entropy loss upon complexation that cannot be overcome by enthalpic effects. In contrast, more rigid thiourea derivatives bind more favorably and, as a consequence of their electron-poor nature, reduce the reaction barriers. As there is a very fine balance including small enthalpic binding, product inhibition is not observed.

Counterintuitively, a highly coordinating solvent, such as water, does *not* override the catalytic effect. While the reactions are accelerated by polar interactions of water, even without a catalyst, addition of only 1 mol% catalyst still leads to detectable rate accelerations, that is, solvent and additive do not necessarily compete, but may operate in a complementary fashion, as predicted computationally.[46]

Hence, we have identified a neutral system that relays its ability to lower the activation energies of a subset of Diels–Alder reactions through specific hydrogen bonds.[53] Finally, this allows the bold question as to whether the "hunt" for a "Diels–Alder-ase" is still meaningful.[5]

Experimental Section

Materials: All thiourea derivatives,[95] *N*-benzylidene-aniline *N*-oxide,[96, 97] 1,3-diphenyl-propenone,[98] 3-phenyl-1-pyridin-2-yl-propenone,[99] and 3-phenyl-1-pyridin-3-yl-propenone[100] were synthesized following the procedures reported in the literature. Methyl vinyl ketone (Fluka), isopropyl vinyl ether (Acros), methacrolein (Acros), and crotonaldehyde (Acros) were distilled immediately before use. Cyclopentadiene was prepared from its dimer (Aldrich) by thermal retro-Diels–Alder reaction immediately before use. All solvents used were of the highest purity available. Deuterated chloroform was stored over sodium bicarbonate.

Kinetics: All NMR measurements were recorded on a Bruker Aspect 300 NMR spectrometer. The Diels–Alder reactions were carried out in a 5-mm standard NMR tube containing 0.5 mL of a solution of 0.1M dienophile, 1.0M **9**, and the respective amount of catalyst (in the case of ketone dienophiles **8a–e** 1 mol%, in the case of aldehyde dienophiles **8f**,**g** 20 mol%) in the chosen solvent. Since the solubility of **9** and the thioureas in water is very low, 0.1 equiv *tert*-butyl alcohol were used as solubilizers for all reactions in water (also in those without catalyst for proper comparison). The Diels–Alder reactions of **8a**,**b** were carried out at 20°C and were recorded over 2 h. All other Diels–Alder reactions were carried out at 40°C and recorded over 40 h. Pseudo-first-order rate constants were calculated with a fitting program. The 1,3-dipolar cycloaddition reactions were also carried out in a 5-mm standard NMR tube containing 0.5 mL of a solution of 0.1M **11**, 1.0M dipolarophile, and 0.1M catalyst in deuterated chloroform at 60°C and analyzed after 20 h. All reactions were repeated and the results were averaged.

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