A Systematic Study of Ligand Effects on a Lewis-Acid-Catalyzed Diels−Alder Reaction in Water. Water-Enhanced Enantioselectivity

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Abstract: The influence of a series of diamine ligands and α-amino acid ligands on the rate and enantioselectivity of the Ni^{2+}- and Cu^{2+}-catalyzed Diels−Alder reaction between 3-phenyl-1-(2-pyridyl)-2-propen-1-ones and cyclopentadiene in water has been investigated. Equilibrium constants and enthalpies and entropies for binding of the dienophile to the catalyst−ligand complex as well as rate constants, activation enthalpies, and entropies for the subsequent reaction with the diene have been determined using UV−vis spectroscopy. Ligand-accelerated catalysis is observed for several aromatic α-amino acid ligands. This is likely to be a consequence of arene−arene interaction between the aromatic ring of the α-amino acid ligand and the pyridine ring of the dienophile and for which quantitative evidence is provided. The same interaction also induces up to 74% enantioselectivity in the Diels−Alder reaction. This is the first example of enantioselectivity in a Lewis-acid-catalyzed organic reaction in water. Most importantly, water significantly enhances the enantioselectivity.

Introduction

The influence of ligands coordinated to Lewis acid catalysts on the rate and particularly the enantioselectivity of organic reactions is one of the most extensively studied topics in homogeneous catalysis.[1] Unfortunately, the approach is still largely based on trial and error. This is a consequence of the difficulties encountered in establishing the exact catalytic mechanism. This is partly a result of the fact that enantioselective Lewis acid catalysis has, so far, been strictly limited to organic solvents. Particularly in these media, ion pairing and clustering of catalyst and reactants often complicate mechanistic analysis.[2] This problem is significantly reduced when water can be used as the solvent.[3] The use of water has important additional benefits: it is nontoxic, it forms no threat to the environment, and it often facilitates workup procedures and catalyst regeneration.[4]

However, the use of water as a solvent has so far been incompatible with enantioselective Lewis acid catalysis. Even trace amounts of water often exert detrimental effects on enantioselectivity. Only a few documented examples exist where small amounts of water in the reaction mixture are tolerated.[5] In exceptional cases, a few equivalents of water have been reported to induce modest enhancements of the enantioselectivity.[6] To the best of our knowledge, no examples of enantioselective Lewis acid catalysis in pure water have been reported, even though water has been used successfully as a solvent for an increasing number of catalytic reactions.[4]

We envisaged important benefits when water is used as solvent for enantioselective Lewis-acid-catalyzed reactions. For our studies, we have selected the Diels−Alder reaction since the mechanism of Lewis acid catalysis of this process is straightforward and well understood. Moreover, in the absence[7] as well as in the presence[8] of Lewis acid catalysts, the rate of the Diels−Alder reaction can experience a beneficial influence of water.[9] We have recently been able to measure the equilibrium constants and rate constants associated with individual steps of the catalytic cycle of the aqua−metal-ion-catalyzed Diels−

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(2) Only a few quantitative studies have been reported. See, for example: Kitamura, M.; Suga, S.; Oka, H.; Noyori, R. *J. Am. Chem. Soc.* **1998**, *120*, 9800.

(3) This is illustrated by mechanistic studies of the effect of achiral ligands on decarboxylation [(a) Rund, J. V.; Plane, R. A. *J. Am. Chem. Soc.* **1964**, *86*, 367. (b) Hay, R. W.; Leong, K. N. *J. Chem. Soc., Chem. Commun.* **1967**, 800. (c) Rund, J. V.; Claus, K. G. *J. Am. Chem. Soc.* **1967**, *89*, 2256. (d) Rund, J. V.; Claus, K. C. *Inorg. Chem.* **1968**, *7*, 860. (e) Claus, K. G.; Rund, J. V. *Inorg. Chem.* **1969**, *8*, 59. (f) Leong, K. N.; Lister, M. W. *Can. J. Chem.* **1971**, *50*, 1461. (g) Raghavan, N. V.; Leussing, D. L. *J. Am. Chem. Soc.* **1977**, *99*, 2188] and hydrolytic reactions [(h) Hay, R. W.; Morris, P. J. *J. Chem. Soc. A* **1971**, 1524. (i) Angelici, R. J.; Allison, J. W. *Inorg. Chem.* **1971**, *10*, 2238. (j) Hay, R. W.; Morris, P. J. *J. Chem. Soc., Dalton Trans.* **1973**, 56. (k) Nakon, R.; Rechani, P. R.; Angelici, R. J. *J. Am. Chem. Soc.* **1974**, *96*, 2117. (l) Schneider, H.; Rammo, J.; Hettich, R. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1716.].

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(5) (a) Desimoni, G.; Faita, G.; Righetti, P. P. *Tetrahedron Lett.* **1996**, *37*, 3027. (b) Desimoni, G.; Faita, G.; Invernizzi, A. G.; Righetti, P. *Tetrahedron* **1997**, *53*, 7671. (c) Kanemasa, S.; Oderaotoshi, Y.; Sakagushi, S.; Yamamoto, H.; Tanaka, J.; Wada, E.; Curran, D. P. *J. Am. Chem. Soc.* **1998**, *120*, 3074.

(6) Mikami, K.; Kotera, O.; Motoyama, Y.; Sakagushi, H. *Synlett* **1995**, 975.

(7) The beneficial influence of water on the Diels−Alder reaction has already been reported in 1973 (Eggelte, T. A.; de Koning, H.; Huisman, H. O. *Tetrahedron* **1973**, *29*, 2491) and has become generally recognized by the work of Breslow et al. (Rideout, D. C.; Breslow, R. J. *J. Am. Chem. Soc.* **1980**, *102*, 7816). For recent references, see: (a) Otto, S.; Blokzijl, W.; Engberts, J. B. F. N. *J. Org. Chem.* **1994**, *59*, 5372. (b) Engberts, J. B. F. N. *Pure Appl. Chem.* **1995**, *67*, 823. (c) Otto, S. Ph.D. Thesis, University of Groningen, 1998.

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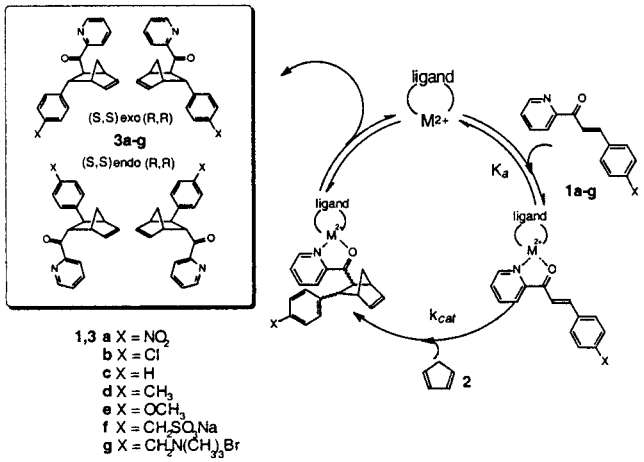
Scheme 1



Alder reaction of substituted dienophiles 3-phenyl-1-(2-pyridyl)-2-propen-1-ones (**1a**−**g**) with cyclopentadiene (**2**) in water.[8a,b]

We have since extended our investigations to the influence of ligands on these steps. Our goals were threefold: (1) to find ligands that induce an acceleration of the Lewis-acid-catalyzed Diels−Alder reaction in water;[10] (2) to find ligands that induce enantioselectivity in this process; and (3) to provide a detailed mechanistic understanding. In this paper, we will demonstrate that these three goals can be reached through a systematic study. *In the course of this study, we report the first example of enantioselective Lewis acid catalysis of an organic reaction in water*.[11] Most significantly, water is observed to increase the enantioselectivity. Strong indications exist that this is a general phenomenon. These results open the way for new applications of water as a solvent for enantioselective reactions.

Results and Discussion

We will describe the effect of ligands on the Lewis-acid-catalyzed Diels−Alder reaction of substituted dienophiles 3-phenyl-1-(2-pyridyl)-2-propen-1-ones (**1a**−**g**) with cyclopentadiene (**2**) in water. The catalytic cycle for this reaction is shown in Scheme 1.[8a,b] The reaction produces four different products: (*R*,*R*)- and (*S*,*S*)-*exo*-**3** as well as (*R*,*R*)- and (*S*,*S*)-*endo*-**3**, enabling assessment of the influence of ligands on the endo−exo ratio[12] as well as on the enantioselectivity. Ligand effects on the overall rate of the Diels−Alder reaction can be separated into influences on the equilibrium constant for binding of the dienophile to the catalyst (K_a) and influences on the rate constant for reaction of the complex with cyclopentadiene (k_{cat}).

Previous studies have demonstrated that Co^{2+}, Ni^{2+}, Cu^{2+}, and Zn^{2+} exhibit pronounced catalytic activity toward the Diels−Alder reaction under investigation.[8a,b] In aqueous solutions, these ions generally form octahedral complexes. Copper(II) ion occupies a special position among these catalysts. Due to the Jahn−Teller effect, coordination to the four equatorial sites is stronger than that to the two remaining axial positions.[13] Consequently, in the absence of special geometrical constraints in the ligands, four-coordinated copper(II) complexes are generally characterized by a square planar geometry. In contrast, there is usually no intrinsic preference for axial over equatorial coordination in Co^{2+}, Ni^{2+}, and Zn^{2+} complexes in aqueous solution. In view of the higher catalytic activity of Ni^{2+} and, particularly, Cu^{2+} ions, our study of the effect of ligands has been focused on catalysis by these two ions.

Two classes of ligands have been examined in detail: diamine ligands and α-amino acid ligands. Both classes are known to form well-defined and stable complexes with transition metal ions in water.[14] The stability constants of all ligand−catalyst complexes reported in this paper are several orders of magnitude higher than those for the catalyst−dienophile complexes, ensuring that the ligands are not displaced by the substrate.

Diamine Ligands. Our choice for diamine ligands was inspired by the beneficial effect that has been reported for aromatic amine ligands in the transition-metal-ion-catalyzed decarboxylation of oxaloacetate and derivatives thereof.[3d,e,g]

Aiming at ligand-accelerated catalysis, we have investigated the effects of a series of aromatic diamines on the rate of the Diels−Alder reaction of **1c** with **2**. The results are summarized in Table 1.

Binding of **1c** to copper(II) ions is invariably hampered by the presence of the diamine ligands. On a simple statistical basis, a reduction of the equilibrium constant can be anticipated, since the ligand can be expected to block coordination sites on the metal ion. For square-planar-coordinated copper(II) ions, this effect will cause bidentate ligands to reduce K_a by 50%. The effects of ethylenediamine and dimethylethylenediamine can be explained on this statistical basis. 2,2′-Bipyridine and 1,10-phenanthroline show a further reduction of the equilibrium constant for binding of the dienophile. This might well be a result of a steric repulsion between the α-pyridine proton of the dienophile and an α-pyridine proton of the ligand (Scheme 2). Note that, in the ternary complex containing the 2-(aminomethyl)pyridine ligand, this interaction can be avoided by positioning the pyridine ring of the dienophile trans with respect to the ligand pyridine ring.

Interestingly, the rate constants for Diels−Alder reactions of the ternary complexes with **2** are remarkably similar. Only with 2,2′-bipyridine and 1,10-phenanthroline as ligands is a significant change in reactivity observed. It might well be that the inability of these complexes to adopt a planar geometry hampers the interaction between the copper ion and the dienophile, resulting in a decrease of the rate constant of the catalyzed Diels−Alder reaction. Similar interactions between Cu(II)-coordinated dienophile and ligand are likely to influence enantioselectivity in Cu(II)−α-amino acid-catalyzed Diels−Alder reactions (vide supra).

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(9) We have recently demonstrated that micelles can even further increase the efficiency of a Lewis-acid-catalyzed Diels−Alder reaction: Otto, S.; Engberts, J. B. F. N.; Kwak, J. C. T. *J. Am. Chem. Soc.* **1998**, *120*, 9517.

(10) Some examples have been reported. See ref 3d,e, and g. For a review on ligand-accelerated catalysis, see: Berrisford, D. J.; Bol, C.; Sharpless, K. B. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1059.

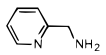
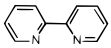
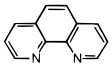
(11) Preliminary communication: Otto, S.; Boccaletti, G.; Engberts, J. B. F. N. *J. Am. Chem. Soc.* **1998**, *120*, 4238.

(12) A preliminary investigation demonstrated that the endo−exo selectivity of the Diels−Alder reaction of **1c** with **2** is not significantly influenced by the presence of ligands: the effects of ethylenediamine, 2,2′-bipyridine, 1,10-phenanthroline, glycine, L-tryptophan, and L-abrine have been studied. The endo−exo ratio observed for the copper(II)-catalyzed reaction in the presence of these ligands never deviated more than 2% from the endo−exo ratio of 93:7 obtained for catalysis by copper aqua ion.[8b]

(13) Martell, A. E.; Hancock, R. D. *Metal Complexes in Aqueous Solutions*; Plenum Press: New York, 1996.

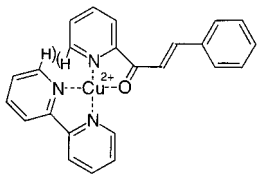
(14) Martell, A. E. *Stability Constants of Metal−Ion Complexes;* Chemical Society: London, 1971.

Table 1. Influence of Diamine Ligands on the Equilibrium Constant for Binding of **1c** to the Ligand−Metal Ion Complex (K_a) and the Second-Order Rate Constant (k_{cat}) for Reaction of the Ternary Complex with Diene **2**[a]

ligand			Cu^{2+}		Ni^{2+}	
structure	name	equiv[b]	K_a (M^{-1})	k_{cat} (M^{-1} s^{-1})	K_a (M^{-1})	k_{cat} (M^{-1} s^{-1})
H_2O			1.16×10^3	2.56	686	9.46×10^{-2}
	ethylenediamine	1	4.58×10^2	2.91	437	9.76×10^{-2}
		2			136	8.73×10^{-2}
	2-(aminomethyl)pyridine	1	3.74×10^2	3.12		
	2,2′-bipyridine	1	1.78×10^2	0.838	519	7.43×10^{-2}
		2			337	1.02×10^{-1}
	1,10-phenanthroline	1	1.78×10^2	0.626	565	8.20×10^{-2}
		2			372	9.03×10^{-2}
	N,N′-dimethylethylenediamine	1	4.12×10^2	2.46	800	9.75×10^{-2}
		2			693	8.19×10^{-2}

[a] All measurements were performed at constant ionic strength (2.00 M using KNO_3 as background electrolyte) and at pH 7−8. [b] Ligand/catalyst ratio.

Scheme 2



The data for Ni^{2+} ions can be explained on the basis of a simple statistical argument. Bidentate ligand reduces the equilibrium constant for binding of the dienophile by one-third if 1 equiv of ligand is added, and by two-thirds for 2 equiv.[15] The rate constant of the Ni^{2+}-catalyzed Diels−Alder reaction is barely sensitive to the presence of ligands.

In sum, significant ligand-accelerated catalysis of the Diels−Alder reaction between **1c** and **2** using the diamine ligands appears not to be feasible. Nevertheless, the study of these diamine ligands has provided us with some important structural details (vide supra).

Effects of α-Amino Acid Ligands on Rate and Equilibrium Constants. The naturally occurring α-amino acids form a class of readily available, strongly coordinating ligands, which exhibit broad structural variations. Moreover, their availability in enantiomerically pure form offers opportunities for enantioselective catalysis. Some derivatives of these compounds have been used successfully as chiral units in enantioselective catalysis in organic solvents.[16]

At neutral, or slightly acidic pH, α-amino acids tend to coordinate to transition metal ions in their deprotonated form, resulting in the formation of a five-membered ring, which is usually flat.[17]

The effects of a series of α-amino acids on the Diels−Alder reaction of **1c** with **2** has been investigated. The results are shown in Table 2. The aliphatic α-amino acids induce a reduction of the equilibrium constant for binding of the dienophile to the copper ion (K_a) by roughly 50%, as anticipated on the basis of statistics. However, when L-phenylalanine is used as ligand, this reduction is significantly less pronounced. For L-tyrosine, L-tryptophan, and derivatives thereof, *the equilibrium constant is even larger than that for binding of the dienophile to the copper aqua ion*. Compared to the bulkiest of the aliphatic α-amino acids, L-leucine ($\Delta G^{\ominus}_{compl} = -15.5$ kJ/mol), L-abrine ($\Delta G^{\ominus}_{compl} = -21.1$ kJ/mol) enhances the affinity of the catalyst for the dienophile by 5.6 kJ/mol.

We contend that a specific interaction between the aromatic system of the α-amino acid ligand and that of the coordinated dienophile (arene−arene interaction[18]) is responsible for the enhanced stability of the ternary complex (Scheme 3). In ternary complexes in aqueous solutions, this type of ligand−ligand interaction is well documented.[19] In the extreme case of the 5-hydroxy-L-tryptophan−Cu^{2+}−1,10-phenanthroline complex, a stability increase of 12.7 kJ/mol was observed when compared to the analogous complexes of nonaromatic α-amino acids.[19k] Crystal structures of complexes of copper(II) with aromatic amine ligands and α-amino acids[19m,o−q] and dipeptides[19n] have been published, demonstrating a stacked arrangement of the aromatic moieties.

(15) Only for N,N′-dimethylethylenediamine is a different behavior encountered. One equivalent of this ligand *raises* K_a above the value for the nickel aqua ion. It is not unlikely that the methyl groups of the ligand hinder coordination of the water molecules in the two remaining equatorial positions of the complex, facilitating their displacement by the dienophile.

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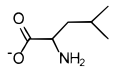
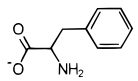
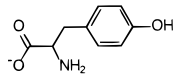
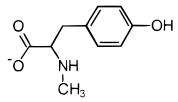
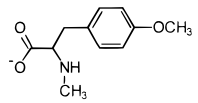
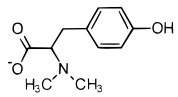
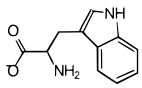
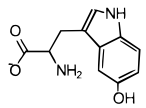
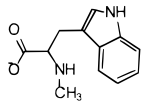
(17) Laurie, S. H. In *Comprehensive Coordination Chemistry*; Wilkinson, G., Gillard, R. D., McCleverty, J. A., Eds.; Pergamon Press: Oxford, 1997; p 739.

(18) The term "arene−arene interaction" is used to denote the noncovalent interactions between two aromatic systems, without specifying their nature.

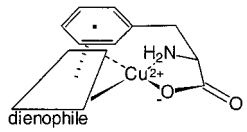
(19) (a) Naumann, C. F.; Sigel, H. *J. Am. Chem. Soc.* **1974**, *96*, 2750. (b) Granot, J. *J. Am. Chem. Soc.* **1978**, *100*, 6745. (c) Sigel, H.; Scheller, K. H.; Milburn, R. M. *Inorg. Chem.* **1984**, *23*, 1933. For ternary complexes containing α-amino acids, see: (d) Arena, G.; Cali, R.; Cucinotta, V.; Musumeci, S.; Rizzarelli, E.; Sammartano, S. *J. Chem. Soc., Dalton Trans.* **1983**, 1271. (e) Sigel, H.; Fischer, B. E.; Farkas, E. *Inorg. Chem.* **1983**, *22*, 925. (f) Malini-Balakrishnan, R.; Scheller, K. H.; Haring, U. K.; Tribolet, R.; Sigel, H. *Inorg. Chem.* **1985**, *24*, 2067. (g) Fischer, B. E.; Sigel, H. *J. Am. Chem. Soc.* **1980**, *102*, 2998. (h) Sigel, H.; Schneller, K. H.; Haring, U. K.; Malini-Balakrishnan, R. *Inorg. Chim. Acta* **1983**, *79*, 277. (i) Dubler, E.; Haring, U. K.; Scheller, K. H.; Baltzer, P.; Sigel, H. *Inorg. Chem.* **1984**, *23*, 3785. (j) Sigel, H.; Tribolet, R.; Scheller, K. H. *Inorg. Chim. Acta* **1985**, *100*, 151. (k) Yamauchi, O.; Odani, A. *J. Am. Chem. Soc.* **1985**, *107*, 5938. (l) Odani, A.; Deguchi, S.; Yamauchi, O. *Inorg. Chem.* **1986**, *25*, 62. (m) Masuda, H.; Sugimori, T.; Odani, A.; Yamauchi, O. *Inorg. Chim. Acta* **1991**, *180*, 73. (n) Sugimori, T.; Shibakawa, K.; Masuda, H.; Odani, A.; Yamauchi, O. *Inorg. Chem.* **1993**, *32*, 4951. (o) Sugimori, T.; Masuda, H.; Ohata, N.; Koiwai, K.; Odani, A.; Yamauchi, O. *Inorg. Chem.* **1997**, *36*, 576. (p) Aoki, K.; Yamazaki, H. *J. Chem. Soc., Dalton Trans.* **1987**, 2017. (q) Sugimori, T.; Masuda, H.; Yamauchi, O. *Bull. Chem. Soc. Jpn.* **1994**, *67*, 131. (r) Kim, S.; Martin, B. *J. Am. Chem. Soc.* **1984**, *106*, 1707.

Table 2. Influence of α-Amino Acid Ligands on the Equilibrium Constant for Binding of **1c** to the Ligand−Cu^{2+} Complex (K_a) and the Second-Order Rate Constant (k_{cat}) for Reaction of This Ternary Complex with Diene **2**[a] and the Enantioselectivity of This Reaction in Water[b]

ligand				
structure	name	K_a (M^{-1})	k_{cat} (M^{-1} s^{-1})	ee[c] (%)
H_2O		1.16×10^3	2.56	−
	glycine	6.29×10^2	1.89	−
	L-valine	5.71×10^2	1.90	3[d]
	L-leucine	5.14×10^2	2.01	3[d]
	L-phenylalanine	8.66×10^2	2.01	17
	L-tyrosine	1.40×10^3	1.68	36
	*N*-methyl-L-tyrosine	2.45×10^3	2.07	74
	*N*-methyl-*p*-methoxy-L-phenylalanine	2.04×10^3	2.83	67
	*N*,*N*-dimethyl-L-tyrosine	1.66×10^3	2.92	73
	L-tryptophan	3.02×10^3	1.44	33
	5-hydroxy-L-tryptophan	4.89×10^3	1.15	29
	L-abrine[e]	5.05×10^3	1.47	74

[a] All measurements were performed at constant ionic strength (2.00 M using KNO_3 as background electrolyte) and at pH 4.6−5.2. [b] 10 mol % of $Cu(NO_3)_2$; 17.5 mol % of ligand; conditions as outlined in the Experimental Section. [c] Only the results for the major (>90%) endo isomer of the Diels−Alder adduct are shown. [d] 250 mol % of catalyst was used. [e] N^{α}-Methyl-L-tryptophan.

Scheme 3



Despite the extensive studies on the effects of the arene−arene interactions on the *stability* of ternary complexes, their influence on the *kinetics* of a chemical transformation have not been investigated. Particularly, the chiral nature of the α-amino acid ligands offers possibilities for enantioselective catalysis. The Lewis-acid-catalyzed Diels−Alder reaction between **1** and **2** allows for such kinetic and stereochemical investigations.

From the data in Table 2, it is apparent that almost all α-amino acid ligands induce a modest deceleration of the Diels−Alder reaction of **1c** with **2**. In general, these ligands have a larger influence on the rate of the reaction than most of the diamines in Table 1. Most likely, this difference can be ascribed to the fact that the α-amino acids coordinate in their deprotonated form, whereas the diamine ligands are neutral. The negatively charged α-amino acid oxygen in the coordination sphere of the catalyst reduces its Lewis acidity. Fortunately, this effect is modest, and for *N*-methyl-*p*-methoxy-L-phenylalanine and *N*,*N*-dimethyl-L-tyrosine it is even absent. Apparently, the arene−arene interactions do not necessarily lead to a reduction of the rate constant of the Diels−Alder reaction, even though the presence of the aromatic ring of the ligand in the vicinity of the reacting double bond of the dienophile most likely hinders approach of the diene.

Table 3. Gibbs Energies, Enthalpies, and Entropies of Activation of the Diels−Alder Reaction of Several Copper(Ligand)(**1c**) Complexes with **2** in Water at 25 °C at pH 5−6 and Ionic Strength of 6.00 mM[a]

ligand	$\Delta^{\ddagger}G^{\ominus}$ (kJ/mol)	$\Delta^{\ddagger}H^{\ominus}$ (kJ/mol)	$T\Delta^{\ddagger}S^{\ominus}$ (kJ/mol)
water	72.1 ± 0.1	50.3 ± 1.2	−21.8 ± 1.1
glycine	72.7 ± 0.1	32.7 ± 1.9	−40.0 ± 1.9
L-tryptophan	73.2 ± 0.1	40.4 ± 1.5	−32.8 ± 1.6
L-abrine	72.6 ± 0.1	48.3 ± 1.8	−24.3 ± 1.8

[a] Ionic strengths were adjusted using KNO_3.

From the temperature dependence of the rate constants, we have determined the enthalpy and entropy of activation for the reaction of ternary Cu(ligand)(**1c**) complexes with **2**. The results are shown in Table 3. Almost complete enthalpy−entropy compensation is observed. In general, this behavior is associated

with changes in the hydration of the reactants during the reaction, i.e., changes in hydrogen bonding (an enthalpic effect) with concomitant changes in orientational freedom of the water molecules (an entropic effect). More specifically, the results in Table 3 are likely to reflect the influence of the α-amino acid ligands on the changes in the hydrophobic hydration shells of the reactants during the reaction.[20] In this activation process, parts of these shells are broken down. Usually, this breakdown is accompanied by a dominating gain in entropy. However, when defects (dangling hydrogen bonds) occur in hydrophobic hydration shells, the gain in entropy will be largely replaced by a gain in enthalpy associated with the re-formation of hydrogen bonds. We suggest that the introduction of the glycine ligand, due to its charged character,[21] induces defects in the hydrophobic hydration shell of the reactants. Note that, in the stacked conformation, the L-tryptophan and L-abrine ligands shield the charged centers from interaction with water. Consequently, the hydrophobic hydration shell surrounding the reactants is likely to be less defective in the presence of these ligands than in the presence of glycine. Consequently, the activation enthalpies and entropies resemble more closely those for catalysis by copper aqua ion.

In conclusion, despite the decrease of k_{cat} in the presence of the aromatic α-amino acid ligands, the significant increase of K_a that is induced by these ligands indicates that, under suitable conditions, ligand-accelerated catalysis by aromatic α-amino acids is feasible (vide supra).

Effect of α-Amino Acids on Enantioselectivity. We envisaged that the attractive interaction between the pyridine ring of the dienophile and the aromatic group of the chiral α-amino acid ligands in ternary copper(II) complexes might well lead to shielding of one face of the dienophile to approach by the diene. This prompted us to investigate the effect of these ligands on the enantioselectivity of the copper(II)-catalyzed Diels−Alder reaction of **1** with **2**.

Indeed, it turned out that the Diels−Alder products **3** can be obtained in up to 74% enantiomeric excess (Table 2).[11,22] To the best of our knowledge, these results constitute the first example of enantioselectivity in a chiral Lewis-acid-catalyzed organic transformation in aqueous solution.

Analogous nickel(II)-catalyzed Diels−Alder reactions failed to induce significant enantioselectivity, which is not surprising in view of the large number of conceivable geometries of the ligand−nickel(II)−dienophile complex. Moreover, preliminary studies demonstrated that the arene−arene interaction is less pronounced for ternary nickel(II) complexes than for the corresponding copper(II) complexes.[23]

Despite the availability of relevant mechanistic parameters in the form of the rate constants and binding constants given in Table 2, rationalization of the observed enantioselectivities is still rather complicated, and therefore some additional information has been gathered.

First, the pH dependence of the enantioselectivity of the reaction between **1c** and **2** catalyzed by the copper(L-tryptophan) complex has been studied. Above pH 5, the enantioselectivity reaches a plateau value, indicating that it is the deprotonated form of the α-amino acid ligand that induces enantioselectivity. The diminished enantioselectivities observed at lower pH most likely result from protonation of the carboxylate group of the α-amino acid, which decreases the affinity of this ligand for the copper(II) ion and consequently favors catalysis by the achiral copper aqua ion. Furthermore, protonation of the pyridine ring of **1c** will result in Brønsted-acid catalysis[8b] of the reaction, leading to a racemic product mixture.

Second, the catalyst:dienophile ratio has been varied from 8 mM:1 mM to 1 mM:10 mM. This change did not significantly alter the enantioselectivity of the copper(L-tryptophan)-catalyzed reaction, despite the fact that the former solution is homogeneous and the latter is heterogeneous. This is a strong indication that, as anticipated, the Diels−Alder reaction proceeds through the ternary dienophile−copper(II)−ligand complex and also that the extent of displacement of the ligand by the dienophile is insignificant.

Likewise, the influence of the ligand:catalyst ratio on the enantioselectivity has been investigated. With 0.5 equiv of ligand, we obtained 78% of the major versus 22% of the minor enantiomer. Under these conditions, enantioselectivity is already close to the limiting value at high ligand:catalyst ratios (87% of the major enantiomer). Note that, at ligand:catalyst ratios larger than 1, the high stability constant of the Cu(II)−ligand complex ensures that virtually no copper aqua ion is present in solution.

The strongly nonlinear dependence of ee on the ligand:catalyst ratio is not unusual in enantioselective catalysis.[24] The results demonstrate that, even when 50% of the copper catalyst is present as the achiral aqua ion, still most of the reaction (76%) is mediated by the chiral copper(L-abrine) complex. Hence, as anticipated from the rate and equilibrium data in Table 2, *ligand-accelerated catalysis is taking place*.[25]

Additional mechanistic information has been obtained through a study of the influence of structural variation of the aromatic α-amino acid ligands on the rate and equilibrium data and the enantioselectivity (Table 2). Noteworthy in this respect is the large influence of N-methylation on the enantioselectivity. Going from L-tyrosine to *N*-methyl-L-tyrosine or from L-tryptophan to *N*-methyl-L-tryptophan, the enantiomeric excess is increased dramatically. The large effect of the methyl substituent can be rationalized by considering the four different possible geometries that can be adopted by the ternary copper(α-amino acid ligand)-(dienophile) complex (Scheme 4). These geometries differ with respect to the coordination environment around the central copper ion (cis or trans) and the conformation of the α,β-unsaturated ketone (cisoid or transoid). The cis complexes **4a** and **4c** most likely experience a steric repulsion between the pyridine α-hydrogen atom of the dienophile and the methyl group of the α-amino acid. This repulsion is absent in the trans complexes **4b** and **4d**. Hence, the methyl substituent in the α-amino acid ligand induces a preference for a trans geometry in the ternary complex. Note that we have observed a similar steric repulsion in the ternary copper(2,2′-bipyridine)(**1c**) and copper(1,10-phenanthroline)(**1c**) complexes (vide infra).

(20) Enforced hydrophobic interactions determine, for a large part, the enthalpy and entropy of activation of uncatalyzed Diels−Alder reactions in water. See: Blokzijl, W.; Blandamer, M. J.; Engberts, J. B. F. N. *J. Am. Chem. Soc.* **1991**, *113*, 4241.

(21) The addition of salts has been reported to induce similar changes in enthalpy and entropy of activation of Diels−Alder reactions. See: Hunt, I.; Johnson, C. D. *J. Chem. Soc., Perkin Trans. 2* **1991**, 1051.

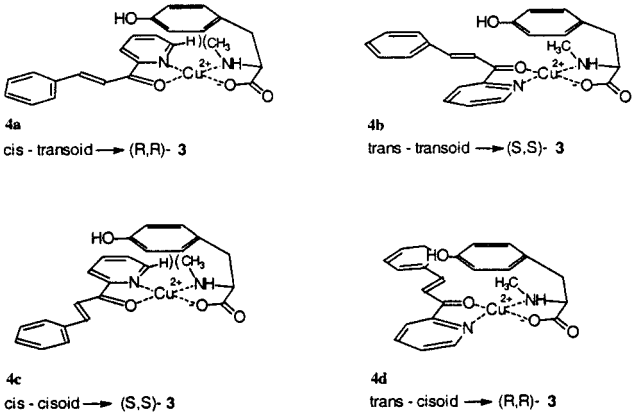
(22) Note that the rate and equilibrium constants have been measured in the presence of background electrolyte (2.00 M ionic strength, using KNO_3), whereas the solutions used for determining the enantioselectivity contained merely catalyst and reacting species. Control experiments have ascertained that enantioselectivity is not significantly affected by the appreciable concentrations of KNO_3.

(23) An equilibrium constant for binding of **1c** to the nickel(II)(L-tryptophan) complex of 805 M^{-1} has been obtained, compared to 530 M^{-1} in the presence of glycine.

(24) See ref 2 and references therein.

(25) As pointed out by a reviewer, the rate and equilibrium constants at 6 mM ionic strength (where k_{cat} and K_a for the Cu(H_2O) and Cu(L-abrine) ions are 0.901 M^{-1} s^{-1}, 573 M^{-1} and 0.671 M^{-1} s^{-1}, 2.44 × 10^3 M^{-1}, respectively) predict 76% of the reaction to be mediated by Cu(L-abrine). This number is in perfect agreement with the 76% calculated from the enantiomeric excess.

Scheme 4



Our interpretation is further supported by literature studies on the crystal structures of copper(II) complexes containing two α-amino acid ligands. For N-unsubstituted α-amino acid ligands, solid complexes have been isolated of both the cis and trans geometry.[17] In contrast, it appears that copper(II) complexes containing two N-alkylated α-amino acid ligands crystallize exclusively in the trans form.[26]

Since there is no indication to assume that the reactivities of the cis complexes exceed those of the trans complexes, we infer that the reaction is mediated mainly by **4b** or **4d**. Note that endo attack of **2** on the lower face of **4b** results in *endo*-(*S*,*S*)-**3c**, whereas the corresponding reaction of **4d** produces *endo*-(*R*,*R*)-**3c**. Hence, upon elucidation of the absolute configuration, the predominant reaction pathway can be identified. Unfortunately, despite extensive effort,[27] we have not been able to clarify this point.

Investigations into the Nature of the Arene−Arene Interaction. In the literature, different types of interactions have been suggested as contributing to the arene−arene interactions. London dispersion forces are likely to be of influence.[28] In water, also hydrophobic interactions may be important.[29] Finally, electrostatic interactions as well as donor−acceptor interactions have been invoked.[30]

In an attempt to identify which of these interactions dominates the arene−arene interactions in the ternary copper(α-amino acid)(dienophile) complexes, we have determined the enthalpy and entropy changes associated with this process. Table 4 compares the changes in Gibbs energy, enthalpy, and entropy upon binding of **1c** to copper aqua ion and complexes of copper with glycine (no arene−arene interactions possible), L-tryptophan (weak arene−arene interactions), and L-abrine (stronger arene−arene interactions).

If hydrophobic interactions were dominating the arene−arene interactions, an entropic driving force would be expected at low ionic strength, gradually becoming more enthalpy-driven with increasing salt concentration.[31] This is not observed. The arene−arene interaction is clearly enthalpy-driven and counteracted by entropy. Moreover, entropies and enthalpies change only weakly upon increasing the ionic strength from 6 mM to 2 M. Hence, hydrophobic interactions are not the major driving force for the arene−arene interactions. The fact that modest enantioselectivities are observed in organic solvents further underlines this conclusion.

An alternative driving force could involve a donor−acceptor interaction. In principle, the electron-poor pyridine ring that is coordinated to the copper cation could act as an electron acceptor in combination with the electron-rich aromatic ring of the α-amino acid. The fact that donating substituents on the α-amino acid increase the efficiency of the arene−arene interaction (Table 2) supports this view. Furthermore, a charge-transfer band is observed between 300 and 400 nm for the complexes that exhibit efficient arene−arene interactions.[32] The latter observation demonstrates that the orbitals of the dienophile and the α-amino acid ligand are sufficiently close for overlap. However, as correctly pointed out by Cozzi et al.,[33] the occurrence of a charge-transfer band in itself cannot be considered as evidence for a donor−acceptor interaction. The charge-transfer band owes its existence to the possibility of forming a charge-separated excited state, which normally contributes little to ground-state stability.

If donor−acceptor interactions were operative, then one would expect that electron donation or withdrawal by substituents on the dienophile affects these interactions. Consequently, one might anticipate an increase of the substituent effect on the equilibrium constant for binding of the dienophile to the copper(ligand) complex in the presence of aromatic α-amino acids, beyond the value that is obtained for binding to the copper aqua ion. However, no indication for such behavior is observed. A plot of the Gibbs energies of complexation of **1a**−**g** to the copper(II)(L-tryptophan) complex versus those for binding to the copper aqua ion is shown in Figure 1. A straight line is obtained with a slope of 1.01 ($r = 0.999$), demonstrating that the contribution of arene−arene interaction in stabilizing the ternary **1**(copper)(L-tryptophan) complexes is constant (2.42 ± 0.07 kJ/mol), irrespective of the substituent on **1**. Evidently, the Hammett ρ-value describing the substituent effect on binding of the dienophile to the copper(L-tryptophan) complex (−0.52) is, within experimental error, equal to that for binding to the copper aqua ion (−0.51). These observations demonstrate that substituents on the phenyl ring of the dienophile do not have a significant influence on the magnitude of the arene−arene interaction. Also, the enantioselectivity of the reactions of **1b**[34] and **1g** with **2** catalyzed by copper(L-abrine) in water is, within experimental error, equal to the enantioselectivity observed for **1c**.

From the absence of a significant substituent effect on the arene−arene interaction as well as on the enantioselectivity, we

(26) Sabolovic, J.; Rasmussen, K. *Inorg. Chem.* **1995**, *34*, 1221.

(27) Extensive efforts aimed at obtaining crystals of several derivatives of **3** suitable for X-ray diffraction have been, as yet, unsuccessful. Attempts were made using oxim, semicarbazone, and several hydrazone derivatives of **3b**. We have also tried to crystallize **3g** after exchange of the bromide ion for tartrate. Finally, attempts to crystallize several ternary L-α-amino acid−Cu(II)−**3** complexes were also unsuccessful.

(28) (a) Hunter, C. A.; Sanders, J. K. M. *J. Am. Chem. Soc.* **1990**, *112*, 5525. (b) Jaffe, R. L.; Smith, G. D. *J. Chem. Phys.* **1996**, *105*, 2780.

(29) (a) Frieden, E. *J. Chem. Educ.* **1975**, *52*, 754. (b) Scheraga, H. A. *Acc. Chem. Res.* **1979**, *12*, 7.

(30) (a) Hunter, C. A. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1584. (b) Diez-Barra, E.; Merino, S.; Sanchez-Verdu, P.; Torres, J. *Tetrahedron* **1997**, *33*, 11437.

(31) (a) Wetlaufer, D. B.; Malik, S. N.; Stoller, L.; Coffin, R. L. *J. Am. Chem. Soc.* **1964**, *86*, 508. (b) Aveyard, R.; Heselden, R. *J. Chem. Soc., Faraday Trans. 1* **1975**, *71*, 312.

(32) Charge-transfer bands have been observed previously in other systems in which the occurrence of arene−arene interactions has been suggested. See ref 19m and the following: Corey, E. J.; Loh, T.; Roper, T. D.; Azimioara, M. D.; Noe, M. *J. Am. Chem. Soc.* **1992**, *114*, 8290.

(33) Cozzi, F.; Cinquini, M.; Annuziata, R.; Siegel, J. S. *J. Am. Chem. Soc.* **1993**, *115*, 5330.

(34) Interestingly, after one cystallisation from isooctane, the major enantiomer of **3b** can be obtained in higher than 99% ee by evaporation of the mother liquor. Unfortunately, the oily product mixture still contained both enantiomers of the exo isomer, which could not be separated by chromatography.

Table 4. Gibbs Energies, Enthalpies, and Entropies of the Binding of **1c** to Different Copper(II)−Amino Acid Complexes in Water at 25 °C at pH 5−6 and Ionic Strengths of 2.00 M and 6.00 mM[a]

	$\Delta G^{\ominus}$ (kJ/mol)		$\Delta H^{\ominus}$ (kJ/mol)		$T\Delta S^{\ominus}$ (kJ/mol)	
ligand	$\mu = 6$ mM	$\mu = 2$ M	$\mu = 6$ mM	$\mu = 2$ M	$\mu = 6$ mM	$\mu = 2$ M
water	-15.7 ± 0.3	-17.7 ± 0.2	-21.9 ± 1.0	-18.7 ± 0.7	-6.2 ± 1.0	-1.0 ± 0.7
glycine	-14.2 ± 0.3	-16.0 ± 0.3	-12.8 ± 0.7	-14.1 ± 1.2	1.4 ± 0.7	1.9 ± 1.2
L-tryptophan	-18.7 ± 0.2	-19.9 ± 0.2	-23.9 ± 0.7	-25.0 ± 1.3	-5.2 ± 0.7	-5.1 ± 1.3
L-abrine	-19.4 ± 0.3	-21.1 ± 0.3	-29.8 ± 2.0	-34.0 ± 2.5	-10.4 ± 2.0	-12.9 ± 2.5

[a] Ionic strengths were adjusted using KNO_3.

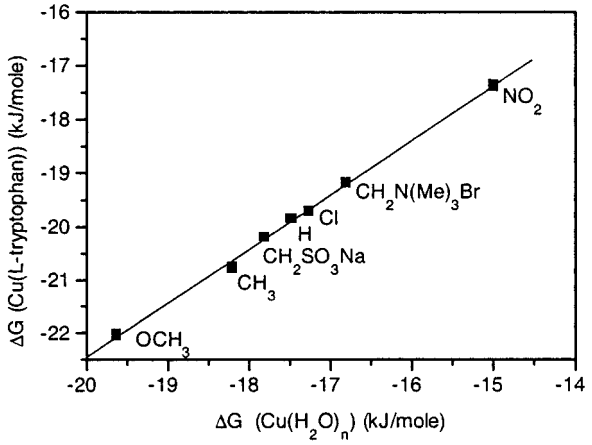


Figure 1. Gibbs energies of complexation of **1a**−**g** to the copper(II)-(L-tryptophan) complex versus those for complexation to the copper aqua ion.

conclude that the arene−arene interaction is not primarily driven by donor−acceptor interactions.

Since neither hydrophobic interactions nor donor−acceptor interactions are predominantly driving the arene−arene interaction, we contend that London dispersion and electrostatic forces govern these interactions.

Solvent Effects on the Enantioselectivity.[35] Having available, for the first time, a reaction that is catalyzed by Lewis acids in water in an enantioselective fashion, the important question arises of how water influences the enantioselectivity compared with nonaqueous solvents. Consequently, the copper-(II)-catalyzed reaction between **1c** and **2** in the presence of L-tryptophan and L-abrine has been performed in a number of organic solvents. To reduce the influence of ion pairing,[36] we used copper(II) triflate instead of copper(II) nitrate in the organic solvents. For deprotonation of the α-amino acid ligand, triethylamine was used instead of the potentially coordinating sodium hydroxide, which is employed in aqueous media. Table 5 summarizes the results.

Note that the reaction time in water is considerably shorter than that in organic solvents, despite the fact that the concentration of diene used for the reaction in water was less than one-third of that for the reaction in the organic solvents. Contrary to the organic solvents, the reaction mixture in water is heterogeneous. It might well be that the low solubility of the Diels−Alder product (**3c**) in this solution reduces inhibition of the reaction by this compound. Product inhibition is likely to be more pronounced in the homogeneous organic media.

Table 5. Enantiomeric Excess and Reaction Times for the Copper(L-Abrine)-Catalyzed Diels−Alder Reaction of **1c** with **2** in Different Solvents at 0 °C

solvent	time (days)	ee (%)[c]
water[a]	3	74
1,1,1-trifluoroethanol[b]	12	40
ethanol[b]	10	39
acetonitrile[b]	7	17
THF[b]	8	24
chloroform[b]	11	44
dichloromethane[b]	12	17

[a] Conditions: $[Cu(NO_3)_2] = 1.0$ mM; [L-abrine] = 1.75 mM; [**1c**] = 10 mM; [**2**] = 24 mM. One equivalent of NaOH was used to deprotonate the α-amino acid. [b] Conditions: $[Cu(OTf)_2] = 1.0$ mM; [L-abrine] = 1.75 mM; [**1c**] = 10 mM; [**2**] = 80 mM. One equivalent of triethylamine was used to deprotonate the α-amino acid. [c] Only the results for the major (>90%) endo isomer of the Diels−Alder adduct are shown.

Due to the prolonged reaction times and higher concentrations of **2** in organic solvents, some dimerization of the diene occurs during the reaction, resulting in contaminated product mixtures after workup. In contrast, the reactions in water yield quantitatively the ^{1}H NMR-pure Diels−Alder adducts.

Most importantly, enantioselectivity benefits considerably from the use of water as the reaction medium. We cannot exclude that this effect could be a result of water exerting a favorable influence on the cisoid−transoid equilibrium. Unfortunately, little is known about the factors that affect this equilibrium. Alternatively, and more likely, water enhances the efficiency of the arene−arene interactions. There is literature support for this suggestion.[19b,37] This enhancement can be at least partially attributed to a contribution from hydrophobic interactions.[38] The arene−arene interaction brings two nonpolar aromatic ring systems into close contact. In water, such a process will inevitably be accompanied by a release of part of the water molecules from the hydrophobic hydration shells of these groups. This provides the stacked form of the ternary complex in water with additional stability relative to organic solvents. Furthermore, the low polarizability of water is likely to favor the London dispersion interactions between the arene groups.

Outlook

We have provided compelling and quantitative evidence for the occurrence of arene−arene interactions in the Lewis-acid-catalyzed Diels−Alder reaction of **1** with **2**. These interactions influence not only the rate but also the enantioselectivity of this process. Not only do these results form the first link between aqueous coordination chemistry and enantioselective catalysis, but they also constitute the first example of enantioselective Lewis-acid catalysis of an organic reaction in water.

(35) Some studies of solvent effects on the enantioselectivity of Diels−Alder reactions catalyzed by chiral Lewis acids have been published. The sometimes dramatic effects have been brought down to influences on ion pairing and the geometry of the dienophile−Lewis acid complex. See: (a) Jaquith, J. B.; Guan, J.; Wang, S.; Collins, S. *Organometallics* **1995**, *14*, 1079. (b) Johannsen, M.; Jorgensen, K. A. *J. Chem. Soc., Perkin Trans. 2* **1997**, 1183.

(36) Evans, D. A.; Murry, J. A.; von Matt, P.; Norcross, R. D.; Miller, S. J. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 798.

(37) (a) Mitchell, P. R. *J. Chem. Soc., Dalton Trans.* **1980**, 1079. (b) Breault, G. A.; Hunter, C. A.; Mayers, P. C. *J. Am. Chem. Soc.* **1998**, *120*, 3402.

(38) Note that, even though hydrophobic interactions are not primarily driving arene−arene interactions, they are likely to enhance the efficiency of these interactions in water compared to organic solvents.

Most importantly, we have demonstrated that these interactions benefit considerably from the use of water as the solvent. Previously, other authors have suggested the occurrence of arene−arene interactions not only in enantioselective Diels−Alder reactions[16c,32] but also in many other transformations *in organic solvents*.[39] This suggests a considerable potential for water-promoted enantioselective catalysis. Our efforts in this field are continuing.

Conclusions

The influence of a series of diamine ligands and α-amino acid ligands on the rate and enantioselectivity of the Diels−Alder reaction between 3-phenyl-1-(2-pyridyl)-2-propen-1-ones (**1a**−**g**) and cyclopentadiene (**2**) in water has been investigated. Whereas the diamine ligands do not improve the catalytic efficiency, attachment of aromatic α-amino acid ligands to the copper(II) ion leads to an increase in the overall rate of the Diels−Alder reaction. This example of ligand-accelerated catalysis can be attributed to an increased binding of **1** to the copper(ligand) complex. The enhanced stability of the resulting complex relative to the aqua−copper(**1**) complex is a result of an arene−arene interaction between the aromatic ring of the amino acid ligand and the pyridine ring of **1**. The strength of this interaction amounts to 5.6 kJ/mol. The arene−arene interaction shields one face of the dienophile from attack by the diene, enabling enantioselective catalysis, producing **3** in up to 74% ee. The fact that ligand-accelerated catalysis is taking place is also apparent from the strongly nonlinear dependence of the enantioselectivity on the chiral ligand:catalyst ratio. To the best of our knowledge, this is the first example of enantioselectivity in a Lewis-acid-catalyzed organic reaction in water. Most importantly, comparison of the enantioselectivity in water with that in organic solvents reveals that water significantly promotes enantioselectivity. Mechanistic studies demonstrate that, in water, the arene−arene interaction that is underlying enantioselectivity is enthalpy-driven and seems to be mainly governed by London dispersion interactions and electrostatic forces. Hydrophobic interactions, though of minor importance in the overall strength of the arene−arene interaction, are likely to be partly responsible for the enhancement of enantioselectivity by water when compared to organic solvents. We infer these promising results to be the first step toward a more frequent use of water in enantioselective catalysis.

Experimental Section

Materials. $Cu(NO_3)_2 \cdot 3H_2O$ (Merck), $Cu(OTf)_2$ (Aldrich), $Ni(NO_3)_2 \cdot 6H_2O$ (Merck), KNO_3 (Merck), 2,2′-bipyridine (Merck), 1,10-phenanthroline (Merck), and *N*,*N*′-dimethylethylenediamine (Aldrich) were of the highest purity available. Ethylenediamine (Aldrich) and 2-(aminomethyl)pyridine (Aldrich) were distilled prior to use. Glycine (Fluka), L-valine (Fluka), L-leucine (Aldrich), L-phenylalanine (Jansen), L-tyrosine (Aldrich), *N*-methyl-L-tyrosine (Bachem), *N*-methyl-*p*-methoxy-L-phenylalanine (Bachem), L-tryptophan (Acros), 5-hydroxy-L-tryptophan (Sigma), and *N*-methyl-L-tryptophan (L-abrine, Aldrich) were of the highest purity available. *N*,*N*-Dimethyl-L-tyrosine was synthesized as described by Bowman.[40] Dimineralized water was distilled twice in a quartz distillation unit. Ethanol (Merck), chloroform (Merck), and THF (Merck) were of the highest purity available. Acetonitrile (Janssen) was run over basic aluminum oxide prior to use. Cyclopentadiene (**2**) was prepared from its dimer (Merck-Schuchardt) immediately before use. The preparation of dienophiles **1a**−**g** has been described previously.[8b,9] Europium tris(3-(trifluormethylhydroxymethylene)-d-camphorate) was obtained from Aldrich.

Equilibrium Constants and Enthalpies and Entropies of Complexation. Equilibrium constants for binding of **1a**−**g** were determined by following methods described previously.[8b] Solutions containing copper(II) or nickel(II) α-amino acid complexes were prepared by adding a clear solution (heating may be required) of the ligand in 1−5 mL of water, containing 1 equiv of sodium hydroxide, to a solution of the transition metal salt in 1−5 mL of water in a volumetric flask. The required amount of potassium nitrate was added, together with an amount of water sufficient to fill 95% of the volume. After dissolution of the potassium nitrate and thermal equilibration, the pH was adjusted to the desired value using diluted nitric acid, and filling of the volumetric flask with water was completed.

The enthalpies of complexation of **1c** to the copper(II)−amino acid ligand complexes have been calculated from the values of K_a at 20, 25, 30, 40, and 50 °C using the van't Hoff equation.[41] Complexation entropies have been calculated from the corresponding Gibbs energies and enthalpies.

Rate Constants and Enthalpies and Entropies of Activation. Kinetic experiments were performed using a Perkin-Elmer λ2, λ5, or λ12 spectrophotometer by following methods described previously.[8b] Values for k_{cat}, given in Tables 1 and 2, were calculated using the following equation:

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

Enthalpies and entropies of activation were calculated from the temperature dependence of k_{cat}. Apparent second-order rate constants were determined at 20, 25, 30, and 35 °C. Values of k_{cat} were calculated from these values and the equilibrium constants determined at the same temperatures.

Endo−Exo Selectivity. In a typical experiment, 105 mg (0.50 mmol) of **1c**, dissolved in a minimal amount of ethanol, and 100 mg (1.50 mmol) of **2** were added to a solution of 1.21 g (5 mmol) of $Cu(NO_3)_2 \cdot 3H_2O$ and 5 mmol of ligand in 500 mL of water in a 500-mL flask. α-Amino acid-containing solutions required addition of 1 equiv of sodium hydroxide. When necessary, the pH was adjusted to 5 (α-amino acids) and 7.5 (amines). The flask was sealed carefully, and the solution was stirred for 2−4 h, followed by extraction with ether. After the solution was dried over sodium sulfate, the ether was evaporated. The endo:exo ratios were determined from the ^{1}H NMR spectra of the product mixtures as described previously.[8b]

Enantioselective Catalysis. In a typical procedure, a solution of 0.175 mmol of L-α-amino acid and 0.175 mmol of NaOH in 1 mL of water was added to a solution of 0.100 mmol of $Cu(NO_3)_2$ in 100 mL of water in a 100-mL flask. The pH was adjusted to 6.0−6.5. The catalyst solution was cooled to 0 °C, and a solution of 1.0 mmol of **1c** in a minimal amount of ethanol was added, together with 2.4 mmol of **2**. The flask was sealed carefully, and the reaction mixture was shaken thoroughly. After being stirred for 48 h at 0 °C the suspension was extracted with ether, affording **3c** in quantitative yield. After evaporation of the ether from the aqueous layer (rotary evaporator), the catalyst solution can be reused without a significant decrease in enantioselectivity.

The procedure in organic solvents differed in the facts that $Cu(OTf)_2$ was used instead of $Cu(NO_3)_2 \cdot 3H_2O$ and that 1 equiv of ethylenediamine was used to deprotonate the amino acid ligand.

Determination of the Enantiomeric Excess. The enantiomeric excess of **3c** has been determined by HPLC analysis using a Daicel Chiracel OD column and eluting with a 60/1 (v/v) hexane (HPLC grade)/2-propanol (p.a.) mixture. At a flow of 1 mL/min, the retention times for the different isomers of **3c** were 6.3 (exo, major enantiomer), 7.1 (exo, minor enantiomer), 7.7 (endo, major enantiomer), and 10.7 min (endo, minor enantiomer).

The enantiomeric excess for **3b** and **3g** has been determined from ^{1}H NMR measurements (Varian VXR 300 MHz) in the presence of

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(40) Bowman, R. E.; Stroud, H. H. *J. Chem. Soc.* **1950**, 1342.

(41) Atkins, P. W. *Physical Chemistry*, 4th ed., Oxford University Press: Oxford, 1990; p 219.

the chiral europium tris(3-(trifluormethylhydroxymethylene)-d-camphorate) ($Eu(tfc)_3$) shift reagent. To a solution of 100 mg of Diels−Alder adduct in 0.7 mL of $CDCl_3$ were added 10−25-μL portions of a solution of 30 mg of $Eu(tfc)_3$ in 250 μL of $CDCl_3$, and the ^{1}H NMR spectrum was recorded. For the enantiomers of *endo*-**3g**, the signals of one of the vinyl protons ($\delta = 5.82$ ppm in the absence of shift reagent) were baseline separated after addition of 65 μL (0.2 equiv) of the solution of the shift reagent. For **3b**, the singlet of the phenyl protons at 7.15 ppm (in the absence of shift reagent) was monitored. After addition of 125 μL (0.5 equiv) of the solution of the shift reagent, the enantiomeric excess was determined after integration of the signal of the minor enantiomer (7.06 ppm, s, 4H) and of half of the significantly shifted and splitted signal of the major enantiomer (7.25 ppm, d, 2H).

Determination of the enantiomeric excess of **3c** was also performed using $Eu(tfc)_3$. Results obtained using this methods agreed within 2% with the outcome of the HPLC analysis.

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Supporting Information Available: Plot of the enantiomeric excess of the Cu(L-tryptophan)-catalyzed Diels−Alder reaction of **1c** with **2** as a function of pH and UV−vis absorption spectra of **1c** in water and in water containing 3.0 mM Cu(glycine), Cu(*N*-methyl-L-tyrosine), and Cu(L-abrine), showing a charge-transfer band for the aromatic α-amino acids (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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