A Chiral Lewis-Acid-Catalyzed Diels−Alder Reaction. Water-Enhanced Enantioselectivity

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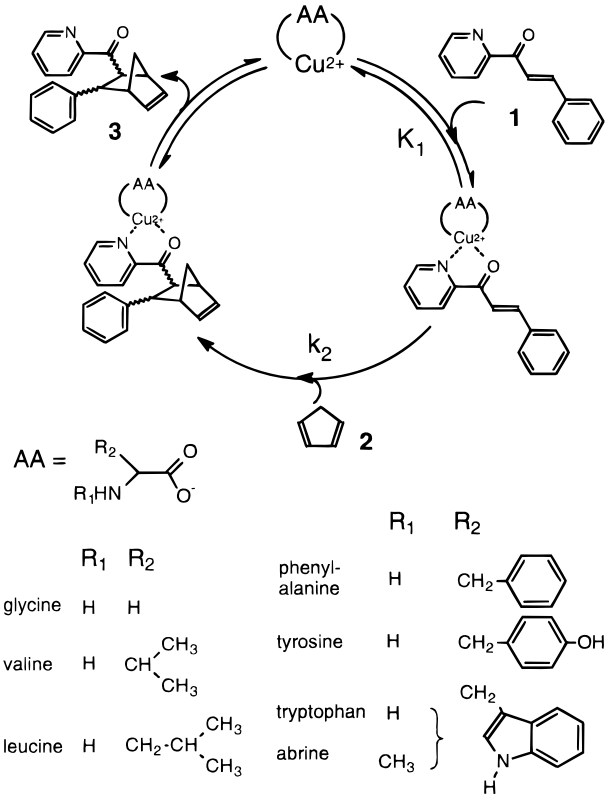
Water is becoming increasingly popular as a medium for organic reactions.[1] Apart from the obvious economic and environmental benefits,[2] the aqueous medium can have favorable effects on many organic transformations.[3] In the field of Lewis-acid catalysis, the use of water is still in its infancy.[4] Accordingly, reports on Lewis-acid catalysis of Diels−Alder reactions in water[5] or mixtures of organic solvents with small amounts of water[6] are scarce. Examples of *enantioselective* Lewis-acid-catalyzed Diels−Alder reactions in water have been completely lacking to date.

In organic solvents, enantioselective Lewis-acid catalysis of Diels−Alder reactions has been studied extensively.[7] The choice of the solvent for these reactions is rather limited. Donating solvents are generally avoided since they exert detrimental effects on rate and enantioselectivity.[8] Nevertheless, on the basis of our previous work on Lewis-acid catalysis of Diels−Alder reactions in water,[5a,b] we envisaged that even in aqueous media enantioselective catalysis should be possible.

In recent studies,[5a,b] we have already shown that water can have a beneficial effect on the rate of the Lewis-acid-catalyzed Diels−Alder reaction of 3-phenyl-1-(2-pyridyl)-2-propen-1-one (**1**) with cyclopentadiene (**2**) (Scheme 1). We now report that for this reaction enantioselectivity can be induced by coordinating chiral commercially available α-amino acids to a catalytically active metal ion. Derivatives of α-amino acids have already been reported to induce large enantioselectivities in Diels−Alder reactions in organic solvents.[8a,9]

In the presence of 10 % percent of copper(II) complexes of glycine, L-valine, L-leucine, L-phenylalanine, L-tyrosine, L-tryptophan, and *N*α-methyl-L-tryptophan (L-abrine), the Diels−Alder adduct **3** is obtained after 48 h in yields generally exceeding 90%.[10] Most interestingly, enantioselectivity is observed for the chiral ligands (Table 1). With L-abrine, an enantiomeric excess (ee) of 74% can be achieved. The catalyst solution can be reused without decrease in enantioselectivity. To the best of our knowledge, this is the first example of an enantiomeric excess in a chiral Lewis-acid-catalyzed reaction in water.

Scheme 1



Significant enantioselectivities are observed exclusively for the α-amino acids containing aromatic side groups. This suggests that arene−arene interactions are important in discriminating between the two pathways leading to the enantiomeric Diels−Alder adducts. The importance of these interactions was further assessed by examining the effect of the α-amino acid ligands on the following: (1) the equilibrium constants (K_1 in Scheme 1) for binding of the dienophile to the copper−ligand complex and (2) the second-order rate constants (k_2) for reaction of **2** with the thus-formed complex. The results are shown in Table 1. When compared to the aquo complex, the presence of the aliphatic α-amino acids glycine, L-valine, and L-leucine at the copper center causes a decrease of the equilibrium constants for binding of **1** to this copper ion. Presumably, this effects is a consequence of the reduction of the number of coordination sites available on the copper center in combination with a reduction of the Lewis acidity of the metal ion as a result of the presence of the Lewis-basic α-amino acid ligand.

Interestingly, for the aromatic α-amino acids an additional and counteractive effect is operative, which *raises* the equilibrium

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(10) In a typical procedure a solution of 0.175 mmol of L-abrine 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. The pH was adjusted to 6−6.5. The catalyst solution was cooled to 0 °C, and a solution of 1.0 mmol of **1** in a minimal amount of ethanol was added, together with 2.0 mmol of **2**. After 48 h of stirring at 0 °C, the reaction mixture was extracted with ether affording 0.94 mmol (94%) of **3**. All attempts to determine the absolute configuration of **3** and several derivatives thereof by X-ray diffraction have been as yet unsuccessful, due to problems in obtaining suitable crystals.

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Table 1. Effects of Ligands on the Equilibrium Constants (K_1)[a] for Binding of **1** to the Copper(II)−Ligand Complex, the Second-order Rate Constants (k_2)[a] for Reaction of **2** with This Complex, and the Enantioselectivity[b] of the Latter Process at 25 °C[c]

ligand	10^{-3} K_1 (M^{-1})[d]	k_2 (M^{-1} s^{-1})[d]	ee (%)[e,f,g]
water	1.2	2.56	0
glycine	0.74	1.89	0
L-valine	0.57	1.90	3
L-leucine	0.51	2.01	3
L-phenylalanine	0.87	2.01	14
L-tyrosine	1.4	1.68	26
L-tryptophan	3.0	1.44	25
L-abrine	5.0	1.47	74[h]

[a] Determined as described previously.[5b] [b] Determined by HPLC analysis using a Daicel Chiracel OD column, eluting with a 60:1 hexane/2-propanol mixture. [c] α-Amino acid solutions were adjusted to pH 4.6−4.9 (glycine pH 5.7). [d] Constant ionic strength (2.00 M) was ensured by adding KNO_3. [e] Conditions: $[Cu(NO_3)_2]$ = [α-amino acid] = 2.4 mM, [**1**] = 0.96 mM, [**2**] = 2.4 mM. [f] Only the results for the major endo (>90%) isomer of the Diels−Alder adduct are shown. [g] Reproducible to within 2%. [h] At 0 °C, pH 6.0 and 1.75 equiv of L-abrine relative to $Cu(NO_3)_2$.

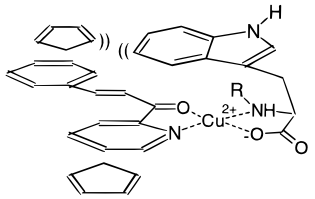

Figure 1. Transition-state assembly suggested[15] for the aqueous Lewis-acid-catalyzed Diels−Alder reaction of **1** with **2**.

constant even above the value observed for the aquo complex. This implies that an attractive interaction has to be involved, most likely between the aromatic ring of the α-amino acid and the pyridine ring of **1** as depicted in Figure 1. There is literature precedent for this type of interaction in the fields of aqueous coordination chemistry[11] as well as enantioselective catalysis.[9c,d,12]

Surprisingly, the second-order rate constants of the reaction are not sensitive to variation of the ligand. Coordination of a strongly Lewis-basic α-amino acid ligand to Cu^{2+} reduces the Lewis acidity of this ion, so that activation of **1** is somewhat less efficient in the presence of α-amino acids, but the effects are small.

Table 2. Solvent Effects on the Enantioselectivity of the Diels−Alder Reaction of **1** with **2**, Catalyzed by Cu(L-abrine)$^+$ at 0 °C

medium	ee (%)[a,b]
acetonitrile[c]	17
THF[c]	24
ethanol[c]	39
chloroform[c]	44
water[d]	74

[a] Only the results for the major (>90%) endo isomer of the Diels−Alder adduct are shown. [b] Reproducible to within 2%. [c] Conditions: $[Cu(OTf)_2]$ = 1.00 mM; [L-abrine] = $[Et_3N]$ = 1.75 mM; [**1**] = 10 mM; [**2**] = 80 mM. [d] Conditions: see footnote 10.

Finally, we compared the results obtained in water with the enantioselectivity in organic solvents. Table 2 clearly demonstrates that enantioselectivity benefits considerably from the use of water as the solvent. This is in line with literature observations that arene−arene interactions are less efficient in organic solvents than in water.[13]

Since arene−arene interactions are held responsible for the enantioselectivity in many reactions involving chiral catalysts, we infer that the enhancement of enantioselectivity by water might well be a general phenomena. Moreover, we want to point out that water can be expected to facilitate mechanistic studies of the interactions underlying enantioselectivity. Two effects that usually complicate the study of enantioselective catalysis in organic solvent, ion pairing[14] and clustering of the catalyst species, will normally not occur in water. The remaining rate and equilibrium constants of the different catalytic steps can be determined with relative ease, as is exemplified in this paper.

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(15) We are currently investigating whether the coordination sphere of the copper ion is actually trans and whether the dienophile reacts in the s-trans configuration.