Asymmetric Catalysis

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DNA-Based Catalytic Enantioselective Michael Reactions in Water**

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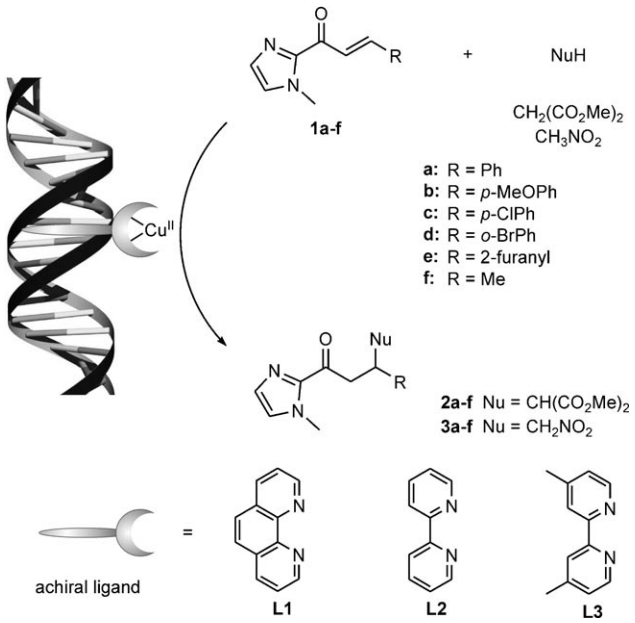
The increasing appreciation of the special properties of water as a reaction medium, combined with the potential advantages of replacing organic solvents by water, have fueled the development of catalytic methodologies for use in water or aqueous media.[1] Despite significant progress in the area of catalytic asymmetric C–C bond-forming reactions in water,[2] many challenges remain. For example, a particularly important transformation is the catalytic enantioselective Michael addition reaction, in which an enone substrate undergoes conjugate addition with a carbon nucleophile. The reaction can be catalyzed by Lewis acids.[3] To our knowledge, only two examples of transition-metal-catalyzed enantioselective Michael reactions in water have been reported to date. Maximum *ee* values of 83[4] and 86% *ee*[5] have been obtained by using Ag^{I}- or Pd^{II}-based catalysts, respectively.[6,7] Here we report a highly enantioselective Michael reaction in water that is mediated by a DNA-based catalyst.

An emerging approach in aqueous-phase catalysis is the use of hybrid catalysts, which combine the catalytic power of transition-metal complexes with the chiral architecture of biopolymers.[8] Enantioselective catalysis has been achieved for a number of reactions through the use of protein-based hybrid catalysts.[9] The double helix of DNA represents a very attractive scaffold for hybrid catalysis, and we have demonstrated that its chirality can be transferred to a catalytic reaction, that is, the Cu^{II}-catalyzed asymmetric Diels–Alder reaction.[10] This was achieved by binding a copper complex, based on an achiral ligand, to DNA in a noncovalent fashion. To date, two families of ligands have been investigated. Initially, a metal-binding domain was linked through a short spacer to a DNA intercalator.[10a] In an improved and much simpler design, the DNA-binding moiety was integrated into the metal-binding domain. Enantioselectivities of up to 99% *ee* were obtained in the Diels–Alder reaction of azachalcone with cyclopentadiene by using ligands of this class.[10b] Furthermore, it was demonstrated that the catalytic reactions could be performed on a synthetically relevant scale.[10c]

Encouraged by these results, we decided to explore the scope and versatility of the DNA-based catalysis concept further by applying it to the catalytic asymmetric Michael reaction in water.[11,12] α,β-Unsaturated 2-acylimidazoles (**1a**–**f**), which can bind to Cu^{II} ions in a bidentate fashion under aqueous conditions, were selected as the enone substrates. An additional attractive feature of these compounds is that following the catalyzed reaction, the *N*-methylimidazole auxiliary is readily displaced, thus giving rapid access to interesting chiral building blocks. This novel class of substrate has been applied recently with considerable success in a variety of reactions, such as carbonyl anion additions, Friedel–Crafts alkylations, nitrone cycloadditions, and also the DNA-based catalytic asymmetric Diels–Alder reaction.[10c,13] Nitromethane and dimethyl malonate, both of which readily enolize, were employed as nucleophiles.

The DNA-based catalyst was self-assembled from salmon testes DNA (st-DNA) and the appropriate copper complex. The reaction of **1a** (Scheme 1) with 100 equivalents of



Scheme 1. Schematic representation of the asymmetric Michael addition reaction catalyzed by complexes formed between copper(II) ions and achiral ligands (L1–L3) in the presence of DNA.

dimethyl malonate was used to screen for the most efficient catalytic system (Table 1). An excess of the nucleophile was necessary to achieve good conversion (see below). Reactions were performed at 5 °C and pH 6.5, the optimum conditions with regard to both conversion and enantioselectivity.[14] The reaction mixture was heterogeneous, as a result of the low solubility of **1a** in water. Nevertheless, in all cases the reaction proceeded cleanly, with only formation of the Michael

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Table 1: Results of Michael addition reactions catalyzed by DNA/[Cu(L1–L3)$(NO_3)_2$].[a]

	[Cu(L*n*)$(NO_3)_2$]		Substrate		$CH_2(CO_2Me)_2$		CH_3NO_2	
	[mM]	L	R	equiv[b]	conv [%][c]	*ee* [%][d]	conv [%][c]	*ee* [%][d]
1	0.3	–	Ph (**1a**)	3.3	26	<2	0	n.d.[l]
2	0.3	L1		3.3	4	56 (−)	–	–
3	0.3	L2		3.3	90	80 (−)	–	–
4	0.3	L3		3.3	quant.	91 (−)	97	85 (−)
5[e]	0.3			3.3	54	–	36	–
6	0.3			3.3	92[f]	92 (−)	65[g]	85 (−)
7	0.15			6.6	quant.	92 (−)	61	85 (−)
8	0.05			19.8	66	92 (−)	–	–
9	0.3			6.6	quant.	87 (−)	quant.	84 (−)
10[h]	0.3			6.6	quant. (86)[i]	85 (−)	96 (90)[i]	84 (−)
11	0.3			13.3	quant.	91 (−)	58	83 (−)
12	0.3			20	quant.	90 (−)	69	83 (−)
13	0.3			33	40	89 (−)	–	–
14	0.3		*p*-MeOPh (**1b**)	3.3	94	86	89	82
15	0.3		*p*-ClPh (**1c**)	3.3	75	90	72	85
16	0.3		*o*-BrPh (**1d**)	3.3	quant.	99 (−)	70	94
17[j]	0.3			6.6	87 (80)[i]	99 (−)	–	–
18[j,k]	0.3			6.6	79 (72)[i]	99 (−)	–	–
19	0.3			13.3	34	98 (−)	–	–
20	0.3		2-furanyl (**1e**)	3.3	96	86	quant.	87
21	0.3		Me (**1f**)	3.3	92	58	95	62

[a] Typical experiments were carried out with salmon testes DNA (1.3 mg mL^{-1}) in MOPS buffer (20 mM pH 6.5) for 3 days at 5 °C using 100 equiv of dimethyl malonate or 1000 equiv of nitromethane, with respect to enone. [b] Equivalents of substrate **1a–f** with respect to Cu^{II} ions. [c] Conversion values were determined by ^{1}H NMR spectroscopy and are the average of duplicate experiments (standard deviation: ±3%). [d] The *ee* values were determined by analytical chiral HPLC. [e] Reaction performed without DNA. [f] 40 equiv of dimethyl malonate. [g] 200 equiv of nitromethane. [h] Reaction performed on a 80-mg scale [i] Yield of isolated product after column chromatography. [j] Reaction performed on a 1-mmol scale. [k] Using recycled catalyst solution from entry 17. [l] Not determined.

addition product **2a** (entries 2–4). In the absence of a ligand, that is, with only $[Cu(H_2O)_3(NO_3)_2]$ and DNA, low conversion and no enantioselectivity was observed (entry 1). The reactivity decreased even further when 1,10-phenanthroline (L1) was used as the ligand, but a moderate *ee* value was obtained (entry 2). In contrast, a significantly increased activity and enantioselectivity was found by using 2,2′-bipyridyl (L2) as the ligand (entry 3). However, the best results were obtained with 4,4′-dimethyl-2,2′-bipyridine (L3), which resulted in full conversion and an enantioselectivity of 91% *ee* (entry 4). In all cases the (−) enantiomer was obtained in excess. Remarkably, the reaction proved to be not only accelerated by the presence of a ligand, but it was also accelerated by DNA; in the absence of DNA, only 54% conversion was observed over the same reaction time (entry 5). On the basis of these results $[Cu(L3)(NO_3)_2]$ was selected as the catalyst of choice and further experiments were performed using this catalytic system.

Decreasing the amount of dimethyl malonate to 40 equivalents with respect to **1a** resulted in a slight drop in the conversion (entry 6). The concentration of $[Cu(L3)(NO_3)_2]$ could be lowered to 0.15 mM (15 mol%), using the same DNA concentration, without affecting the conversion (entry 7). However, reduced conversion was observed at 0.05 mM $[Cu(L3)(NO_3)_2]$ (entry 8). In both cases the *ee* value remained the same, thus indicating that decreasing the $[Cu(L3)(NO_3)_2]$/DNA base pair ratio does not affect the enantioselectivity. However, lowering the DNA concentration did result in a slightly lower *ee* value.[14] Conversely, the amount of **1a** could be increased up to 20 equivalents with respect to the Cu^{II} concentration (5 mol% catalyst loading) and still obtain full conversion with 90% *ee* (entries 9–12). Further increasing the amount of **1a** led to a decrease in the conversion, but without a decrease in the enantioselectivity (entry 13).

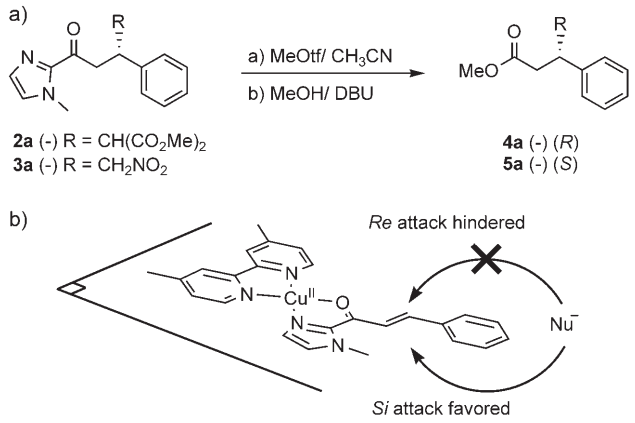
Nitromethane is also a good nucleophile in this reaction, although it proved to be somewhat less reactive than dimethyl malonate; 1000 equivalents of nitromethane were required to achieve full conversion. The origin of this reduced reactivity is unclear. The pK_a values of nitromethane and dimethyl malonate are 10.3[15] and 13,[16] respectively, which suggests that the reactivity is not directly related to the acidity of the nucleophiles. The corresponding Michael adduct was obtained with very good enantioselectivity when nitromethane was used as the nucleophile (85% *ee*, entry 4). Higher $[Cu(L3)(NO_3)_2]$ loadings were generally required with nitromethane because of its lower reactivity. Decreasing the catalyst concentration resulted in a significant decrease in the conversion (entry 7) and, similarly, using larger amounts of **1a** also led to a rapid decrease in the conversion (entries 11 and 12).

The scope of the reaction was investigated using α,β-unsaturated 2-acylimidazole substrates **1a–f**, which contain different R groups.[13a,c] Good to excellent conversion was observed in all cases, with the corresponding Michael addition product being the sole product detected.[17] Very good enantioselectivities, ranging from 82–94% for nitromethane and from 86–99% in the case of dimethyl malonate as the nucleophile (entries 14–20), were obtained when R = aryl. In both cases the Michael acceptor containing an *ortho*-bromophenyl substituent gave rise to the highest enantioselectivities (entry 16). A significant decrease in the enantioselectivity was obtained when R = Me (entry 21). Replacement of the *N*-methylimidazole moiety in the substrate with a noncoordinating group (namely, phenyl) resulted in a complete loss of activity, thereby underlining the importance of the bidentate coordination of the substrate to the Cu^{II} ion.[14]

The reaction of **1d** with dimethyl malonate was performed on a preparative scale, namely, 1 mmol **1d** (291 mg). The corresponding Michael adduct **2d** was obtained in 80% yield (87% conversion) and 99% *ee* after column chromatography (entry 17). This catalyst solution was then reused for another reaction on a 1 mmol scale without significant decrease in the *ee* value or yield; from this experiment **2d** was obtained in

72% yield and 99% *ee* (entry 18). These results demonstrate the potential of the DNA-based catalyis concept for applications in synthesis.

To gain insight into the stereochemical course of the catalytic reaction the Michael adducts **2a** and **3a** were isolated from an 80-mg-scale reaction (entry 10) in 86 and 90% yields and 85 and 84% *ee*, respectively. The imidazole groups of **2a** and **3a** (Scheme 2) were methylated using methyl triflate[13b] and then treated with methanol to give the corresponding optically active carboxylic esters **4a** and **5a** (Scheme 2). Measurement of the optical rotation of **4a**



Scheme 2. a) Synthesis of **4a** and **5a** and b) schematic representation of the stereochemistry of the attack of the nucleophile in the DNA-based catalytic asymmetric Michael addition.

($[\alpha]_D^{25} = -10.8\ \mathrm{deg\,cm^3\,g^{-1}\,dm^{-1}}$) allowed us to conclude that the *R* enantiomer had been formed,[18] whereas the optical rotation of **5a** ($[\alpha]_D^{25} = -14.5\ \mathrm{deg\,cm^3\,g^{-1}\,dm^{-1}}$) indicates that the *S* enantiomer was formed in this case.[19] Consequently, the DNA-based catalyst system appears to direct the nucleophile towards attack on the *Si* face of the Michael acceptor (Scheme 2). This approach coincides with the face from which cyclopentadiene reacts in the related DNA-based catalytic enantioselective Diels–Alder reaction, which suggests that the DNA shields the *Re* face of the coordinated α,β-unsaturated 2-acylimidazole substrate.[10c] Current efforts are aimed at elucidating the structure of the DNA-bound activated complex.

In conclusion, we have developed a highly enantioselective Michael reaction in water by using a simple DNA-based catalyst. Enantioselectivities of up to 99% *ee* could be obtained by using nitromethane and dimethyl malonate as the nucleophiles and α,β-unsaturated 2-acylimidazoles as the Michael acceptors. To our knowledge these represent the highest enantioselectivities obtained in the catalytic Michael addition in water to date. The reactions can be performed on a preparative scale and the catalyst can be recycled. These results are a clear demonstration of the versatility of the DNA-based catalysis concept.

Experimental Section

Representative procedure for the [Cu(L3)$(NO_3)_2$]/DNA-catalyzed Michael addition reaction: A catalyst solution of the copper(II) complex (0.3 mM) and salmon testes DNA (1.3 mg mL^{-1}) in 20 mM 3-(*N*-morpholine)propanesulfonic acid (MOPS) buffer at pH 6.5 was prepared by adding a solution of salmon testes DNA (10 mL, 2 mg mL^{-1} in 30 mM MOPS buffer, pH 6.5; prepared 24 h in advance) to a solution of [Cu(L3)$(NO_3)_2$] in water (5 mL, 0.9 mM). A fresh stock solution of Michael acceptor (30 μL) in CH_3CN was then added. After addition of dimethyl malonate (174 μL) or nitromethane (1 mL) at 0 °C, the reaction mixture was kept for 3 days at 5 °C with continuous inversion. The product was isolated by extraction with Et_2O (2 × 10 mL). After drying the reaction mixture (Na_2SO_4) and removal of the solvent, the crude product was analyzed by NMR spectroscopy and HPLC.

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