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DNA-Accelerated Copper Catalysis of Friedel–Crafts Conjugate Addition/Enantioselective Protonation Reactions in Water

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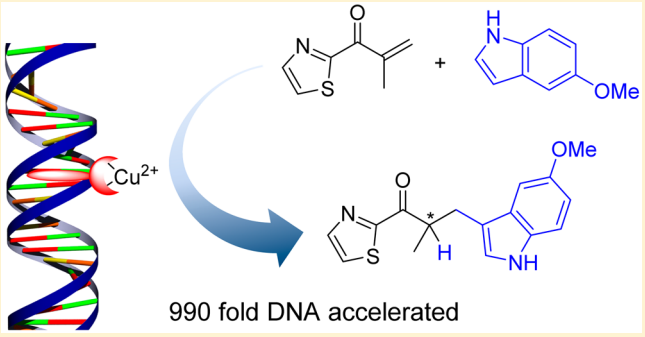
Supporting Information

ABSTRACT: DNA-induced rate acceleration has been identified as one of the key elements for the success of the DNA-based catalysis concept. Here we report on a novel DNA-based catalytic Friedel–Crafts conjugate addition/enantioselective protonation reaction in water, which represents the first example of a reaction that critically depends on the >700- to 990-fold rate acceleration caused by the presence of a DNA scaffold. The DNA-induced rate acceleration observed is the highest reported due to the environment presented by a biomolecular scaffold for any hybrid catalyst, to date. Based on a combination of kinetics and binding studies, it is proposed that the rate acceleration is in part due to the DNA acting as a pseudophase, analogous to micelles, in which all reaction components are concentrated, resulting in a high effective molarity. The involvement of additional second coordination sphere interactions is suggested by the enantioselectivity of the product. The results presented here show convincingly that the DNA-based catalysis concept, thanks to the DNA-accelerating effect, can be an effective approach to achieving a chemically challenging reaction in water.



INTRODUCTION

Metalloenzymes are often considered to be the perfect metal catalysts, since they catalyze chemically challenging reactions with high activities and selectivities under mild conditions. The catalytic reactivity of a metalloenzyme is due to the metal ion, whose reactivity is controlled by its ligands. However, what makes metalloenzymes such exceptional catalysts is the involvement of the second coordination sphere. This is made up of functional groups provided by the amino acid side chains from the protein, which provide a variety of supramolecular interactions that contribute to binding, activating, and directing substrates and stabilizing transition states. The field of artificial metalloenzymes aims to exploit these second coordination sphere interactions to confer enzyme-like activity and selectivity to transition metal catalysts, by embedding metal complexes in biomolecular scaffolds such as proteins or DNA. The resulting hybrid catalysts have been applied successfully in a variety of catalytic reactions, resulting in high enantioselectivities.[1,2] In several cases this was accompanied by an additional rate acceleration compared to the metal complex alone. In most cases, this rate acceleration was modest, but in a few cases significant rate accelerations of up to almost 100-fold have been reported.[1a,3,4]

Duplex DNA has proven to be a very attractive scaffold for the creation of hybrid catalysts.[5] Using a combination of a transition metal complex and DNA, excellent enantioselectivities have been achieved in a variety of Lewis acid catalyzed[6,7] and even some organometallic reactions.[8] Especially in the case of reactions catalyzed by a DNA-based catalyst assembled from the copper(II) complex of 4,4′-dimethyl-2,2′-bipyridine (Cu-dmbipy) and salmon testis DNA (st-DNA), also a significant rate acceleration, i.e., up to 60-fold in the Diels–Alder reaction, was observed compared to the reactions catalyzed by the copper complex alone, in the absence of DNA.[4a]

Recent studies have shown for the (Cu-dmbipy) complex that groove binding is the predominant DNA-binding mode.[9] Additionally, it was found that the DNA has a beneficial effect on the binding of the azachalcone substrate to the Cu(II) center due to the fact that both bind to DNA.[10] The resulting increased effective molarity was hypothesized to be an important contributor to the rate acceleration observed in the Diels–Alder reaction.

A particularly interesting case is the catalytic asymmetric Friedel–Crafts alkylation of indoles with α,β-unsaturated 2-acyl(1-methyl)imidazole substrates in water, giving rise to the formation of the corresponding alkylated products with enantioselectivities up to 93%.[7] Importantly, this was accompanied by a 30-fold increase in reaction rate due to the presence of DNA.[7]

These results inspired us to investigate α-substituted enones as substrate. Conjugate addition of indoles to α-substituted enones followed by enantioselective protonation represents a powerful method for the synthesis of nonracemic tertiary

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carbon stereocenters which are present in many important chiral molecules.[11,12]

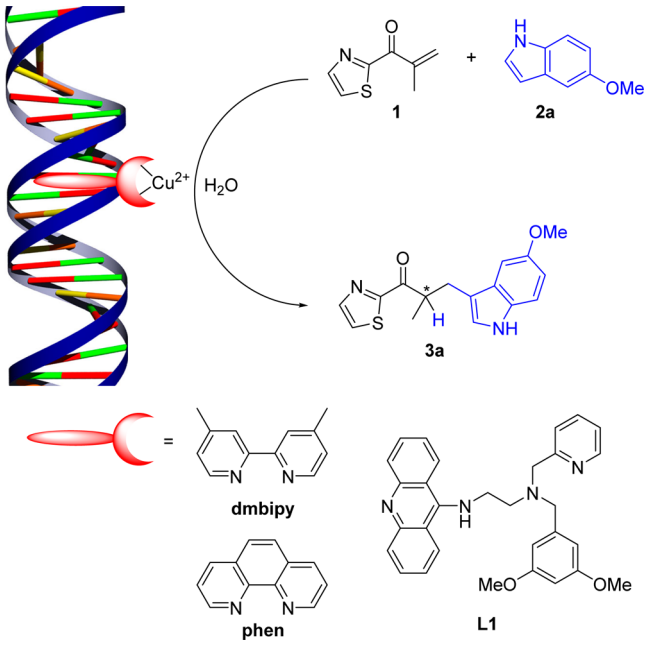
This transformation appears deceptively simple: it involves the transfer of a proton from a donor to a prochiral acceptor, often a transient enolate species that is generated *in situ* by a conjugate addition to an α-substituted enone.[13−15] Yet, there are several aspects that make this a highly challenging reaction, especially when using water as reaction medium: the small size of protons, which makes them difficult to control, potential racemization of the products, the high mobility of protons in water, and the question how to achieve kinetic control over the protonation step. Enzymes capable of catalyzing enantioselective protonations, which rely on water as medium and as the proton source, solve this problem by limiting access of bulk water into their hydrophobic active sites.[11] Indeed, examples of nonenzymatic catalytic enantioselective protonation reactions in water are rare;[14b] most current methods therefore involve either strict anhydrous conditions or the use of a limited amount of a protic cosolvent.[16]

Here we report on the DNA-based catalytic Friedel−Crafts alkylation/enantioselective protonation reaction, which represents the first example of a reaction that critically depends on the >700-fold DNA-induced rate acceleration to proceed efficiently.

RESULTS AND DISCUSSION

Catalysis. The conjugate addition of 5-methoxy-1*H*-indole (**2a**) to 2-methyl-1-(thiazol-2-yl)prop-2-en-1-one (**1**) was selected as the benchmark reaction. Upon addition of the indole to the β position and subsequent protonation, a chiral tertiary carbon center is obtained at the α position. (Scheme 1). A thiazole auxiliary moiety, which is needed to ensure bidentate binding of **1** to the catalytic Cu(II) ion,[17] was used instead of the commonly used *N*-methyl imidazole moiety, since the latter is incompatible with the α-methyl group due to steric hindrance upon binding to Cu(II). Substrate **1** was prepared by reaction of 2-(trimethylsilyl)thiazole with methacrolein, followed by oxidation of the alcohol to the ketone with MnO_2. The latter step was performed immediately prior to the catalytic experiments, since it was found that upon storage **1** dimerizes via a hetero Diels−Alder reaction (Supporting Information).

Scheme 1. DNA-Based Catalytic Tandem Friedel−Crafts Alkylation/Enantioselective Protonation and Ligands Used in This Study



Starting from the catalytic conditions used in the previously reported asymmetric DNA-based catalyzed Friedel−Crafts alkylation of indoles,[7a] after an optimization study, it was decided to use a 1:1 ratio of substrates **1** and **2a**, 15 mol % [0.15 mM] of $[Cu(dmbipy)(NO_3)_2]$ and 0.67 mg/mL of st-DNA [1 mM in base pairs] in MES buffer pH 5.0 at 4 °C, for 18 h as standard conditions (Table S1). In the absence of Cu(II), no significant conversion was obtained both in the absence and in the presence of DNA (Table S1, entries 13, 14).

A moderate conversion and no significant ee in the product was obtained when $[Cu(NO_3)_2]$/st-DNA was used as catalyst (entry 1). Using the Cu(II) complex of the ligand dmbipy in combination with st-DNA resulted in high conversion, and the product **3a** was obtained with a promising ee of 59% (Table 1, entry 3). Surprisingly, in the reaction without DNA, i.e., using $[Cu(dmbipy)(NO_3)_2]$ alone, almost no conversion was obtained in the same time (Table 1, entry 4). This was the first indication of a very strong DNA acceleration effect in this reaction (see below). Using higher concentrations of st-DNA in the $[Cu(dmbipy)(NO_3)_2]$ catalyzed reaction did not further improve conversion or ee. However, reducing the DNA concentration to 0.5 mM in base pairs did give rise to a lower conversion and ee (Table S2).

Table 1. Results of the Catalytic Friedel−Crafts Conjugate Addition/Enantioselective Protonation Reaction of 1 with 2a[a]

entry	catalyst	[st-DNA] (mM)	conv[b](%)	ee[b](%)
1	$[Cu(NO_3)_2].3H2O$	1	41	<5
2	$[Cu(NO_3)_2].3H2O$		14	
3	$[Cu(dmbipy)(NO_3)_2]$	1	90	59
4	$[Cu(dmbipy)(NO_3)_2]$		1	
5	$[Cu(phen)(NO_3)_2]$	1	71	<5
6	$[Cu(L1)(NO_3)_2]$	1	66	−53

[a]Typical reaction conditions: **1** (1 mM), **2a** (1 mM), Cu-dmbipy (0.15 mM), st-DNA (1 mM in base pairs) in 20 mM MES pH 5.0 at 4 °C, for 18 h. [b]Conversion (reproducibility ±5%) and ee values (reproducibility ±3%) were determined by HPLC.

Using the related copper complex $[Cu(phen)(NO_3)_2]$ also no significant ee was obtained (Table 1, entry 5). Application of a first generation ligand L1 (Table 1, entry 6) resulted in preferential formation of the opposite enantiomer of the product with a moderate enantioselectivity of 53%.

The nucleophile scope was investigated using indoles containing various substitution patterns, in the reaction with enone **1** as substrate (Table 2). It is worth noting that the synthesis of all the corresponding products (**3a−u**) proceeded efficiently only in the presence of $[Cu(dmbipy)(NO_3)_2]$ in combination with DNA as catalyst; in the absence of DNA, all reactions proved to be very slow. Indeed, as a consequence, the racemic reference products required for validating chiral HPLC separation of enantiomers were best prepared by racemization of the product obtained in the DNA-based catalytic reaction (Supporting Information).[18]

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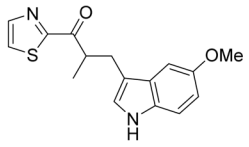
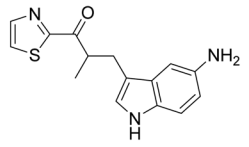
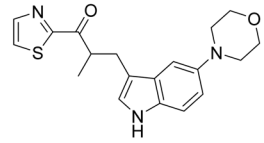
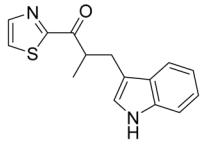
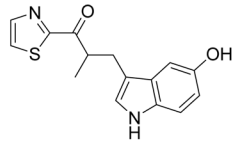
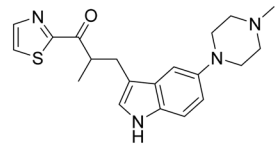
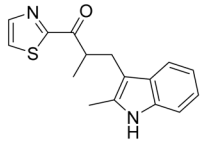
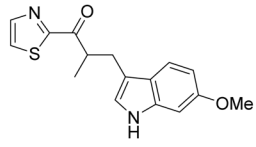
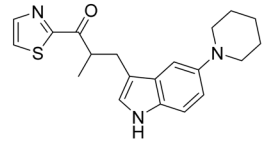
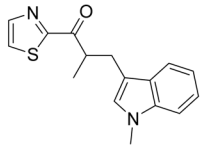
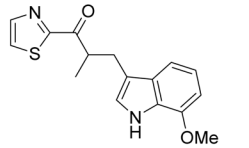
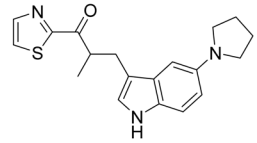
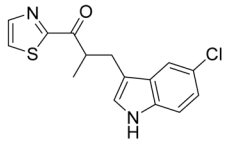
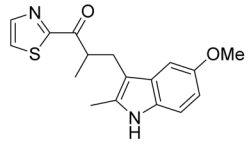
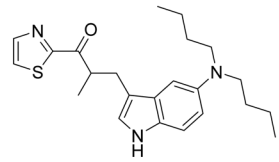
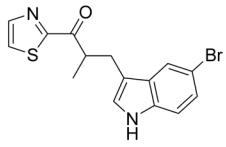
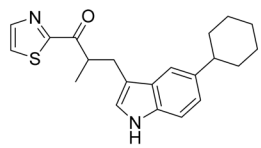
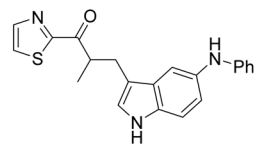
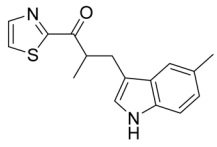
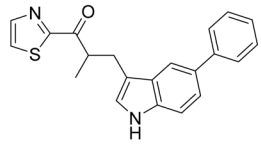
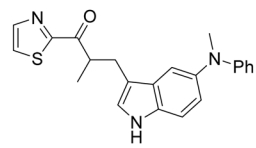
Table 2. Scope of Indoles[a]

1 2a-v 3a-v

Entry	Product, yield[b] / ee (%)[c]	Entry	Product, yield[b] / ee (%)[c]	Entry	Product, yield[b] / ee (%)[c]
1	 **3a**, 81 / 59	8	 **3h**, 43 / 52	15	 **3p**, 83 / 84
2	 **3b**, 54 / 32	9	 **3i**, 66 / 41	16	 **3q**, 40 / 74
3	 **3c**, 65 / <5	10	 **3j**, 75 / 11	17	 **3r**, 87 / 79
4	 **3d**, 45 / 6	11	 **3k**, 77 / 29	18	 **3s**, 84 / 79
5	 **3e**, 80 / 27	12	 **3l**, 70 / 5	19	 **3t**, 87 / 69
6	 **3f**, 86 /29	13	 **3m**, 49 / 8	20	 **3u**, 72 / 48
7	 **3g**, 52 / 54	14	 **3n**, 33 / 8	21	 **3v**, no conv

[a]Typical reaction conditions: **1** (1 mM), **2a−v** (1 mM), Cu-dmbipy (0.15 mM), st-DNA (1 mM in base pairs) in 20 mM MES pH 5.0 at 4 °C, for 18 h. [b]Isolated yields after column chromatography. [c]Ee values determined by HPLC (reproducibility ±3%).

In general, reaction products **3a−u** were obtained in moderate to good yields. Using 1*H*-indole gave rise to 32% ee of the product **3b** (entry 2). Indoles with methyl groups as substituents at positions 1 and 2 resulted in the formation of the corresponding reaction products in good yields but almost no enantioselectivity (entries 3, 4, and 12). Indoles containing

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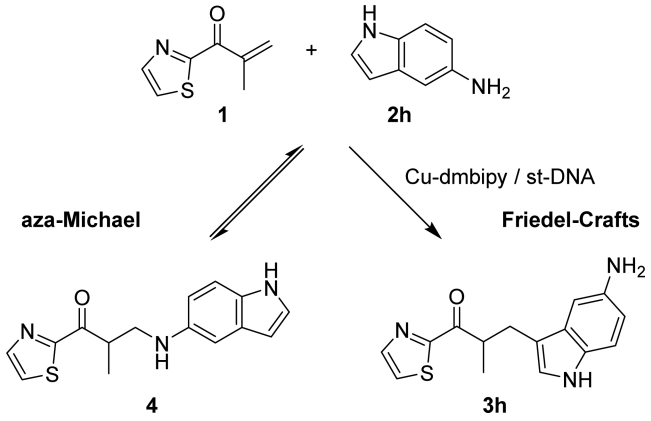
electron withdrawing groups at the 5 position gave rise to the reaction products with modest enantioselectivities, i.e., less than <30% (entries 5, 6). The presence of electron donating groups, such as MeO, Me, NH_2 or OH as substituents at the 5 position of the indole, gave the corresponding products with ee values of 41 to 59% (entries 1, 7–9). Switching the position of the methoxy group to the 6 or 7 position led to low enantioselectivity (Table 2, entries 10, 11). Using alkyl or aryl substituents at this position, only low ee's were obtained (entries 13, 14). Since the highest ee's were obtained with electron donating substituents, a variety of derivatives containing tertiary amine groups at the 5 position were tested (Table 2, entries 15–21). Indeed, significantly higher ee's were observed, with the highest enantioselectivity achieved in the case of 5-morpholinoindole, i.e., 84% ee (Table 2, entry 15). A variety of synthetic self-complementary oligonucleotides were evaluated in this reaction (Table S3). The enantioselectivity of **3p** was indeed found to be DNA sequence dependent, albeit that no improvement in ee compared to st-DNA was observed. In the case of *N*-methyl-*N*-phenyl-1*H*-indol-5-amino (**3u**), no product formation was observed (Table 2, entry 16).

A particularly interesting case is the reaction of **1** with 5-aminoindole (**2h**): while the catalyzed reaction between enone **1** and 5-aminoindole in the presence of DNA resulted in formation of the desired Friedel–Crafts alkylation product, in the absence of DNA the exclusive formation of the aza-Michael product **4** was observed (Scheme 2). Thus, the presence of

Scheme 2. Aza-Michael and Friedel–Crafts Alkylation/ Enantioselective Protonation Reaction of 1 with 2h



DNA completely alters the chemoselectivity of the reaction. It has to be noted that the aza-Michael addition also does not necessarily require Cu(II) catalysis; formation of **4** was also observed in the absence of catalyst.

The reaction between enone **1** and **2h** catalyzed by $[Cu(dmbipy)(NO_3)_2]$ in the presence of DNA was followed in time (Figure S1). At the beginning of the reaction, the formation of product **3h** was observed concomitantly with the formation of aza-Michael addition product **4**. However, after several hours, only product **3h** was observed. This can be explained by considering that the aza-Michael addition is reversible, while the Friedel–Crafts alkylation is irreversible.

Kinetic Studies. Intrigued by the observed dramatic difference in reactivity in the absence and presence of DNA, the reaction was subjected to a kinetic study. For this, the reactions between enone **1** and three representative indoles, i.e., 5-methoxyindole (**2a**), 2-methylindole (**2c**), and 5-morpholinoindole (**2p**), which give rise to moderate, low, and high ee's, respectively, were selected. The formation and ee of products were followed in time, and aliquots from the reaction mixture were analyzed by normal phase high-performance liquid chromatography (np-HPLC).[19] Using 1 equiv of enone with respect to indole the reaction progress was fitted to an overall second order reaction in all cases (Supporting Information).

The reactions catalyzed by $[Cu(dmbipy)(NO_3)_2]$ only, in the absence of st-DNA, were found to be very slow, in agreement with the results obtained at preparative scale (vide supra). The low reactivity of α-substituted enones toward conjugate addition, which is in marked contrast to the much faster reaction observed with β-methyl substituted enones, has been noted before in the literature.[20] In the case of the reaction with 2-methylindole (**2c**) in the absence of DNA, HPLC and ^{1}H NMR analysis showed that, in addition to small quantities of **3c**, a number of side products were formed (Figure S2). Therefore, the kinetic parameters were not determined for this reaction. No side products were observed in the reaction with **2a** or **2p**.

In the presence of DNA, clean conversion to the corresponding product was observed for all three indoles. Moreover, in all three cases the reaction was significantly faster in the presence of DNA (Figure S2, Table S4). This result shows that there is no direct correlation between enantioselectivity and DNA-induced rate acceleration. The DNA acceleration effect, defined as the ratio of the apparent second order rate constant k_{app} for the reaction in the presence of DNA and the k_{app} for the reaction without DNA ($k_{app(DNA)}/k_{app(noDNA)}$), using 0.22 mM concentration of indole, i.e., 1 equiv with respect to **1**, was determined to be ~990- and 700-fold in the case of **2a** and **2p**, respectively (Table S4). This represents, to the best of our knowledge, the largest rate acceleration due to the biomolecular scaffold reported for a reaction catalyzed by a hybrid catalyst, to date.

The ee of the products **3a**, **3c**, and **3p** remained constant over the course of the reaction, which suggests that the reaction is essentially irreversible under the reaction conditions employed.

A plot of the observed pseudo first order rate constant k_{obs} versus initial indole concentration gave a straight line in the case of **2a** (Figure 1) and **2c** (Figure S1), consistent with a first order dependence on indole. In the case of 5-morpholino

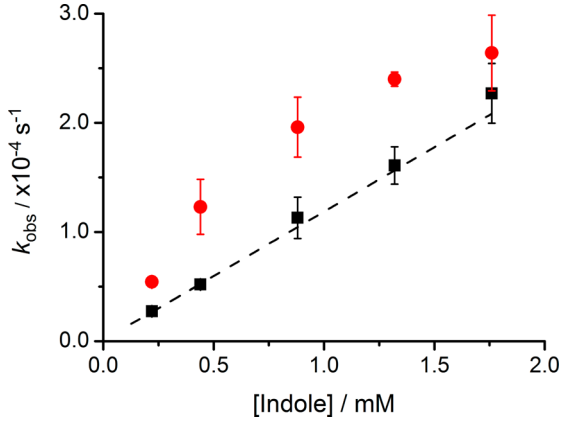


Figure 1. Kinetics of the Cu(II)-dmbipy/st-DNA catalyzed reaction of **1** with **2a** (black squares) and **2p** (red circles) as a function of indole concentration.

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indole (**2p**) a small but significant deviation from linearity was observed, suggesting saturation behavior (Figure 1).

The deuterium isotope effect on the reaction was determined by performing the DNA-based catalytic reactions in D_2O at pD = 5.4. First, the α-deuterated products **3a**-*d* and **3p**-*d* were prepared by performing the DNA-based catalytic reaction at preparative scale in D_2O at pD 5.4. ^1H and ^{13}C NMR analysis confirmed the formation of the α-deuterated products with >99% deuterium incorporation with ee's similar to those obtained for the results obtained for the corresponding α-protonated products **3a** and **3p**. The deuterated product **3a**-*d* was treated overnight with Cu(II)-dmbipy/st-DNA under the normal reaction conditions, i.e., in H_2O, MES buffer at pH 5, at 25 °C. NMR analysis of the product showed that in this time no D/H exchange had occurred, further confirming that the reaction is irreversible.

The kinetics were determined for the reaction between enone **1** and 1 equiv of indoles **2a**, **2c**, and **2p** in D_2O and compared to those in H_2O. A large primary kinetic deuterium isotope effect k_H/k_D = 5.1, 5.9, and 2.1 was measured in the case of indoles **2a**, **2c**, and **2p**, respectively (Table S5). This was confirmed for the reaction of **1** with **2a** in a competition experiment in a 90:10 mixture of D_2O and H_2O. ^1H NMR analysis of the product showed 50% incorporation of D at the α carbon, which corresponds to a $k_H/k_D \sim 5$ (Figure S4). Significant primary kinetic isotope effects have been reported in Sc^{3+} and organocatalyzed tandem conjugate additions/enantioselective protonations.[14b,15a]

Indole–DNA Binding Studies. The binding affinity of 5-methoxyindole (**2a**) and 5-morpholindole (**2p**) for DNA was determined by titration of st-DNA to indole, monitored by fluorescence spectroscopy at pH 5.0 (Figure S5). A moderate binding constant was measured for **2a** (Table 3, entry 1).

Table 3. Binding Constants for Binding of Indoles 2a and 2p to st-DNA at Various pH Values

entry	indole	pH	K_b (DNA)/M^{-1}	ee/%
1	**2a**	5.0	$3.42 \pm 0.16 \times 10^2$	59
2	**2p**	5.0	$1.45 \pm 0.11 \times 10^3$	84
3	**2p**	7.5	$4.28 \pm 0.23 \times 10^2$	19
4	**2p**	10	$2.19 \pm 0.03 \times 10^2$	3

However, **2p** exhibits a 1 order of magnitude stronger binding to DNA at pH 5.0 (Table 3, entry 2). This binding constant is in the same range as that previously observed for the copper(II) complexes with DNA.[6k] The higher binding affinity of **2p** was tentatively ascribed to an additional interaction with DNA provided by the protonated morpholine moiety. This is in agreement with reports that the presence of a morpholine moiety in the structure of DNA intercalating agents enhances the binding of DNA at acid pH values due to additional favorable electrostatic interactions.[21] This additional interaction of the DNA with **2p** could also be a reason for the higher ee's obtained in the case of **3p** compared to, for example, **3a**.

Using UV spectroscopy, the pK_a value of 5-morpholinoindole was determined to be 4.6 (Figure S6), which means that at pH 5 a significant fraction of **2p** is protonated. Indeed, at higher pH the K_b decreased to values similar to those obtained for **2a**. Performing the catalysis at these higher pH values also resulted in a significantly decreased enantioselectivity of the product.

These data suggest that, under the conditions of catalysis, ~60% of **2p** is bound to the DNA. The fact that, in addition to Cu(II)-dmbipy, **2p** also binds to DNA explains the saturation behavior observed in the kinetic experiments: at higher concentrations, **2p** starts to compete with Cu(II)-dmbipy for binding to DNA. Due to the DNA-accelerating effect, only the DNA-bound Cu(II)-dmbipy contributes to the observed reaction rate. Therefore, a lower fraction of Cu-dmbipy bound to DNA causes an overall slower reaction than expected, based on the overall concentration of Cu(II)-dmbipy present. This was indeed observed.

Implications for Mechanism. It is quite remarkable that, using the DNA-based catalytic system reported here, enantioselective protonation can be achieved in water as the reaction medium. A possible reason could be that the first hydration sphere in the DNA grooves, where the reaction most likely occurs,[9,10] is more structured than bulk water due to the interactions of the water molecules with the DNA and/or the copper ion.[6h,22] This will result in a transferable proton that is spatially well positioned with respect to the enolate intermediate, resulting in a preferred protonation from one prochiral face of the enolate and, hence, enantioselectivity in the product.

The combination of the enantioselectivities achieved, the measured large primary kinetic deuterium isotope effects, and the irreversibility of the reactions confirm that not only is the protonation step under kinetic control, which is a prerequisite for achieving enantioselectivity,[12,14] it is even part of the rate limiting step. This is surprising in view of the fact that proton transfer rates to enolates are generally diffusion controlled.[23]

An alternative possibility is that the reaction does not proceed via a stepwise mechanism involving a discrete enolate intermediate, but instead involves a concerted mechanism in which the conjugate addition of the indole to the β position occurs concurrently with the proton transfer to the α carbon. This would also require a transferable proton that is appropriately positioned within the microenvironment where the reaction occurs, i.e., the DNA groove. Both mechanisms are in agreement with the kinetic data presented above, and both would also rationalize the enantioselectivity achieved in the reaction, even though it takes place in aqueous medium.

Origin of DNA-Induced Rate Acceleration. Arguably, one of the most intriguing findings of this study is the large rate acceleration observed in the presence of DNA: the catalytic reactions proceed at least >700- and up to 990-fold faster in the presence of DNA compared to Cu-dmbipy alone, i.e., in the absence of DNA. This represents the highest rate acceleration reported due to the biomolecular scaffold in the field of artificial metalloenzymes, to date. DNA-accelerated catalysis has been observed before in DNA-based catalytic Diels–Alder reactions and Friedel–Crafts alkylation reactions with β-substituted enones, albeit that the acceleration factor in these cases was at least 1 order of magnitude lower.[4,7] It was proposed to be one of the key reasons for the selective catalysis achieved with the Cu(II)-dmbipy/st-DNA catalyst, despite the fact that the Cu(II) complex has only a moderate binding affinity for DNA: due to the DNA acceleration, the contribution of catalysis by unbound metal complex to the overall result is negligible.[4a] Yet, at that time there was no insight into the origins of the DNA-acceleration effect. The present study, in combination with a recent spectroscopic study on the binding of the Cu(II) complexes and enone substrates to DNA,[9,10] allows the assignment of the high effective molarity of all reaction components within the DNA structure as one of the key contributing factors. All reaction components, i.e., Cu(II)-

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dmbpy,[6k] enone,[10] and indole substrates, bind to DNA with moderate affinity. This aspect is important, because it ensures that, at any given time, all three components, i.e., Cu-dmbipy, enone (**1**), and indole **2**, are bound simultaneously in significant amounts, while there is still enough dynamics for the components to encounter each other and reaction to occur. In the case of high binding affinity of one of the components, this would outcompete the other components, resulting in saturation/inhibition behavior, as to some extent was observed with indole **2p**.

Thus, the DNA acts as a pseudophase, analogous to micellar aggregates in Lewis acid assisted micellar catalysis, in which all components, i.e., Cu-dmbipy, enone (**1**), and indole **2**, are concentrated.[24] The high effective molarity results in more efficient binding of the enone to the Cu(II) complex, and the resultant active substrate complex will always have indole substrate in close proximity, resulting in a fast reaction. However, the enantioselectivity achieved in the catalyzed Friedel–Crafts/enantioselective protonation reactions shows that effective molarity is not the only effect that contributes to the catalysis. Instead, this suggests the presence of chiral microenvironments within the DNA pseudophase in which additional second coordination sphere interactions favor the selective formation of one enantiomer of the product.

CONCLUSION

Here we have reported a novel DNA-based catalytic Friedel–Crafts conjugate addition/enantioselective protonation reaction in water, which critically depends on the DNA-induced rate acceleration. Indeed, the rate acceleration observed in this system is the highest reported due to the presence of a biomolecular scaffold for any hybrid catalyst to date. This high DNA-induced reactivity is of key importance for this reaction to occur both efficiently and (enantio-)selectively. The high effective molarity of all reaction partners plays a key role in the observed rate acceleration: the DNA binds all reaction components and thus acts as a pseudophase in which all reaction components are concentrated, analogous to micelles. The enantioselectivity of the product clearly suggests the involvement of additional second coordination sphere interactions. The results presented here show that the DNA-based catalysis concept, thanks to the DNA-accelerating effect, can be an effective approach to achieving a chemically challenging reaction in water.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b08295.

Results of control and additional experiments and full experimental details (PDF)

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Notes

The authors declare no competing financial interest.

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