On the Role of DNA in DNA-based Catalytic Enantioselective Conjugate Addition Reactions†

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A kinetic study of DNA-based catalytic enantioselective Friedel–Crafts alkylation and Michael addition reactions showed that DNA affects the rate of these reactions significantly. Whereas in the presence of DNA, a large acceleration was found for the Friedel–Crafts alkylation and a modest acceleration in the Michael addition of dimethyl malonate, a deceleration was observed when using nitromethane as nucleophile. Also, the enantioselectivities proved to be dependent on the DNA sequence. In comparison with the previously reported Diels–Alder reaction, the results presented here suggest that DNA plays a similar role in both cycloaddition and conjugate addition reactions.

Introduction

DNA has emerged as a versatile scaffold for synthesis and catalysis.[1,2,3] Particularly its ubiquitous chiral structure is attractive for applications in enantioselective catalysis. In our concept of DNA-based asymmetric catalysis, transfer of chirality is achieved by placing a catalytically active metal complex, based on a non-chiral ligand, in close proximity to the DNA-helix, using non-covalent interactions.[4] As a result the catalyzed reaction is directed towards the selective formation of one of the enantiomers of a chiral product, resulting in an enantiomeric excess (Fig. 1). This concept has been applied successfully to some of the archetypical C–C bond forming reactions such as the copper catalyzed Diels–Alder,[5] Michael addition[6] and Friedel–Crafts alkylation reaction;[7] in all cases ee's > 90% could be achieved. Recently, using this and related approaches, the scope of DNA-based catalysis has been extended to include hydrolytic kinetic resolution of epoxides,[8] allylic aminations[9] and aldol reactions.[10]

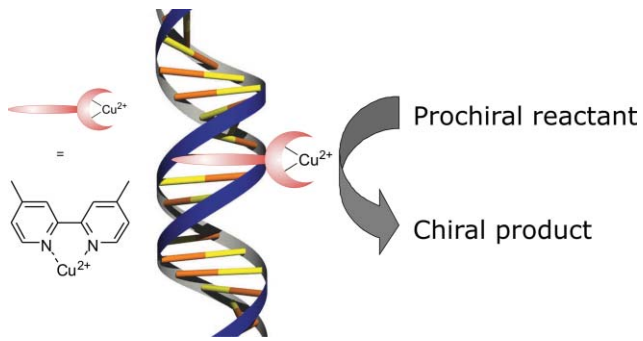

Fig. 1 Schematic representation of the concept of DNA-based asymmetric catalysis and the Cu^{II} complex of 4,4′-dimethyl-2,2′-bipyridine.

In case of the DNA-based copper catalyzed Diels–Alder reaction, kinetic studies have demonstrated that the role of DNA in the reactions can be quite different, depending on the nature of the copper complex. Using ligands of the first generation, which comprise an acridine intercalator that is attached *via* a spacer to an aminomethyl pyridine metal binding moiety, it was found that the catalyzed reaction is slightly slower in the presence of DNA.[11] Hence, in this case the role of DNA is primarily that of chiral scaffold. In contrast, using ligands of the second generation, in particular 4,4′-dimethyl-2,2′-bipyridine (dmbipy), the Diels–Alder reaction proved to be DNA-accelerated; rate accelerations of up to two orders of magnitude were observed in the presence of DNA.[12] In the latter case the DNA is more than a chiral scaffold and apparently participates actively in the catalytic event. Moreover, it was found that both the enantioselectivity and the rate acceleration were DNA sequence dependent, with the sequences that give rise to the highest ee's in the catalyzed reactions, also result in the strongest acceleration of this reaction.

In the light of the intriguing role of DNA in the Diels–Alder reaction, it was decided to explore the effect of DNA on the kinetics of the DNA-based copper catalyzed Michael addition and Friedel–Crafts alkylation reaction (Scheme 1). Both these reactions involve a conjugate addition of an anionic enolate-type or a neutral π nucleophile, respectively, to an α,β-unsaturated 2-acyl imidazole. Preliminary studies have indicated that in some cases indeed the reaction was DNA-accelerated. The goal of the present study was to determine the effect of DNA on the kinetics of DNA-based copper catalyzed conjugate additions, using Cu-dmbipy, which proved to be the most enantioselective catalysts in all these cases. Furthermore, a comparison between the observed effects in the Michael addition, Friedel–Crafts and Diels–Alder reaction is made, which sheds new light on the role of DNA in these reactions.

Results and Discussion

Since in both the Michael additions and Friedel–Crafts alkylations the highest enantioselectivities were obtained with Cu^{2+}-dmbipy/salmon testes DNA (st-DNA), this catalytic system was selected for further study. First-order reactions with respect to the nucleophiles were observed by time-dependent UV measurements both in the absence and presence of DNA, following the

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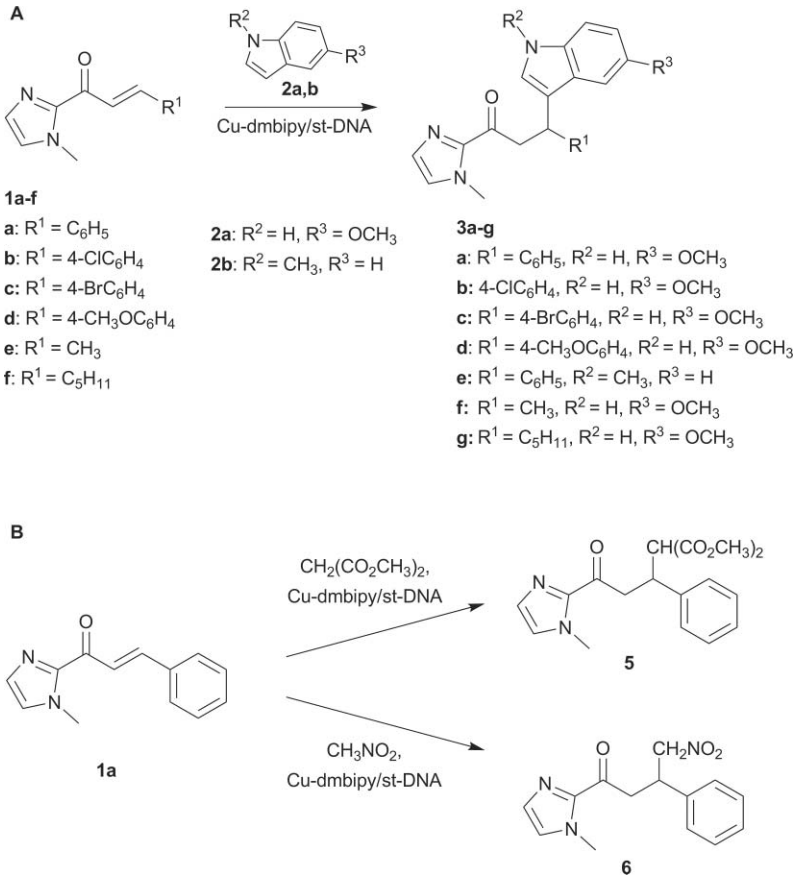
† Electronic supplementary information (ESI) available: characterization details of all reaction products



Scheme 1 DNA-based catalytic Friedel–Crafts alkylation (A) and Michael addition reactions (B).

methods developed by Engberts *et al.*[13] A large excess of Cu^{2+}-dmbipy/st-DNA with respect to the substrate was used, so that the dissociation of the addition product from the complex could be ignored in the overall reaction rate. Care should be exercised in extrapolating the data to turnover conditions, as it has been observed in some cases that the product dissociation step is rate limiting.[14]

Friedel–Crafts Alkylations

The kinetics of the asymmetric DNA-based Friedel–Crafts reaction of **2a** with **1f** were briefly studied before and a significant 30 fold rate acceleration was observed in the presence of st-DNA.[7] The generality of this phenomenon was investigated by a study of the effect of substituents at both the enone and the indole moiety. The results are shown in Table 1. In all cases, the presence of st-DNA had a significant positive effect on the rate of the reaction; rate accelerations ranged from 9–27 fold, depending on the enone used. The fastest reactions as well as the highest rate accelerations were found with enones carrying electron-withdrawing substituents such as 4-Cl or 4-Br at the aromatic moiety of the enone (entries 2–3). On the other hand, an electron-donating substituent such as 4-OCH_3 (entry 4) resulted in a slower reaction and a less pronounced acceleration by DNA than for the parent enone **1a**. Using *N*-methylindole **2b** as the π-nucleophile resulted in a smaller rate enhancement in the presence of DNA (entry 5). For the enones carrying an aliphatic substituent at the β carbon, an increase of the chain length resulted in a slightly lower addition rate, especially in the presence of DNA (entries 6 and 7). In general, no clear trend between the DNA acceleration factor and the ee of the product is apparent, which is in contrast with observations made previously for the Diels–Alder reaction.[12]

Table 1 Apparent second-order rate constants for the Friedel–Crafts reaction of substituted indoles to various enones.[a]

Entry	Product	Ee (%)[b]	k_{app} (DNA)[c]	k_{app} (no DNA)[c]	k_{DNA}/k_{noDNA}
1	**3a**	57	7.75×10^{-2}	4.31×10^{-3}	18
2	**3b**	79	0.135	6.45×10^{-3}	21
3	**3c**	66	0.235	8.96×10^{-3}	26
4	**3d**	69	4.62×10^{-2}	3.73×10^{-3}	12
5	**3e**	75	6.33×10^{-2}	7.02×10^{-3}	9.0
6	**3f**	83	0.842	3.10×10^{-2}	27
7	**3g**	80	0.429	2.72×10^{-2}	16

[a] Determined at 25 ± 0.2 °C. [b] Determined before on a semi-preparative scale.[7] [c] Values are given in $M^{-1}s^{-1}$, values are based on at least 4 experiments; errors in the rate constants were ≤ 9% in all cases.

Michael addition

The kinetic values for the Michael addition reaction of dimethyl malonate and nitromethane to **1a** are listed in Table 2. The Michael addition of dimethylmalonate and nitromethane to **1a** to give the Michael adducts **5** and **6**, respectively, was studied at pH 5.5, 6.5 and pH 7.5. The rate of the reactions was pH dependent with the

Table 2 The effect of pH on the ee and the rate of the Michael addition of dimethylmalonate and nitromethane to **1a**

Entry	pH	Ee (%)[a]	k_{app} (DNA)[b]	k_{app} (no DNA)[b]	$k_{DNA}/k_{no\ DNA}$
With $CH_2(CO_2CH_3)_2$:					
1[c]	5.5	95	n.d.[d]	n.d.[d]	
2	6.5	92	3.3×10^{-3}	1.0×10^{-3}	3.3
3	7.5	90	6.7×10^{-3}	1.1×10^{-3}[e]	6.1
With CH_3NO_2:					
4[c]	5.5	74	n.d.[d]	n.d.[d]	
5	6.5	85	1.2×10^{-4}	5.0×10^{-4}	0.24
6	7.5	77	6.0×10^{-4}	1.1×10^{-3}	0.55

[a] experiments performed on a semi-preparative scale using 100 eq of $CH(CO_2CH_3)_2$ or 1000 eq CH_3NO_2.[6] [b] Determined in duplicate, values are given in M^{-1} s^{-1}, errors in the rate constants were ≤ 15% in all cases. [c] MES buffer was used instead of MOPS. [d] n.d. = not determined: values were too low to be accurately determined. [e] Reactions were run in triplicate using the same batch of or Cu^{2+}-dmbipy solution with a fixed excess of the nucleophile (300 eq.).

fastest reaction observed at pH 7.5 (entries 3 and 6). This was expected since the actual nucleophilic species in the reactions is the enolate of dimethyl malonate and nitromethane. At pH 5.5 (using MES buffer instead of MOPS), incomplete conversion and significantly lower enantioselectivity was observed for the addition of nitromethane to **1a** to give **6** (entry 4). Dimethylmalonate as nucleophile did result in full conversion at pH 5.5 after 3 days, giving **5** in a slightly higher ee than at pH 6.5 (entry 2). The reaction rates for the addition of both nucleophiles at pH 5.5 were very low, and no reliable data could be extracted from time-dependent UV spectroscopy measurements.

In general, the reactions with dimethyl malonate (entries 1–3) are significantly faster than those with nitromethane (entries 4–6). From the pK_a values of both nucleophiles, an opposite effect would be expected; nitromethane's pK_A of ~10 in water[15] is 3 units lower than that of dimethylmalonate (pK_A around 13).[16] This means that in the buffer used, at a given initial concentration of nucleophile, approximately 1000 times more of deprotonated nitromethane is present than of deprotonated dimethylmalonate. However, this is not reflected in the reaction rates of the respective addition reactions in the presence or absence of DNA.

The observation that pK_a values and nucleophilicities are not correlated was made before.[17] Indeed, the anion of dimethylmalonate is about 3 orders of magnitude more nucleophilic than the anion of nitromethane for the nucleophilic addition to benzhydrilium ions in methanol.[17c] This was attributed to the notion that reactivity of these anions is controlled more by solvation than by their intrinsic properties, such as their basicities.

The effect of DNA on the reactions is also quite different for both Michael donors. The reactions with nitromethane are decelerated in the presence of DNA; 2–4 fold lower reaction rates were observed. In contrast, the addition of dimethylmalonate to **1a** is moderately accelerated by the presence of DNA. Indeed, in reactions at a preparative scale, a much smaller excess of dimethylmalonate is needed to obtain full conversion in the addition, as compared to nitromethane.

DNA sequence dependence of conjugate additions

For the Friedel–Crafts alkylation of 5-methoxyindole **2a** by the enones **1d** and **1e**, a remarkable effect of the DNA sequence on the ee of the reaction product has been observed (Table 3, entries 1–6). In the reaction with **1e**, the self-complementary oligonucleotide d(TCA GGG CCC TGA)$_2$ gave an increase of enantioselectivity from 83% (st-DNA, entry 4) to 93% (entry 5). In contrast, the reaction with **1d** showed a considerably lower ee with this oligonucleotide than with st-DNA (49% and 69%, respectively) (entries 1 and 2). In view of the significant rate acceleration of the Friedel–Crafts reaction by DNA, sequence-dependent reaction rates were measured to determine whether the rate of reaction is correlated to the ee of the product, as was the case in the DNA-based asymmetric Diels–Alder reaction. Oligonucleotide d(TCA GAG CTC TGA)$_2$, inducing a lower ee than st-DNA in both adducts **3d** and **3f**, was included in the study as well (entries 3 and 6).

Table 3 Sequence-dependent enantioselectivity and apparent second-order rate constants[a] in the DNA-based catalytic Friedel–Crafts alkylation and Michael addition reactions

Entry	Product	DNA	Ee (%)[a]	k_{app}/M^{-1} s^{-1}[b]
Friedel–Crafts reaction:				
1	**3d**	st-DNA	69	3.10×10^{-2}
2		d(TCA GGG CCC TGA)$_2$	49	1.52×10^{-2}
3		d(TCA GAG CTC TGA)$_2$	32	1.45×10^{-2}
4	**3f**	st-DNA	83	0.63
5		d(TCA GGG CCC TGA)$_2$	93	0.66
6		d(TCA GAG CTC TGA)$_2$	65	0.31
Michael addition:				
7	**5**	d(TC GGG AT CCC GA)	86	2.2×10^{-3}
8		d(TCA GGG CCC TGA)	93	2.6×10^{-3}
9		d(TC GG AA TT CC GA)	76	2.7×10^{-3}
10		d(TCG CGA TCG CGA)	71	1.2×10^{-3}
11		d(TCG CGT ACG CGA)	74	1.5×10^{-3}
12		st-DNA	90	6.5×10^{-3}
13		no DNA	—	1.9×10^{-3}

[a] Determined under standard conditions.[6,7] [b] Determined at 18 ± 0.2 °C, values are based on at least 3 experiments, errors are <9% in for the Friedel–Crafts reactions (entries 1–6) and <20% for the Michael addition reactions (entries 7–13).

The influence of the DNA sequence on the reaction rate is small, despite the substantial effect on the enantioselectivity of the product. No significant rate increase caused by the oligonucleotide d(TCA GGG CCC TGA)$_2$ relative to st-DNA in the addition of **2a** to **1e** was observed (entries 4 and 5). The oligonucleotide d(TCA GAG CTC TGA)$_2$, which induces a lower ee in **3f** than st-DNA, also gives a lower reaction rate, although the effect is rather small (entry 6). The same holds for the reaction between **1d** and **2a**, displaying a lower enantioselectivity using both oligonucleotides than using st-DNA (entries 1–3); in these cases reaction rates are a factor 2 lower compared to st-DNA.

For the Michael reaction of enone **1a** with dimethylmalonate, apparent rate constants and ee's were determined for a selection of synthetic oligonucleotides (entries 7–11). Oligonucleotide d(TC GGG AT CCC GA)$_2$ was chosen as the parent sequence because the binding mode of a few transition metal complexes to this synthetic duplex has been studied.[18,19,20] Variation in the number of consecutive deoxyguanines (3, 2 or 1) and the central AT sequence (present, absent or inversed) showed interesting effects in the DNA-based Diels–Alder reaction. Indeed, the highest ee, that is 93% (entry 8), for the Michael addition were found with d(TCAGGGCCCTGA)$_2$ which also gave the highest ee's in the Diels–Alder reaction of azachalcone with cyclopentadiene and the

Friedel–Crafts alkylation of **2a** with **1e**. There appears to be some relation between the ee and the apparent rate constant, albeit that the effects are too small to justify any conclusions. It is likely that the optimal DNA sequence has not been identified yet, as catalysis in the presence of st-DNA proceeds at least 2.5 times faster than in the presence of the tested synthetic oligonucleotides.

Comparison Friedel–Crafts *vs.* Michael reaction

From the enantioselectivities and kinetic data presented above it is apparent that the DNA-based catalytic asymmetric Michael additions and Friedel–Crafts alkylations, both conjugate addition reactions, have some common characteristics, but there are also notable differences. Both reactions types can be catalyzed efficiently by a DNA-based catalyst, giving rise to excellent enantioselectivities. Moreover, the enantioselectivities are DNA-sequence dependent, but different substrates have different sequence requirements.

However, a major difference is the effect DNA has on the rate of the catalyzed reactions. The presence of DNA causes significant rate accelerations up to 27 fold in the Friedel–Crafts alkylation. However, in the Michael addition with dimethylmalonate only a modest rate acceleration, that is, up to 3-fold, was found in the presence of DNA. Using nitromethane as the Michael donor even a significant deceleration of the reaction was observed. These differences are tentatively explained by considering the nature of the nucleophilic species. Whereas the Friedel–Crafts alkylations involve conjugate addition of a charge neutral aromatic π-nucleophile, the Michael addition involves an anionic enolate-type nucleophile, which can be expected to experience significant charge repulsion from the negatively charged DNA backbone. Hence, approach of the nucleophile to the copper coordinated enone, which is bound to the DNA, is unfavorable resulting in a less accelerated or even decelerated reaction.

Considering this, the good ee's obtained for **6** are particularly noteworthy, considering that the binding constant $K_b = 1.12 \pm 0.02 \times 10^4$ M^{-1},[5] which means that ~5% unbound Cu^{2+}-dmbipy is present in solution. The free complex, that is, not bound to DNA, catalyzes the addition of nitromethane up to 5 times more efficiently, giving rise to racemic product. Hence, ee's up to 85% can only be achieved if the conjugate addition catalyzed by Cu^{2+}-dmbipy/DNA is almost completely enantioselective.

Implications for the role of DNA in catalysis

Comparison of the results presented here for the DNA-based catalytic enantioselective conjugate additions with those previously reported for the Diels–Alder reaction reveal some striking similarities.

The enantioselectivities are sequence dependent, with the highest ee's obtained with sequences containing stretches of G's. Particularly noteworthy is that in the majority of reactions investigated, that is, the Diels–Alder reaction of azachalcone with cyclopentadiene, the Friedel–Crafts alkylation of **2a** with **1e** and the Michael addition of dimethyl malonate to **1a**, the self-complimentary oligonucleotide d(TCA GGG CCC TGA)$_2$ proved to give rise to the highest ee's.

Interestingly, the stereochemistry of the catalyzed reactions is predictable; in all cases the product resulting from the attack of the diene or nucleophile from the *Si* face of the enone is obtained in excess.[6,7,21] This suggests a similar enantiodiscriminating mechanism applies to all three reaction class investigated.

Also in all cases the DNA sequence has an influence on the rate of the reaction, albeit that this effect is less pronounced in the conjugate addition reactions than in the Diels–Alder reaction. In the Diels–Alder reaction, rate accelerations of up to 2 orders of magnitude were found whereas in the Friedel–Crafts reaction this is up to 1 order of magnitude and in the Michael addition of dimethyl malonate only a 3–4 fold increase was observed. However, in the latter case the repulsive interaction between the anionic nucleophile and the DNA negatively affects the rate acceleration (*vide supra*).

Combined these observations suggest that DNA plays a similar role in the Diels–Alder, Michael addition and Friedel–Crafts alkylation reactions. Since these reactions involve structurally different activated complexes, it is unlikely that transition state stabilization by the DNA is a major contributor to all. Instead, these three reaction classes have a structurally very similar ground state. Therefore, it is hypothesized that it is here that DNA exerts its influence, resulting in enantioselectivity and rate acceleration.

The Michael addition of nitromethane is the only exception to date, since it is decelerated by the presence of DNA. At present the origin of this deceleration is unknown and will be studied further.

Experimental

Catalytic experiments, general procedure. To an ice-cold solution (prepared 24 h in advance) of DNA (final concentration 1.3 mg mL^{-1} or 2 mM in base pairs) in MOPS buffer (final concentration 20 mM, pH 6.5 or 7.5), a solution of [Cu(dmbipy)$(NO_3)_2$] in doubly distilled water was added to a final concentration of 0.3 mM. The solution was equilibrated by gentle mixing, and the enone was added as a stock solution in acetonitrile. The nucleophile was added neat or as a stock solution in acetonitrile, and the reaction was mixed by continuous inversion at 5 °C. Experiments were run until full conversion was obtained, unless noted otherwise. After the indicated time,[6,7] the reaction mixture was extracted with ethyl acetate (3 × 5 mL). After drying (Na_2SO_4) and removal of the solvent, the crude product was analyzed by ^{1}H-NMR to determine conversion and HPLC on a chiral stationary phase for ee. The ee values are based on at least 2 experiments and are reproducible within 2%.

Determination of rate constants using time-dependent UV-Vis spectroscopy. Rate constants for a variety of DNA-based Michael additions to enones were determined under similar conditions as described by Boersma *et al.*[12] Freshly dialyzed st-DNA (final concentration 0.67 mg mL^{-1} in 20mM MOPS pH 6.5) was used, and this was pre-equilibrated at 5 °C for 18h with Cu^{2+}-dmbipy at a final concentration of 0.15 mM (1 complex per ~6–7 base pairs). After transfer of the solution thus obtained to a cuvette, the substrate was added to give a final concentration of 6.0 μM (Michael additions) or 14 μM (Friedel–Crafts reactions). The appropriate amount of the nucleophile (typically to a final concentration of 0.9 mM (dimethylmalonate), 9.0 mM (nitromethane) or 0.5–2.0 mM (**2a**,**b**) was then added as a stock solution in acetonitrile (nitromethane and indoles) or 20 mM MOPS pH 6.5 (dimethylmalonate) and the cuvette was gently shaken. The UV absorption was monitored 335 nm (Michael additions to **1a**) or 340 nm (Friedel–Crafts alkylations

to **1a–f**) at a temperature of 25.0 ± 0.2 °C. For the reactions with half-lives of more than approx. one hour, apparent rate constants were determined by initial-rate kinetics with the following expression:[13] $k_1 = \frac{d(A_{enone})}{dt} \cdot \frac{1}{d \cdot \Delta\varepsilon \cdot [enone]_0}$, in which $d(A_{enone})/dt$ is the slope of the decrease of absorption in time, d the pathlength of the cuvette (1 cm), $\Delta\varepsilon$ the difference in extinction coefficients of the substrate and the product (determined separately) and $[enone]_0$ is the initial substrate concentration. Apparent second-order rate constants were then deduced from the slope of a plot of these values of k_1 *versus* the concentration of nucleophile. For faster reactions (complete conversion within several hours, *viz.* Friedel–Crafts alkylations of **2a**,**b** by **1e–f**), the decrease of absorption in time (A_t) was curve-fitted using Grafit 3.0 (Erithacus Software Ltd., 1992) to the exponential equation $A_t = A_\infty + A_0 \cdot e^{-k1 \cdot t}$, giving apparent rate constants k_1 directly.

Synthesis of substrates and identification of products. Enone substrates **1a–f**[22] were synthesized according to published procedures. Indoles **2a**,**b** were commercially available from Sigma-Aldrich and used without further purification. Analytical data of adducts **3b**,**d–f**, **5** and **6** were in accordance with literature.[6,7] Addition products, for which initial-rate kinetics were used to study rate constants, were synthesized independently as a racemate, starting from 0.25 mmol of enone, 0.25 mmol of copper(II) nitrate and 5 eq. of the appropriate nucleophile in 5 mL of distilled water overnight. The adducts were purified by flash-column chromatography and their molar extinction coefficients were determined in a concentration range close to that of the catalytic reactions (typically 4–40 μM).

3-(5-methoxy-1*H*-indol-3-yl)-1-(1-methyl-1*H*-imidazol-2-yl)-3-phenyl-1-propanone (3a). Purified by flash column chromatography (SiO_2, hexane–ethyl acetate 1 : 2, R_f 0.25), giving a light brown solid, mp 139 °C (dec.); ^{1}H NMR: δ 8.07 (br s, 1H), 7.38 (d, J 8.0, 2H), 7.20–7.26 (m, 2H), 7.11–7.20 (m, 3H), 7.09 (d, J = 2.4, 1H), 6.98 (s, 1H), 6.92 (d, J = 2.2, 1H), 6.78 (dd, J = 8.8, 2.4, 1H), 5.01 (t, J = 7.6, 1H), 4.01 (dd, J = 16.3, 7.4, 1H), 3.90 (s, 3H), 3.82 (dd, J = 16.4, 7.8, 1H), 3.75 (s, 3H);^{13}C NMR: δ 190.88 (s), 153.48 (s), 144.22 (s), 142.98 (s), 131.61 (s), 128.69 (d), 128.18 (d), 127.81 (d), 126.98 (s), 126.95 (d), 126.00 (d), 122.15 (d), 118.74 (s), 111.83 (d), 111.68 (d), 101.10 (d), 55.64 (q), 45.29 (t), 37.92 (d), 35.94 (q) MS (ESI) m/z 382 ([M+Na]$^+$), 360 ([M+H]$^+$), 236, 213; HRMS calcd for $C_{22}H_{22}N_3O_2$ ([M+H]$^+$): 360.1707, found: 360.1700; HPLC: Chiralpak AD, heptane/*i*-PrOH 80/20, flow 1.0 mL min^{-1}, T_r 19.1, 26.9 min.

3-(4-bromophenyl)-3-(5-methoxy-1*H*-indol-3-yl)-1-(1-methyl-1*H*-imidazol-2-yl)-1-propanone (3c). Purified by flash column chromatography (SiO_2, hexane–ethyl acetate 1 : 2, R_f 0.29), ^{1}H NMR: δ 8.50 (br s, 1H), 7.55 (d, J = 7.9, 1H), 7.12–7.22 (m, 3H), 7.09 (t, J = 7.5, 1H), 7.04 (d, J = 2.4, 1H), 6.96–7.01 (m, 3H), 6.77 (dd, J = 2.4, 8.8, 1H), 5.47 (t, J = 7.7, 1H), 4.18 (dd, J = 8.1, 16.2, 1H), 3.90 (s, 3H), 3.76 (s, 3H), 3.56 (dd, J = 6.7, 16.2, 1H); ^{13}C NMR: δ 190.40 (s), 153.72 (s), 143.16 (s), 143.06 (s), 132.66 (d), 131.56(s), 129.46 (d), 128.91 (d), 127.64 (d), 127.16 (s), 122.36 (d), 124.10 (s), 118.00 (s), 112.27 (d), 111.66 (d), 101.27 (d), 55.68 (q), 44.39 (t), 37.16 (d), 36.11 (q); MS (ESI) m/z 462 ([M+Na]$^+$), 460 ([M+Na]$^+$), 440 ([M+H]$^+$), 438 ([M+H]$^+$), 422, 420, 316, 314, 293, 291, 122; HRMS calcd for $C_{22}H_{21}BrN_3O_2$ ([M+H]$^+$): 438.0812, found: 438.0805; HPLC: Chiralpak AD, heptane/*i*-PrOH 90/10, flow 1.0 mL min^{-1}, T_r 37.1, 46.8 min.

3-(5-methoxy-1*H*-indol-3-yl)-1-(1-methyl-1*H*-imidazol-2-yl)-1-octanone (3g). Purified by flash column chromatography (SiO_2, hexane–ethyl acetate 2 : 1, R_f 0.21), giving a brown oil. ^{1}H NMR: δ 7.83 (br s, 1H), 7.20 (d, J = 9.0, 1H), 7.12 (d, 0.91, 1H), 7.05 (dd, J = 2.4, 17.7, 2H), 6.96 (s, 1H), 6.81 (dd, J = 2.4, 8.7, 1H), 3.85 (s, 3H), 3.82 (s, 3H), 3.63–3.69 (m, 1H), 3.44–3.57 (m, 2H), 1.71–1.82 (m, 2H), 1.20–1.31 (m, 6H), 0.82 (t, 7.9, 3H), ^{13}C NMR: δ 192.3 (s), 153.5 (s), 143.2 (s), 131.4 (s), 128.6 (d), 127.3 (s), 126.7 (d), 121.8 (s), 119.1 (s), 111.7 (d), 111.6 (d), 101.0 (d), 55.8 (q), 45.6 (t), 36.0 (t), 36.0 (d), 32.2 (q), 31.9 (t), 27.1 (t), 22.5 (t), 14.0 (q); MS (ESI) m/z 376 ([M+Na]$^+$), 354 ([M+H]$^+$), 149; HRMS calcd for $C_{21}H_{28}N_3O_2^+$ ([M+H]$^+$): 354.2176, found: 354.2184; HPLC: Regis (*R*,*R*)-Whelk-O 1, 0.04% diethylamine in heptane/*i*-PrOH 80/20, flow 0.5 mL min^{-1}, T_r 35.6, 42.3 min.

Conclusions

In the DNA-based catalytic enantioselective Michael addition and Friedel–Crafts alkylation reaction, the role of the DNA is not limited to that of a chiral scaffold. It was shown that in both these conjugate addition reactions, the DNA affects the reaction rate, with the largest rate accelerations observed in case of the Friedel–Crafts alkylation. In the case of the Michael addition the effect is dependent on the Michael donor: with dimethylmalonate a modest increase of reaction rate was observed, whereas with nitromethane a deceleration of the reaction was found in the presence of DNA. The lower rates found for the Michael addition compared to the Friedel–Crafts alkylation were attributed to charge repulsion between the anionic nucleophile and the negatively charged DNA backbone

From a comparison with the DNA-based catalytic enantioselective Diels–Alder reaction, it was found that the role of DNA is comparable in both reaction classes, suggesting that similar factors play a role in the observed enantioselectivity and reaction rate acceleration. It is suggested that the DNA predominantly has an effect on the ground state of these reactions.

Based on the observed generallity of the DNA-induced enantioselectivity and rate acceleration, it is envisioned that the DNA-based catalysis concept can be applied to other enantioselective transition metal catalyzed reactions as well.

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