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Ligand denticity controls enantiomeric preference in DNA-based asymmetric catalysis†

Arnold J. Boersma,[a] Bas de Bruin,[b] Ben L. Feringa*[a] and Gerard Roelfes*[a]

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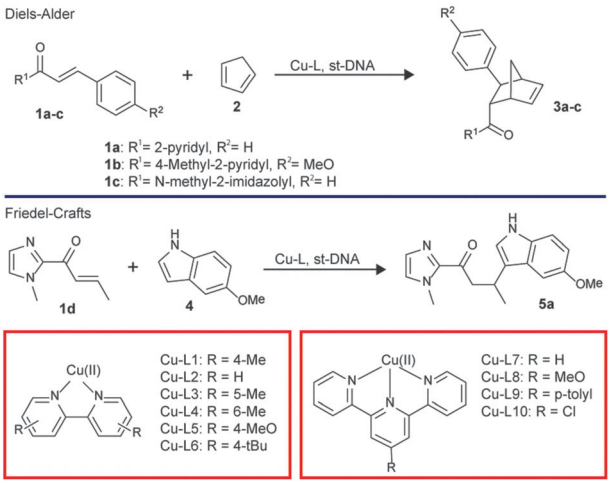
DNA-based catalysis can be used to control the enantioselectivity of copper-catalysed Diels–Alder and Friedel–Crafts reactions to produce either enantiomer of the product by changing the denticity of the ligand coordinated to the Cu(II) ion, even though the DNA adopts a right handed helical conformation only.

Artificial metalloenzymes have shown great potential in enantioselective catalysis.[1,2] Using protein or DNA as a chiral host for catalytically active transition metal complexes, excellent enantioselectivities have already been achieved in a variety of reactions. However, one of the major challenges in this area is how to obtain both enantiomers of the product in a selective fashion at will, since the biomolecular host is generally available as a single enantiomer. In protein based artificial metalloenzymes, a combination of chemical optimisation of the ligand and mutagenesis of the host protein can be used to obtain the opposite enantiomer of the reaction product of the catalysed reaction.[3] Here we show that control over the enantiomeric preference in DNA-based asymmetric catalysis is achieved by changing the denticity of the poly-pyridine-type ligand bound to the transition metal.

DNA-based asymmetric catalysis involves binding of a catalytically active metal complex of an achiral ligand to DNA *via* a covalent linkage or supramolecular interactions.[4,5] The proximity to the DNA allows for the chiral environment of the DNA-helix to direct a catalysed reaction towards selective formation of one of the enantiomers of a chiral product. Especially the supramolecular approach has been applied successfully to the archetypal C–C bond forming reactions; the Diels–Alder reaction,[6] the Michael addition,[7] and the Friedel–Crafts alkylation.[8] In all these cases excellent enantioselectivities, and in multiple cases even up to 99% ee, have been found using the Cu(II) complex of 4,4′-dimethyl-2,2′-bipyridine (Cu–L1) in combination with salmon testes DNA (st-DNA). Interestingly, an analysis of the absolute configuration of



Scheme 1 DNA-based catalytic asymmetric reactions and Cu(II) complexes of bi- and terpyridine ligands used in this study.

the Diels–Alder, Michael and Friedel–Crafts product revealed that the enantiomeric outcome of the reaction is predictable: the reactant, that is the diene or nucleophile, always attacks the Cu(II) bound enone substrate from the same π-face.[6–8] This suggests a similar mechanism of enantioselection induced by DNA for all three reaction classes. With the first generation DNA-based catalysts, which are based on acridine intercalators and give only moderate enantioselectivity in the aforementioned C–C bond forming reactions, control over the enantiomeric outcome of the reaction was achieved by variation of the ligand structure.[9] However, the 2,2′-bipyridine derived ligands of the second generation such as L1, which induce the highest ee's in these reactions, offer much less opportunities for structural variation. For this reason we have investigated the possibility of changing the structure of the substrate bound complex by variation of the ligand denticity, by comparison of a series of bi- and terpyridine ligands in DNA-based asymmetric catalysis (Scheme 1).

The DNA-based catalysts were prepared *via* self-assembly of Cu–L with st-DNA. The Cu–L/st-DNA catalysed Diels–Alder reaction between aza-chalcone **1a** and cyclopentadiene **2** was used as the benchmark reaction.[10] This reaction results in the formation of the *endo* and *exo* isomers, with the *endo* isomer being the major product. Therefore only the enantiomeric excess of the *endo* isomer is discussed.

[a] *Stratingh Institute for Chemistry, University of Groningen, Nijenborgh 4, 9747 AG Groningen, The Netherlands. E-mail: b.l.feringa@rug.nl, j.g.roelfes@rug.nl*
[b] *Van't Hoff Institute for Molecular Sciences, University of Amsterdam, Science Park 904, 1098 XH Amsterdam, The Netherlands*

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Table 1 Effect of ligand structure on the ee obtained in DNA-based asymmetric catalysis[a]

	Cu–L	Reactants		Conversion[b] (%)	*Endo* : *exo*[c]	ee[c] (%)
Diels–Alder reaction						
1[d]	Cu–L1	**1a**	**2**	Full	>99 : 1	99 (+)
2[d]	Cu–L2	**1a**	**2**	Full	98 : 2	90 (+)
3	Cu–L3	**1a**	**2**	Full	98 : 2	89 (+)
4	Cu–L4	**1a**	**2**	Full	95 : 5	40 (−)
5	Cu–L5	**1a**	**2**	Full	99 : 1	95 (+)
6	Cu–L6	**1a**	**2**	Full	98 : 2	92 (+)
7	Cu–L7	**1a**	**2**	23	89 : 11	60 (−)
8	Cu–L8	**1a**	**2**	20	92 : 8	79 (−)
9	Cu–L9	**1a**	**2**	Full	94 : 6	28 (−)
10	Cu–L10	**1a**	**2**	17	92 : 8	71 (−)
11	Cu–L1	**1b**	**2**	25	>99 : 1	>+99[e]
12	Cu–L7	**1b**	**2**	10	92 : 8	−92[e]
13[f]	Cu–L1	**1c**	**2**	>80	99 : 1	97 (2*S*,3*S*)
14	Cu–L7	**1c**	**2**	15	82 : 18	42 (2*R*,3*R*)
Friedel–Crafts alkylation						
15[g]	Cu–L1	**1d**	**4**	Full	—	83 (+)
16	Cu–L7	**1d**	**4**	20	—	50 (−)

[a] Reactions performed with 1 mM substrate, 8 mM **2** (or 5 mM **4**), 0.3 mM Cu–L, 2 mg ml^{-1} st-DNA, in 20 mM mops buffer pH 6.5, for 3 days at 5 °C. All data averaged over two experiments. [b] Determined by ^{1}H-NMR. [c] Determined by HPLC. [d] Data from ref. 6*a*. [e] + and − sign correspond to elution order on the HPLC (first and second, respectively). [f] Data taken from ref. 6*b*. [g] Data taken from ref. 8.

First, a series of bidentate ligands with varying substitution patterns were investigated. Based on the results of the catalysis, it can be concluded that the substitution pattern on the bipyridine ligand has a significant effect on the enantioselectivity of the Diels–Alder reaction (Table 1, entries 1–6). In particular, substitution at the 4 and 4′-position of the ligand gave rise to an increase of the ee of the (+)-enantiomer compared to Cu–L2, which has no substituents. Since the substitution of the 4 and 4′-position is too remote to have a direct effect on the coordination of **1a** to the copper(II) ion, it is likely that substituents at this position enforce a more favourable binding geometry around the copper(II)–ligand complex in the DNA in order to affect higher ee's in the catalysed reaction. Notably, Cu–L6, which contains bulky *tert*-butyl groups at the 4- and 4′-position, still gives rise to a higher ee than Cu–L2 (entry 6). A methyl substituent at the 5 and 5′-position induced a similar ee as Cu–L2 (entry 3). Surprisingly, when the methyl groups are placed at the 6 and 6′-position, the (−)-enantiomer of the Diels–Alder product was obtained with an ee of 40% (entry 4). This is the opposite enantiomer than produced by the non-substituted or 4,4′- and 5,5′-substituted bipyridine complexes in st-DNA.

Catalysts based on the terpyridine-type ligands L7–L10 gave invariably rise to an excess of the (−)-enantiomer (entries 7–10), albeit that the ee's were generally lower than those obtained with the bipyridine ligands (Table 1, entry 7). An electron donating or withdrawing substituent at the 4 position of the central pyridine moiety led to an improved ee (entries 8 and 10), whereas a large tolyl substituent at the same position caused a significantly decreased ee (entry 9). This suggests that the substituents influence the ee by steric effects mainly, as opposed to electronic effects. Notably, the catalysts based on terpyridine-type ligands gave rise to a significantly lower conversion compared to bipyridine-type ligands as well as a lower *endo* : *exo* ratio. An exception is when using L9: in this case full conversion was achieved (entry 9).

The inversion of the enantiomeric outcome of the catalysed reaction upon going from the bipyridine ligand L1 to the terpyridine-type ligands is independent of the substrate and reaction-type. In the presence of Cu–L7/st-DNA, the Diels–Alder reaction between **1c** and **2** gave **3c** with an ee of 42% (2*R*,3*R*-enantiomer), compared to 97% ee of the 2*S*,3*S*-enantiomer in the case of Cu–L1 (entries 13,14), and the Friedel–Crafts reaction between **1d** and **4** induced an ee of 50% of the (−)-enantiomer (entry 16), compared to 83% ee of the (+)-enantiomer in the case of Cu–L1 (entry 15). The most dramatic differences in enantiomeric outcome were obtained in the Diels–Alder reaction of **1b** with **2**; using Cu–L1/st-DNA or Cu–L7/st-DNA as catalyst, the corresponding Diels–Alder product was obtained with > +99 and −92% ee, respectively (Table 1, entries 11 and 12; in this case the + and − sign indicate elution order from the chiral HPLC: first and second, respectively).

These results indicate that the geometry of the Cu(II)–substrate complex is crucial to the enantiomeric preference observed. To shed some light on the geometries of the Cu(II)–substrate complexes, DFT calculations of the structure of [Cu–L1(**1b**)$(H_2O)]^{2+}$, $[Cu–L1(\mathbf{1b})_2]^{2+}$ and [Cu–L7(**1b**)$(H_2O)]^{2+}$ were performed in the absence of DNA. Different geometrical isomers of these complexes were examined, of which the most stable ones are depicted in Fig. 1.

Attempts to optimise the octahedral bis-aqua complex $[Cu–L1(\mathbf{1b})(H_2O)_2]^{2+}$ led spontaneously to the mono-aqua complex $[Cu–L1(\mathbf{1b})(H_2O)]^{2+}\cdot H_2O$, which is best described as a 5-coordinate trigonal bipyramidal complex to which an additional water molecule hydrogen bridges with both the carbonyl moiety of the coordinated substrate and the aqua ligand. The 5-coordinate mono-aqua complex $[Cu–L1(\mathbf{1b})(H_2O)]^{2+}$ without this additional hydrogen bonded water molecule was calculated to be ~9 kcal mol^{-1} (b3-lyp, def-TZVP) less stable than $[Cu–L1(\mathbf{1b})(H_2O)]^{2+}\cdot H_2O$.

Formation of the bis-substrate adduct $[Cu–L1(\mathbf{1b})_2]^{2+}$ from the mono-substrate adduct $[Cu–L1(\mathbf{1b})(H_2O)]^{2+}\cdot H_2O$ and an additional substrate molecule is energetically favoured

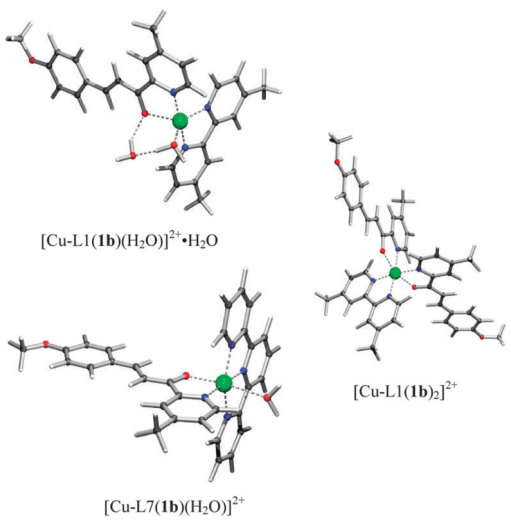

Fig. 1 DFT optimised geometries of $[Cu–L1(\mathbf{1b})(H_2O)]^{2+}\cdot H_2O$, $[Cu–L1(\mathbf{1b})_2]^{2+}$, and [Cu–L7(**1b**)$(H_2O)]^{2+}$ in the absence of st-DNA.

($\Delta E \approx 19$ kcal mol^{-1}) according to DFT. The relevance of the bis-substrate adduct to DNA-based catalysis is not yet clear, since this depends for example on the kinetics of the catalysed reaction, the rate of complex formation, and the influence of DNA on these parameters. However, the fact that the carbonyl oxygen is coordinated at the axial position suggests that the enone in this case is less activated (see below) and, thus, most likely less reactive.

[Cu–L7(**1b**)(H_2O)]$^{2+}$ was found to have an octahedrally coordinated Cu^{2+} ion with the pyridine nitrogen atoms and the pyridyl nitrogen of the substrate occupying the equatorial plane and the carbonyl oxygen and a water molecule at the axial positions.[11]

The combined experimental and theoretical results, even if these were obtained for the catalyst in the absence of DNA‡, strongly suggest that the different structure of the ternary complex Cu–L1–**1b** compared to Cu–L7–**1b** is related to the observed inversion in enantiomeric preference of the catalysed Diels–Alder reaction. Changing the binding geometry of the substrate apparently causes the chiral pocket created by the DNA to favour the opposite enantiomer, either by shielding or facilitating the attack of the diene or nucleophile from the opposite face of the enone. This also rationalises the results obtained when using L4: the proximal methyl groups of ligand L4 should force the substrate to adopt a different binding geometry, more reminiscent of the structure of [Cu–L7(**1b**)(H_2O)]$^{2+}$. The proposed structures also account for the observed differences in activity of the bipyridine compared to the terpyridine based catalysts, with the exception of Cu–L9. In Cu–L1–**1b**, the carbonyl oxygen is coordinated on a pseudo-equatorial site, which results in a better activation of **1b**, compared to Cu–L7–**1b**, where it is bound at the axial position.[12] An intriguing aspect of the calculated structure of Cu–L1–**1b** is the water molecule that was found to bridge the carbonyl oxygen of **1b** and the Cu(II) coordinated water molecule *via* hydrogen bonding. Although it cannot be established at present whether such a bridging interaction could be present in the DNA-based system, it does constitute an example of a second coordination sphere interaction that could be important for the observed stereochemistry and catalytic activity.

In conclusion, in the present communication it is shown that DNA-based catalysis can be used to produce both enantiomers of the product of the catalysed reaction selectively by judicious choice of ligands for the Cu(II) ion, even though salmon testes DNA adopts a right handed helical conformation only. This enantiomeric preference was demonstrated to be related to the denticity of the ligand and the resulting structure of the substrate bound copper complex. In contrast to Cu–L1/st-DNA, which has been shown to be competitive with conventional homogeneous catalysts in several reactions,[13] further optimization of the Cu-terpy type catalysts, *i.e.* to enhance their catalytic activity, is required for synthetic applications. Current investigations are directed towards elucidating the structure of the substrate coordinated complexes when bound to DNA and identifying the second coordination sphere interactions that are important for enantioselective catalysis.

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Notes and references

‡ Computational studies of the Cu–L–**1b** complex bound to DNA, such as docking experiments, are at present not feasible. A key requirement for obtaining useful data from docking experiments is knowledge about the DNA binding mode of these complexes, *e.g.* intercalation *vs.* groove binding. However, to date this information is not available.

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