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DNA-based asymmetric catalysis
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Chapter 2
Highly enantioselective DNA-based asymmetric catalysis

In this chapter a new approach to DNA-based asymmetric catalysis is presented, which enables high enantioselectivities in the Cu(II)-catalyzed Diels–Alder reaction to be achieved. The results presented demonstrate that the DNA is the source of chirality in these reactions and that the close contact between DNA and the copper complex allows for direct transfer of this chirality during the catalyzed reaction. It is shown that \( \alpha, \beta \)-unsaturated 2-acyl imidazoles are an alternative and practical class of dienophiles for the DNA-based catalytic asymmetric Diels–Alder reaction in water. The Diels–Alder products are obtained with excellent diastereoselectivity and enantioselectivity, and the imidazole auxiliary is readily displaced.

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G. Roelfes, A. J. Boersma, B. L. Feringa, Chem. Commun. 2006, 635
A. J. Boersma, B. L. Feringa, G. Roelfes, Org. Lett. 2007, 9, 3647
2.1 Introduction

Recently, a novel DNA-based asymmetric catalysis concept based on the modular assembly of a DNA-based catalyst, i.e. DNA with extended catalytic functionality, attached in a non-covalent manner, was introduced by our group. This catalytic ensemble comprises a copper complex of a non-chiral ligand, which incorporates a metal binding site, a spacer and a covalently attached intercalator, i.e. 9-amino acridine. As a result, the active Cu(II) centre is brought into proximity of the chiral environment of the DNA double helix, allowing asymmetric induction during the reaction. With this approach an enantiomeric excess of 50% for the major (endo) isomer and up to 90% for the minor (exo) isomer could be achieved for copper catalyzed Diels–Alder reactions. Although the ligand in the acridine-based systems is achiral, the corresponding copper complex is chiral, which raises the possibility that the transfer of chirality from DNA to the catalyzed reaction in this system proceeds via the preferred formation of one of the enantiomers of the copper complex. This concept of converting of an achiral ligand–metal complex to a chiral complex by an exogenous chiral source has been well established in asymmetric catalysis.

Scheme 1: Schematic representation of the asymmetric Diels–Alder reaction catalyzed by a DNA-based catalyst.

In this chapter, a new and simplified approach to DNA-based catalysts is introduced (Scheme 1), in which chirality is transferred directly from DNA to the catalyzed reactions. For this purpose achiral copper complexes based on bidentate ligands known to bind to DNA (Figure 1) are employed. Only the DNA binding-mode of the copper complexes
Highly enantioselective DNA-based asymmetric catalysis

Based on L1 and L2 has been determined, and these complexes were shown to intercalate DNA. Since in this approach the metal binding site and the DNA anchor are integrated into one moiety, a spacer is no longer required. As a result the reactive Cu(II) centre is expected to be brought into even closer contact with the double helix. Furthermore, the copper(II) is expected to have a similar coordination geometry in all these cases, and hence the opportunity arises to study the effect of the size of the ligand on the enantiomeric excess of the Diels–Alder product obtained. This new approach gives rise to a dramatic increase in enantioselectivity of the Cu(II) catalyzed asymmetric Diels–Alder reaction compared to our earlier system.

![Ligands L1-L8](image)

**Figure 1**: Ligands used in DNA-based asymmetric catalysis.

### 2.2 The binding of achiral polyaromatic bidentate ligands to DNA

The DNA-based catalysts investigated initially, in this study, consist of salmon testes DNA (st-DNA) bound to a series of Cu(II) complexes based on simple achiral polyaromatic bidentate ligands, e.g. dipyrido[3,2-a:2',3'-c]phenazine (dpq, L1), dipyrido[2,2-d:2',3'-f]quinoxaline (dpq, L2), phenanthroline (phen, L3) and 2,2'-bipyridine (bpy, L4) (Figure 1). The series L1–L4 was chosen in order to study the effect of the size of the planar ligand on the ee, while the coordination geometry of copper(II) remains similar. The binding constants to DNA were determined from a titration of DNA to the Cu(II) complexes, which resulted in a decrease in the absorption of the Cu(II) complexes. The data was subsequently treated by the method of Meehan\(^{23}\) (see also experimental section). It was found that the Cu(II) complexes, [Cu(L)(NO\(_2\))\(_2\)], where L = L1–L4, exhibit moderate to strong binding to DNA, with binding constants ranging from 8 \times 10^5 M\(^{-1}\) to 9.3 \times 10^5 M\(^{-1}\) (Table 1, entries 1–4).

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Table 1: Results of Diels–Alder reactions of 1 with 2a–c, catalyzed by DNA–Cu(L)(NO$_3$)$_2$.

<table>
<thead>
<tr>
<th>Entry</th>
<th>L</th>
<th>$K_{b}^{DNA}$/M$^{-1}$</th>
<th>Dienophile</th>
<th>Endo/exo</th>
<th>ee (%)$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>L1</td>
<td>8 ± 3 × 10$^5$</td>
<td>2a</td>
<td>96:4</td>
<td>49 (+)</td>
</tr>
<tr>
<td>2</td>
<td>L2</td>
<td>7.2 ± 1.2 × 10$^5$</td>
<td>2a</td>
<td>95:5</td>
<td>61 (+)</td>
</tr>
<tr>
<td>3</td>
<td>L3</td>
<td>1.3 ± 0.1 × 10$^5$</td>
<td>2a</td>
<td>96:4</td>
<td>73 (+)</td>
</tr>
<tr>
<td>4</td>
<td>L4</td>
<td>9.4 ± 0.3 × 10$^5$</td>
<td>2a</td>
<td>98:2</td>
<td>90 (+)</td>
</tr>
<tr>
<td>5$^c$</td>
<td>L4</td>
<td>—</td>
<td>2a</td>
<td>97:3</td>
<td>89 (+)</td>
</tr>
<tr>
<td>6$^d$</td>
<td>L4</td>
<td>—</td>
<td>2a</td>
<td>97:3</td>
<td>89 (+)</td>
</tr>
<tr>
<td>7</td>
<td>L4</td>
<td>—</td>
<td>2b</td>
<td>97:3</td>
<td>92 (+)</td>
</tr>
<tr>
<td>8$^e$</td>
<td>L4</td>
<td>—</td>
<td>2c</td>
<td>94:6</td>
<td>83 (+)</td>
</tr>
<tr>
<td>9$^f$</td>
<td>L5</td>
<td>—</td>
<td>2a</td>
<td>93:7</td>
<td>&lt;5</td>
</tr>
<tr>
<td>10$^f$</td>
<td>Py$^g$</td>
<td>—</td>
<td>2a</td>
<td>92:8</td>
<td>6 (+)</td>
</tr>
<tr>
<td>11$^b$</td>
<td>—</td>
<td>—</td>
<td>2a</td>
<td>95:5</td>
<td>10 (–)</td>
</tr>
<tr>
<td>12$^h$</td>
<td>—</td>
<td>—</td>
<td>2a</td>
<td>n.d.$^i$</td>
<td>&lt;5</td>
</tr>
<tr>
<td>13$^k,l$</td>
<td>L1</td>
<td>—</td>
<td>2a</td>
<td>94:6</td>
<td>-</td>
</tr>
<tr>
<td>14</td>
<td>L6</td>
<td>5.2 ± 0.3 × 10$^5$</td>
<td>2a</td>
<td>&gt;99:1</td>
<td>91 (+)</td>
</tr>
<tr>
<td>15</td>
<td>L7</td>
<td>1.5 ± 0.1 × 10$^4$</td>
<td>2a</td>
<td>98:2</td>
<td>92 (+)</td>
</tr>
<tr>
<td>16$^c$</td>
<td>L7</td>
<td>—</td>
<td>2b</td>
<td>&gt;99:1</td>
<td>95</td>
</tr>
<tr>
<td>17</td>
<td>L7</td>
<td>—</td>
<td>2c</td>
<td>98:2</td>
<td>90</td>
</tr>
<tr>
<td>18</td>
<td>L8</td>
<td>1.12 ± 0.02 × 10$^4$</td>
<td>2a</td>
<td>&gt;99:1</td>
<td>99 (+)</td>
</tr>
<tr>
<td>19$^c$</td>
<td>L8</td>
<td>—</td>
<td>2a</td>
<td>99:1</td>
<td>98 (+)</td>
</tr>
<tr>
<td>20</td>
<td>L8</td>
<td>—</td>
<td>2b</td>
<td>&gt;99:1</td>
<td>&gt;99</td>
</tr>
<tr>
<td>21</td>
<td>L8</td>
<td>—</td>
<td>2c</td>
<td>&gt;99:1</td>
<td>97</td>
</tr>
</tbody>
</table>

$^a$ All experiments were carried out with st-DNA (1.3 mg mL$^{-1}$), 0.3 mM [Cu(L)(NO$_3$)$_2$], 1 mM 2a–c and 15 mM cyclopentadiene 1 in MOPS buffer (20 mM pH 6.5) for 3 d at 5 °C, unless noted otherwise.$^b$ For the endo isomer. $^c$ 0.05 mM [Cu(L)(NO$_3$)$_2$]. $^d$ Calf thymus DNA. $^e$ Conversion 50%. $^f$ Cu(II) complex prepared in situ. $^g$ 2 eq. with respect to Cu(II). $^h$ At room temperature. $^i$ In the absence of Cu(II). $^j$ Not determined due to the low conversion. $^k$ In the absence of DNA. $^l$ Conversion 52%. Evidence for DNA-binding was further extracted from CD spectroscopy. Although achiral compounds do not give rise to a CD signal, when bound to DNA an induced CD effect is observed.$^m$ Indeed, DNA gave rise to an induced CD effect (Figure 2), in the region where only the copper(II) ligands L1 – L4 absorb (λ 300 – 400 nm). Hence, the complexes are
embedded in the chiral environment of the DNA. The binding of the copper(II) complexes to DNA will be investigated in more detail in chapter 3 and 4.

![Figure 2: Induced CD spectra from \([\text{Cu(L1-L4)(NO}_3\text{)}_2]\) (150 \(\mu\)M) combined with salmon testes DNA (0.8 mg/ml) in Mops buffer (20 mM, pH 6.5). a) st-DNA; b) \([\text{Cu(bpy)(NO}_3\text{)}_2]\) / st-DNA; c) \([\text{Cu(dppz)(NO}_3\text{)}_2]\) / st-DNA; d) \([\text{Cu(dpq)(NO}_3\text{)}_2]\) / st-DNA; e) \([\text{Cu(phen)(NO}_3\text{)}_2]\) / st-DNA.]

### 2.3 DNA-based asymmetric catalysis using achiral polyaromatic bidentate ligands

The Diels–Alder reaction of cyclopentadiene 1 with aza-chalcone 2a catalyzed by DNA-based catalysts, assembled from st-DNA\(^7\) and \([\text{Cu(L1–L4)(NO}_3\text{)}_2]\), was performed at 5 °C for 3 d. This ensured >80% conversion in all reactions, with the Diels–Alder product 3a being the sole product formed, according to \(^1\)H-NMR. In the absence of DNA generally a slightly lower conversion was obtained, albeit the product has no ee, whereas hardly any reaction was observed with only DNA and no copper complex, showing the essential role of Cu\(^{2+}\) as Lewis acid in this reaction (entries 12–13). The eno isomer of 3a, which was produced almost exclusively (95%), was obtained with ee’s ranging from 49% for \([\text{Cu(dppe)(NO}_3\text{)}_2]\) to a remarkable 90% for \([\text{Cu(bpy)(NO}_3\text{)}_2]\) (entries 1–4). This is considerably higher than those obtained previously with either the acridine-based catalysts or Cu(II)–amino acid complexes.\(^8,9\) Since, due to the symmetric, planar nature of ligands 4–
Chapters 1 and 2.doc

Chapter 2

6, the Cu(II) complexes are achiral, these results demonstrate the direct transfer of chirality from DNA to the catalyzed Diels–Alder reaction. Even though [Cu(bpy)(NO\textsubscript{3})\textsubscript{2}] is chiral as a result of the small twist between the two pyridyl groups (see chapter 4), this twist is generally quite small and does not lead to significantly different geometries around the Cu(II) centre. Therefore, it is unlikely that the chirality in the complex is responsible for the observed enantioselectivity and, hence, in this case most likely also is direct chirality transfer from DNA.

Ligands L1–L4 provide a similar coordination environment to the Cu(II) ion and, hence, the relationship between the DNA binding strength of the complexes and the enantioselectivity observed in DNA-based catalysis can be established readily by comparison of the complexes’ catalytic properties. Interestingly, within this homologous series, an inverse correlation was observed between the DNA binding strength of the Cu(II) complex and the ee in the product; the weakest DNA-binder in this series, [Cu(bpy)(NO\textsubscript{3})\textsubscript{2}], provided the highest ee (Table 1). Catalysts based on 2-aminomethylpyridine (L5) or pyridine (py) itself did not provide significant enantiointic selectivity in the reaction (entries 9, 10), whereas in the absence of ligand (i.e. only Cu(NO\textsubscript{3})\textsubscript{2} and DNA), 10% ee of the opposite enantiomer was obtained (entry 11). These results demonstrate that a copper complex capable of binding to DNA, although not necessarily with high affinity, is an absolute requirement in obtaining high enantioselectivity.

In view of the excellent results obtained with 2,2’-bipyridine, a series of bidentate bipyridine-type ligands were investigated. The pyridyl–imidazole ligands L6 and L7 provided up to 92% ee for 3a and 95% in case of 3b (entries 14–16). However, the best results were obtained with the Cu\textsuperscript{2+} complex of 4,4'-dimethyl-2,2'-bipyridine (dmbpy, L8), i.e. complete endo selectivity and virtually complete enantioselectivity (entry 18). Upon lowering the concentration of [Cu(dmbpy)](NO\textsubscript{3})\textsubscript{2} the reaction became somewhat slower, i.e. 45% vs. 28% conversion at 30 and 5 mol% catalyst, respectively, after 5.5 h. However, in both cases the reaction is essentially complete within 24 h and the enantioselectivity was not affected noticeably (entries 18, 19).

When the ratio of DNA base pairs : [Cu(bpy)(NO\textsubscript{3})\textsubscript{2}] was lowered, either by reducing the DNA concentration or increasing the complex concentration, a slight decrease in ee was observed. Considering the DNA-binding strength of [Cu(bpy)(NO\textsubscript{3})\textsubscript{2}] and the number of available binding sites, this is not unexpected: at higher complex DNA ratios relatively more of the copper complex will remain unbound and be available, in solution, to catalyze the Diels–Alder reaction in a racemic fashion, resulting in a lower overall ee. This underscores further the need for the reaction to take place in close proximity to the DNA in order to obtain enantioselectivity.

The R group on the dienophile was found to be amenable to variation. Substrates 2b and 2c were converted efficiently to the corresponding Diels–Alder product with very high enantioselectivity (entries 7, 8, 14, 15, 18 and 19), albeit with lower conversion for 2b and
with considerable amounts of a side-product, in the case of the sterically demanding substrate 2c. This side-product was the result of the Michael addition of water to 2c and was formed as a racemate.

### 2.4 Dienophile requirements

Further investigation of the substrate scope of the asymmetric Diels-Alder reaction with aza-chalcone type dienophiles, revealed that the substituent at the alkene moiety of the dienophile was amenable to variation, but the 2-acyl pyridine moiety proved to be essential for both catalysis and enantioselectivity. However, the 2-acyl pyridine moiety of the substrate limits the synthetic potential of the catalytic system, since the pyridyl moiety is not removed readily or transformed after the Diels-Alder reaction. Therefore, we sought to replace the 2-pyridyl moiety by an alternative, removable auxiliary, which still allows for efficient binding to Cu\(^{2+}\) under aqueous conditions. Using the well known 3-alkenoyl-1,3-oxazolidinones 4, which have two carbonyl oxygens available for coordination to Cu\(^{2+}\), no conversion was observed. Also, \(\alpha,\beta\)-unsaturated-1-acyl-3,5-dimethylpyrazoles 5, \(\alpha,\beta\)-unsaturated-1-acyl-pyrazoles 6 and substrate 7 did not show conversion. Apparently, \(\alpha,\beta\)-unsaturated amides are not reactive enough, and a more electron-withdrawing carbonyl containing moiety is required.

Recently, \(\alpha,\beta\)-unsaturated-1-acyl-3,5-dimethylpyrazoles 5 were reported as substrates for the catalytic Diels-Alder reaction using chiral copper complexes. Although generally good yields and enantioselectivities were reported, only limited success was obtained in pure water. Evans et al. have demonstrated that \(\alpha,\beta\)-unsaturated 2-acyl imidazoles are good substrates in a variety of Lewis-acid catalyzed reactions e.g., Friedel-Crafts reactions and 1,3-dipolar cycloadditions. This substrate class was also employed in the conjugate addition of in situ formed carbonyl anions under aqueous conditions, although not in pure water. Subsequently, the imidazole group has been transformed into a good leaving group by treatment with methyl triflate, allowing substitution by a nucleophile. These features make \(\alpha,\beta\)-unsaturated 2-acyl imidazoles a very attractive class of substrates for DNA-based catalytic asymmetric Diels-Alder reactions.

![Figure 3: Potential dienophiles for DNA-based asymmetric catalysis.](image-url)
2.5 Diels-Alder reactions using α,β-unsaturated 2-acyl imidazoles

α,β-unsaturated 2-acyl imidazoles 8a-f (Scheme 2) were prepared via aldol condensation of 2-acyl-1-methylimidazole and the appropriate aldehyde, as described previously. Although cyclohexyl carboxaldehyde can, in principle, also form an enolate, dienophile 8f was the only product observed from cyclohexyl carboxaldehyde and 2-acyl-1-methylimidazole. 1-(1-Methyl-1H-imidazol-2-yl)-propenone (8h) was prepared by addition of lithiated imidazole to acrolein, followed by oxidation of the allylic alcohol with MnO₂. Dienophile 8h is prone to polymerization, and therefore was prepared freshly prior to use.

Initially a series of DNA-based catalysts from both classes investigated to date, i.e., using ligands of the acridine1 (L9 – L12) and the bipyridine (L3, L4, L8) type, were screened in the Diels-Alder reaction of 8a with 1 (Table 3). The DNA-based catalyst was formed through self-assembly by mixing solutions of salmon testes DNA (st-DNA), which is inexpensive and readily available, and the appropriate copper complex. For screening purposes the catalyst loading was 30 mol % with respect to substrate, but this can be lowered to 5 mol % without a significant effect on the enantioselectivity (vide supra). The reaction was initiated by addition of 10 equivalents of cyclopentadiene (1), and continued for 3 d at 5 °C, after which the cyclopentadiene was depleted. The Diels-Alder product is the only product formed.

The catalytic reaction is ligand accelerated, in the absence of a ligand, i.e., using only Cu(NO₃)₂, no conversion was observed (entry 1). The catalysts based on the acridine ligands (L9-L12) gave rise to good conversion and moderate ee’s (entries 2-5). Although the enantioenermic preference was always the same, significant variations in the e.e. were observed, compared to aza-chalcone 2a. For example, complexes based on ligands L9 and L10 gave a lower enantiomeric excess, whereas the copper complex based on ligand L12 gave rise to a significantly higher enantioselectivity. In contrast, using the copper complexes of the bipyridine class ligands (L3, L5, and L8), comparable results are seen for aza-chalcone 2a and α,β-unsaturated 2-acyl imidazole 8a with respect to both the
enantiomeric excess, i.e., e.e.'s up to 97%, and enantiomeric preference, albeit with low conversion in the case of ligands L3 and L4. Surprisingly, using the catalyst based on L8 90% conversion was obtained, indicating that this catalyst is much more reactive, with 97% e.e. of the (+) enantiomer. Based on these results, it was evident that the copper complex of L8 is the catalyst of choice, and all further experiments were performed using this catalytic system.

**Table 3:** Screening of ligands for the copper(II) catalyzed Diels-Alder reaction of α,β-unsaturated 2-acyl imidazole 1a and cyclopentadiene 1 in the presence of DNA.

<table>
<thead>
<tr>
<th>entry</th>
<th>ligand</th>
<th>% conversion(^a) of 8a</th>
<th>% ee(^c) of 9a</th>
<th>% ee(^d,e) of 3a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-</td>
<td>&lt;5</td>
<td>n.d.(^f)</td>
<td>10 (+)</td>
</tr>
<tr>
<td>2</td>
<td>L9</td>
<td>61</td>
<td>10 (+)</td>
<td>48 (+)</td>
</tr>
<tr>
<td>3</td>
<td>L10</td>
<td>83</td>
<td>16 (-)</td>
<td>49 (-)</td>
</tr>
<tr>
<td>4</td>
<td>L11</td>
<td>78</td>
<td>29 (+)</td>
<td>37 (+)</td>
</tr>
<tr>
<td>5</td>
<td>L12</td>
<td>93</td>
<td>68 (+)</td>
<td>37 (+)</td>
</tr>
<tr>
<td>6</td>
<td>L3</td>
<td>17</td>
<td>68 (+)</td>
<td>72 (+)</td>
</tr>
<tr>
<td>7</td>
<td>L4</td>
<td>25</td>
<td>87 (+)</td>
<td>90 (+)</td>
</tr>
<tr>
<td>8</td>
<td>L8</td>
<td>90</td>
<td>97 (+)</td>
<td>99 (+)</td>
</tr>
</tbody>
</table>

\(^a\) All experiments were carried out with salmon testes DNA (1.3 mg mL\(^{-1}\)), 0.3 mM [Cu(L)(NO\(_3\))]\(_2\)], 1 mM 8a in 15 mL MOPS buffer (20 mM, pH 6.5) for 3 d at 5 °C, unless noted otherwise. \(^b\) Determined by \(^1\)H-NMR. \(^c\) For the endo isomer. \(^d\) Only 3a obtained with conversions >80%. \(^e\) n.d. = not determined.
2.6 Substrate scope

The substrate scope of the reaction was investigated using α,β-unsaturated 2-acyl imidazoles 8b-h (Table 4). All substrates underwent efficient Diels-Alder reactions with cyclopentadiene, catalyzed by Cu-L8/salmon testes DNA. The Diels-Alder product was the sole product; no side products were detected by NMR and HPLC analysis. In all cases the endo diastereomer was obtained almost exclusively and with an excellent enantiomeric excess.

**Table 4:** Substrate scope of the Diels-Alder reaction with α,β-unsaturated 2-acyl imidazoles catalyzed by CuL8(NO$_3$)$_2$/st-DNA.$^a$

<table>
<thead>
<tr>
<th>entry</th>
<th>R (substrate)</th>
<th>endo: exo</th>
<th>% ee$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph (8a)</td>
<td>99:1</td>
<td>97 (+) (25,35)</td>
</tr>
<tr>
<td>2$^c$</td>
<td>Ph (8a)</td>
<td>99:1</td>
<td>98 (+) (25,35)</td>
</tr>
<tr>
<td>3</td>
<td>p-MeOPh (8b)</td>
<td>99:1</td>
<td>98</td>
</tr>
<tr>
<td>4$^d$</td>
<td>p-CIPh (8c)</td>
<td>n.d.</td>
<td>96</td>
</tr>
<tr>
<td>5$^e$</td>
<td>o-BrPh (8d)</td>
<td>96:4</td>
<td>94</td>
</tr>
<tr>
<td>6</td>
<td>2-furan (8e)</td>
<td>97:4</td>
<td>94</td>
</tr>
<tr>
<td>7</td>
<td>cyclohexyl (8f)</td>
<td>94:6</td>
<td>88</td>
</tr>
<tr>
<td>8</td>
<td>Me (8g)</td>
<td>&gt;99:1</td>
<td>86</td>
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<td>9</td>
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<td>&gt;99:1</td>
<td>88</td>
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<td>10</td>
<td>H (8h)</td>
<td>98:2</td>
<td>80</td>
</tr>
<tr>
<td>11$^f$</td>
<td>H (8h)</td>
<td>99:1</td>
<td>83</td>
</tr>
</tbody>
</table>

$^a$ All experiments were carried out with st-DNA (1.3 mg mL$^{-1}$), 0.3 mM [Cu(L8)(NO$_3$)$_2$], 2 mM 8 in 45 mL MOPS buffer (20 mM, pH 6.5) for 3 d at 5 °C, unless noted otherwise. $^b$ For the endo isomer. $^c$ 1 mM 8, 0.05 mM Cu(L8)(NO$_3$)$_2$. $^d$ Conversion ~50%. $^e$ Conversion ~70%.

The best results were obtained when the R substituent in the enone was an aromatic group, with ee’s ranging from 94-98%. The electronic nature of the substituent on the aryl ring, i.e., electron donating or electron withdrawing, or the position on the aryl ring did not

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influence the ee significantly (entry 2-6). In the case of R = p-CIPh and o-BrPh (entry 4 and 5), the conversion was somewhat decreased, most likely caused by the low solubility of 8c and 8d. When R is a 2-furanyl group, which is a convenient handle for further functionalization, an excellent ee was obtained (entry 7). Dienophiles 8f-8h, which contain alkyl groups or are unsubstituted, also gave rise to high enantioselectivity, i.e., e.e. = 80-88%, although the enantioselectivity is somewhat lower compared to substrates with an aromatic R group (entries 7, 8, and 10). The catalyst loading could be reduced to 5 mol % without affecting the endo:exo selectivity and the enantioselectivity (entries 2, 9, and 11).

2.7 Synthetic application and absolute configuration

To demonstrate that the present reaction is practical from a synthetic point of view, the DNA-based catalytic asymmetric Diels–Alder reaction of 8a with 1 was performed on a 1.0 mmol (210 mg, 2 mM) scale, with 5 mol % Cu-L8, and 1.4 mg/mL st-DNA. Product 9a was obtained in 70% isolated yield (85% conversion), and 96% ee after column chromatography. Using the procedure of Evans et al., the imidazole of 9a was first methylated using methyl triflate, followed by treatment with methanol. The corresponding methyl ester 10 was obtained in 41% isolated yield (80% conversion of the Diels–Alder product; see Scheme 3), the ee was not determined. The optical rotation of the product was [α]D20 = +126.8° (c = 0.401, CHCl₃). From comparison with literature values ([α]D20 = -130.2°, >95% ee in the 2R,3R-enantiomer) it can be concluded that the Diels–Alder product is obtained from the st-DNA-based catalytic reaction as the 2S,3S-enantiomer.

![Scheme 3](image_url)


2.8 Conclusions

A new and simple approach to DNA-based asymmetric catalysis is presented, which enables very high enantioselectivities in the Cu(II) catalyzed Diels–Alder reaction to be achieved. Through this approach the assembly of DNA-based catalysts in a modular fashion from DNA and achiral copper complexes of simple and readily available achiral pyridine-based ligands is realized. The results demonstrate that the DNA is the source of
chirality in these reactions and that the close contact between DNA and the copper complex allows for direct transfer of the chirality during the catalyzed reaction. The virtually complete regioselectivity (up to >99% endo) and excellent enantioselectivity (up to 99% ee) of the catalyzed Diels–Alder reactions in water, reported here, are testimony of the potential of DNA-based asymmetric catalysis.

It was demonstrated that α,β-unsaturated 2-acyl imidazoles are an alternative and practical class of dienophiles for the DNA-based catalytic asymmetric Diels-Alder reaction in water. The Diels-Alder products are obtained with excellent diastereoselectivity and enantioselectivity, and the imidazole auxiliary is readily displaced. In chapters 6 and 7 new DNA-based catalytic reactions using this class of substrates are explored.

### 2.9 Experimental section

**General remarks**

Salmon testes DNA was obtained from Sigma. Dienophiles 1a-b, 8 [Cu(dppz)(NO$_3$)$_2$], 4 [Cu(dpq)(NO$_3$)$_2$], 4 2-(2-pyridyl)imidazole L6, 22 ligands L9-L12, 1 and dienophiles 8b, 8c, 8d, and 8e 4 were prepared following published procedures. Cyclopentadiene was freshly prepared from its dimer prior to use. 1H-NMR, and 13C-NMR spectra were recorded on a Varian 400 (400 and 100 MHz) or Varian 300 (300 and 75 MHz) in CDCl$_3$. Chemical shifts (δ) are quoted in ppm using residual solvent as internal standard (δ$_C$ 77.0 and δ$_H$ 7.26 for CDCl$_3$). Mass spectra (HRMS) were recorded on an AEI MS-902. Optical rotations were measured on a Schmidt and Haensch Polartronic MH8. Enantiomeric excess determination was performed by HPLC analysis using UV-detection. Flash chromatography was performed using silica gel 60 Å (Merck, 200-400 mesh). Circular Dichroism spectra were measured on a JASCO J-715 spectropolarimeter, with a temperature control attachment.

**Physical methods**

Equilibrium binding constants to salmon testes DNA were determined by UV/Vis titration, following the procedure of Meehan. 23 After dissolution of salmon testes DNA (2 mg/ml), the stock solution was dialyzed extensively against Mops buffer (20 mM pH 6.5) prior to use. The concentration in base pairs was determined spectrophotometrically, using $\varepsilon_{260} = 12800$ M$^{-1}$ cm$^{-1}$. 24 The absorbance ratio of $\lambda_{260}/\lambda_{280}$ was 1.8-1.9, indicating the DNA was sufficiently free of protein. The $K_b$ was determined by titration of DNA to a solution of copper complex in buffered solution. Concentrations of copper complexes generally were 30 µM, or 15 µM in case of [Cu(dppz)(NO$_3$)$_2$] and [Cu(dpq)(NO$_3$)$_2$]. Under conditions where the ratio of bound complex : DNA base pairs approaches zero, the $K_b$ can determined using:
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\[
\frac{D}{\Delta \epsilon_{ap}} = \frac{1}{\Delta \epsilon} D + \frac{1}{\Delta \epsilon K_b}
\]

where \(\Delta \epsilon_{ap} = |\epsilon_a - \epsilon_f|\), \(\Delta \epsilon = |\epsilon_b - \epsilon_f|\), \(\epsilon_a\), \(\epsilon_f\), and \(\epsilon_b\) are the apparent, free and bound extinction coefficients for the complex, respectively, and \(D\) is the DNA concentration in base pairs. In a plot of \(D/\Delta \epsilon_{ap}\) vs. \(D\), \(K_b\) is given by the ratio of the slope to the y intercept (Figure 4).

Figure 4: A representative plot of the UV/Vis titration of salmon testes DNA to Cu-L8 for the equilibrium binding constant determination following the procedure of Meehan. \(^{23}\)

Synthesis

Catalytic Diels-Alder reactions, representative procedure

A buffered solution (20 mM Mops, pH 6.5) of DNA bound catalyst (1.3 mg/ml salmon testes DNA and 0.3 mM \([\text{Cu(bpy)(NO}_3\text{)}_2]\)) was prepared by mixing a solution of salmon testes DNA (10 ml of a 2 mg/ml solution in 30 mM Mops, prepared 24 h in advance) with an aqueous solution of catalyst (5 ml of a 0.9 mM solution, prepared by adding a solution of \([\text{Cu(bpy)(NO}_3\text{)}_2]\) dissolved in a minimal amount of DMSO, to 5 ml \(H_2O\)). An aliquot of a stock solution of dienophile 2a in \(CH_3CN\) (30 µL of a 0.5 M soln., final conc. 1 mM) was added and the mixture was cooled to 5 °C. The reaction was started by addition of cyclopentadiene (21 µL, final conc. 15 mM) and mixed by continuous inversion for 3 days, followed by extraction of the product with diethyl ether. After \(^1H\)-NMR analysis the ee was
determined by chiral HPLC. Selected products were purified by column chromatography and analyzed by HPLC to confirm the results obtained from analysis of the crude product.

**Synthesis of copper complexes**

\[ \text{[Cu(phenanthroline)(NO}_3\text{)\textsubscript{2}]} \text{ ([Cu(L3)(NO}_3\text{)\textsubscript{2}])} \text{.} \]

Following the procedure as described for \[ \text{[Cu(dppz)(NO}_3\text{)\textsubscript{2}]}\text{,} \]

starting from phenanthroline (70 mg, 0.35 mmol) and Cu(NO\textsubscript{3})\textsubscript{2}·3H\textsubscript{2}O (94 mg, 1.1 eq), \[ \text{[Cu(phen)(NO}_3\text{)\textsubscript{2}]} \text{ was obtained as a blue solid. Yield: 114 mg, 0.31 mmol, 89 \%}. \]

Anal. Calcd for C\textsubscript{12}H\textsubscript{8}CuN\textsubscript{4}O\textsubscript{6}: C, 39.19 H, 2.19 N, 15.23. Found: C, 39.25 H, 2.09 N, 15.15.

\[ \text{[Cu(2,2'-bipyridine)(NO}_3\text{)\textsubscript{2}]} \text{ ([Cu(L4)(NO}_3\text{)\textsubscript{2}])}. \]

Following the procedure as described for \[ \text{[Cu(dppz)(NO}_3\text{)\textsubscript{2}]}\text{,} \]

starting from 2,2'-bipyridine (60 mg, 0.39 mmol) and Cu(NO\textsubscript{3})\textsubscript{2}·3H\textsubscript{2}O (100 mg, 1.1 eq), \[ \text{[Cu(bpy)(NO}_3\text{)\textsubscript{2}]} \text{ was obtained as a blue solid. Yield: 86 mg, 0.25 mmol, 64 \%}. \]

Anal. Calcd for C\textsubscript{10}H\textsubscript{8}CuN\textsubscript{4}O\textsubscript{6}: C, 34.94 H, 2.35 N, 16.30. Found: C, 35.1 H, 2.30 N, 16.15.

\[ \text{[Cu(2-(2-pyridyl)imidazole)(NO}_3\text{)\textsubscript{2}·H}_2\text{O]} \text{ ([Cu(L6)(NO}_3\text{)\textsubscript{2}])}. \]

To a solution of 2-(2-pyridyl)imidazole \[ L_6 \text{ (74 mg, 0.51 mmol) in ethanol (10 mL) was added Cu(NO}_3\text{)\textsubscript{2}·3H}_2\text{O (123 mg, 0.51 mmol). The mixture was shaken until a clear green solution was obtained. The solution was placed in an ether bath for 2 d. The green crystals were filtered and washed with water and ethanol. Yield: 65 mg, 38 \%}. \]

Anal. Calcd for C\textsubscript{8}H\textsubscript{9}CuN\textsubscript{5}O\textsubscript{7}: C, 27.40 H, 2.59 N, 19.97. Found: C, 27.6 H, 2.49 N, 19.74.

\[ \text{[Cu(2-(2-pyridyl)benzimidazole)(NO}_3\text{)\textsubscript{2}·H}_2\text{O]} \text{ ([Cu(L7)(NO}_3\text{)\textsubscript{2}])}. \]

To a solution of Cu(NO\textsubscript{3})\textsubscript{2}·3H\textsubscript{2}O (97 mg, 0.39 mmol) in a mixture of acetone (4 mL) and ethanol (0.3 ml) was added a solution of 2-(2-pyridyl)benzimidazole \[ L_7 \text{ (75 mg, 0.38 mmol) in ethyl acetate (4 ml), through a small cotton plug. The dark green solution was filtered and the vial was closed with a cotton plug, allowing for slow evaporation of acetone. After one night a dark green solid had precipitated, which was washed with a small volume of ethyl acetate. Yield: 135 mg, 89 \%}. \]

Anal. Calcd for C\textsubscript{12}H\textsubscript{11}CuN\textsubscript{5}O\textsubscript{7}: C, 35.96 H, 2.77 N, 17.47. Found: C, 36.30 H, 2.83 N, 17.04.

\[ \text{[Cu(4,4'-dimethyl-2,2'-dipyridyl)(NO}_3\text{)\textsubscript{2}]} \text{ ([Cu(L8)(NO}_3\text{)\textsubscript{2}])}. \]

To a solution of Cu(NO\textsubscript{3})\textsubscript{2}·3H\textsubscript{2}O (0.10 g, 0.41 mmol) in ethanol was added 4,4'-dimethyl-2,2'-dipyridyl \[ L_8 \text{ (38 mg, 0.24 mmol), dissolved in ethanol. The solution was placed in an ethyl acetate bath and left standing for 2 d. The blue solid was filtered and washed with ethanol. Yield: 49 mg, 59 \%}. \]

Anal. Calcd for C\textsubscript{12}H\textsubscript{12}CuN\textsubscript{4}O\textsubscript{6}: C, 38.8 H, 3.25 N, 15.07. Found: C, 38.5 H, 3.14 N, 14.80.

**Synthesis of dienophiles**

\[ (E)-4,4\text{-dimethyl-1-(2-pyridinyl)-2-penten-1-one} \text{ (2c).} \]

This compound was prepared following the procedure as described for \[ 2a. \]

Starting from 2-acetylpyridine (2.06 g, 17 mmol) and pivaldehyde (1.42 g, 16.5 mmol), after column chromatography (SiO\textsubscript{2}, n-
heptane/ethyl acetate 8:1), 2c was obtained as a white solid. Yield: 706 mg, 3.7 mmol, 22%.

1H-NMR (CDCl₃, 400 MHz) δ 1.18 (s, 9H), 7.24 (dd, J = 15.8 Hz, J = 0.8 Hz, 1H), 7.46 (m, 1H), 7.54 (d, J = 16.5 Hz, 1H), 7.84 (m, 1H), 8.12 (d, J = 7.3 Hz, 1H), 8.71 (m, 1H).

1H-NMR (CDCl₃, 100 MHz) δ 28.71 (q), 34.39 (s), 119.32 (d), 122.81 (d), 126.65 (d), 136.85 (d), 148.76 (d), 154.29 (s), 159.89 (d), 190.04 (d); Anal. Calcd for C₁₂H₁₅NO:
C, 76.16 H, 7.99 N, 7.40. Found: C, 76.1 H, 8.04 N, 7.45.

3-Cyclohexyl-1-(1-methyl-1H-imidazol-2-yl)-propene (8f).

A solution of 2-acetyl-1-methylimidazole (1.2 g, 10 mmol), cyclohexane carbaldehyde (1.1 g, 10 mmol), and KOH (0.1 g) in 20 mL EtOH was stirred overnight. After addition of brine (30 mL) and water (10 mL) the mixture was extracted with EtOAc (3×75 mL). The organic fractions were combined and dried on sodium sulfate. After concentration the crude product was purified using column chromatography (SiO₂, 30% EtOAc:hexanes) providing 8f as a colourless oil (0.33 g, 15%).

1H-NMR (CDCl₃, 400 MHz) δ 1.02-1.28 (m, 5H), 1.53-1.76 (m, 5H), 2.13-2.19 (m, 1H), 3.95 (s, 3H), 6.96 (s, 1H), 6.98 (dd, J = 15.8 Hz, J = 6.8 Hz, 1H), 7.07 (s, 1H), 7.28 (dd, J = 15.8 Hz, J = 1.4 Hz, 1H).

13C-NMR (CDCl₃, 100 MHz) δ 25.9 (t), 26.1 (t), 31.9 (t), 36.4 (q), 41.0 (d), 123.9 (d), 127.2 (d), 129.3 (d), 153.7 (d), 155.3 (s), 181.9 (s). HRMS Calcd for C₁₃H₁₈N₂O 218.1419, found 218.1408.

1-(1-Methyl-1H-imidazol-2-yl)-propene (8h).

To a solution of 1-methylimidazole (0.51 g, 6.2 mmol) in 20 mL THF cooled to –78 °C, was added 3.9 mL n-BuLi (1.6 M in hexanes). After stirring for 5 min the solution was slowly warmed to room temperature, followed by cooling again to –78 °C. Dropwise addition of acrolein (0.35 g, 6.2 mmol) resulted in a colour change to red. Loss of colour was observed after the addition was completed. The mixture was quenched with water (6.5 mL), warmed to room temperature, and 60 mL water and 60 mL EtOAc were added. The combined organic layers were dried on Na₂SO₄, filtered and concentrated. The crude residue was dissolved in 30 mL CH₂Cl₂. MnO₂ (5 g, 57 mmol) was added, and the reaction was stirred vigorously at room temperature for 45 min. The reaction mixture was filtered over a celite pad and concentrated. After purification over a short column (SiO₂, EtOAc) 8h (0.20 g, 24%) was obtained as a colourless oil, which was used immediately.

1H-NMR (CDCl₃, 400 MHz) δ 4.02 (s, 3H), 5.83 (dd, J = 10.4 Hz, J = 2.0 Hz, 1H), 6.48 (dd, J = 17.5 Hz, J = 1.8 Hz, 1H), 7.04 (s, 1H), 7.16 (s, 1H), 7.65 (dd, J = 17.4 Hz, J = 10.5 Hz, 1H).

13C-NMR (CDCl₃, 100 MHz) 36.2 (q), 127.3 (d), 128.8 (d), 129.4 (t), 132.6 (d), 143.4 (s), 180.6 (s). HRMS Calcd for C₇H₈N₂O 136.0636, found 136.0642.

Synthesis of Diels-Alder products

The Diels-Alder products were generally obtained as a mixture of endo and exo diastereomers, which were not separated. The NMR data of the endo isomer are presented.
In case of 3c, 3d, and 3e, the intensity of the C2 carbon peak of the imidazoles in $^{13}$C-NMR was too low, and could not be detected.

**[3-(tert-Butyl)bicyclo[2.2.1]hept-5-en-2-yl](2-pyridinyl)methanone (3c).** Purified by column chromatography (SiO$_2$, CH$_2$Cl$_2$:n-pentane 4:1). $^1$H-NMR (CDCl$_3$, 400 MHz) $\delta$ 0.89 (s, 9H), 1.38 (m, 1H), 1.80 (m, 1H), 1.90 (dd, $J = 6.2$ Hz, $J = 1.5$ Hz, 1H), 2.76 (dd, $J = 2.9$ Hz, $J = 1.5$ Hz, 1H), 3.22 (m, 1H), 4.26 (dd, $J = 6.2$ Hz, $J = 2.9$ Hz, 1H), 5.69 (dd, $J = 5.5$ Hz, $J = 2.6$ Hz, 1H), 6.43 (dd, $J = 5.5$ Hz, $J = 2.9$ Hz, 1H), 7.44 (m, 1H), 7.78 (m, 1H), 7.97 (d, 1H, $J = 7.7$ Hz), 8.71 Hz (d, $J = 4.8$ Hz, 1H); MS (CI): 256 (M$^+$1); HRMS Calcd for C$_{17}$H$_{21}$NO 255.1623, found 255.1613.

**[3-(3-Phenyl-bicyclo[2.2.1]hept-5-en-2-yl)-(1-methyl-1H-imidazol-2-yl)]methanone (9a).** A white solid was obtained after purification by column chromatography (SiO$_2$, 10% EtOAc:n-pentane). $[\alpha]_{D}^{20} = +211^\circ$ (c = 0.1 CHCl$_3$); $^1$H-NMR (CDCl$_3$, 400 MHz, endo isomer) $\delta$ 1.59 (d, $J = 8.5$ Hz, 1H), 2.03 (d, $J = 8.5$ Hz, 1H), 3.04 (s, 1H), 3.35 (d, $J = 5.2$ Hz, 1H), 3.60 (s, 1H), 3.96 (s, 3H), 4.37 (m, 1H), 5.89 (dd, $J = 5.5$ Hz, $J = 2.6$ Hz, 1H), 6.50 (dd, $J = 5.5$ Hz, $J = 3.2$ Hz, 1H), 7.00 (s, 1H), 7.14 – 7.17 (m, 2H), 7.24 – 7.31 (m, 4H). $^{13}$C-NMR (CDCl$_3$, 400 MHz) $\delta$ 45.7 (q), 48.25 (d), 48.28 (d), 49.5 (t), 49.7 (d), 55.1 (d), 125.9 (d), 126.7 (d), 127.6 (d), 128.4 (d), 128.9 (d), 132.8 (d), 139.5 (d), 143.1 (s), 144.2 (s), 192.4 (s). HRMS Calcd for C$_{18}$H$_{18}$N$_2$O 278.1419, found 278.1420. Anal. Calcd for C$_{18}$H$_{18}$N$_2$O: C, 77.67 H, 6.52 N, 10.06. Found: C, 77.34 H, 6.58 N, 9.81. Product ratios and e.e.’s were determined by HPLC analysis (Chiralcel-OD, n-heptane/iPrOH 99:1, 1 ml/min. Retention times: 17.5, 20.9 (exo isomer), 19.0 (+), 26.2 (+) min (endo isomer).

**[3-(4-Methoxy-phenyl)-bicyclo[2.2.1]hept-5-en-2-yl)]-(1-methyl-1H-imidazol-2-yl)]methanone (9b).** A white solid was obtained after purification by column chromatography (SiO$_2$, 20% EtOAc:n-pentane). $^1$H-NMR (CDCl$_3$, 400 MHz, endo isomer) $\delta$ 1.58 (d, $J = 8.6$ Hz, 1H), 2.02 (d, $J = 8.5$ Hz, 1H), 2.98 (s, 1H), 3.29 (d, $J = 5.4$ Hz, 1H), 3.59 (m, 1H), 3.77 (s, 3H), 3.96 (s, 3H), 4.34 (dd, $J = 5.2$ Hz, $J = 3.5$ Hz, 1H), 5.88 (dd, $J = 5.6$ Hz, $J = 2.7$ Hz, 1H), 6.50 (dd, $J = 5.6$ Hz, $J = 3.1$ Hz, 1H), 6.79 – 6.83 (m, 2H), 7.00 (s, 1H), 7.14 – 7.20 (m, 2H), 7.24 (s, 1H). $^{13}$C-NMR (CDCl$_3$, 400 MHz) $\delta$ 36.3 (q), 45.1 (d), 48.2 (d), 49.4 (t), 50.0 (d), 55.1 (d), 55.3 (d), 113.8 (d), 126.7 (s), 128.6 (d), 129.0 (d), 132.7 (d), 136.3 (d), 139.5 (d), 143.2 (s), 157.8 (s), 192.6 (s). HRMS Calcd for C$_{19}$H$_{20}$N$_2$O$_2$ 308.1525, found 308.1535. Product ratios and e.e.’s were determined by HPLC analysis (Chiralcel-OD, heptane/iPrOH 98:2, 1 ml/min. Retention times: 12.2, 16.6 (exo isomer), 13.4, 20.8 min (endo isomer).
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[3-(4-Chloro-phenyl)-bicyclo[2.2.1]hept-5-en-2-yl)-(1-methyl-1H-imidazol-2-yl)-methanone (9c). A white solid was obtained after purification by column chromatography (SiO2, 20% EtOAc:n-pentane). 1H-NMR (CDCl3, 400 MHz, endo isomer) δ 1.53 (dd, J = 8.8 Hz, J = 1.6 Hz, 1H), 1.91 (d, J = 8.5 Hz, 1H), 2.94 (s, 1H), 3.24 (dd, J = 5.3 Hz, J = 1.7 Hz, 1H), 3.54 (s, 1H), 3.90 (s, 3H), 4.24 (dd, J = 5.3 Hz, J = 3.5 Hz, 1H), 5.93 (dd, J = 5.5 Hz, J = 2.7 Hz, 1H), 6.53 (dd, J = 5.6, J = 3.1, 1H), 6.95 (s, 1H), 7.08 (m, 1H), 7.16 (m, 4H). 13C-NMR (CDCl3, 100 MHz) δ 36.3 (q), 45.2 (d), 46.3 (d), 47.6 (d), 49.5 (t), 49.6 (d), 55.3 (d), 126.9 (d), 128.4 (d), 129.0 (d), 129.1 (d), 131.6 (s), 132.9 (d), 139.3 (d), 142.8 (s), 192.2 (s). HRMS Calcd for C18H17N2OCl 312.1029, found 312.1041. Product ratios and e.e.’s were determined by HPLC analysis (Chiralcel-AD, n-heptane/iPrOH 98:2, 1 ml/min. Retention times: 13.8, 23.5 min (endo isomer).

[3-(2-Bromo-phenyl)-bicyclo[2.2.1]hept-5-en-2-yl)-(1-methyl-1H-imidazol-2-yl)-methanone (9d). A white solid was obtained after purification by column chromatography (SiO2, 20% EtOAc:n-pentane). 1H-NMR (CDCl3, 400 MHz, endo isomer) δ 1.57 (dd, J = 8.4 Hz, J = 1.6 Hz, 1H), 1.95 (d, J = 8.6 Hz, 1H), 3.02 (s, 1H), 3.55 (m, 2H), 3.97 (s, 3H), 4.51 (dd, J = 5.3 Hz, J = 3.5 Hz, 1H), 5.95 (dd, J = 5.5 Hz, J = 2.8 Hz, 1H), 6.55 (dd, J = 5.5 Hz, J = 3.2 Hz, 1H), 7.01 (s, 1H), 7.04 – 7.09 (m, 1H), 7.14 (d, J = 0.8 Hz, 1H), 7.23 – 7.31 (m, 1H), 7.47 – 7.57 (m, 2H). 13C-NMR (CDCl3, 100 MHz) δ 36.3 (q), 46.3 (d), 47.6 (d), 49.2 (t), 50.2 (d), 52.3 (d), 126.9 (d), 127.3 (d), 127.5 (d), 127.9 (d), 128.9 (d), 133.1 (d), 133.4 (d), 138.7 (d), 143.0 (s), 191.9 (s). HRMS Calcd for C18H17N2OBr 358.0504, found 358.0522. Product ratios and e.e.’s were determined by HPLC analysis (Chiralcel-AD, n-heptane/iPrOH 99:1, 1 ml/min. Retention times: 11.0, 14.1 (exo isomer), 15.9, 21.0 min (endo isomer).

(3-Furan-2-yl-bicyclo[2.2.1]hept-5-en-2-yl)-(1-methyl-1H-imidazol-2-yl)-methanone (9e). A white solid was obtained after purification by column chromatography (SiO2, 10% EtOAc:pentane). 1H-NMR (CDCl3, 400 MHz, endo isomer) δ 1.56 (d, J = 8.8 Hz, 1H), 1.99 (d, J = 8.7 Hz, 1H), 3.05 (s, 1H), 3.31 (d, J = 4.6 Hz, 1H), 3.59 (s, 1H), 3.96 (s, 3H), 4.41 (dd, J = 4.2 Hz, J = 3.8 Hz, 1H), 5.87 (dd, J = 5.3 Hz, J = 2.7 Hz, 1H), 6.10 (dd, J = 2.4 Hz, 1H), 6.26 (s, 1H), 6.43 (dd, J = 5.1 Hz, J = 3.4 Hz, 1H), 7.02 (s, 1H), 7.17 (s, 1H), 7.29 (s, 1H). 13C-NMR (CDCl3, 100 MHz) δ 39.7 (q), 48.6 (t), 49.0 (d), 49.1 (d), 53.3 (d), 104.8 (d), 110.0 (d), 126.8 (d), 129.0 (d), 132.8 (d), 138.4 (d), 141.1 (d), 157.9 (s), 191.7 (s). HRMS Calcd for C16H16N2O2 268.1211, found 268.1208. Product ratios and e.e.’s were determined by HPLC analysis (Chiralcel-OD, n-heptane/iPrOH 98:2, 1 ml/min. Retention times: 8.8, 11.6 (exo isomer), 9.9, 13.5 min (endo isomer).
(3-Cyclohexyl-bicyclo[2.2.1]hept-5-en-2-yl)-(1-methyl-1H-imidazol-2-yl)-methanone (9f). A colourless oil was obtained after column chromatography (SiO$_2$, 10% EtOAc:n-pentane). $^1$H-NMR (CDCl$_3$, 400 MHz, endo isomer) $\delta$ 0.75 – 1.25 (m, 6H), 1.43 (d, J = 7.0 Hz, 1H), 1.59 – 1.72 (m, 6H), 1.95 (d, J = 12.7 Hz, 1H), 2.88 (s, 1H), 3.34 (s, 1H), 3.92 (s, 1H), 3.95 (s, 3H), 5.76 (dd, J = 5.5 Hz, J = 2.7 Hz, 1H), 6.34 (dd, J = 5.4 Hz, J = 3.3 Hz, 1H), 7.01 (s, 1H), 7.16 (s, 1H). $^{13}$C-NMR (CDCl$_3$, 100 MHz) $\delta$ 26.2 (t), 26.6 (t), 32.5 (t), 36.3 (q), 42.2 (d), 44.6 (d), 47.9 (t), 48.7 (d), 52.8 (d), 126.7 (d), 128.8 (d), 131.8 (d), 139.3 (d), 143.1 (s), 193.5 (s). HRMS Calcd for C$_{18}$H$_{16}$N$_2$O$_2$ 284.1889, found 284.1857. Product ratios and e.e.’s were determined by HPLC analysis (Chiralcel-OD, n-heptane/iPrOH 99:1, 1 ml/min. Retention times: 6.7, 7.5 (exo isomer), 8.3, 9.3 min (endo isomer).

(3-Methyl-bicyclo[2.2.1]hept-5-en-2-yl)-(1-methyl-1H-imidazol-2-yl)-methanone (9g). A colourless oil was obtained after purification by column chromatography (SiO$_2$, 10% EtOAc:n-pentane). $^1$H-NMR (CDCl$_3$, 400 MHz, endo isomer) $\delta$ 1.17 (d, J = 7.0 Hz, 3H), 1.46 (dd, J = 8.5 Hz, J = 1.6 Hz, 1H), 1.78 (d, J = 8.5 Hz, 1H), 2.03 (m, 1H), 2.53 (s, 1H), 3.36 (s, 1H), 3.74 (dd, J = 3.9 Hz, J = 3.9 Hz, 1H), 3.95 (s, 3H), 5.81 (dd, J = 5.6 Hz, J = 2.8 Hz, 1H), 6.34 (dd, J = 5.6 Hz, J = 3.2 Hz, 1H), 7.00 (s, 1H), 7.15 (s, 1H). $^{13}$C-NMR (CDCl$_3$, 100 MHz) $\delta$ 20.6 (q), 36.0 (q), 36.7 (d), 47.2 (d), 49.1 (t), 49.8 (d), 56.0 (d), 126.6 (d), 128.8 (d), 131.8 (d), 138.8 (d), 143.4 (s), 193.5 (s). HRMS Calcd for C$_{13}$H$_{16}$N$_2$O$_2$ 216.1262, found 216.1263. Product ratios and e.e.’s were determined by HPLC analysis (Chiralcel-AD, n-heptane/iPrOH 99:1, 1 ml/min. Retention times: 7.3, 8.1 (exo isomer), 8.7, 9.5 min (endo isomer).

Bicyclo[2.2.1]hept-5-en-2-yl-(1-methyl-1H-imidazol-2-yl)-methanone (9h). A colourless oil was obtained after column chromatography (SiO$_2$, 33% EtOAc:n-pentane). $^1$H-NMR (CDCl$_3$, 400 MHz, endo isomer) $\delta$ 1.44 – 1.51 (m, 2H), 1.53 – 1.57 (m, 1H), 1.85 – 1.92 (m, 1H), 2.96 (s, 1H), 3.44 (s, 1H), 3.94 (s, 3H), 4.20 (m, 1H), 5.80 (dd, J = 5.6 Hz, J = 2.9 Hz, 1H), 6.24 (dd, J = 5.5 Hz, J = 3.0 Hz, 1H), 6.99 (s, 1H), 7.15 (s, 1H). $^{13}$C-NMR (CDCl$_3$, 100 MHz) $\delta$ 28.5 (t), 36.2 (d), 43.2 (d), 47.4 (q), 48.2 (t), 50.5 (d), 126.5 (d), 128.8 (d), 131.4 (d) 137.7 (d), 143.4 (s), 193.5 (s). HRMS Calcd for C$_{12}$H$_{14}$N$_2$O 202.1106, found 202.1111. Product ratios and e.e.’s were determined by HPLC analysis (Chiralcel-OD, n-heptane/iPrOH 99:3:0.7, 1 ml/min. Retention times: 10.1 (exo isomers), 11.7, 12.6 min (endo isomer).

Cu(L8)(NO$_3$)$_2$/DNA catalyzed Diels-Alder cycloaddition on a 1.0 mmol scale.

In a 500 mL Schott bottle was combined 19 mg Cu(L7)(NO$_3$)$_2$ (0.050 mmol), 166 mL water, and 333 mL of a salmon testes DNA solution (2 mg/mL in 30 mM MOPS buffer, pH 6.5; prepared 24h in advance), respectively. After cooling for an hour at 0 ºC, 8a (212 mg, 40
1.0 mmol, in 2 mL DMSO) was added, and the reaction was started by addition of cyclopentadiene (0.67 mL, 7.0 mmol). The components were mixed for three days by continuous inversion. The reaction mixture was extracted with EtOAc, dried on Na$_2$SO$_4$ and concentrated. Purification by column chromatography yielded 3a as a white crystalline powder (194 mg, 70% yield).

**2S,3S-3-Phenyl-bicyclo[2.2.1]hept-5-ene-2-carboxylic acid methyl ester (10).** To a 2 dram-oven dried vial under N$_2$ atmosphere was added 3a (24 mg, 0.09 mmol), powdered 4 Å mol. sieves (10 mg) and acetonitrile (0.6 mL). The mixture was stirred at room temperature and methyl triflate (11 µL, 0.1 mmol) was added. After stirring for 3h, MeOH (0.6 mL) and DBU (0.15 mL) were added. The mixture was stirred for another 20 min and subsequently diluted with 30 mL EtOAc, washed with bicarbonate and brine, dried on sodium sulfate and concentrated. Column chromatography (SiO$_2$, 1:25 EtOAc:n-pentane) provided 10 as a colourless oil (8.0 mg, 41%). [$\alpha$]$_{D}^{20}$ = +126.8º (c = 0.401 CHCl$_3$).

**1H-NMR (CDCl$_3$, 400 MHz, endo isomer)** $\delta$ 1.53 (d, J = 9.3 Hz, 1H), 1.74 (d, J = 8.7 Hz, 1H), 2.96 (t, J = 4.2 Hz, 1H), 3.00 (s, 1H), 3.06 (d, J = 4.2 Hz, 1H), 3.24 (s, 1H), 3.62 (s, 3H), 6.07 (dd, J = 5.6 Hz, J = 2.8 Hz, 1H), 6.38 (dd, J = 5.5 Hz, J = 3.2 Hz, 1H), 7.14 – 7.17 (m, 1H), 7.21 – 7.29 (m, 1H). The NMR data were in accordance with those published.$^{21}$

### 2.10 References

7. Calf thymus DNA proved equally effective in this reaction compared with st-DNA (Table 1, entry 6), demonstrating that this system is not dependent on the DNA source.
19. DNA concentration was kept at 1.3 mg/mL, which means that the Cu-L8/DNA base pair ratio in this case was 1:40.
20. The same yield and purity of 10 was observed without column chromatography of Diels-Alder product 8a.