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Asymmetric copper-catalyzed Diels-Alder reaction revisited: control of the structure of bis(oxazoline) ligands.

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Abstract

Synthesis of 1,4-bis(oxazoline) ligands bearing a bicyclo[2,2,2]backbone derived from 9,10-dihydro-9,10-ethanoanthacene trans-dicarboxylic acid was revisited. Starting from L- or D-amino alcohols and either (S,S) or (R,R)-dihydroethano trans-dicarboxylic acid, a complete series of ligands was evaluated in the copper-catalyzed Diels-Alder reaction. The most efficient ligands with a phenyl substituent on the oxazoline ring afforded enantiomeric excess up to 98%. This is different from previous results indicating that the best enantioselectivity involved a diastereomeric ligand with the meso-backbone.

Keywords: Chiral bis(oxazoline) synthesis; Bicyclo[2.2.2] backbone; Diels-Alder catalysis; Copper; Enantioselectivity.

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1. Introduction

Chiral bis(oxazoline) ligands have emerged as one class of important and efficient $C_2$-symmetric ligands in numerous metal-catalyzed asymmetric transformations.\textsuperscript{1-9} Among them, a novel class of oxazoline ligands with multiple elements of chirality has been synthesized from readily available chiral diacid and chiral amino alcohol (Fig. 1). Besides the central chirality element in the oxazoline moiety, these ligands possess an additional chirality element in the backbone such as 1,3-dioxolane $\text{I}$,\textsuperscript{10-12} bicyclo[2,2,1] $\text{II}$, [2,2,2] $\text{III}$,\textsuperscript{13} cyclohexane $\text{IV}$,\textsuperscript{14,15} and cyclopentane $\text{V}$.\textsuperscript{16}

![Fig. 1.](image)

Although the Diels-Alder reaction between acrylimide dienophiles and cyclopentadiene was the most successful application of the Cu(II)-bis(oxazoline) catalytic system with enantiomeric excess up to 99%,\textsuperscript{17-31} its application with the ligands $\text{I}$, $\text{II}$, $\text{III}$, $\text{IV}$ and $\text{V}$ was less effective in enantioselectivity. In particular, the ligand $\text{III}$, previously introduced by Takacs et al.,\textsuperscript{13} has particularly focused our attention since the best enantioselectivity (75%) in the Diels-Alder reaction surprisingly involves the meso-backbone and poor results were obtained with the other chiral configurations. Moreover, the authors\textsuperscript{13} indicated that a phenomenon of epimerization was observed during the synthesis of these ligands. These results inspired us to reinvestigate the synthesis of these ligands with more convenient routes to better control the stability of their relative configuration.
In the present work we revisit this class of bis(oxazoline) ligands in which the two oxazolines are separated by a dihydroethanoanthracene backbone (Figure 1, III). With the goal to rationalize and optimize the results obtained in catalysis, a more convenient preparation of the ligand was first described and the four diastereomers were prepared in pure form. The effect of structure change of the ligands on the stereochemical outcome of the asymmetric copper-catalyzed Diels-Alder reaction between N-acryloyloxazolidinone or N-crotonyloxazolidinone and cyclopentadiene was then fully investigated yielding high enantiomeric excess (up to 98%). As expected, the best ees were obtained with pure R,R and S,S bis(oxazoline), provided that the chirality of the backbone matched correctly the chirality of the bis(oxazoline).

2. Results and Discussion

The bis(oxazoline) ligands were synthesized from the corresponding 9,10-dihydro-9,10-ethanoanthacene trans-(11S,12S) and trans-(11R,12R) dicarboxylic acid (1) as shown in Scheme 1. After chiral separation with brucine,32 conversion of the diacid into the corresponding acid dichloride by reaction with the oxalyl chloride16 was accomplished within 1 h. After removing the solvent and excess oxalyl chloride, the product was used in the next step without purification. Overnight reaction with 2.2 equiv of the amino alcohol in the presence of triethylamine afforded the expected bis-hydroxyamide 3 as a white solid in 60-85% yield. The 1H NMR analysis confirmed the presence of the desired product as a single diastereomer. It should be noted that some epimerization occurs with the previously requisited procedure13 in forming the diamide intermediate.

Conversion of bis(hydroxyamide) 3 to the corresponding bis(oxazoline) 4 was carried out in one step by reaction with diethylaminosulfur trifluoride in CH2Cl2 at -78°C followed by
base induced cyclisation\textsuperscript{16,9} in 50-80\% yield. For the ligand 4d, the bis(hydroxyamide) 3d was first converted into the bis(amide) dichloride with SOCl\textsubscript{2} and then the cyclization was achieved with aqueous NaOH in 73\% yield. The dihydroxyamide 6 with the meso-backbone was synthesized from the anhydride 5 (not the acid)\textsuperscript{33} and the (R)-phenylglycinol in the presence of the coupling reagent N-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline (EEDQ) in 77\% yield.\textsuperscript{34,16}

The corresponding meso-bis(oxazoline) ligand 7 was prepared using a similar route with diethylaminosulfur trifluoride in CH\textsubscript{2}Cl\textsubscript{2} at -78°C. After purification on column chromatography, the \textsuperscript{1}H NMR spectrum shows peaks corresponding to ligands 4a and 4e'(15\%) due to epimerization (Fig. 2(A)). The \textsuperscript{1}H NMR analysis confirms the progressive disappearance of 7 after 24h (50\%, Fig. 2(B)) and after 48 hours, there is total conversion into the ligands 4a and 4e' in a ratio 53/47 (Fig. 2(C)).
Scheme 1.
Fig. 2

An X-ray structure of the bis(oxazoline) ligand 4a has been solved (Fig. 3).35 X-ray diffraction analysis shows that the two chiral oxazoline rings are slightly twisted pushing the two oxazolinyl phenyl towards the metal centre. In contrast, X-ray structure of the other diastereomer ligand 4e' (using the (R)-phenyl glycino1 and trans-(11R,12R)-dicarboxylic acid 1),13 showed that the two oxazolinyl phenyl are far away from the metal centre in the complex.
Fig. 3.

The Diels-Alder reaction of N-acryloyloxazolidinone 8a or N-crotonyloxazolidinone 8b\textsuperscript{19} and cyclopentadiene in the presence of various chiral catalysts derived from the ligands 4 and Cu(II) triflate was then investigated. The catalytic results are summarized in Table 1.
Table 1.

Diels-Alder reaction of 8 with cyclopentadiene catalyzed by Cu(II)(OTf)₂/bis(oxazoline) complexes¹

![Diels-Alder reaction diagram]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand</th>
<th>Time (min)</th>
<th>Temp (°C)</th>
<th>Yield (%)</th>
<th>endo/exo² (%)</th>
<th>eeendo³ (%) (config.)</th>
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<tbody>
<tr>
<td>1</td>
<td>4a</td>
<td>5</td>
<td>20</td>
<td>95</td>
<td>94/6</td>
<td>93 (R)</td>
</tr>
<tr>
<td>2</td>
<td>4a'</td>
<td>10</td>
<td>20</td>
<td>80</td>
<td>75/25</td>
<td>21 (R)</td>
</tr>
<tr>
<td>3</td>
<td>4b</td>
<td>30</td>
<td>20</td>
<td>80</td>
<td>85/15</td>
<td>16 (R)</td>
</tr>
<tr>
<td>4</td>
<td>4c</td>
<td>240</td>
<td>20</td>
<td>50</td>
<td>88/12</td>
<td>10 (S)</td>
</tr>
<tr>
<td>5</td>
<td>4d</td>
<td>10</td>
<td>20</td>
<td>80</td>
<td>88/12</td>
<td>20 (R)</td>
</tr>
<tr>
<td>6</td>
<td>4e</td>
<td>5</td>
<td>20</td>
<td>95</td>
<td>94/6</td>
<td>94 (S)</td>
</tr>
<tr>
<td>7</td>
<td>4e'</td>
<td>15</td>
<td>20</td>
<td>82</td>
<td>76/24</td>
<td>22 (S)</td>
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<tr>
<td>8</td>
<td>4f</td>
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<td>80</td>
<td>90/10</td>
<td>76 (R)</td>
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<td>9</td>
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<td>88/12</td>
<td>77 (R)</td>
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<td>4a²</td>
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<td>85</td>
<td>93/7</td>
<td>89 (R)</td>
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<td>11</td>
<td>4a</td>
<td>5</td>
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<td>95</td>
<td>96/4</td>
<td>95 (R)</td>
</tr>
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<td>12</td>
<td>4a</td>
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<td>98/2</td>
<td>98 (R)</td>
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<td>13</td>
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<td>96/4</td>
<td>96 (S)</td>
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<td>14</td>
<td>4e</td>
<td>45</td>
<td>-40</td>
<td>92</td>
<td>98/2</td>
<td>98 (S)</td>
</tr>
</tbody>
</table>

¹Molar ratio of metal/ligand/diene/dienophile: 1/1.2/150/50.

²Isolated yield of cycloadducts after silica gel chromatography.

³Determined by ¹H NMR and HPLC.

⁴Determined by chiral HPLC (Chiralcel OD-H column) and comparison of known optical rotation.

⁵Ligand prepared from the racemic trans-dicarboxylic acid 1 and (-)-(R)-phenylglycinol.

⁶N-crotonyloxazolidinone as dienophile.

From the results of Table 1, it is shown that the ligands 4a and 4e with the phenyl substituted oxazoline gave the best ee (93-94%) and endo/exo diastereoselectivity (94/6) (entries 1 and 6). With the ligand 4a' or 4e', in which the chirality of the oxazoline ring has
been inverted, the ee was decreased (21%), as well as the diastereoselectivity (75/25) (entries 2 and 7). The ligands with \textit{i}-Pr 4b and \textit{t}-Bu 4c gave low ee (< 20%) (entries 3 and 4). The high reactivity of the catalyst leads to short reaction times (5-10mn) with yields in the range 80-95%, excepted for the bulky \textit{t}-Bu group (50% yield) in which a longer reaction time was necessary (4 hours). We also decided to test N-crotonyloxazolidinone 8b as a substrate to compare our results with those previously reported.\textsuperscript{13} In our hands, the \textit{endo}-cycloadduct 9 was obtained with 89% ee and R configuration, using 4a as ligand (entry 10), whereas it was previously reported\textsuperscript{13} an enantiomeric excess of 28% with S configuration in a similar situation.

The effect of temperature was studied with ligands 4a and 4e. The highest ee and diastereoselectivity was obtained at -40°C (98% and 98/2 respectively) (entries 12 and 14).

The influence of substitution both on the oxazoline ring and on the backbone moiety has been investigated with the goal of better understanding the stereocontrol of the Cu(II)-catalyzed reaction. According to the structure (Fig. 3), we have prepared and tested the four diastereomeric ligands 4 with the phenyl group on the oxazoline ring (as represented in Fig. 4). By changing combination of the enantiomers derived from (+) or (-)-\textit{trans}-dicarboxylic acid and aminoalcohol, the stereochemistry of the four asymmetric centres can be adjustable. There are two sets of enantiomer pairs corresponding to the ligands 4a, 4e and 4a’, 4e’. The two phenyl groups on the oxazoline ring of ligand 4a and 4e are placed nearer to the reaction centre than those of 4a’ and 4e’, and consequently, have a larger effect on the enantioselectivity (93% versus 21%). These results show that the degree of asymmetric induction depends of the chirality on the oxazoline ring in 4a and 4a’ or 4e and 4e’. Furthermore, with the ligands 4a and 4a’ or 4e and 4e’, the same \textit{endo}-9(R) or 9(S) -cycloadduct was obtained. The sense of asymmetric induction was logically inverted with the
enantiomeric ligands 4a and 4e or 4a’ and 4e’ but also with the ligands 4a and 4e’ or 4a’ and 4e. These results demonstrate that the chiral sense of enantioselection was determined by the chirality of the backbone. To complete the study, it was also noted that ligand 4d with no substituent on the oxazoline ring gave an enantioselectivity of 20% (entry 5). This value was similar to the enantioselectivity obtained with ligand 4a’ (entry 2).

In our hands, the ligand 7 gave an ee = 77% for endo-9 (R)-cycloadduct (entry 9). Actually, this value is very close to that obtained with the ligand 4f derived from the racemic trans-dicarboxylic acid 1 and (-)-(R)-phenylglycinol, ee = 76% endo-9(R)-cycloadduct (entry 8). Taking into account the epimerization observed in the NMR study, an epimerization of the ligand 7 may also occur in the catalytic conditions. Since the epimerization is time dependent, a study of the ee obtained using ligand 7 over the time course of the catalytic reaction might be necessary. However, the short time of the catalytic reaction (<5 min) makes this study too difficult. It should be noted that previous results\textsuperscript{13} gave an ee of 75% for endo-9(R)-cycloadduct, quite similar to our results (77% ee).

![Fig. 4.](image-url)
3. Conclusion

In conclusion, the synthesis of bis(oxazoline) ligands with four asymmetric centres by combination of the two chiral sources derived from the dihydroethanoanthracene diacid and aminoacids are revisited, and well-structured chiral ligands have been isolated and characterized. The copper-catalyzed asymmetric Diels-Alder reaction between N-acryloyloxazolidinone and N-crotonyloxazolidinone with cyclopentadiene was carried out with these chiral ligands. The best adapted combination for the ligands 4a and 4e gave ees up to 98% at -40°C. Studies on the potential of these ligands for other metal-catalyzed asymmetric reactions are now in progress.

4. Experimental

4.1. General
All reactions were performed under argon. Solvent was distilled from appropriate drying agent, CH$_2$Cl$_2$ from CaH$_2$. Commercially available reagents were used without further purification unless otherwise stated. All reactions were monitored by TLC with Merck precoated aluminium foil sheets (silica gel 60 with fluorescent indicator UV$_{254}$). Column chromatographies were carried out using silica gel from Acros (0.063-0.200 mm). Melting points were measured on a banc Kofler. $^1$H NMR and $^{13}$C NMR in CDCl$_3$ were recorded using Bruker (Advance 400dpx) spectrometer at 400 and 100 MHz respectively. The following abbreviations are used in connexion with NMR: s=singlet, d=doublet, t=triplet, q=quartet and m=multiplet. Chiral HPLC analysis was performed on a Varian Prostar 218 system equipped with a Chiralcel OD-H column. Optical rotations were recorded with a Perkin-Elmer 341 polarimeter. High resolution mass spectra were performed by the Centre Regional de Mesures Physiques de l’Ouest (CRMPO) at Rennes, France, on a Q-Tof2 spectrometer in ESI positif mode.
4.2. General procedure of preparation of bis-hydroxyamides 3a, 3a’, 3b, 3c, 3d, 3e, 3e’, 3f and 6

Oxalyl chloride (3 equiv) was added dropwise to a cooled suspension (0°C) of the trans-diacide (-)-1 or (+)-1 and dimethylformamide (15 mol %) in CH₂Cl₂ (5 mL/mmol) under argon. The reaction mixture was stirred at room temperature for 2 h to give a yellow solution of the trans-diacide chloride (-)-2 or (+)-2. The solvent and excess oxalyl chloride were removed in high vacuum, the residue was taken up in CH₂Cl₂ (4 mL/mmol) and added slowly to a cold solution (0°C) of the corresponding amino alcohol (2.2 equiv) and Et₃N (5 equiv) in CH₂Cl₂ (2 mL/mmol) under argon. Stirring was continued for 16 h at room temperature. After evaporation, the crude product was purified by column chromatography (Hexane-EtOAc-MeOH).

4.2.1. (11S,12S)-Bis[(2’-hydroxy-1’-((R)-phenylethyl))-amido-9,10-dihydro-9,10-ethanoanthacene 3a

The product was synthesized according to the general procedure described above from 9,10-dihydro-9,10-ethanoanthacene trans-(11S,12S)-dicarboxylic acid 1 (0.5 g, 1.7 mmol) and (-)-(R)-phenylglycinol (0.65 g, 3.74 mmol). Purification by column chromatography (hexane-EtOAc, 1:9) yielded a white solid (840 mg, 93%): m.p. = 147-148 °C; [α]D20 = -34 (c 1.44, CHCl₃); ¹H NMR (400 MHz, CDCl₃): δ = 2.91 (s, 2H), 3.66 (br s, 4H), 4.59 (s, 2H), 4.90 (br s, 2H), 7.06-7.32 (m, 18H); ¹³C NMR (100 MHz, CDCl₃): δ = 46.8, 49.6, 55.8, 66.07, 123.4, 125.4, 126.3, 126.7, 127.6, 128.6, 138.8, 140.1, 143.0, 173.5; HRMS [ESI]: m/z calcld for C₃₄H₃₂N₂O₄Na: 555.2259 (M+Na)⁺, found: 555.2255.

4.2.2. (11S,12S)-Bis[(2’-hydroxy-1’-(S)-phenylethyl)]-amido-9,10-dihydro-9,10-ethanoanthacene 3a’
The product was synthesized according to the general procedure described above from 9,10-dihydro-9,10-ethanoanthacene trans-(11S,12S)-dicarboxylic acid 1 (0.5 g, 1.7 mmol) and (+)-(S)-phenylglycinol (0.65 g, 3.74 mmol). Purification by column chromatography (EtOAc-MeOH, 0:1) yielded a white solid (720 mg, 80%): m.p. = 174 °C; [α]D²⁰ = +32 (c 0.84, CHCl₃); ¹H NMR (400 MHz, CDCl₃): δ = 2.96 (s, 2H), 3.68 (dd, J = 6.4, 11.6 Hz, 2H), 3.73 (dd, J = 3.6, 11.4 Hz, 2H), 4.59 (s, 2H), 4.90 (dd, J = 7.2, 11.2 Hz, 2H), 7.00-7.04 (m, 6H), 7.16-7.22 (m, 8H), 7.28, 7.58 (2d, J = 8 Hz, 4H); ¹³C NMR (100 MHz, CDCl₃): δ = 45.9, 48.9, 56.2, 65.6, 123.4, 125.3, 125.9, 126.7, 127.3, 128.4, 139.6, 140.4, 143.3, 173.5; HRMS [ESI]: m/z calcd for C₃₄H₃₂N₂O₄Na: 555.2259 (M+Na)⁺, found: 555.2255.

4.2.3. (11S,12S)-Bis[(2’-hydroxy-1’-(S)-isopropylethyl)]-amido-9,10-dihydro-9,10-ethanoanthacene 3b

The product was synthesized according to the general procedure described above from 9,10-dihydro-9,10-ethanoanthacene trans-(11S,12S)-dicarboxylic acid 1 (0.5 g, 1.7 mmol) and (+)-L-Leucinol (0.438 g, 3.74 mmol). Purification by column chromatography (hexane-EtOAc, 9:1) yielded a white solid (635 mg, 80%): m.p. = 134-135 °C; [α]D²⁰ = -18 (c 0.55, CHCl₃); ¹H NMR (400 MHz, CDCl₃): δ = 0.78, 0.80 (2d, J = 6.4 Hz, 12H), 1.09-1.16, 1.22-1.29 (2m, 4H), 1.39-1.47 (m, 2H), 2.88 (s, 2H), 3.23 (dd, J = 6.8, 11.4 Hz, 2H), 3.46 (dd, J = 3.6, 11.6 Hz, 2H), 3.85 (br s, 2H), 4.46 (s, 2H), 7.00-7.06 (m, 4H), 7.21, 7.24 (2d, J = 6.8 Hz, 4H); ¹³C NMR (100 MHz, CDCl₃): δ = 22.0, 23.2, 24.8, 40.2, 46.9, 49.6, 65.4, 123.2, 125.4, 126.21, 140.3, 143.2, 173.8; HRMS [ESI]: m/z calcd for C₃₀H₄₅N₂O₄Na: 515.2885 (M+Na)⁺, found: 515.2883.

4.2.4. (11S,12S)-Bis[(2’-hydroxy-1’-(S)-tert-buty lethyl)]-amido-9,10-dihydro-9,10-ethanoanthacene 3c
The product was synthesized according to the general procedure described above from 9,10-dihydro-9,10-ethanoanthacene *trans*-\((11S,12S)\)-dicarboxylic acid 1 (1.0 g, 3.4 mmol) and (+)-(S)-*tert*-Leucinol (0.876 g, 7.48 mmol). Purification by column chromatography (EtOAc:MeOH, 4:1) yielded a white solid (1.27 g, 77%): m.p.= 220 °C; \([\alpha]_{365}^{20} = +57 \ (c \ 0.95\ , \ CHCl_3)\); \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta = 2.90 \ (s, \ 2H), 2.92 \ (t, \ J = 6.8 \ Hz, \ 2H), \ 3.36-3.43 \ (m, \ 2H), 3.73-3.79 \ (m, \ 4H), 4.62 \ (s, \ 2H), \ 7.10-7.17 \ (m, \ 4H), 7.28, \ 7.42 \ (2d, \ J = 6.4 \ Hz, \ 4H)\); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta = 26.8, 33.5, 46.3, 50.5, 59.6, 62.4, 123.2, 125.7, 126.3, 126.4, 140.2, 143.4, 174.7\); HRMS [ESI]: \(m/z\) calcd for C\(_{30}\)H\(_{40}\)N\(_2\)O\(_4\)Na: 515.2885 (M+Na)\(^+\), found: 515.2887.

4.2.5. (11S,12S)-Bis[\(2'\)-hydroxy-ethyl]-amido-9,10-dihydro-9,10-ethanoanthacene 3d

The product was synthesized according to the general procedure described above from 9,10-dihydro-9,10-ethanoanthacene *trans*-\((11S,12S)\)-dicarboxylic acid 1 (1 g, 3.40 mmol), and ethanolamine (0.457 g, 7.48 mmol) in THF (5 ml/mmold). Recrystallization from methanol yielded a white solid (578 mg, 45%): m.p.= 262 °C; \([\alpha]_{D}^{20} = +40 \ (c \ 2.25, \ CH_3OH)\); \(^1\)H NMR (400 MHz, CD\(_3\)OD): \(\delta = 3.28-3.33 \ (m, \ 6H), 3.56 \ (t, \ J = 6 \ Hz, \ 4H), 4.60 \ (s, \ 2H), 7.09 \ (quintuplet, \ J = 7.2 \ Hz, \ 4H), 7.24 \ (d, \ J = 6.8 \ Hz, \ 2H), 7.35 \ (d, \ J = 6.4 \ Hz, \ 2H)\); \(^{13}\)C NMR (100 MHz, CD\(_3\)OD): \(\delta = 40.9, 46.5, 59.7, 122.0, 123.8, 124.9, 139.1, 141.7, 172.6\); HRMS [ESI]: \(m/z\) calcd for C\(_{22}\)H\(_{24}\)N\(_2\)O\(_4\)Na: 403.1633 (M+Na)\(^+\), found: 403.1633.

4.2.6. (11R,12R)-Bis[\(2'\)-hydroxy-1'-(S)-phenylethyl]-amido-9,10-dihydro-9,10-ethanoanthacene 3e

The product was synthesized according to the general procedure described above from 9,10-dihydro-9,10-ethanoanthacene *trans*-\((11R,12R)\)-dicarboxylic acid 1 (0.5 g,1.7 mmol) and (+)-(S)-phenylglycinol (0.65 g, 3.74 mmol). Purification by column chromatography (hexane-EtOAc, 1:9) yielded a white solid (820 mg, 91%): m.p.= 137-138 °C; \([\alpha]_{D}^{20} = +30 \ (c \ 0.51,
CHCl₃; ¹H NMR (400 MHz, CDCl₃): δ = 2.92 (s, 2H), 3.64 (m, 4H), 4.58 (s, 2H), 4.89 (dd, J = 5.0, 11.8 Hz, 2H), 7.04-7.30 (m, 18H); ¹³C NMR (100 MHz, CDCl₃): δ = 46.1, 50.1, 55.8, 66.7, 123.5, 125.5, 126.5, 126.6, 127.8, 128.8, 138.5, 140.0, 143.0, 173.6; HRMS [ESI]: m/z calcd for C₃₄H₃₂N₂O₄Na: 555.2259 (M+Na)⁺, found: 555.2255.

4.2.7. (11R,12R)-Bis[(2’-hydroxy-1’-(R)-phenylethyl)]-amido-9,10-dihydro-9,10-ethanoanthacene 3e’

The product was synthesized according to the general procedure described above from 9,10-dihydro-9,10-ethanoanthacene trans-(11R,12R)-dicarboxylic acid 1 (0.5 g, 1.7 mmol) and (-)-(R)- phenylglycinol (0.65 g, 3.74 mmol). A white precipitate was formed in the solution and it was filtered, washed with CH₂Cl₂ and dried in vacuum to provide the corresponding bis(hydroxyamide) (768 mg, 85%): m.p.= 148-150°C; [α]D²⁰ = -31 (c 0.71, CHCl₃); ¹H NMR (400 MHz, CDCl₃): δ = 3.19 (s, 2H), 3.75 (br s, 4H), 4.69 (s, 2H), 4.95 (br d, 2H), 7.02 (dd, J = 4.0, 8.4 Hz, 2H), 7.19-7.31 (m, 14H), 7.90 (d, J = 7.2 Hz, 2H); ¹³C NMR (100 MHz, CDCl₃): δ = 46.7, 49.3, 56.1, 65.7, 123.4, 125.4, 125.6, 126.0, 126.0, 126.7, 128.5, 139.4, 140.4, 143.3, 173.5; HRMS [ESI]: m/z calcd for C₃₄H₃₂N₂O₄Na: 555.2259 (M+Na)⁺, found: 555.2255.

4.2.8. (11S,12S+11R,12R)-Bis[(2’-hydroxy-1’-(R)-phenylethyl)]-amido-9,10-dihydro-9,10-ethanoanthacene 3f

The product was synthesized according to the general procedure described above from racemic- 9,10-dihydro-9,10-ethanoanthacene trans-dicarboxylic acid 1 (0.5 g, 1.7 mmol) and (-)-(R)- phenylglycinol (0.65 g, 3.74 mmol). Purification by column chromatography (EtOAc), yielded a white solid (690 mg, 76%): m.p.= 150 °C; [α]D₅₈⁹ = -33 (c 1.94, CHCl₃); ¹H NMR (400 MHz, CDCl₃): δ = 3.08 (s, 2H), 3.66 (br s, 4H), 4.60 (s, 2H), 4.87 (br s, 2H), 6.93-7.22 (m, 16H), 7.77 (d, J = 7.2 Hz, 2H); ¹³C NMR (100 MHz, CDCl₃): δ = 45.9, 49.3,
4.2.9. Bis[(2'-hydroxy-1'-(R)-phenylethyl)]-amido-9,10-dihydro-9,10-ethanoanthacene 6

The product was synthesized from the cis-9,10-dihydro-9,10-ethanoanthacene dicarboxylic anhydride 5 (225mg, 0.9 mmol), (-)-(R)- phenylglycinol (156mg, 0.9 mmol) and N-Ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline (247 mg, 1.0 mmol) in 10 ml of THF at ambient temperature for 48 h. Purification by column chromatography (EtOAc-MeOH , 9:1) yielded a white solid (185 mg, 77%): m.p.= 125-127 °C; [α]_{D}^{20} = -73 (c 0.82 , CHCl₃); ¹H NMR (400 MHz , CDCl₃): δ = 3.12 (dd, J = 12.0, 22.8 Hz, 2H), 3.23, 3.26 (2d, J = 6.8 Hz, 1H), 3.57-3.63 (m 2H), 3.73, 3.75 (2d, J = 3.6 Hz, 1H), 4.040 (dd, J = 7.2,14.4 Hz, 1H), 4.41 (br s, 1H), 4.80 (m, 1H), 4.90 (m, 1H), 7.02-7.36 (m, 18H); ¹³C NMR (100 MHz, CDCl₃): δ = 46.2, 47.0, 49.4, 50.6, 55.5, 56.2, 65.2, 65.6 123.5, 123.6, 124.5, 126.3, 126.4, 126.9, 127.0, 127.1, 127.2, 127.7, 128.7, 128.7, 138.8, 139.3, 139.5, 141.9, 142.4, 142.8, 172.4, 173.1; HRMS [ESI]: m/z calcd for C₃₄H₃₂N₂O₄Na: 555.22598 (M+Na)^+, found: 555.2257.

4.3. General procedure of preparation of bis(oxazoline) 4a, 4a’, 4b, 4c, 4d, 4e, 4e’, 4f, and 7

Diethylaminosulfur trifluoride (2.2 equiv) was added dropwise to a cooled suspension (-78°C) of the corresponding bis-hydroxyamide in dry CH₂Cl₂ (10 mL/mmol) under argon. After stirring for 3-5 h at the indicated temperature, anhydrous K₂CO₃ (3 equiv) was added and the reaction mixture was allowed to warm to room temperature. A saturated aqueous NaHCO₃ solution was added and after phase separation the aqueous layer was extracted with CH₂Cl₂. After drying over MgSO₄ and evaporation, the crude product was purified by column chromatography (Hexane-EtOAc).
4.3.1. (11S,12S)-Bis[(4'R)-phenyloxazoline]-9,10-dihydro-9,10-ethanoanthacene 4a

The product was synthesized from 3a (0.7 g, 1.31 mmol) according to the general procedure described above. Purification by column chromatography (hexane-EtOAc, 3:2) yielded a white solid (513 mg, 78%): m.p. = 85-86 °C; [α]D<sup>20</sup> = +83 (c 0.96, CHCl<sub>3</sub>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ = 3.68 (s, 2H), 4.01 (t, J = 8.0 Hz, 2H), 4.57 (t, J = 9.2 Hz, 2H), 4.82 (s, 2H), 5.01 (t, J = 8.4 Hz, 2H), 7.08-7.27 (m, 14H), 7.34, 7.38 (2d, J = 6.4 Hz, 4H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ = 42.9, 47.0, 69.3, 75.3, 123.9, 125.1, 126.1, 126.3, 126.6, 127.4, 128.6, 140.5, 142.4, 142.5, 168.8; HRMS [ESI]: m/z calcd for C<sub>34</sub>H<sub>29</sub>N<sub>2</sub>O<sub>2</sub>: 497.2229 (M+H)<sup>+</sup>, found: 497.2229.

4.3.2. (11S,12S)-bis[(4'S)-phenyloxazoline]-9,10-dihydro-9,10-ethanoanthacene 4a'

The product was synthesized from 3a' (0.50 g, 0.94 mmol) according to the general procedure described above. Purification by column chromatography (hexane-EtOAc, 3:2) yielded a white solid (300 mg, 68%): m.p. = 177 °C; [α]D<sup>20</sup> = +31 (c 0.87, CHCl<sub>3</sub>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ = 3.83 (s, 2H), 3.86 (t, J = 8.0 Hz, 2H), 4.50 (dd, J = 8.4, 10.0 Hz, 2H), 4.78 (s, 2H), 4.92 (t, J = 8.8 Hz, 2H), 6.40 (d, J = 8.4 Hz, 4H), 7.05-7.18 (m, 12H), 7.23, 7.36 (2d, J = 6.8 Hz, 4H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ = 43.1, 46.5, 69.1, 75.9, 124.5, 124.9, 126.3, 126.4, 127.2, 128.4, 140.9, 142.0, 142.1, 169.2; HRMS [ESI]: m/z calcd for C<sub>34</sub>H<sub>29</sub>N<sub>2</sub>O<sub>2</sub>: 497.2229 (M+H)<sup>+</sup>, found: 497.2229.

4.3.3. (11S,12S)-Bis[(4'S)-isopropyloxazoline]-9,10-dihydro-9,10-ethanoanthacene 4b

The product was synthesized from 3b (0.5 g, 1.0 mmol) according to the general procedure described above. Purification by column chromatography (hexane-EtOAc, 2:3) yielded a white solid (295 mg, 63%): m.p. = 67-69 °C; [α]D<sup>20</sup> = -11 (c 0.52, CHCl<sub>3</sub>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ = 0.65, 0.71 (2d, J = 6.8 Hz, 12H), 0.78, 0.92 (2 quintuplets, J = 7.2 Hz, 4H), 1.30 (septuplet, J = 6.8 Hz, 2H), 3.46 (s, 2H), 3.69 (t, J = 7.2 Hz, 2H), 3.80 (quintuplet, J = 7.6 Hz,
2H), 4.13 (t, J = 8.0 Hz, 2H), 4.60 (s, 2H), 6.97-7.05 (m, 4H); 7.13, 7.27 (2d, J = 6.8 Hz, 4H);

$^{13}$C NMR (100 MHz, CDCl$_3$): δ = 22.6, 22.7, 24.9, 42.3, 45.8, 46.9, 64.0, 73.4, 124.0, 124.6,
125.8, 126.1, 140.6, 141.8, 166.9; HRMS [ESI]: m/z calcd for C$_{30}$H$_{37}$N$_2$O$_2$: 457.2855,
(M+H)$^+$, found: 457.2857.

4.3.4. (11S,12S)-Bis[(4'S)-tert-butyloxazoline]-9,10-dihydro-9,10-ethanoanthacene 4c

The product was synthesized from 3c (0.5 g, 1.02 mmol) according to the general procedure
described above. Purification by column chromatography (hexane-EtOAc, 3:1) yielded a
white solid (404 mg, 86%): m.p.= 84-86 °C; [α]$_D^{20}$ = -19 (c 0.51 , CHCl$_3$); $^1$H NMR (400
MHz , CDCl3): δ = 3.56 (s, 2H), 3.59 (t, J = 9.2 Hz, 2H), 3.86 (t, J = 8.4 Hz, 2H), 4.07 (t, J =
8.4 Hz, 2H), 4.60 (s, 2H), 6.92, 6.98 (2t, J = 7.2 Hz,4H), 7.10, 7.23 (2d, J = 7.2 Hz, 4H); $^{13}$C
NMR (100 MHz, CDCl$_3$): δ = 25.6, 32.9, 43.0, 46.5, 69.1, 75.3, 123.7, 124.9, 125.97, 126.0,
140.8, 142.3, 167.2; HRMS [ESI]: m/z calcd for C$_{30}$H$_{37}$N$_2$O$_2$: 457.2855 (M+H)$^+$,
found:457.2855.

4.3.5. (11S,12S)-Bis(oxazoline)-9,10-dihydro-9,10-ethanoanthacene 4d

The bis(hydroxyamide) 3d (250 mg, 0.66 mmol) in CH$_2$Cl$_2$ (5 ml) was treated with SOCl$_2$
(1.56 g, 13.1 mmol). After 15 min, the solution was heated at reflux for 3 h, then recooled to
room temperature and washed sequentially with cold water (10 ml), 0.1 M K$_2$CO$_3$ (2 x 10 ml),
and saturated aqueous NaCl (10ml). After drying over MgSO$_4$ and evaporation, the crude
bisamide dichloride was obtained as a white solid (175 mg, 93%): $^1$H NMR (400 MHz ,
CDCl3): δ = 2.84 (s, 2H), 3.45 (m, 8H), 4.55 (s, 2H), 7.04-7.11 (m, 4H), 7.24, 7.29 (2d, J =
6.4 Hz, 4H). HRMS [ESI]: m/z calcd for C$_{22}$H$_{22}$N$_2$O$_2$Cl$_2$Na: 439.0956 (M+Na)$^+$, found:
439.0957.

A mixture of the crude bisamide dichloride, 170mg (0.41 mmol), and NaOH (500 mg, 30
mmol) in 50% aqueous MeOH (5 ml) was heated under reflux for 4 hours. After cooling, the
mixture was extracted with CH$_2$Cl$_2$ and washed with saturated aqueous NaCl. Column chromatography on silica (EtOAc/MeOH, 9:1) yielded the ligand 4d as a white solid (102 mg, 73%): m.p. = 95-98 °C, 0.102 g (73%). [α]$_D^{20}$ = +34 (c 1.23, CHCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$): δ = 3.38 (s, 2H), 3.44-3.64 (m, 4H), 4.06-4.16 (m, 4H), 4.62 (s, 2H), 6.99-7.05 (m, 4H), 7.15, 7.25 (2d, J = 6.4 Hz, 4H); $^{13}$C NMR (100 MHz, CDCl$_3$): δ = 42.7, 46.9, 54.1, 67.8, 123.8, 124.7, 126.0, 126.2, 140.4, 142.3, 168.4; HR MS [ESI]: m/z calcd for C$_{22}$H$_{21}$N$_2$O$_2$: 345.1603 (M+H)$^+$, found: 345.1611.

4.3.6. (11R,12R)-Bis[(4'S)-phenyloxazoline]-9,10-dihydro-9,10-ethanoanthacene 4e

The product was synthesized from 3e (0.5 g, 0.94 mmol) according to the general procedure described above. Purification by column chromatography (hexane-EtOAc, 3:2) yielded a white solid (440 mg, 68%): m.p. = 81-82 °C; [α]$_D^{20}$ = -82 (c 0.65, CHCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$): δ = 3.58 (s, 2H), 3.92 (t, J = 8.0 Hz, 2H), 4.48 (t, J = 8.4 Hz, 2H), 4.72 (s, 2H), 54.90 (t, J = 8.0 Hz, 2H), 6.96-7.18 (m, 14H), 7.24, 7.28 (2d, J = 6.4 Hz, 4H); $^{13}$C NMR (100 MHz, CDCl$_3$): δ = 43.1 46.5, 69.1, 75.9, 124.5, 124.9, 126.3, 126.3, 126.4, 127.2, 128.4, 140.9, 142.0, 142.1, 169.2; HRMS [ESI]: m/z calcd for C$_{34}$H$_{29}$N$_2$O$_2$: 497.2229 (M+H)$^+$, found: 497.2229.

4.3.7. (11R,12R)-Bis[(4'R)-phenyloxazoline]-9,10-dihydro-9,10-ethanoanthacene 4e'

The product was synthesized from 3e' (0.5 g, 0.94 mmol) according to the general procedure described above. Purification by column chromatography (hexane-EtOAc, 3:2) yielded a white solid (407 mg, 63%): m.p. = 178 °C; [α]$_D^{20}$ = -33 (c 0.87, CHCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$): δ = 3.83 (s, 2H), 3.87 (t, J = 8.0 Hz, 2H), 4.50 (dd, J = 8.4, 10.0 Hz, 2H), 4.78 (s, 2H), 4.92 (t, J = 8.8 Hz, 2H), 6.41 (d, J = 7.2 Hz, 4H), 7.05-7.18 (m, 10H), 7.23, 7.36 (2d, J = 6.8 Hz, 4H); $^{13}$C NMR (100 MHz, CDCl$_3$): δ = 43.1, 46.5, 69.1, 75.9, 124.5, 124.9, 126.3,
126.3, 126.4, 127.2, 128.4, 140.9, 142.0, 142.1, 169.2; HRMS [ESI]: \textit{m/z} calcd for C$_{34}$H$_{29}$N$_2$O$_2$: 497.2229 (M+H)$^+$, found: 497.2229.

4.3.8. (11S,12S+11R,12R)-Bis[(4'R)-phenyloxazoline]-9,10-dihydro-9,10-ethanoanthacene 4f

The product was synthesized from 3f (0.5 g, 0.94 mmol) according to the general procedure described above. Purification by column chromatography (hexane-EtOAc, 3:2) yielded a white solid (230 mg, 52%): m.p.= 91-95 °C; [\alpha]_D$^{20}$ = +13 (c 10, CHCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 3.58 (s, 2H), 3.83 (s, 2H), 3.87, 3.91 (2t, J = 8.0 Hz, 4H), 4.45-4.53 (m, 4H), 4.72 (s, 2H), 4.78 (s, 2H), 4.87-4.95 (m, 4H), 6.41 (d, J = 8.0 Hz, 4H), 6.96-7.37 (m, 32H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ = 42.8, 43.1, 46.5, 47.0, 69.1, 69.2, 75.3, 75.9, 123.8, 124.5, 124.8, 125.1, 126.1, 126.2, 126.3, 126.4, 126.5, 127.2, 127.4, 128.4, 128.5, 140.9, 142.1, 142.3, 142.5, 168.8, 169.2; HRMS [ESI]: calcd for C$_{34}$H$_{29}$N$_2$O$_2$: 497.2229 (M+H)$^+$, found: 497.2229.

4.3.9. Bis[(4'R)-phenyloxazoline]-9,10-dihydro-9,10-ethanoanthacene 7

The product was synthesized from 6 (0.3 g, 0.56 mmol) according to the general procedure described above. Purification by column chromatography (hexane-EtOAc, 3:2) yielded a white solid (90 mg, 54%): m.p.= 60-62 °C; [\alpha]_D$^{20}$ = +43, c 0.58, CHCl$_3$; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 3.18 (d, J = 10.8 Hz, 1H), 3.35 (t, J = 8.4 Hz, 1H), 3.43 (d, J = 8.4 Hz, 1H), 3.54 (dd, J = 2 Hz, 1H), 4.04, 4.07 (2d, J = 8.4 Hz, 1H), 4.29, 4.31 (2d, J = 8.4 Hz, 1H), 4.56 (d, J = 2 Hz, 1H), 4.81 (s, 1H), 4.93 (t, J = 9.2 Hz, 2H), 5.03 (t, J = 9.4 Hz, 1H), 6.84-7.25 (m, 17 H), 7.42-7.44 (m, 1H). $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ = 41.6, 41.7, 46.5, 48.8, 69.0, 69.1, 74.6, 74.8, 123.5, 124.0, 124.6, 125.7, 126.3, 126.4, 126.5, 126.7, 126.9, 127.1, 127.3, 128.4, 128.6, 140.7, 141.2, 142.3, 142.4, 142.6, 143.7, 168.0, 168.2. HRMS [ESI]: \textit{m/z} calcd for C$_{34}$H$_{29}$N$_2$O$_2$: 497.2229 (M+H)$^+$, found: 497.2229.
4.4. General procedure for asymmetric Diels-Alder reaction

A mixture of Cu(II)(OTf)$_2$ (5 μmol, 10 mol %) and the ligand 4 (6 μmol,) in dry CH$_2$Cl$_2$ (0.2 ml) was stirred for 0.5 h at room temperature under argon. The dienophile (50 μmol in 50 μl CH$_2$Cl$_2$) and freshly distilled cyclopentadiene (150 μmol) were then respectively added. The reaction was monitored by TLC and stopped after consumption of the starting substrate. The reaction mixture was purified on silica gel with hexane-ethyl acetate (3:1) to give a mixture of endo and exo isomers of cycloadducts 9. The yield was calculated on the basis of the isolated products. The endo/exo ratio was determined by $^1$H NMR analysis and confirmed by HPLC analysis. The enantiomeric excess of the cycloadduct was determined by chiral HPLC analysis: Daicel Chiralcel OD-H column, hexane-i-PrOH, 95:5, flow rate = 1 ml/min, detection: 220 nm. The absolute configuration of the cycloadduct endo-9 product was assigned based upon the comparison of the sign of optical rotation with the literature values: (+) for (R)-9 and (-) for (S)-9.

Supplementary data

Copies of $^1$H and $^{13}$C NMR spectra of bis(hydroxyamide) 3a, 3a’, 3b, 3c, 3d, 3e, 3e’, 3f and 6, copies of $^1$H and $^{13}$C NMR spectra of bis(oxazoline) 4a, 4a’, 4b, 4c, 4d, 4e, 4e’, 4f and 7, HPLC chromatograms of selected Diels-alder reactions, X-ray crystallographic data of ligand 4a.

Legends

**Fig. 1.** Structure of various chiral bis(oxazoline) ligands linked with a rigid backbone.

**Fig. 2.** $^1$H NMR study of the epimerization of ligand 7 in CDCl$_3$

(A) After purification; Time: 1h
(B) Time: 24h

(C) Time: 48h

**Fig. 3.** ORTEP drawing and atom labeling of ligand 4a

**Fig. 4.** Cu(II)-complexes of the four diastereomeric ligands 4 and the correlation between structure of the ligand and configuration of the cycloadduct

**Scheme 1.** Synthesis of different chiral bis(oxazoline) with a dihydroethanoanthracene backbone.

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**References and notes**

35. Crystal structure data deposited at the Cambridge Crystallographic Data Centre with deposit number CCDC 935282.