Synthesis of novel chiral bisoxazoline ligands with a norbornadiene backbone: use in the copper-catalyzed enantioselective Henry reaction

Rabia DELİKUŞ1, Emine ÇAKIR1, Nadir DEMİREL1, Metin BALCI2, Betül KARATAS1,*

1Department of Chemistry, Faculty of Arts and Sciences, Ahi Evran University, Kırşehir, Turkey
2Department of Chemistry, Faculty of Arts and Sciences, Middle East Technical University, Ankara, Turkey

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Abstract: Novel chiral bisoxazoline ligands based on norbornadiene were synthesized and used for the asymmetric Henry reaction. Various aromatic aldehydes were converted into chiral β-nitro alcohols with high yields and moderate to acceptable enantioselectivities under the optimized reaction conditions.

Key words: Asymmetric synthesis, Henry reaction, chiral bisoxazolines, nitroaldol, copper

1. Introduction

In recent years, chiral bisoxazoline-metal complexes have proven to be versatile chiral catalysts able to catalyze a wide range of reactions.1–4 The short and efficient synthesis of bisoxazoline ligands, the flexibility in ligand design, coordination to a large number of transition metals, and excellent enantioselectivity in many reactions make these ligands indispensable in asymmetric catalysis.

The nitroaldol or Henry reaction is one of the important C–C bond forming reactions in organic chemistry.5–7 It involves the addition of a nitroalkane having an α-hydrogen atom to a carbonyl compound to form a β-nitro alcohol that can be transformed into valuable oxygen- and nitrogen-containing derivatives. Despite the early discovery of the Henry reaction in 1895, catalyst-controlled asymmetric versions of this reaction were undocumented until 1992.8 Since then, various chiral catalytic systems were developed involving the use of BINOL,8–10 bisoxazolines,11–26 bisoxazolidines,27,28 cinchona alkaloids,29–31 zinc complexes,32–34 salen-cobalt35 and salen-chromium36 complexes, amino alcohols,37–43 diamines,44–49 chiral Schiff bases,50–56 and tetrahydro-bisisoquinoline ligands.57,58

To the best of our knowledge, there is still a limited number of papers on the synthesis of chiral bisoxazoline ligands forming five-22 and seven-membered19 chelates with metals and their application in the asymmetric Henry reaction. Herein we report the synthesis of novel bisoxazoline ligands 1a–e and 2 forming seven-membered metal chelates where the oxazoline groups are attached to the sp² carbon backbone and their use in the copper-catalyzed asymmetric Henry reaction (Figure).

*Correspondence: bkaratas@ahievran.edu.tr
2. Results and discussion

2.1. Preparation of the bisoxazoline ligands 1a – e and 2

The synthesis of diacyl chloride 5 used in the preparation of the chiral bisoxazoline ligands 1a – e and 2 starts with the reaction of cyclopentadiene and dimethyl acetylenedicarboxylate. The Diels–Alder reaction of these compounds at room temperature yielded the diester 3 quantitatively. Heating compound 3 in THF/MeOH/H$_2$O in the presence of KOH at 50 °C gave dicarboxylic acid 4 in 83% yield. Finally, compound 4 was treated with oxalyl chloride in the presence of a catalytic amount of DMF at 0 °C to give diacyl chloride 5 in 79% yield according to the literature with some modifications as indicated in the experimental part (Scheme 1).

Diagram:


Diacyl chloride 5 was treated with various chiral $\beta$-amino alcohols 6a – e and 7 in the presence of triethylamine at 0 °C to afford bis(hydroxy amides) 8a – e and 9 in 65% – 96% yields according to the procedure published by Evans et al. Their subsequent reaction with diethylaminosulfur trifluoride (DAST) at −78 °C yielded bisoxazoline ligands 1a – e and 2 in 45% – 88% yields (Scheme 2).
2.2. Copper-catalyzed asymmetric Henry reaction

Initially the reactivity and selectivity of chiral bisoxazoline ligands 1a–e and 2 in the copper-catalyzed Henry reaction were investigated (Table 1). The reaction between p-nitrobenzaldehyde and nitromethane in the presence of 6 mol% ligand and 5 mol% of Cu(OAc)$_2$ was chosen as a model system.\textsuperscript{19} The reactions were carried out at room temperature in 2-propanol and completed in 2–6 days. The first results showed that varying the substituents on the oxazoline ring had remarkable effects on the enantioselectivity of the reactions. The chiral bisoxazoline ligand 1a with a Ph group resulted in the lowest ee value among all ligands (entry 1). Ligand 1b with a Bn group presented higher enantioselectivity than did 1c with an i-Pr group (entry 2 vs. 3). Ligand 1d with a sterically hindered t-Bu group and ligand 2b with two stereogenic centers on the oxazoline ring decreased the enantioselectivity dramatically (entries 4 and 6). The highest ee value was obtained with ligand 1e with a sec-Bu group, which was the ligand of choice yielding a nitroaldol product 11a with 44% ee (entry 5).

In order to find the optimal conditions for the copper-catalyzed Henry reaction, the catalyst loading was changed. Lowering the catalyst amount from 5 mol% to 3 mol% or increasing it to 10 mol% slightly decreased the enantioselectivity (entries 7 and 8). On the other hand, the addition of triethylamine as a base promoter lowered the enantioselectivity substantially (entry 9). Replacing Cu(OAc)$_2$ with Cu(OTf)$_2$ or with Cu(OAc)$_2$.H$_2$O did not help to increase the enantioselectivity of the Henry reactions (entries 10 and 11).

The best solvent for the asymmetric Henry reaction was found to be 2-propanol (Table 2, entry 1). The other polar protic solvents (MeOH and EtOH) resulted in lower ee values (entries 2 and 3). Moreover, polar aprotic solvents (Et$_2$O, THF, CH$_2$Cl$_2$ etc.) presenting lower ee values were also not suitable for this reaction (entries 4–9). As a result, the best reaction conditions for the enantioselective Henry reaction was obtained by using 6 mol% ligand 1e and 5 mol% Cu(OAc)$_2$ in 2-propanol at room temperature.
After optimizing the reaction conditions, the asymmetric Henry reaction was performed with various aromatic aldehydes (Table 3). In general, the reactions were slow, but better enantiomeric excesses were obtained with these aldehydes than with \( p \)-nitrobenzaldehyde (54%–67% ee, entries 2–11 vs. entry 1). Ortho-, meta-, and para-methoxybenzaldehydes (10c–e) showed acceptable enantioselectivities (61%–67% ee, entries 3–5), whereas it was slightly lower for \( p \)-ethoxybenzaldehyde (10f) (54% ee, entry 6). Benzaldehydes having electron
withdrawing groups except for 10a did not decrease the enantioselectivity much (entries 8 and 9).

Benzaldehyde (10b) with 63% ee showed better enantioselectivity than 1-naphthaldehyde (10j) and cinnamaldehyde (10k) (entry 2 vs. entries 10 and 11).

Table 3. Henry reaction of nitromethane with various aldehydes.\textsuperscript{a}

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Product</th>
<th>Time (days)</th>
<th>Yield\textsuperscript{b} (%)</th>
<th>ee\textsuperscript{c} (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4-NO\textsubscript{2}C\textsubscript{6}H\textsubscript{4}</td>
<td>11a</td>
<td>2</td>
<td>80</td>
<td>44</td>
</tr>
<tr>
<td>2</td>
<td>Ph</td>
<td>11b</td>
<td>7</td>
<td>80</td>
<td>63</td>
</tr>
<tr>
<td>3</td>
<td>2-MeOC\textsubscript{6}H\textsubscript{4}</td>
<td>11c</td>
<td>13</td>
<td>69</td>
<td>61</td>
</tr>
<tr>
<td>4</td>
<td>3-MeOC\textsubscript{6}H\textsubscript{4}</td>
<td>11d</td>
<td>13</td>
<td>98</td>
<td>67</td>
</tr>
<tr>
<td>5</td>
<td>4-MeOC\textsubscript{6}H\textsubscript{4}</td>
<td>11e</td>
<td>13</td>
<td>71</td>
<td>60</td>
</tr>
<tr>
<td>6</td>
<td>4-EtOC\textsubscript{6}H\textsubscript{4}</td>
<td>11f</td>
<td>7</td>
<td>85</td>
<td>54</td>
</tr>
<tr>
<td>7</td>
<td>4-MeC\textsubscript{6}H\textsubscript{4}</td>
<td>11g</td>
<td>7</td>
<td>97</td>
<td>60</td>
</tr>
<tr>
<td>8</td>
<td>4-ClC\textsubscript{6}H\textsubscript{4}</td>
<td>11h</td>
<td>14</td>
<td>19</td>
<td>56</td>
</tr>
<tr>
<td>9</td>
<td>3-BrC\textsubscript{6}H\textsubscript{4}</td>
<td>11i</td>
<td>13</td>
<td>89</td>
<td>62</td>
</tr>
<tr>
<td>10</td>
<td>1-Naphthyl</td>
<td>11j</td>
<td>7</td>
<td>98</td>
<td>54</td>
</tr>
<tr>
<td>11</td>
<td>PhCH=CH\textsubscript{2}</td>
<td>11k</td>
<td>7</td>
<td>95</td>
<td>60</td>
</tr>
</tbody>
</table>

\textsuperscript{a}All reactions were performed at room temperature on a 0.2 mmol scale with 2 mmol nitromethane, 6 mol % of ligand 1e and 5 mol % of Cu(OAc)\textsubscript{2} in 2-propanol.

\textsuperscript{b}Values are isolated yields after chromatographic purification.

\textsuperscript{c}Enantiomeric excess was determined by HPLC using a Chiralcel OD-H column.

The moderate to acceptable enantiomeric excesses obtained in the copper-catalyzed Henry reaction might be the result of distortion in the $C_2$-symmetry of the ligands 1a–e and 2. The norbornadiene backbone not only enlarges the chelate but also breaks the $C_2$-symmetry apparent by the signal doubling of the ligands in the $^1$H and $^{13}$C NMR spectra.

Although bisoxazoline ligands forming six-membered metal chelates result in excellent enantioselectivity in the copper-catalyzed Henry reactions, their seven-membered derivatives exhibit rather lower enantioselectivity. For example, the reaction of $p$-nitrobenzaldehyde (10a) with nitromethane presents 81% ee, when inda-box ligand 12 forming six-membered metal chelate is used (Scheme 3).\textsuperscript{12} However, cyclopropane based ligand 13 forming seven-membered metal chelate results in lower stereoselectivity (68% ee).\textsuperscript{13} Moreover, when a bisoxazoline ligand forming seven-membered metal chelate with two oxazoline groups attached to sp\textsuperscript{2} carbon atoms (ligands 14a and 14b), stereoselectivity of the copper-catalyzed Henry reaction further decreased to 13% and 28% ee respectively.\textsuperscript{21} Our norbornadiene based bisoxazoline ligands 1a–e and 2 are examples of ligands forming seven-membered metal chelate having two oxazoline groups attached to sp\textsuperscript{2} carbon atoms. Under the guidance of these studies, it might be argued that these type of ligands show lower stereoselectivity but still ligand 1e with 44% ee exhibits higher enantioselectivity than ligands 14a and 14b in the enantioselective Henry reaction between $p$-nitrobenzaldehyde (10a) and nitromethane (Table 1, entry 5 vs. Scheme 3).

In conclusion, a series of novel chiral bisoxazoline ligands 1a–e and 2 having a norbornadiene backbone were synthesized in five steps in 45%–88% yields. They were used as chiral ligands in the copper-catalyzed
asymmetric Henry reaction. With the optimized reaction conditions, various \( \beta \)-nitro alcohols \(11a-k\) were obtained with 44\%–67\% enantiomeric excesses. Application of the bisoxazoline ligands \(1a-e\) and \(2\) in other asymmetric catalytic reactions is currently under investigation.

\[
\begin{align*}
\text{Cu(OAc)}_2 \cdot \text{H}_2\text{O} & \quad \text{EtOH, 25 °C} \quad 81\% \text{ ee} \\
\text{Cu(OAc)}_2 & \quad \text{i-PrOH, 0 °C} \quad 68\% \text{ ee}
\end{align*}
\]

Scheme 3. Comparison of the enantioselectivity of ligands \(12, 13, 19\) and \(14\) in the copper-catalyzed Henry reaction of \(p\)-nitrobenzaldehyde (\(10a\)) with nitromethane.

3. Experimental

3.1. General

Reagents obtained from commercial suppliers were used without further purification unless otherwise noted. Preparation of bisoxazoline ligands and \( \beta \)-nitro alcohols was performed in flame-dried glassware under a static pressure of nitrogen. Solvents were dried prior to use following standard procedures. Technical grade solvents for chromatography (hexane and ethyl acetate) were distilled before use. Reactions were monitored by thin layer chromatography using Merck silica gel 60 Kieselgel F254 TLC (aluminum sheets 20 × 20 cm) and column chromatography was performed on silica gel 60 (40–63 \( \mu \text{m}, 230–400 \text{ mesh, ASTM} \)) from Merck using the indicated solvents. \(^1\)H and \(^{13}\)C NMR spectra were recorded in CDCl\(_3\) on a Bruker-Biospin (DPX-400) instrument. AB signals in the \(^1\)H NMR spectra were denoted by the symbol “\(\bigtriangleup\).” Infrared spectra were recorded on a Thermo Scientific Nicolet iS10 FT-IR spectrometer. Enantiomeric ratios were determined by analytical HPLC analysis on a Shimadzu LC-20A Prominence instrument with a chiral stationary phase using Daicel OD-H columns (\(n\)-hexane:i-propanol mixtures as solvent). Optical rotations were measured on a Rudolph Research Analytical Autopol III polarimeter. Melting points (mp) were determined on a Thomas-Hoover capillary melting point apparatus and were not corrected. High resolution mass spectrometry (HRMS) was performed using an Agilent Technologies 6224 TOF LC/MS instrument.

3.2. Procedure for the preparation of bicyclo[2.2.1]hepta-2,5-diene-2,3-dicarbonyl dichloride (5)

To a dichloromethane suspension (325 mL) of compound 4 and DMF (0.6 mL, 7.8 mmol) at 0 °C was added oxalyl chloride (15.4 mL, 180 mmol) slowly via a syringe. The reaction mixture was stirred at this temperature
until a clear solution was obtained. Subsequently, the solvent was evaporated under reduced pressure and the residue was distilled under vacuum (bp 88 °C; Lit: bp 85–87 °C/0.45 mmHg) to give analytically pure diacyl chloride 5 (16.8 g, 79%, pale yellow oil).

3.3. General procedure for the preparation of bis(hydroxy amides) 8 and 9

To a solution of β-amino alcohol (10.0 mmol) in CH₂Cl₂ (25 mL) at 0 °C was added triethylamine (25 mmol). Then a dichloromethane solution (5 mL) of compound 5 (5.0 mmol) was added dropwise to the reaction mixture at this temperature. The ice bath was removed and the reaction mixture was stirred for 30 min at room temperature. The reaction mixture was extracted with HCl (1 N, 8 mL), NaHCO₃ solution (8 mL), and H₂O (3 × 20 mL) consecutively. The organic phase was dried over MgSO₄ and the solvent was removed under reduced pressure to afford crude bis(hydroxy amide) as a white solid.

3.3.1. (1R,4S)-N²,N³-bis((S)-2-hydroxy-1-phenylethyl)bicyclo[2.2.1]hepta-2,5-diene-2,3-dicarboxamide (8a):

White solid; mp 79–80 °C (Rf = 0.30 ethyl acetate:methanol = 99:1). Yield: 96%. Purified by column chromatography using ethyl acetate:methanol = 95:5. [α]D²⁸ = +4.3 (c = 0.440 g/100 mL, CHCl₃). ¹H NMR (400 MHz, CDCl₃): δ 8.58 (d, J = 7.9 Hz, 1H, NH), 8.27 (d, J = 6.6 Hz, 1H, NH), 7.29–7.20 (m, 10H, Ar-H), 6.89–6.85 (m, 2H, 5-H, 6-H), 5.11–5.06 (m, 2H, NCH), 3.96 (br. s, 2H, 1-H, 4-H), 3.85–3.77 (m, 4H, OCH₂), 2.11 (d, J = 6.8 Hz, 1H, 7-Hₐ), 1.96 (d, J = 6.8 Hz, 1H, 7-Hₐ); ¹³C NMR (100 MHz, CDCl₃): 165.1 [165.0], 154.4 [153.3], 142.6 [142.1], 138.9 [138.9], 129.1 [129.0], 128.0 [128.0], 127.0, 71.4, 66.8 [66.6], 56.4 [56.1], 54.6, [54.5]. IR (ATR): ν 3305, 3028, 2939, 2872, 1638, 1596, 1521, 1495, 1454, 1291, 1070, 1028, 756, 698 cm⁻¹. HRMS (ESI⁺): m/z calcd for C₂₅H₂₆N₂O₄H: 419.1971; found: 419.2005 [M+H]⁺.

3.3.2. (1R,4S)-N²,N³-bis((S)-1-hydroxy-3-phenylpropan-2-yl)bicyclo[2.2.1]hepta-2,5-diene-2,3-dicarboxamide (8b):

White solid, mp 52–53 °C (Rf = 0.33 ethyl acetate:methanol = 99:1). Yield: 82%. Purified by column chromatography using ethyl acetate:methanol = 95:5. [α]D⁰ = −81.6 (c = 0.690 g/100 mL, CHCl₃). ¹H NMR (400 MHz, CDCl₃): δ 8.05 (d, J = 7.7 Hz, 1H, NH), 7.83 (d, J = 7.3 Hz, 1H, NH), 7.25–7.21 (m, 4H, Ar-H), 7.18–7.14 (m, 6H, Ar-H), 6.79 (br. s, 2H, 5-H, 6-H), 4.17–4.14 (m, 2H, NCH), 3.84 (s, 1H, 1-H), 3.80 (s, 1H, 4-H), 3.64♭ (dt, J = 11.2, 3.2 Hz, 2H, OCH), 3.52♭ (ddd, J = 11.2, 5.3, 1.8 Hz, 2H, OCH), 2.84 (dd, J = 7.2, 4.9 Hz, 4H, CH₂), 2.02♭ (d, J = 6.8 Hz, 1H, 7-Hₐ), 1.91♭ (d, J = 6.8 Hz, 1H, 7-Hₐ); ¹³C NMR (100 MHz, CDCl₃): δ: 165.3 [165.1], 153.9 [153.3], 142.5 [141.9], 137.9 [137.9], 129.5 [129.5], 128.8 [128.8], 126.9 [126.9], 71.2, 64.4 [64.2], 54.4 [54.4], 35.6, 37.2; IR (ATR): ν 3309, 3026, 2939, 2871, 1636, 1594, 1523, 1496, 1454, 1292, 1033, 743, 698 cm⁻¹; HRMS (ESI⁺): m/z calcd for C₂₇H₃₀N₂O₄H: 447.2284; found: 447.2308 [M+H]⁺.
3.3.3. \((1R,4S)-N^2,N^3\text{-bis((S)-1-hydroxy-3-methylbutan-2-yl)bicyclo[2.2.1]hepta-2,5-diene-2,3-dicarboxamide (8c)}:\)

White solid, mp 86–87 °C \((R_f = 0.22\text{ ethyl acetate:methanol = 99:1). Yield: 65%}. \left[α\right]^{34}_D = -78.5 \text{ c = 0.275 g/100 mL, CHCl}_3\). \(^1\)H NMR \((400 \text{ MHz, CDCl}_3\) \(δ: 8.00 \text{ (d, } J = 8.3 \text{ Hz, 1H, NH), 7.75 \text{ (d, } J = 7.8 \text{ Hz, 1H, NH), 6.90–6.86 \text{ (m, 2H, 5-H, 6-H), 3.93 (br. s, 2H, 1-H, 4-H), 3.77–3.71 \text{ (m, 2H, NCH), 3.68–3.57 \text{ (m, 4H, OCH}_2\), 2.11 (d, } J = 7.0 \text{ Hz, 1H, 7-H}_A\), 1.96 (d, } J = 7.0 \text{ Hz, 1H, 7-H}_B\), 1.92–1.82 \text{ (m, 2H, CH), 0.91 (d, } J = 8.0 \text{ Hz, 6H, CH}_3\), 0.90 (d, } J = 6.8 \text{ Hz, 3H, CH}_3\), 0.88 (d, } J = 6.8 \text{ Hz, 3H, CH}_3\); \(^{13}\)C-NMR \((100 \text{ MHz, CDCl}_3\)\(δ: 166.9 [165.7], 153.9 [153.2], 142.6 [142.1], 71.3, 64.1 [63.9], 57.8 [57.8], 54.5, 29.4 [29.4], 19.7 [19.7], 19.1 [19.0]; IR (ATR): \(\nu = 3428, 3268, 2963, 2935, 2869, 1632, 1574, 1532, 1461, 1317, 1291, 1024, 712, 607 \text{ cm}^{-1}; HRMS (ESI\(^+\)): m/z calcd for C\(_{19}\)H\(_{30}\)N\(_2\)O\(_4\)H: 351.2284; found: 351.2298 \([M+H]^+\).\)

3.3.4. \((1R,4S)-N^2,N^3\text{-bis((S)-1-hydroxy-3,3-dimethylbutan-2-yl)bicyclo[2.2.1]hepta-2,5-diene-2,3-dicarboxamide (8d)}:\)

White solid, mp 185–186 °C \((R_f = 0.12\text{ ethyl acetate:methanol = 99:1). Yield: 73%}. The reaction was performed at 0 °C and after the addition of diacetyl chloride 5, the reaction mixture was stirred at this temperature for 30 min. Extraction was done according to the general method. Purified by column chromatography using ethyl acetate:methanol = 95:5. \(\left[α\right]^{20}_D = -46.7 \text{ c = 0.75 g/100 mL, CHCl}_3\). \(^1\)H NMR \((400 \text{ MHz, CDCl}_3\) \(δ: 7.86 \text{ (d, } J = 9.0 \text{ Hz, 1H, NH), 7.58 \text{ (d, } J = 8.5 \text{ Hz, 1H, NH), 6.93–6.91 \text{ (m, 1H, 5-H}_A\) 6.89–6.87 \text{ (m, 1H, 6-H}_B\), 3.94 (br. s, 2H, 1-H, 4-H), 3.86–3.77 \text{ (m, 4H, NCH, OCH)}, 3.56–3.49 \text{ (m, 2H, OCH)}, 2.14 \text{ (d, } J = 6.8 \text{ Hz, 1H, 7-H}_A\), 1.98 \text{ (d, } J = 6.8 \text{ Hz, 1H, 7-H}_B\), 0.92 \text{ [s, 9H, C(CH}_3)_3\), 0.91 \text{ [s, 9H, C(CH}_3)_3\); \(^{13}\)C-NMR \((100 \text{ MHz, CDCl}_3\)\(δ: 166.4 [166.0], 153.7 [153.1], 142.8 [142.0], 71.2, 63.3 [63.3], 60.3 [60.3], 54.6 [54.5], 33.9 [33.8], 27.2; IR (ATR): \(\nu = 3475, 3384, 3246, 2964, 1633, 1595, 1540, 1366, 1294, 1050, 726, 693 \text{ cm}^{-1}; HRMS (ESI\(^+\)): m/z calcd for C\(_{21}\)H\(_{34}\)N\(_2\)O\(_4\)H: 379.2597; found: 379.2620 \([M+H]^+\).\)

3.3.5. \((1R,4S)-N^2,N^3\text{-bis((2S)-1-hydroxy-3-methylpentan-2-yl)bicyclo[2.2.1]hepta-2,5-diene-2,3-dicarboxamide (8e)}:\)

White solid, mp 118–119 °C \((R_f = 0.38\text{ ethyl acetate:methanol = 95:5). Yield: 77%}. Purified by column chromatography using ethyl acetate:methanol = 95:5. \(\left[α\right]^{34}_D = -84.4 \text{ (c = 0.205 g/100 mL, CHCl}_3\). \(^1\)H-NMR \((400 \text{ MHz, CDCl}_3\) \(δ: 8.04 \text{ (d, } J = 8.2 \text{ Hz, 1H, NH), 7.80 \text{ (d, } J = 8.1 \text{ Hz, 1H, NH), 6.94–6.90 \text{ (m, 2H, 5-H, 6-H), 3.97 (br. s, 2H, 1-H, 4-H), 3.88–3.82 \text{ (m, 2H, NCH), 3.73–3.63 \text{ (m, 4H, OCH}_2\), 2.16 \text{ (br. dt, } J = 6.8, 1.3 \text{ Hz, 1H, 7-H}_A\), 2.01 \text{ (br. dt, } J = 6.8, 1.4 \text{ Hz, 1H, 7-H}_B\), 1.73–1.62 \text{ (m, 2H, CH}_2\text{CH}_3\), 1.62–1.42 \text{ (m, 2H, CH}_2\text{CH}_3\), 1.23–1.09 \text{ (m, 2H, CH}_2\text{CH}_3\), 0.95 \text{ (d, } J = 6.8 \text{ Hz, 3H, CH}_3\), 0.92 \text{ (d, } J = 6.8 \text{ Hz, 3H, CH}_3\), 0.89 \text{ (t, } J = 7.4 \text{ Hz, 3H, CH}_2\text{CH}_3\), 0.88 \text{ (t, } J = 7.3 \text{ Hz, 3H, CH}_2\text{CH}_3\); \(^{13}\)C-NMR \((100 \text{ MHz, CDCl}_3\)\(δ: 165.8 [165.6], 153.8 [153.2], 142.5 [142.1], 71.3, 63.5, 56.5 [56.5], 54.4, 35.9, 25.8, 15.7, 11.6 [11.5]; IR (ATR): \(\nu = 3349, 2963, 2933, 2874, 1588, 1571, 1509, 1375, 1292, 1069, 1043, 1032, 762, 707, 600 \text{ cm}^{-1}; HRMS (ESI\(^+\)): m/z calcd for C\(_{21}\)H\(_{34}\)N\(_2\)O\(_4\)H: 379.2597; found: 379.2560 \([M+H]^+\).\)
3.3.6. \((1R,4S)\)-\(N^2,N^3\)-Bis((1\(S,2R\))-2-hydroxy-1,2-diphenylethyl)bicyclo[2.2.1]hepta-2,5-diene-2,3-dicarboxamide (9):

White solid, mp 97–98 °C (\(R_f = 0.71\) ethyl acetate:n-hexane:3:1). Yield: 75%. \([\alpha]_D^{19} = +112.0 (c = 0.515 g/100 mL, CHCl_3)\). 1H NMR (400 MHz, CDCl_3) \(\delta\): 8.73 (d, \(J = 7.8\) Hz, 1H, NH), 8.25 (d, \(J = 8.4\) Hz, 1H, NH), 7.18–7.08 (m, 12H, Ar-H), 7.02–6.94 (m, 8H, Ar-H) 6.89 (dd, \(J = 4.7, 3.2\) Hz, 1H, 5-\(H_A\)), 6.84 (dd, \(J = 4.7, 3.2\) Hz, 1H, 6-\(H_A\)), 5.30–5.26 (m, 2H, NCH), 5.08 (d, \(J = 4.2\) Hz, 1H, OCH), 5.04 (d, \(J = 4.2\) Hz, 1H, NCH). MS: 2955, 2924, 2857, 1741, 1652, 1453, 1364, 1235, 1030, 1028, 758, 698 cm \(^{-1}\); HRMS (ESI\(^{+}\): m/z calcd for \(C_{37}H_{34}N_2O_4\)H: 571.2591; found: 571.2624 [\(M+H\)]\(^{+}\).

3.4. General procedure for the preparation of bisoxazoline ligands 1 and 2

To a dichloromethane solution (4 mL) of bis(hydroxy amide) (0.25 mmol) in a flame-dried Schlenk tube at 78 °C was added diethylaminosulfur trifluoride (0.1 mL, 0.75 mmol). After stirring at this temp. for 10 min, CH\(_2\)Cl\(_2\) (20 mL) was added and the mixture was washed with saturated aqueous NaHCO\(_3\) (10 mL) and H\(_2\)O (15 mL) consecutively. The organic phase was dried over MgSO\(_4\) and concentrated in vacuo to yield the crude product. Purification by column chromatography (ethyl acetate:n-hexane = 1:1) resulted in isolation of the bisoxazoline ligand as yellow oil, which was directly used for catalysis.

3.4.1. \((1R,4S)\)-2,3-Bis((3\(S\))-4\(^\prime\)-phenyl-4,5\(^\prime\)-dihydrooxazol-2\(^\prime\)-yl)bicyclo[2.2.1]hepta-2,5-diene (1a):

Yellow oil (\(R_f = 0.42\) ethyl acetate:n-hexane = 1:1). Yield: 45%. \([\alpha]_D^{10} = -50.7 (c = 0.623 g/100 mL, CHCl_3)\). 1H NMR (400 MHz, CDCl_3) \(\delta\): 7.30–7.20 (m, 10H, Ph), 6.93 (br. t, \(J = 2.0\) Hz, 2H, 5-H, 6-H), 5.25 (t, \(J = 8.4\) Hz, 1H, 4\(^\prime\)-H), 5.22 (t, \(J = 8.4\) Hz, 1H, 4\(^\prime\)-H), 4.65 (dd, \(J = 8.4, 10.2\) Hz, 1H, 5\(^\prime\)-H), 4.62 (dd, \(J = 8.4, 10.2\) Hz, 1H, 5\(^\prime\)-H), 4.12 (t, \(J = 8.4\) Hz, 1H, 5\(^\prime\)-H), 4.08 (t, \(J = 8.4\) Hz, 1H, 5\(^\prime\)-H), 4.07 (br. t, \(J = 1.6\) Hz, 2H, 1-H, 4-H), 2.30 (dt, \(J = 6.8, 1.6\) Hz, 1H, 7-H\(_A\)), 2.03 (dt, \(J = 6.8, 1.6\) Hz, 1H, 7-H\(_B\)); 13C NMR (100 MHz, CDCl_3) \(\delta\): 164.4 [164.4], 154.5 [153.0], 142.6 [142.0], 140.0 [139.9], 137.1 [136.9], 128.3, 128.3 [128.3], 128.2 [128.2], 127.9, 127.9 [127.8], 126.8 [126.7], 77.1 [77.1], 71.2, 60.1 [59.7], 54.5 [54.4]; IR (ATR): \(\nu\) 3304, 3029, 1641, 1596, 1496, 1452, 1293, 1090, 1058, 1028, 758, 698 cm \(^{-1}\); HRMS (ESI\(^{+}\): m/z calcd for \(C_{25}H_{22}N_2O_2\)H: 383.1759; found: 383.1754 [\(M+H\)]\(^{+}\).

3.4.2. \((1R,4S)\)-2,3-Bis((3\(S\))-4-benzyl-4,5\(^\prime\)-dihydrooxazol-2\(^\prime\)-yl)bicyclo[2.2.1]hepta-2,5-diene (1b):

Yellow oil (\(R_f = 0.56\) ethyl acetate:n-hexane = 2:1). Yield: 86%. \([\alpha]_D^{10} = -36.4 (c = 0.535 g/100 mL, CHCl_3)\). 1H NMR (400 MHz, CDCl_3) \(\delta\): 7.32–7.28 (m, 5H, Ar-H), 7.23–7.20 (m, 5H, Ar-H), 6.95 (br. s, 2H, 5-H, 6-H), 4.54–4.42 (m, 2H, 4\(^\prime\)-H), 4.24 (t, \(J = 9.0\) Hz, 1H, 5\(^\prime\)-H), 4.20 (t, \(J = 9.0\) Hz, 1H, 5\(^\prime\)-H), 4.07–3.99 (m, 4H, 5\(^\prime\)-H, 1-H, 4-H), 3.23–3.15 (m, 2H, CH\(_2\)Ph), 2.71–2.63 (m, 2H, CH\(_2\)Ph), 2.27 (dd, \(J = 1.5, 6.8\) Hz, 1H, 7-H\(_A\)), 2.06 (dd, \(J = 1.5, 6.8\) Hz, 1H, 7-H\(_B\)); 13C NMR (100 MHz, CDCl_3) \(\delta\): 162.0 [162.0], 147.0 [146.7], 142.5 [142.5], 138.1 [138.0] 129.4 [129.4], 128.7 [128.7], 126.7, 72.0 [71.8] 71.9, 67.9 [67.8], 55.3 [55.1], 41.8 [41.7]; IR (ATR): \(\nu\) 2926, 1630, 1602, 1495, 1453, 1296, 1236, 1031, 1008, 956, 734, 698 cm \(^{-1}\); HRMS (ESI\(^{+}\): m/z calcd for \(C_{27}H_{26}N_2O_2\)H: 411.2072; found: 411.2067 [\(M+H\)]\(^{+}\).
3.4.3. (1R,4S)-2,3-Bis((S)-4′-isopropyl-4′,5′-dihydrooxazol-2′-yl)bicyclo[2.2.1]hepta-2,5-diene (1e):

Yellow oil (Rf = 0.74, ethyl acetate:n-hexane = 2:1). Yield: 78%. [α]D = –41.5 (c = 0.908 g/100 mL, CHCl3). 1H NMR (400 MHz, CDCl3) δ: 6.88–6.86 (m, 1H, 5-H), 6.85–6.83 (m, 1H, 6-H), 4.25–4.17 (m, 2H, 4′-H), 3.99–3.89 (m, 6H, 5′-H, 1-H, 4-H), 2.20 (br, d, J = 6.7 Hz, 1H, 7-HA), 1.96 (br, d, J = 6.7 Hz, 1H, 7-HB), 1.79–1.70 (m, 2H, CH2CH3), 0.93 (d, J = 6.8 Hz, 3H, CH3), 0.91 (d, J = 6.8 Hz, 3H, CH3), 0.84 (d, J = 6.8 Hz, 3H, CH3), 0.81 (d, J = 6.8 Hz, 3H, CH3); 13C NMR (100 MHz, CDCl3) δ: 161.5 [161.4], 146.8 [146.7], 142.7 [142.6], 72.7 [72.7] 71.9, 70.1, 55.3 [55.2], 32.9 [32.8], 19.2 [19.1], 18.3 [18.2]; IR (ATR): ν 2962, 2927, 2872, 1628, 1592, 1364, 1216, 668 cm–1; HRMS (ESI+): m/z calcd for C19H26N2O2H: 315.2072; found: 315.2067 [M+H]+.

3.4.4. (1R,4S)-2,3-Bis((S)-4′-t-butyl-4′,5′-dihydrooxazol-2′-yl)bicyclo[2.2.1]hepta-2,5-diene (1d):

Yellow oil (Rf = 0.48, ethyl acetate:n-hexane = 2:1). Yield: 60%. [α]D = –71.4 (c = 0.440 g/100 mL, CHCl3). 1H NMR (400 MHz, CDCl3) δ: 6.88–6.86 (m, 1H, 5-HA), 6.83–6.81 (m, 1H, 6-HB), 4.20–4.13 (m, 2H, 4′-H), 4.02 (t, 1H, 5′-H), 4.01–3.97 (m, 2H, 5′-H, 1-H), 3.92–3.86 (m, 3H, 5′-H, 4-H), 2.20 (d, J = 6.6 Hz, 1H, 7-HA), 1.95 (d, J = 6.6 Hz, 1H, 7-HB), 0.86 (s, 9H, CH3), 0.83 (s, 9H, CH3); 13C NMR (100 MHz, CDCl3) δ: 161.4 [161.2], 146.7 [146.6], 142.8 [142.5], 76.4 [76.2] 71.9, 68.8 [68.7], 55.2 [55.1], 34.3 [34.1], 26.1 [26.1]; IR (ATR): ν 2955, 2870, 1636, 1478, 1363, 1296, 1236, 1010, 751 cm–1; HRMS (ESI+): m/z calcd for C21H30N2O2H: 343.2385; found: 343.2380 [M+H]+.

3.4.5. (1R,4S)-2,3-Bis((4S)-4-sec-butyl-4′,5′-dihydrooxazol-2′-yl)bicyclo[2.2.1]hepta-2,5-diene (1e):

Yellow oil (Rf = 0.26, ethyl acetate:n-hexane = 1:1). Yield: 80%. [α]D = –79.8 (c = 0.440 g/100 mL, CHCl3). 1H NMR (400 MHz, CDCl3) δ: 6.95–6.93 (m, 1H, 5-HA), 6.92–6.90 (m, 1H, 6-HB), 4.27 (dd, J = 9.8, 8.0 Hz, 1H, 5′-H), 4.24 (dd, J = 9.7, 7.8 Hz, 1H, 5′-H), 4.18–4.09 (m, 2H, 4′-H), 4.03–3.96 (m, 4H, 5′-H, 1-H, 4-H), 2.27 (br, dt, J = 6.6, 1.7 Hz, 1H, 7-HA), 2.02 (br, dt, J = 6.7, 1.3 Hz, 1H, 7-HB), 1.74–1.63 (m, 2H, CH2CH3), 1.61–1.48 (m, 2H, CH2CH3), 1.24–1.13 (m, 2H, CH2CH3), 0.94 (t, J = 7.4 Hz, 3H, CH2CH3), 0.93 (t, J = 7.4 Hz, 3H, CH2CH3), 0.85 (d, J = 6.8 Hz, 3H, CH2CH3), 0.81 (d, J = 6.8 Hz, 3H, CH2CH3); 13C NMR (100 MHz, CDCl3) δ: 161.4 [161.3], 146.6 [146.5], 142.6 [142.5], 71.8, 71.0, 69.5 [69.5], 55.1 [55.1], 39.0 [38.9], 26.3 [26.2], 14.4 [14.3], 11.8; IR (ATR): ν 2961, 2930, 2875, 1634, 1460, 1379, 1296, 1236, 1092, 1010, 960, 751 cm–1; HRMS (ESI+): m/z calcd for C21H30N2O2H: 343.2385; found: 343.2380 [M+H]+.

3.4.6. (1R,4S)-2,3-Bis((4R,5S)-4′,5′-diphenyl-4′,5′-dihydrooxazol-2′-yl)bicyclo[2.2.1]hepta-2,5-diene (2):

Yellow oil (Rf = 0.42, ethyl acetate:n-hexane = 1:3). Yield: 88%. [α]D = +30.0 (c = 0.400 g/100 mL, CHCl3). 1H NMR (400 MHz, CDCl3) δ: 7.25–7.17 (m, 20H, Ar-H), 7.08–7.07 (m, 2H, 5-H, 6-H), 5.30 (d, J = 8.3 Hz, 1H, 4′-H), 5.26 (d, J = 8.3 Hz, 1H, 4′-H), 5.11 (d, J = 7.0 Hz, 1H, 5′-H), 5.09 (d, J = 7.0 Hz, 1H, 5′-H), 4.25–4.24 (m, 2H, 1-H, 4-H), 2.50 (d, J = 6.7 Hz, 1H, 7-HA), 2.18 (d, J = 6.7 Hz, 1H, 7-HB).
7-$H_B$; $^{13}$C NMR (100 MHz, CDCl$_3$)$\delta$: 162.3 [162.2], 147.2 [147.2], 142.8 [142.6], 141.7 [141.6], 140.2 [140.1], 128.8, 128.3 [128.3], 127.8, 127.0, [126.9], 125.9 [125.9], 89.5, 79.0, 72.2, 55.5 [55.5]; IR (ATR): $\nu$ 3063, 3029, 2940, 1633, 1495, 1454, 1295, 1270, 1006, 963, 757, 698 cm$^{-1}$; HRMS (ESI$^+$): m/z calcd for C$_{37}$H$_{30}$N$_2$O$_2$H: 535.2385; found: 535.2380 [M+H]$^+$. 

3.5. General procedure for the catalytic Henry reaction$^{19}$

To Cu(OAc)$_2$ (1.8 mg, 0.01 mmol) in a flame-dried Schlenk tube was added a 2-propanol solution (0.4 mL) of bisoxazoline ligand 1e (4.1 mg, 0.012 mmol) under nitrogen atmosphere at room temperature. After stirring for 1 h, aldehyde (0.2 mmol) and nitromethane (0.122 g, 0.11 mL, 2 mmol) were added via syringe. The reaction was stirred at room temperature until TLC control indicated complete consumption of the aldehyde. The solvent was removed under reduced pressure and the crude product was purified by column chromatography to give the desired nitro alcohol. Enantiomeric excess was determined by HPLC with a Chiralcel OD-H column, and the absolute configurations of the nitroaldol products were assigned by comparing their specific rotations and the HPLC retention times with data from the literature.

3.5.1. ($R$)-1-(4-Nitrophenyl)-2-nitroethanol (11a)$^{12}$

(44% ee, Entry 1, Table 3): Yield 80%. Purified by column chromatography using ethyl acetate:n-hexane = 1:3. HPLC (Chiralcel OD-H column, column temperature 20 $^\circ$C, solvent n-hexane:i-propanol = 80:20, flow rate 1.0 mL/min, $\lambda$ = 230 nm); major ($R$)-enantiomer $t_R = 12.56$ min, minor ($S$)-enantiomer $t_R = 15.59$ min; $[\alpha]_{D}^{25} = -13.2$ ($c = 0.365$ g/100 mL, CHCl$_3$).

3.5.2. ($R$)-2-Nitro-1-phenylethanol (11b)$^{12}$

(63% ee, Entry 2, Table 3): Yield 80%. Purified by column chromatography using ethyl acetate:n-hexane = 1:4. HPLC (Chiralcel OD-H column, column temperature 20 $^\circ$C, solvent n-hexane:i-propanol = 80:20, flow rate 1.0 mL/min, $\lambda$ = 230 nm); major ($R$)-enantiomer $t_R = 8.31$ min, minor ($S$)-enantiomer $t_R = 9.97$ min; $[\alpha]_{D}^{25} = -26.6$ ($c = 0.365$ g/100 mL, CHCl$_3$).

3.5.3. ($R$)-1-(2-Methoxyphenyl)-2-nitroethanol (11c)$^{12}$

(61% ee, Entry 3, Table 3): Yield 69%. Purified by column chromatography using ethyl acetate:n-hexane = 1:4. HPLC (Chiralcel OD-H column, column temperature 20 $^\circ$C, solvent n-hexane:i-propanol = 80:20, flow rate 1.0 mL/min, $\lambda$ = 230 nm); major ($R$)-enantiomer $t_R = 7.44$ min, minor ($S$)-enantiomer $t_R = 8.56$ min; $[\alpha]_{D}^{25} = -37.5$ ($c = 0.325$ g/100 mL, CHCl$_3$).

3.5.4. ($R$)-1-(3-Methoxyphenyl)-2-nitroethanol (11d)$^{58}$

(67% ee, Entry 4, Table 3): Yield 98%. Purified by column chromatography using ethyl acetate:n-hexane = 1:4. HPLC (Chiralcel OD-H column, column temperature 20 $^\circ$C, solvent n-hexane:i-propanol = 80:20, flow rate 1.0 mL/min, $\lambda$ = 230 nm); major ($R$)-enantiomer $t_R = 12.61$ min, minor ($S$)-enantiomer $t_R = 16.24$ min; $[\alpha]_{D}^{25} = -31.5$ ($c = 0.305$ g/100 mL, CHCl$_3$).
3.5.5. \((R)-1-(4\text{-}Methoxyphenyl)\)-2-nitroethanol (11e)\(^{58}\)

(60\% ee, Entry 5, Table 3): Yield 71\%. Purified by column chromatography using ethyl acetate: \(n\)-hexane = 1:4. HPLC (Chiralcel OD-H column, column temperature 20 °C, solvent \(n\)-hexane: \(i\)-propanol = 80:20, flow rate 1.0 mL/min, \(\lambda = 230\) nm); major \((R)\)-enantiomer \(t_R = 11.41\) min, minor \((S)\)-enantiomer \(t_R = 14.05\) min; \([\alpha]_{D}^{19} = -47.7\) (\(c = 0.350\) g/100 mL, CHCl\(_3\)).

3.5.6. (\(-\))-1-(4-Ethoxyphenyl)-2-nitroethanol (11f)\(^{19}\)

(54\% ee, Entry 6, Table 3): Yield 85\%. Purified by column chromatography using ethyl acetate: \(n\)-hexane = 1:4. HPLC (Chiralcel OD-H column, column temperature 20 °C, solvent \(n\)-hexane: \(i\)-propanol = 80:20, flow rate 1.0 mL/min, \(\lambda = 230\) nm); major enantiomer \(t_R = 8.76\) min, minor enantiomer \(t_R = 9.99\) min; \([\alpha]_{D}^{19} = 13.8\) (\(c = 0.600\) g/100 mL, CHCl\(_3\)).

3.5.7. \((R)-1-(4\text{-}Methylphenyl)\)-2-nitroethanol (11g)\(^{58}\)

(60\% ee, Entry 7, Table 3): Yield 97\%. Purified by column chromatography using ethyl acetate: \(n\)-hexane = 1:4. HPLC (Chiralcel OD-H column, column temperature 20 °C, solvent \(n\)-hexane: \(i\)-propanol = 80:20, flow rate 1.0 mL/min, \(\lambda = 230\) nm); major \((R)\)-enantiomer \(t_R = 8.65\) min, minor \((S)\)-enantiomer \(t_R = 10.55\) min; \([\alpha]_{D}^{19} = -27.2\) (\(c = 0.585\) g/100 mL, CHCl\(_3\)).

3.5.8. \((R)-1-(4\text{-}Chlorophenyl)\)-2-nitroethanol (11h)\(^{12}\)

(57\% ee, Entry 8, Table 3): Yield 19\%. Purified by column chromatography using ethyl acetate: \(n\)-hexane = 1:4. HPLC (Chiralcel OD-H column, column temperature 20 °C, solvent \(n\)-hexane: \(i\)-propanol = 80:20, flow rate 1.0 mL/min, \(\lambda = 230\) nm); major \((R)\)-enantiomer \(t_R = 7.80\) min, minor \((S)\)-enantiomer \(t_R = 9.50\) min; \([\alpha]_{D}^{19} = -7.1\) (\(c = 0.350\) g/100 mL, CHCl\(_3\)).

3.5.9. \((R)-1-(3\text{-}Bromophenyl)\)-2-nitroethanol (11i)\(^{63}\)

(62\% ee, Entry 9, Table 3): Yield 89\%. Purified by column chromatography using ethyl acetate: \(n\)-hexane = 1:4. HPLC (Chiralcel OD-H column, column temperature 20 °C, solvent \(n\)-hexane: \(i\)-propanol = 80:20, flow rate 1.0 mL/min, \(\lambda = 230\) nm); major \((R)\)-enantiomer \(t_R = 8.84\) min, minor \((S)\)-enantiomer \(t_R = 11.39\) min; \([\alpha]_{D}^{19} = -26.7\) (\(c = 0.445\) g/100 mL, CHCl\(_3\)).

3.5.10. \((R)-1-(1\text{-}Naphthyl)\)-2-nitroethanol (11j)\(^{12}\)

(54\% ee, Entry 10, Table 3): Yield 98\%. Purified by column chromatography using ethyl acetate: \(n\)-hexane = 1:3. HPLC (Chiralcel OD-H column, column temperature 20 °C, solvent \(n\)-hexane: \(i\)-propanol = 80:20, flow rate 1.0 mL/min, \(\lambda = 230\) nm); major \((R)\)-enantiomer \(t_R = 10.30\) min, minor \((S)\)-enantiomer \(t_R = 16.32\) min; \([\alpha]_{D}^{18} = -4.3\) (\(c = 0.255\) g/100 mL, CHCl\(_3\)).

3.5.11. \((R,E)-1\text{-}Nitro\text{-}4\text{-}phenyl\text{-}3\text{-}buten\text{-}2\text{-}ol (11k)\(^{58}\)

(60\% ee, Entry 11, Table 3): Yield 95\%. Purified by column chromatography using ethyl acetate: \(n\)-hexane = 1:3. HPLC (Chiralcel OD-H column, column temperature 20 °C, solvent \(n\)-hexane: \(i\)-propanol = 80:20, flow
rate 1.0 mL/min, λ = 230 nm); minor (S)-enantiomer \( t_R = 19.83 \) min, major (R)-enantiomer \( t_R = 22.66 \) min; \( [\alpha]_D^{19} = -17.0 \) (c = 0.235 g/100 mL, CHCl₃).

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References