

Bisoxazolines with one and two sidearms: stereodirecting ligands for copper-catalysed asymmetric allylic oxidations of alkenes

Markus Seitz,^a Carmine Capacchione,^{a,c} Stéphane Bellemin-Lapponnaz,^b Hubert Wadepl, ^a Benjamin D. Ward^a and Lutz H. Gade^{*a}

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A series of sidearm functionalized bisoxazoline ligands has been synthesized by reaction of the monolithiated methyl{bis(oxazolonyl)}methane with the appropriate electrophiles, and tested in the copper catalyzed asymmetric allylic oxidation of cyclohexene (“Kharasch–Sosnovski” reaction). The observed enantioselectivities were higher (up to 85% ee) than for the unfunctionalized bisoxazoline (“BOX”) derivatives (*ca.* 60% ee). Regardless of the functional groups incorporated into the sidearm unit, the ee’s obtained for the different derivatives were essentially indistinguishable. This implies that the sidearms do not interfere directly in this reaction and only play an indirect role by virtue of their steric demand. Three of the copper complexes have been characterized by X-ray diffraction, establishing a distorted octahedral coordination geometry around the copper atom in all three cases. In the elongated distorted CuN₂O₄ octahedra, the two nitrogen atoms of the oxazolines and one oxygen atom of each acetate ligand occupy the ‘equatorial’ positions whereas the sidearms do not interact with the metal centres.

Introduction

Bisoxazolines (“BOX”) have been established as a class of “privileged” stereodirecting ligands in asymmetric catalysis.¹ Their transition metal complexes have been employed in a wide range of catalytic transformations, in particular, in Lewis acid catalyzed stereoselective reactions.² They have provided the base for extensive research efforts in the design of new chiral ligands and may be combined with other ligating functions.³ A notable development is the coupling of an additional “sidearm” to the bridging carbon atoms of bisoxazolines.⁴ Tang and coworkers have found that such potentially tricoordinating ligands may provide Cu-based Lewis acid catalysts which display a significantly improved performance in comparison to the BOX-reference system.^{4,5} However, the role of the “sidearm” remains a matter of debate.

There are three conceivable ways in which a “sidearm”, which is attached to the bridging carbon atom of the BOX-ligand may interact with the active centre of a molecular catalyst (Fig. 1). First, if it contains a ligating donor function (D) it may bind directly to the metal centre, as represented for case (a) in Fig. 1. This additional binding interaction is expected to stabilize the complex and to change the electron density of the metal. If the sidearm contains a substrate acceptor function (A), such as a hydrogen bond donating functional group, as in case (b), then an additional orientation of the catalytic substrate may be the result. Finally, the addition of the sidearm may neither lead to a direct interaction with the metal centre nor the substrate but may

influence the activity and selectivity of the catalyst by nature of its steric demand [case (c)] and thus be simply due to the reduction of the active space available for the catalytic conversion.

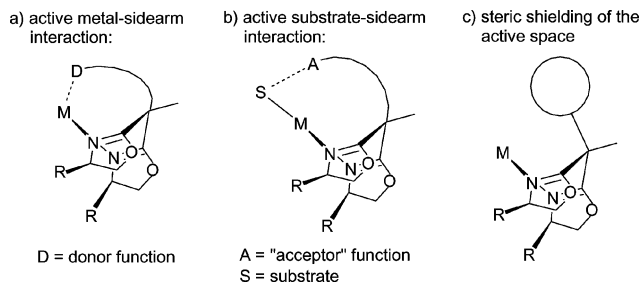


Fig. 1 Possible roles of ligand sidearms in bisoxazolines.

The introduction of the additional ligating “arm” in the podand structure of the bisoxazolines implies the loss of the twofold rotational symmetry of the system, and therefore the reduction of the number of diastereomeric intermediates and transition states in a stereoselective transformation. This complication may be in part offset by the “resymmetrization” of the system upon the introduction of two identical ligand sidearms pointing in opposite directions relative to the bisoxazoline unit. In such a system there may be rapid exchange between the interaction of the two sidearms with the metal centre or the substrate, as is exemplified in Fig. 2 for a bis(donor)-functionalized system. Here again, depending on the catalyst and the type of reaction, the role of the sidearms may also be purely steric.

In our investigation into the catalytic utility of such additionally functionalized stereodirecting bis(oxazoline) ligands⁶ we chose a copper catalyzed reaction in which the copper does not primarily play the role of a Lewis acid. A preparatively useful example of a direct catalytic functionalization of hydrocarbons is the

^aAnorganisch-Chemisches Institut, Universität Heidelberg, Im Neuenheimer Feld 270, 69120, Heidelberg, Germany. E-mail: lutz.gade@uni-hd.de

^bLaboratoire de Chimie Organométallique et de Catalyse, Université Louis Pasteur, 4 rue Blaise Pascal, 67000, Strasbourg, France

^cDipartimento di Chimica, Università degli Studi di Salerno, via S. Allende 84081, Baronissi (SA), Italy

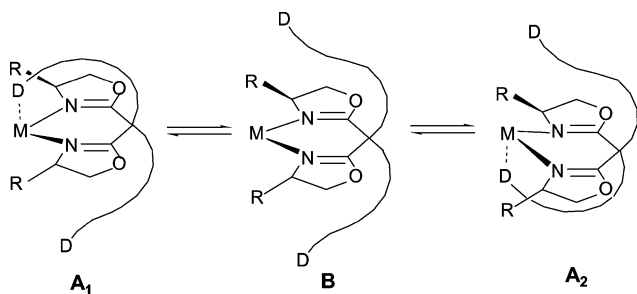


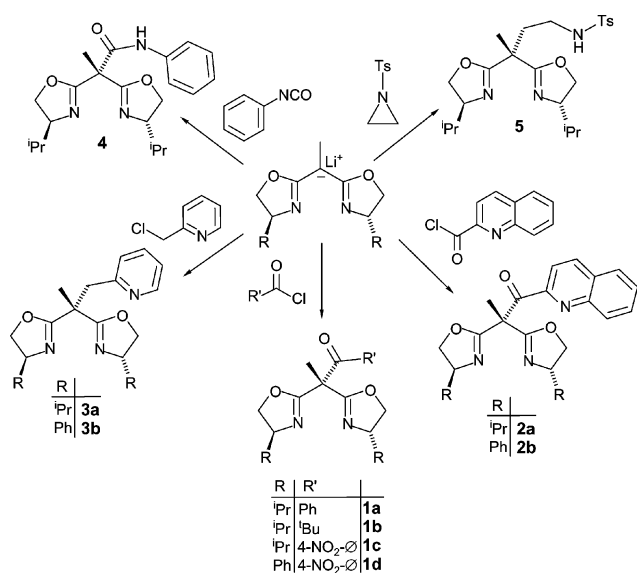
Fig. 2 “Degenerate” interaction of the ligand sidearms in difunctionalized bisoxazolines.

copper-catalyzed Kharasch–Sosnovsky reaction, *i.e.* the allylic acyloxylation of olefins.^{7,8} In the presence of chiral oxazoline-based ligands it has been possible to render this reaction enantioselective,⁹ although a truly efficient asymmetric catalyst has not as yet been found. In this work we report a series of new copper(II)-precatalysts for allylic oxidation and discuss the role that ligand sidearms may play in it.

Results and discussion

Synthesis of the ligands

All sidearm functionalized bisoxazoline ligands employed in this study were synthesized by reaction of the monolithiated methyl{bis(oxazoliny)}methane¹⁰ with the appropriate electrophiles (Scheme 1). The lithiated starting material which was generated *in situ* by deprotonation in the bridgehead position of the corresponding bisoxazoline with ^tBuLi. Reaction of the lithium salt with a range of aroyl and acyl chlorides gave the ligands **1a–d** and **2a, b** while the corresponding transformation with 2-chloromethyl pyridine yielded compounds **3a, b**.



Scheme 1 Synthesis of the bisoxazoline ligands **1–5** containing one sidearm.

Using phenylisocyanate as the electrophilic agent gave bisoxazoline **4**, containing a carboxamido sidearm, whereas ring opening of *N*-tosylaziridine gave rise to compound **5** possessing

a sulfonylamido group in the side chain. For the synthesis of the latter it proved important to use an excess of the lithiated bisoxazoline in order to suppress the oligo- or polymerization of the *N*-tosylaziridine. Compound **5** is characterized by the strong $\nu(\text{RSO}_2\text{N})$ -vibrational bands in the IR spectrum at 1326 cm⁻¹ and 1158 cm⁻¹. After recrystallization from *n*-hexane single crystals of compound **5** were obtained which were suitable for an X-ray structure analysis. Its molecular structure is depicted in Fig. 3 along with important bond lengths and angles.

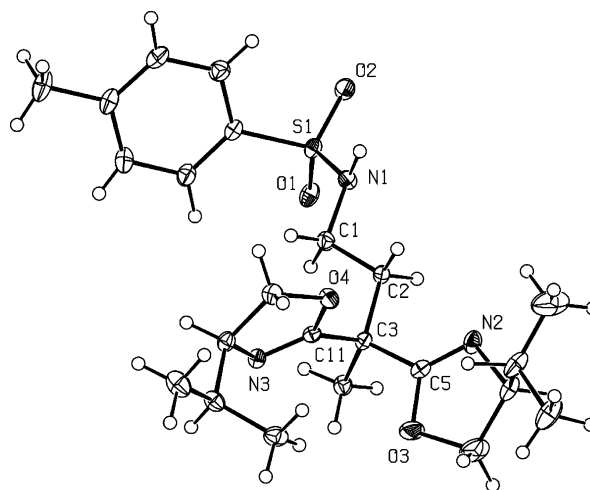


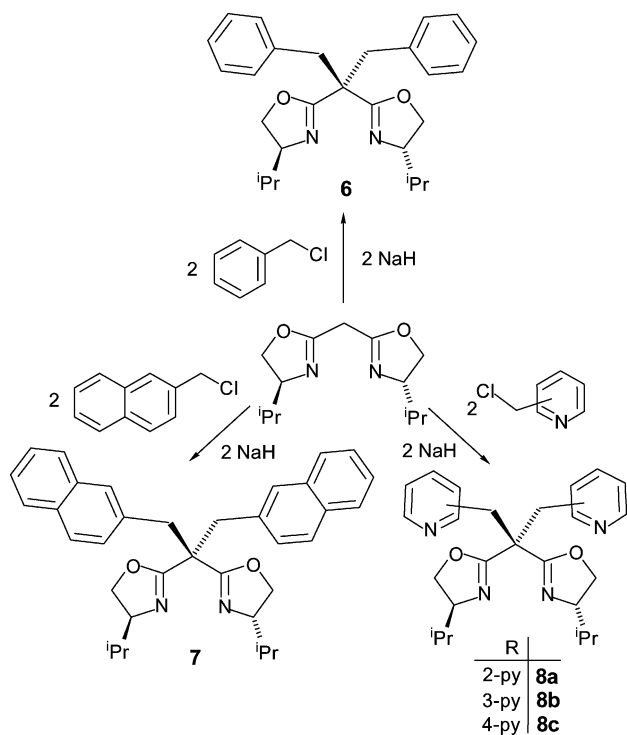
Fig. 3 Molecular structure of compound **5**. Selected bond lengths (Å) and angles (°): C5–N2, 1.263(3); C11–N3, 1.270(2); N1–S1, 1.6107(16); O1–S1, 1.4376(15); O2–S1, 1.4338(15); C5–C3–C11, 106.21(14); N2–C5–O3, 119.10(19); N2–C5–C3, 127.62(18); N3–C11–O4, 118.57(15); N3–C11–C3, 127.36(16); O1–S1–O2, 120.15(8).

The two oxazoline rings in **5** are twisted relative to one another with the two N-atoms, N2 and N3, adopting opposite orientations. This leads to torsion angles N3–C11–C3–C2 120.3(2)° and C2–C3–C5–N2 8.1(3)°. This particular molecular arrangement is thought to be due to the steric demand of the two isopropyl substituents on the oxazoline rings and differs from that present in the copper complex **10** (*vide infra*).

Tetradentate bis(oxazoline) ligands have received less attention than their tridentate counterparts, with very few examples of bisoxazolines incorporating two sidearms on the carbon bridge having been synthesized to date. Their preparation can be easily accomplished by treating the bis(oxazoliny)methane with an excess of sodium hydride and subsequent treatment with the appropriate electrophiles to give the *gem*-disubstituted bis(oxazoline) ligands **6–8** in good yields (Scheme 2).

Asymmetric allylic oxidation of cyclohexene catalyzed by copper complexes containing BOX-derivatives with one and two sidearm(s)

Both the bisoxazoline ligand containing one sidearm as well as those with two were systematically tested as stereodirecting ligands, in combination with a variety of copper salts, in the asymmetric allylic oxidation of cyclohexene which is generally used as the substrate of reference. As the oxidizing agent we employed benzoyl(*tert*-butyl)peroxide. Previous studies have shown that, using the bisoxazolines BOX or pybox as stereodirecting



Scheme 2 Synthesis of the bisoxazoline ligands **6–8** containing two sidearms.

ligands, enantioselectivities of *ca.* 60% ee (with yields of *ca.* 65%) are obtained.

Since Andrus and coworkers have reported that it is possible to induce high stereoselectivity (up to 96%, at low conversion) by using the more electron-deficient *tert*-butyl *p*-nitroperbenzoate as an oxidant,¹¹ we also tested this reagent. The decreased reactivity of the latter, however, limits the usefulness of the method since only very low yields are obtained. The results obtained with the new ligands **1–8** are summarized in Table 1.

The complexes which were tested catalyze the reaction with a moderate degree of selectivity and reactivity at relatively low catalyst loading (5 mol%). The type of copper salt employed does not significantly affect the activity and selectivity, whilst the variation of solvent appears to have an effect (with acetone leading to higher selectivities but lower yields than the commonly used acetonitrile). This observation may be attributed to the solvent dependence of cation–anion interaction in the catalyst.

It is worth noting that the copper complexes of ligands **6** and **8a**, both bearing two substituents on the carbon atom bridging the two oxazoline units (**6**: benzyl; **8a**: 2-pyridyl), display higher selectivity. As previously observed, the use of *p*-NO₂PhCO₃-*t*-Bu significantly enhances the selectivity of the conversion, albeit with decreased reaction rate (Table 2).¹¹ Compared to previous catalysts tested for the Karasch–Sosnovski reaction, the ee values obtained with the catalysts bearing ligands **6** and **8a** are remarkably high (up to 85%). Both ligands differ from one another in functionality and thus potential denticity, however, they are essentially similar as far as the sterics of the bridgehead substituent are concerned.

Table 1 Asymmetric allylic oxidation of cyclohexene using PhCO₃-*t*-Bu as oxidant (isolated yields after reaction times of 5–7 days)

Entry	Ligand	Copper salt	<i>T</i> /°C	Solvent	Yield (%)	ee (%)
1	1b	Cu(OTf) ₂	20	MeCN	49	55
2	1a	Cu(OTf) ₂	20	MeCN	52	60
3	1a	Cu(BF ₄) ₂	20	MeCN	47	54
4	1d	Cu(OTf) ₂	20	MeCN	53	60
5	1c	Cu(OTf) ₂	20	MeCN	41	50
6	2a	Cu(OTf) ₂	20	MeCN	44	51
7	1e	Cu(OTf) ₂	20	MeCN	55	60
8	2b	Cu(OTf) ₂	20	MeCN	45	51
9	3a	Cu(OTf) ₂	20	MeCN	44	61
10	3b	Cu(OTf) ₂	20	MeCN	54	68
11	4	Cu(OCl ₄) ₂	20	MeCN	45	65
12	4	Cu(BF ₄) ₂	20	MeCN	72	60
13	5	Cu(OTf) ₂	20	MeCN	70	60
14	5	Cu(OCl ₄) ₂	20	MeCN	72	60
15	5	Cu(BF ₄) ₂	20	MeCN	72	60
16	5	Cu(OTf) ₂	20	Acetone	59	68
17	5	Cu(OCl ₄) ₂	20	Acetone	67	70
18	5	Cu(BF ₄) ₂	20	Acetone	54	70
19	5	Cu(OTf) ₂	0	MeCN	15	71
20	5	Cu(OCl ₄) ₂	0	MeCN	20	71
21	5	Cu(BF ₄) ₂	0	MeCN	20	71
22	6	Cu(OTf) ₂	20	MeCN	55	80
23	7	Cu(OTf) ₂	20	MeCN	52	77
24	8a	Cu(OTf) ₂	20	MeCN	61	79
25	8a	Cu(OTf) ₂	0	MeCN	59	77
26	8b	Cu(OTf) ₂	20	MeCN	54	55
27	8c	Cu(OTf) ₂	20	MeCN	45	72

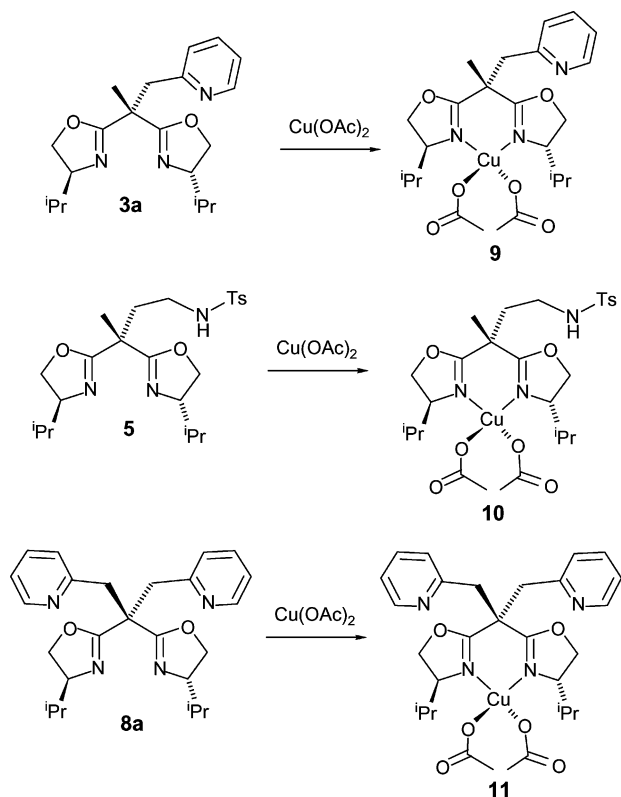
Table 2 Asymmetric allylic oxidation of cyclohexene using *p*-NO₂PhCO₃-*t*-Bu as oxidant (isolated yields after reaction times of 5–7 days)

Entry	Ligand	Copper salt	<i>T</i> /°C	Yield (%)	ee (%)
1	5	Cu(OTf) ₂	20	87	77
2	5	Cu(OCl ₄) ₂	20	63	77
3	5	Cu(BF ₄) ₂	20	73	72
4	5	Cu(OTf) ₂	–15	19	79
5	6	Cu(OTf) ₂	20	52	85
6	7	Cu(OTf) ₂	20	42	84
7	8a	Cu(OTf) ₂	20	60	82
8	8a	Cu(OTf) ₂	0	47	85
9	8b	Cu(OTf) ₂	20	49	65

This observation and that of the lower selectivity observed for the catalysts bearing bisoxazoline ligands with only one sidearm function may suggest that the steric demand of the sidearms rather than binding interaction with the metal or the substrates is responsible for the selectivity of the reaction.

Molecular structures of copper(II) complexes containing BOX-derivatives with one and two sidearms

Reaction of copper(II) acetate monohydrate (2 molar equiv.) with the ligands **3a**, **5** and **8a** (1 molar equiv.) gave the complexes [(ligand)Cu(acetate)₂]**9**, **10** and **11**, respectively (Scheme 3). Single crystals were obtained from toluene solutions layered with *n*-hexane which were subjected to slow diffusion.



Scheme 3 Synthesis of the bisoxazoline–copper(II) complexes **9–11**.

The coordination geometry around the copper atoms is approximately octahedral in all three cases (Figs. 4–6). In the elongated distorted CuN₂O₄ octahedra, the two nitrogen atoms of the oxazolines and one oxygen atom of each acetate occupy the ‘equatorial’ positions. Here, Cu–N and Cu–O distances range from 1.947(6)–1.991(4) Å, respectively. The remaining two oxygen atoms of the acetate ligands approach the ‘axial’ positions, with much larger distances to copper (2.440(3)–2.750(4) Å), and O–Cu–O angles considerably less than 180° (140.8(2)–155.8(1)°). This asymmetrical κ²-acetate coordination is quite common in copper acetate complexes.¹² Most significantly, the additional nitrogen donors (weakly nucleophilic sulfonamide NH in **10**, more strongly nucleophilic pyridine nitrogen atoms in **9** and **11**) do not coordinate to the respective copper centres, nor does there seem to be any significant interaction with the acetate units.

Conclusions

We have studied the influence of “sidearms” in bisoxazoline copper complexes on their catalyst performance in the asymmetric allylic alkylation of cyclohexene as substrate of reference. In general, the observed enantioselectivities have been somewhat higher than for

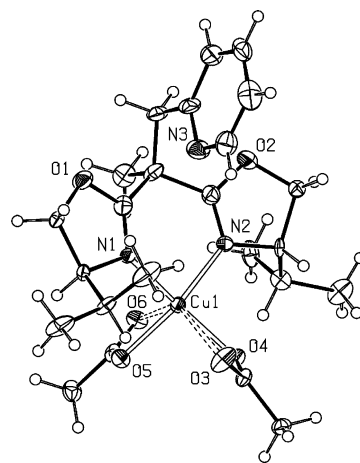


Fig. 4 Molecular structure of compound **9**. Selected bond lengths (Å) and angles (°): Cu1–N1, 1.946(6); Cu1–N2, 1.973(6); Cu1–O4, 1.954(5); Cu1–O5, 1.977(5); Cu1–O3, 2.687(6); Cu1–O6, 2.540(5); N1–Cu1–N2, 90.1(3); O4–Cu1–N2, 93.9(3); N1–Cu1–O5, 92.4(3); N1–Cu1–O4, 158.2(2); N2–Cu1–O5, 154.1(2); O4–Cu1–O5, 93.2(2).

the unfunctionalized bisoxazoline (“BOX”) derivatives. Notably, this effect was observed regardless of the functional groups incorporated into the sidearm unit, the ee’s obtained for the different derivatives being essentially indistinguishable. This leads us to propose that the sidearms do not interfere directly in this reaction, but most probably only play an indirect role by virtue of their steric demand. In other words, we believe that in the case at hand, we observe the third case (c) depicted in Fig. 1. This view is supported by the absence of any interaction of the sidearms with the metal centres or the other ligands established in the X-ray structure analyses of compounds **9–11**. Whether this situation pertains for complexes with other transition metals is not clear and under current investigation.

Experimental

General

All manipulations were performed under nitrogen. Solvents were dried according to standard methods and saturated with nitrogen. The deuterated solvents used for the NMR spectroscopic measurements were degassed by three successive “freeze–pump–thaw” cycles and stored over 4-Å molecular sieves. All other chemicals were used as received. Yields are given for isolated products showing one spot on a TLC plate and no impurities were detectable in the NMR spectrum. 2,2-Bis((*S*)-4-isopropyl-4,5-dihydrooxazol-2-yl)-ethane,¹³ 2,2-bis((*S*)-4-phenyl-4,5-dihydrooxazol-2-yl)-ethane,¹³ bis((*S*)-4-isopropyl-4,5-dihydrooxazol-2-yl)-methane,¹⁰ 2-(2,2-bis((*S*)-4-isopropyl-4,5-dihydrooxazol-2-yl)-propyl)pyridine⁵ (**3a**), (4*S*)-2,2’-(1-phenylmethyl-2-phenylethylidene)bis[4-(1-methylethyl)-4,5-dihydroxazole]¹⁴ (**6**) and *tert*-butyl *p*-nitrobenzoate¹¹ were prepared according to literature procedures. The ¹H and ¹³C NMR spectra were recorded on Bruker Avance DRX 200 or Varian Unity Plus 400 FT-NMR spectrometers at room temperature (295 K). The spectra were referenced relative to tetramethylsilane using the residual protio-solvent (¹H) or the carbon (¹³C) resonance. IR spectra were recorded as thin films between KBr plates using a FT-IR Merlin Excalibur FT3000

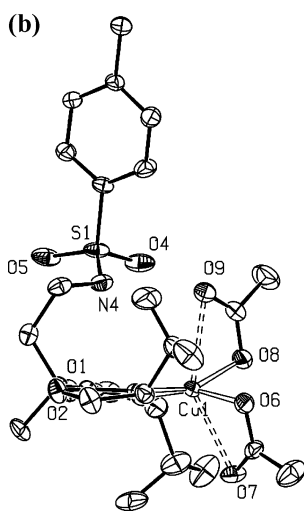
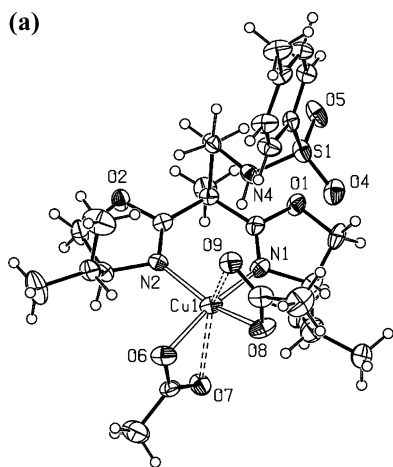


Fig. 5 a) Molecular structure of compound **10**. Selected bond lengths (Å) and angles (°): Cu1–N1, 1.974(4); Cu1–N2, 1.975(4); Cu1–O6, 1.962(4); Cu1–O8, 1.966(4); N4–S1, 1.603(4); O4–S1, 1.434(4); O5–S1, 1.431(4); Cu1–O7, 2.501(3); Cu1–O9, 2.584(3); N1–Cu1–N2, 89.27(14); O8–Cu1–N1, 91.93(16); O6–Cu1–N2, 92.77(16); O8–Cu1–N2, 157.79(14); O6–Cu1–N1, 162.32(14); O6–Cu1–O8, 92.77(15). b) In-plane view of the complex illustrating the orientation of the tosylamido sidearm (hydrogen atoms omitted for clarity).

instrument. Mass spectra (EI or FAB) were recorded on Finnigan MAT TSQ 700 or JEOL JMS-700 spectrometers, high resolution mass spectra (HRMS) were recorded on the latter instrument. Elemental analyses were performed by the microanalytical service at the chemistry department of Heidelberg. Enantiomeric excesses were determined by using a Finnigan Surveyor™ Modular HPLC System equipped with a Chiralpak® AS–H and/or Chiralcel® AD–H columns.

Preparation of the compounds

2,2-Bis((S)-4-isopropyl-4,5-dihydrooxazol-2-yl)-phenyl)-propan-1-one (1a). A 1.70 M solution of *tert*-BuLi (0.16 g, 0.63 mmol) in *n*-hexane was added dropwise to a solution of 2,2-bis((S)-4-isopropyl-4,5-dihydrooxazol-2-yl)-ethane (0.16 g, 0.63 mmol) in THF (45 mL) with stirring at $-78\text{ }^{\circ}\text{C}$. The mixture was allowed

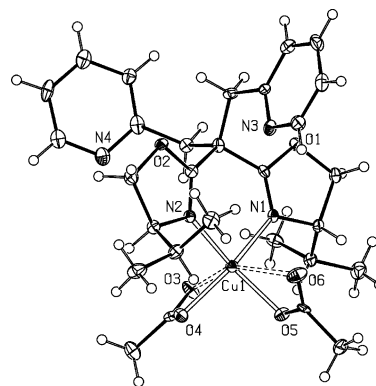
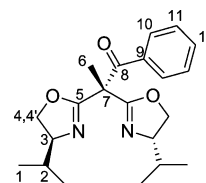


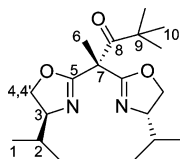
Fig. 6 Molecular structure of compound **11**. Selected bond lengths (Å) and angles (°): Cu1–N1, 1.991(4); Cu1–N2, 1.976(4); Cu1–O4, 1.986(3); Cu1–O5, 1.948(3); N2–Cu1–N1, 89.72(15); N2–Cu1–O4, 92.80(15); O5–Cu1–N1, 95.75(14); O4–Cu1–N1, 156.45(14); O5–Cu1–N2, 153.24(16); O5–Cu1–O4, 92.48(14).

to warm to $-50\text{ }^{\circ}\text{C}$ and stirred for 1 h. This solution was then cooled to $-78\text{ }^{\circ}\text{C}$ and a solution of benzoyl chloride (0.98 g, 0.70 mmol) in THF (5 mL) was slowly added with stirring. The reaction mixture was maintained at $-78\text{ }^{\circ}\text{C}$ for 1 h, slowly warmed to room temperature and then heated to reflux overnight. An aqueous solution of KHCO_3 (50 mL, 10%) was added, and after removal of the organic phase the residue was extracted with dichloromethane ($3 \times 50\text{ mL}$). The organic layer was washed with water and dried over anhydrous Na_2SO_4 . Removal of solvent gave a pale yellow oil which was purified by flash chromatography ($\text{EtOAc}-\text{CH}_2\text{Cl}_2$, 20 : 80) affording **1a** as a colourless oil (0.17 g, 75% yield). ^1H NMR (300 MHz, CDCl_3): δ = 0.84 (d, $^3J_{\text{HH}}$ = 5.3 Hz, 3H, H-1), 0.87 (d, $^3J_{\text{HH}}$ = 5.3 Hz, 3H, H-1), 0.91 (d, $^3J_{\text{HH}}$ = 6.9 Hz, 3H, H-1), 0.95 (d, $^3J_{\text{HH}}$ = 6.8 Hz, 3H, H-1), 1.62–1.86 (m, 2H, H-2), 1.88 (s, 3H, H-6), 3.86–4.10 (m, 4H, H-3), 4.12–4.30 (m, 2H, H-4, H-4'), 7.30 (dd, 2H, H-11), 7.43 (t, $^3J_{\text{HH}}$ = 7.3 Hz, 1H, H-12), 7.91 (d, $^3J_{\text{HH}}$ = 7.2 Hz, 2H, H-10). $\{^1\text{H}\}^{13}\text{C}$ NMR (75.5 MHz, CDCl_3): δ = 17.9–19.0 (C-1), 21.7 (C-6), 32.4 (C-2), 54.3 (C-7), 70.4–70.6 (C-7), 71.9–72.1 (C-3), 127.9 (C-12), 129.3 (C-10/C-11), 132.5 (C-10/C-11), 135.9 (C-9), 165.0 (C-5), 194.3 (C-8). MS (FAB+): $\text{C}_{21}\text{H}_{28}\text{N}_2\text{O}_3$ m/z (%) = 358 (23) $[\text{M} + \text{H}]^+$, 341 (5) $[\text{M} - \text{CH}_3]^+$, 313 (5) $[\text{M} - \text{C}_3\text{H}_7]^+$, 285 (4) $[\text{M} - \text{C}_3\text{H}_7 - \text{CO}]^+$, 253 (30), 251 (19) $[\text{M} - \text{COPh}]^+$, 246 (4), 244 (5) $[\text{M} - \text{C}_6\text{H}_{10}\text{NO}]^+$, 210 (5), 209 (33), 207 (4), 202 (4).

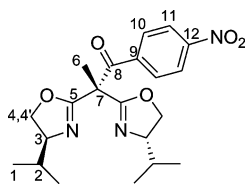


2,2-Bis((S)-4-isopropyl-4,5-dihydrooxazol-2-yl)-4,4-dimethylpentan-3-one (1b). This compound was prepared as a colourless oil from 2,2-bis((S)-4-isopropyl-4,5-dihydrooxazol-2-yl)-ethane (0.50 g, 2.0 mmol), *tert*-BuLi in *n*-hexane (1.5 M, 1.5 mL, 2.2 mmol) and pivaloylchloride (0.48 g, 4.0 mmol) in THF (50 mL) using the same procedure reported for **1a**: yield 0.54 g (81%). ^1H NMR (200 MHz, CDCl_3): δ = 0.83–0.95 (m, 12H, H-1), 1.23 (s, 9H, H-10), 1.67–1.87 (m, 2H, H-2), 1.77 (s, 3H, H-6), 3.86–4.07 (m, 4H, H-3, H-4'), 4.21–4.33 (m, 2H, H-4). $\{^1\text{H}\}^{13}\text{C}$

NMR (50 MHz, CDCl₃): δ = 18.06 (C-1), 18.10 (C-1), 18.85 (C-1), 18.90 (C-1), 21.28 (C-6), 28.42 (C-10), 32.11 (C-2), 32.46 (C-2), 46.10 (C-9), 55.69 (C-7), 70.25 (C-4) 70.47 (C-4), 71.90 (C-3), 72.00 (C-3), 164.58 (C-5), 164.68 (C-5), 208.75 (C-8). IR (film) [ν/cm^{-1}]: 2964 (s), 2907 (m), 2360 (w), 1704 (m), 1662 (s), 1520 (w), 1469 (m), 1335 (m), 1088 (m), 1039 (w), 978 (m). MS (FAB+): C₁₉H₃₂N₂O₃ m/z (%) = 337 (100.0) [M⁺ + H], 459 (2.7) [M⁺ + Na], 253 (9.6) [bisoxazolone⁺ + H]. HRMS (FAB+): 337.2520 (C₁₉H₃₂N₂O₃ requires 337.2520). Calc. for C₁₉H₃₂N₂O₃ (337.25): C 67.82, H 9.59, N 8.33. Found: C 67.60, H 9.66, N 8.10%.

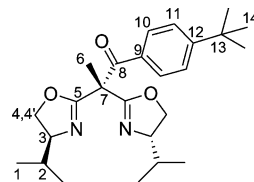


2,2-Bis((S)-4-isopropyl-4,5-dihydrooxazol-2-yl)-1-(4-nitrophenyl)propan-1-one (1c). This compound was prepared as a yellow oil from 2,2-bis((S)-4-isopropyl-4,5-dihydrooxazol-2-yl)ethane (0.50 g, 2.0 mmol), *tert*-BuLi in *n*-hexane (1.5 M, 1.5 mL, 2.2 mmol) and *p*-nitrobenzoylchloride (0.41 g, 2.2 mmol) in THF (50 mL) using the same procedure reported for **1a**: yield 0.23 g (29%). ¹H NMR (200 MHz, CDCl₃): δ = 0.78–0.99 (m, 12H, H-1), 1.60–1.81 (m, 2H, H-2), 1.82 (s, 3H, H-6), 3.80–4.06 (m, 4H, H-3, H-4'), 4.11–4.29 (m, 2H, H-4), 8.13 (d, ³J_{HH} = 9.2 Hz, 2H, H-11), 8.19 (d, ³J_{HH} = 9.2 Hz, 2H, H-10). {¹H}¹³C NMR (50 MHz, CDCl₃): δ = 17.92 (C-1), 18.06 (C-1), 18.56 (C-1), 18.82 (C-1), 21.11 (C-6), 32.31 (C-2), 32.43 (C-2), 54.03 (C-7), 70.45 (C-4), 70.73 (C-4), 71.99 (C-3), 72.11 (C-3), 122.82 (C-11), 130.35 (C-10), 141.20 (C-9), 149.56 (C-12), 164.29 (C-5), 164.31 (C-5), 193.87 (C-8). IR (film) [ν/cm^{-1}]: 3319 (m), 3070 (w), 2360 (w), 1730 (s), 1675 (s), 1530 (vs), 1466 (w), 1346 (m), 1273 (m), 1088 (m), 938 (m). MS (FAB+): C₂₁H₂₇N₃O₅ m/z (%) 402 (15.6) [M⁺ + H], 253 (100.0) [bisoxazolone⁺ + H]. HRMS (FAB+): 402.2053 (C₂₁H₂₈N₃O₅ requires 402.2029).

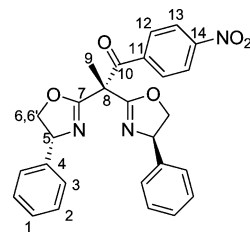


2,2-Bis((S)-4-isopropyl-4,5-dihydrooxazol-2-yl)-1-(4-*tert*-butylphenyl)propan-1-one (1d). This compound was prepared as a colourless oil from 2,2-bis((S)-4-isopropyl-4,5-dihydrooxazol-2-yl)ethane (0.50 g, 2.0 mmol), *tert*-BuLi in *n*-hexane (1.5 M, 1.5 mL, 2.2 mmol) and 4-*tert*-butylbenzoylchloride (0.80 g, 4.0 mmol) in THF (50 mL) using the same procedure reported for **1a**: yield 0.48 g (59%). ¹H NMR (200 MHz, CDCl₃): δ = 0.83–0.97 (m, 12H, H-1), 1.31 (s, 9H, H-14), 1.69–1.84 (m, 2H, H-2), 1.89 (s, 3H, H-6), 3.91–4.10 (m, 4H, H-3, H-4'), 4.19–4.22 (m, 2H, H-4), 7.37 (d, ³J_{HH} = 8.6 Hz, 2H, H-11), 7.90 (d, ³J_{HH} = 8.6 Hz, 2H, H-10). {¹H}¹³C NMR (50 MHz, CDCl₃): δ = 17.86 (C-1), 17.91 (C-1), 18.74 (C-1), 18.97 (C-1), 21.74 (C-6), 31.03 (C-2), 31.13 (C-2), 32.29 (C-14), 35.00 (C-13), 54.31 (C-7), 70.34 (C-4) 70.49 (C-4), 71.85 (C-3), 71.94 (C-3), 124.91 (C-11), 125.22 (C-11), 129.24 (C-10), 129.75 (C-10), 132.97 (C-9), 156.20 (C-12), 165.08 (C-5), 165.15 (C-5), 193.87 (C-8). IR (film) [ν/cm^{-1}]: 3054

(w), 2966 (s), 1728 (m), 1670 (s), 1610 (w), 1518 (m), 1466 (w), 1279 (w), 1188 (w), 1089 (m). MS (FAB+): C₂₅H₃₆N₂O₃ m/z (%) = 413 (100.0) [M⁺ + H], 435 (1.9) [M⁺ + Na], 253 (21.1) [bisoxazolone⁺ + H]. HRMS (FAB+): 413.2787 (C₂₅H₃₇N₂O₃ requires 413.2804). Calc. for C₂₅H₃₇N₂O₃·0.05CHCl₃ (412.56): C 71.89, H 8.68, N 6.69. Found: C 71.84, H 8.86, N 6.41%.

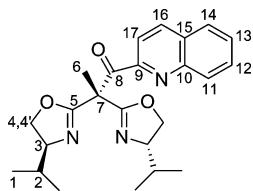


2,2-Bis((R)-4-phenyl-4,5-dihydrooxazol-2-yl)-1-(4-nitrophenyl)propan-1-one (1e). This compound was prepared as a yellow solid from 2,2-bis((S)-4-phenyl-4,5-dihydrooxazol-2-yl)ethane (0.50 g, 1.6 mmol), *tert*-BuLi in *n*-hexane (1.5 M, 1.2 mL, 1.7 mmol) and *p*-nitrobenzoylchloride (0.44 g, 2.4 mmol) in THF (50 mL) using the same procedure reported for **1a**: yield 0.51 g (68%). ¹H NMR (200 MHz, CDCl₃): δ = 2.26 (s, 3H, H-9), 4.00–4.28 (m, 2H, H-6), 4.60–4.72 (m, 2H, H-6'), 5.22–5.36 (m, 2H, H-5), 7.29–7.34 (m, 10H, H-1, H-2, H-3), 8.13 (d, 2H, ³J_{HH} = 9.3 Hz, H-12), 8.19 (d, 2H, ³J_{HH} = 9.3 Hz, H-13). {¹H}¹³C NMR (50 MHz, CDCl₃): δ = 21.11 (C-9), 54.39 (C-8), 69.42 (C-5), 69.63 (C-5), 75.11 (C-6), 75.38 (C-6), 123.06 (C-13), 126.60 (C-1/C-2/C-3), 127.76 (C-1/C-2/C-3), 128.66 (C-1/C-2/C-3), 130.33 (C-12), 140.91 (C-4), 140.99 (C-4), 141.37 (C-11), 149.61 (C-14), 165.66 (C-7), 165.71 (C-7), 193.02 (C-10). IR (KBr) [ν/cm^{-1}]: 3062 (m), 3031 (m), 2962 (m), 1742 (m), 1659 (s), 1569 (s), 1525 (vs), 1454 (m), 1381 (m), 1343 (vs), 1268 (m), 1095 (s), 822 (m). MS (FAB+): C₂₇H₂₃N₃O₅ m/z (%) = 470 (10.8) [M⁺ + H], 321 (100.0) [bisoxazolone⁺ + H]. HRMS (FAB+): 470.1694 (C₂₇H₂₃N₃O₅ requires 470.1716). Calc. for C₂₇H₂₃N₃O₅·0.25CHCl₃: C 65.55, H 4.69, N 8.42. Found: C 65.34, H 4.95, N 8.43%.

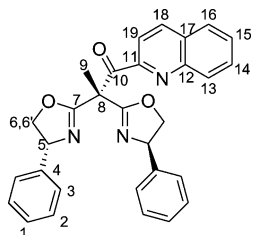


2,2-Bis((S)-4-isopropyl-4,5-dihydrooxazol-2-yl)-1-(quinolin-2-yl)propan-1-one (2a). This compound was prepared as a brown oil from 2,2-bis((S)-4-isopropyl-4,5-dihydrooxazol-2-yl)ethane (0.70 g, 2.8 mmol), *tert*-BuLi in *n*-hexane (1.5 M, 2.1 mL, 3.1 mmol) and quinoline-2-carbonyl chloride (0.94 g, 4.9 mmol) in THF (50 mL) using the same procedure reported for **1a**: yield 0.24 g (21%). ¹H NMR (400 MHz, CDCl₃): δ = 0.86–0.94 (m, 12H, H-1), 1.73–1.87 (m, 2H, H-2), 2.20 (s, 3H, H-6), 3.96–4.09 (m, 4H, H-3, H-4'), 4.14–4.18 (m, 1H, H-4), 4.28–4.32 (m, 1H, H-4), 7.62–7.66 (m, 1H, H-13), 7.74–7.78 (m, 1H, H-12), 7.87 (d, ³J_{HH} = 8.1 Hz, 1H, H-14), 8.08 (d, ³J_{HH} = 8.2 Hz, 1H, H-11), 8.16 (d, ³J_{HH} = 8.6 Hz, 1H, H-17), 8.27 (d, ³J_{HH} = 8.6 Hz, 1H, H-16). {¹H}¹³C NMR (100 MHz, CDCl₃): δ = 17.87 (C-1), 17.89 (C-1), 18.56 (C-1), 18.85 (C-1), 21.83 (C-6), 32.36 (C-2), 53.84 (C-7), 70.42 (C-4), 70.50 (C-4), 71.77 (C-3), 71.89 (C-3), 119.53 (C-17), 127.68 (C-14), 128.59 (C-13), 129.30 (C-15), 129.93 (C-12), 130.31

(C-11), 136.78 (C-16), 146.47 (C-10), 151.28 (C-9), 165.13 (C-5), 165.28 (C-5), 194.85 (C-8). IR (film) [ν/cm^{-1}]: 3057 (m), 2966 (s), 1743 (m), 1674 (s), 1603 (w), 1525 (m), 1464 (w), 1372 (m), 1275 (w), 1240 (w), 1168 (w). MS (FAB+): $\text{C}_{24}\text{H}_{29}\text{N}_3\text{O}_3$ m/z (%) 408 (44.2) [$\text{M}^+ + \text{H}$], 253 (100.0) [bisoxazolone $^+$ + H]. HRMS (FAB+): 408.2283 ($\text{C}_{24}\text{H}_{30}\text{N}_3\text{O}_3$ requires 408.2287).

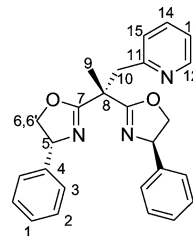


2,2-Bis((R)-4-phenyl-4,5-dihydrooxazol-2-yl)-1-(quinolin-2-yl)propan-1-one (2b). This compound was prepared as a white solid from 2,2-bis((S)-4-phenyl-4,5-dihydrooxazol-2-yl)ethane (0.32 g, 1.0 mmol), *tert*-BuLi in *n*-hexane (1.5 M, 0.8 mL, 1.1 mmol) and quinoline-2-carbonyl chloride (0.29 g, 1.5 mmol) in THF (50 mL) using the same procedure reported for **1a**: yield 0.40 g (84%). ^1H NMR (400 MHz, CDCl_3): δ = 2.33 (s, 3H, H-9), 4.13–4.24 (m, 2H, H-6), 4.56–4.80 (m, 2H, H-6'), 5.26–5.35 (m, 2H, H-5), 7.20–7.33 (m, 10H, H-1, H-2, H-3), 7.56–7.65 (m, 1H, H-15), 7.77 (m, 1H, H-14), 7.88 (m, 1H, H-16), 8.10 (m, 1H, H-13), 8.20 (d, $^3J_{\text{HH}} = 8.5$ Hz, 1H, H-19), 8.29 (d, $^3J_{\text{HH}} = 8.5$ Hz, 1H, H-18). $\{^1\text{H}\}^{13}\text{C}$ NMR (100 MHz, CDCl_3): δ = 21.91 (C-9), 54.02 (C-8), 69.52 (C-5), 69.55 (C-5), 75.51 (C-6), 75.70 (C-6), 119.61 (C-19), 126.84 (C-1/C-2/C-3/C-15/C-16), 127.37 (C-1/C-2/C-3/C-15/C-16), 127.71 (C-1/C-2/C-3/C-15/C-16), 128.51 (C-1/C-2/C-3/C-15/C-16), 128.73 (C-1/C-2/C-3/C-15/C-16), 129.41 (C-17), 130.03 (C-14), 130.39 (C-13), 137.00 (C-18), 142.17 (C-4), 142.23 (C-4), 146.49 (C-12), 151.05 (C-11), 166.82 (C-7), 194.46 (C-10). IR (KBr) [ν/cm^{-1}]: 3058 (m), 3002 (w), 2933 (w), 1716 (m), 1664 (vs), 1564 (m), 1352 (w), 1307 (w), 1129 (m), 1083 (w), 981 (m), 930 (m), 845 (w). MS (FAB+): $\text{C}_{30}\text{H}_{25}\text{N}_3\text{O}_3$ m/z (%) = 476 (100.0) [$\text{M}^+ + \text{H}$], 498 (3.0) [$\text{M}^+ + \text{Na}$]. HRMS (FAB+): 476.1950 ($\text{C}_{30}\text{H}_{26}\text{N}_3\text{O}_3$ requires 476.1974). Calc. for $\text{C}_{26}\text{H}_{26}\text{N}_3\text{O}_3 \cdot 0.3\text{CHCl}_3$: C 71.17, H 4.99, N 8.22. Found: C 71.40, H 5.17, N 8.26%.

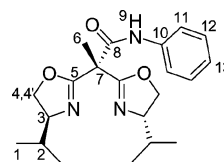


2-(2,2-Bis((R)-4-phenyl-4,5-dihydrooxazol-2-yl)propyl)pyridine (3b). A solution of 1.5 M *tert*-BuLi in *n*-hexane (1.2 mL, 1.7 mmol) was added dropwise to a solution of 2-bis((R)-4-phenyl-4,5-dihydrooxazol-2-yl)ethane (0.50 g, 1.6 mmol) in THF (45 mL) with stirring at -78 °C. The mixture was allowed to warm to -50 °C and stirred for 1 h. This solution was then cooled to -78 °C and a solution of 2-(chloromethyl)-pyridine (0.60 g, 4.7 mmol) in THF (5 mL) was slowly added with stirring. The reaction mixture was maintained at -78 °C for 1 h, slowly warmed to room temperature and then heated to reflux overnight. An aqueous solution of NH_4Cl (50 mL, 10%) was added, and after removal of the organic phase the residue was extracted

with dichloromethane (3 \times 50 mL). The organic layer was washed with water and dried over anhydrous Na_2SO_4 . Removal of the solvent gave a pale yellow oil which was purified by flash chromatography (EtOAc) affording **3b** as a white solid (0.51 g, 78%). ^1H NMR (400 MHz, CDCl_3): δ = 1.73 (s, 3H, H-9), 3.66 (d, $^2J_{\text{HH}} = 13.5$ Hz, 1H, H-10), 3.69 (d, $^2J_{\text{HH}} = 13.5$ Hz, 1H, H-10), 4.16–4.23 (m, 2H, H-6), 4.70–4.76 (m, 2H, H-6'), 5.19–5.30 (m, 2H, H-5), 7.16–7.37 (m, 12H, H-1, H-2, H-3, H-13, H-15), 7.56–7.60 (m, 1H, H-14), 8.59–8.60 (m, 1H, H-12). $\{^1\text{H}\}^{13}\text{C}$ NMR (100 MHz, CDCl_3): δ = 21.64 (C-9), 43.32 (C-10), 44.18 (C-8), 69.51 (C-5), 69.65 (C-5), 75.46 (C-6), 75.51 (C-6), 121.80 (C-13/C-15), 124.96 (C-13/C-15), 126.73 (C-1/C-2/C-3), 126.85 (C-1/C-2/C-3), 127.51 (C-1/C-2/C-3), 127.59 (C-1/C-2/C-3), 128.60 (C-1/C-2/C-3), 128.70 (C-1/C-2/C-3), 136.09 (C-14), 142.25 (C-4), 142.34 (C-4), 149.25 (C-12), 157.30 (C-11), 169.14 (C-7), 169.19 (C-7). IR (KBr) [ν/cm^{-1}]: 3062 (w), 3026 (w), 2945 (w), 2889 (w), 1657 (vs), 1241 (w), 1176 (m), 1096 (s), 972 (s), 921 (w), 764 (s), 701 (m). MS (FAB+): $\text{C}_{26}\text{H}_{25}\text{N}_3\text{O}_2$ m/z (%) = 412 (100.0) [$\text{M}^+ + \text{H}$]. HRMS (FAB+): 412.2041 ($\text{C}_{26}\text{H}_{26}\text{N}_3\text{O}_2$ requires 412.2024). Calc. for $\text{C}_{26}\text{H}_{25}\text{N}_3\text{O}_2 \cdot 0.3\text{CHCl}_3$: C 74.95, H 6.05, N 10.07. Found: C 74.73, H 6.05, N 10.00%.

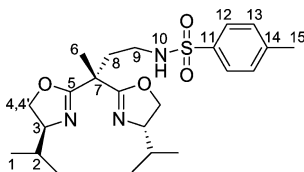


N-Phenyl-2,2-bis((4S)-4-isopropyl-1,3-oxazolin-2-yl)propionamide (4). This compound was prepared as a colourless oil from 2,2-bis((S)-4-isopropyl-4,5-dihydrooxazol-2-yl)ethane (0.16 g, 0.63 mmol), *tert*-BuLi in *n*-hexane (1.7 M, 0.4 mL, 0.68 mmol) and phenyl isocyanate (0.76 mL, 0.70 mmol) in THF (50 mL) using the same procedure reported for **3b**. Purification by flash chromatography (EtOAc– CH_2Cl_2 , 20 : 80) gave the desired product **4** (0.15 g, 64% yield) as a colourless oil. ^1H NMR (300 MHz, CDCl_3): δ = 1.01–0.91 (m, 12H, H-1), 1.83 (sept, $^3J_{\text{HH}} = 6.8$ Hz, 2H, H-3), 1.88 (t, 3H, H-6), 4.05 (m, 2H, H-3), 4.30 (m, 4H, H-4, H-4'), 7.10 (t, $^3J_{\text{HH}} = 7.4$ Hz, 1H, H-13), 7.31 (m, 2H, H-12), 7.60 (d, $^3J_{\text{HH}} = 8.6$ Hz, 2H, H-11), 11.85 (s, 1H, 9-H). $\{^1\text{H}\}^{13}\text{C}$ NMR (75.5 MHz, CDCl_3) δ = 18.1 (C-1), 18.6 (C-1), 22.4 (C-6), 32.5 (C-2), 49.8 (C-7), 70.7 (C-4), 71.9 (C-3), 120.0 (C-13), 129 (C-11/C-12), 129.4 (C-11/C-12), 138.2 (C-10), 165.4 (C-5), 166.0 (C-8). MS (EI): $\text{C}_{21}\text{H}_{29}\text{N}_3\text{O}_3$ m/z (%) 371.4 [M^+ (0.1), 252.3 [$\text{M} - \text{PhCONH}$] $^+$ (10), 209.3 [$\text{M} - (\text{PhCONH} + \text{CH}(\text{CH}_3)_2$)] $^+$ (100). Calc. for $\text{C}_{21}\text{H}_{29}\text{N}_3\text{O}_3$: C, 67.8; H, 7.9; N, 11.3. Found: C, 67.3; H, 7.9; N, 11.2%.

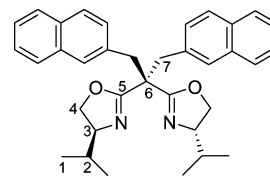


N-(3,3-Bis((S)-4-isopropyl-4,5-dihydrooxazol-2-yl)butyl)-4-methylbenzolsulfonamide (5). This compound was prepared as

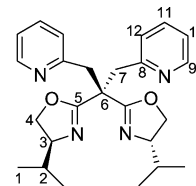
a white solid from 2,2-bis((*S*)-4-isopropyl-4,5-dihydrooxazol-2-yl)ethane (1.10 g, 4.4 mmol), *tert*-BuLi in *n*-hexane (1.5 M, 3.2 mL, 4.8 mmol) and tosylaziridine (0.65 g, 3.3 mmol) in THF (50 mL) using the same procedure reported for **3b**: yield 0.49 g (25%). ¹H NMR (400 MHz, CDCl₃): δ = 0.87–0.89 (m, 6H, H-1), 0.93–0.96 (m, 6H, H-1), 1.44 (s, 3H, H-6), 1.71–1.81 (m, 2H, H-2), 2.05–2.09 (m, 2H, H-8), 2.45 (s, 3H, H-15), 3.07–3.11 (m, 2H, H-9), 3.91–3.99 (m, 4H, H-3, H-4'), 4.19–4.25 (m, 2H, H-4), 7.20–7.22 (m, 1H, H-10), 7.32 (d, ³J_{HH} = 8.4 Hz, 2H, H-13), 7.76 (d, ³J_{HH} = 8.3 Hz, 2H, H-12). {¹H}¹³C NMR (100 MHz, CDCl₃): δ = 17.85 (C-1), 17.91 (C-1), 18.56 (C-1), 18.60 (C-1), 21.47 (C-6), 22.42 (C-15), 32.26 (C-2), 32.42 (C-2), 36.45 (C-8), 39.25 (C-7), 42.29 (C-9), 70.07 (C-4), 70.40 (C-4), 71.53 (C-3), 71.63 (C-3), 127.09 (C-12), 129.46 (C-13), 137.39 (C-11), 142.77 (C-14), 167.91 (C-5), 168.00 (C-5). IR (KBr) [ν/cm⁻¹]: 3081 (m), 2959 (s), 2908 (m), 2866 (m), 1651 (vs), 1474 (m), 1326 (s), 1158 (vs), 1095 (s), 977 (m), 927 (w), 659 (s), 569 (s). MS (FAB+): C₂₃H₃₅N₃O₄S *m/z* (%) = 450 (100.0) [M⁺ + H], 253 (13.2) [bisoxazolium⁺ + H]. [M⁺ + H]. HRMS (FAB+): 450.2437 (C₂₃H₃₇N₃O₄S requires 450.2427). Calc. for C₂₃H₃₆N₃O₄S: C 61.44, H 7.85, N 9.35, S 7.13. Found: C 61.16, H 8.12, N 9.51, S 7.09%.



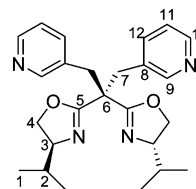
(*S*)-2-(2-((*S*)-4-*tert*-Butyl-4,5-dihydrooxazol-2-yl)-1,3-dinaphthalen-2-yl)propan-2-yl-4-isopropyl-4,5-dihydrooxazole (**7**). A solution of bis((*S*)-4-isopropyl-4,5-dihydrooxazol-2-yl)-methane (0.6 g, 2.5 mmol), in 10 mL of THF was added dropwise to a stirred suspension of NaH (0.30 g, 12.5 mmol) in THF (30 mL) at room temperature. The mixture was then cooled to 0 °C and a solution of 2-(bromomethyl)naphthalene (3.3 g, 12.5 mmol) in THF (10 mL) was slowly added with stirring. The reaction mixture was slowly warmed to room temperature and then heated to reflux overnight. An aqueous solution of NH₄Cl (50 mL, 10%) was carefully added, and after removal of the organic phase the residue was extracted with dichloromethane (3 × 50 mL). The organic layer was washed with water and dried over anhydrous Na₂SO₄. Removal of solvent gave a colourless oil which was purified by flash chromatography (hexane–EtOAc, 90 : 10) affording a colourless sticky solid. (0.72 g, 55%). ¹H NMR (200 MHz, CDCl₃): δ = 0.81 (d, ³J = 6.7 Hz, 6H, H-1), 0.92 (d, ³J = 6.7 Hz, 6H, H-1), 1.69 (m, 2H, H-2), 3.49 (d, ²J = 14 Hz, 2H, H-7), 3.67 (d, ²J = 14 Hz, 2H, H-7), 3.98–3.83 (m, 4H, H-4), 4.24–4.12 (m, 2H, H-3), 7.48–7.38 (m, 6H, Ar–H), 7.84–7.75 (m, 8H, Ar–H). ¹³C NMR (50 MHz, CDCl₃): δ = 18.0 (C-3), 18.9 (C-3), 32.6 (C-2), 40.0 (C-7), 48.6 (C-6), 70.0 (C-4), 72.0 (C-3), 125.4 (Ar), 125.8 (Ar), 127.3 (Ar), 127.3 (Ar), 127.5 (Ar), 127.6 (Ar), 128.8 (Ar), 129.3 (Ar), 132.4 (Ar), 133.3 (Ar), 134.6 (Ar), 166.2 (C-5). MS (FAB+): C₃₅H₃₈N₂O₂ *m/z* (%) = 519.5 (100.0) [M⁺ + H], 577.4 (50) [M – CH₂Naph⁺]. HRMS (FAB+): 519.3008 (C₃₅H₃₉N₂O₂ requires 519.3011).



2-(2,2-Bis((*S*)-4,5-dihydro-4-isopropylloxazol-2-yl)-3-(pyridin-2-yl)propyl)pyridine (**8a**). This compound was prepared as a white solid from bis((*S*)-4-isopropyl-4,5-dihydrooxazol-2-yl)-methane (0.6 g, 2.5 mmol), NaH (0.30 g, 12.5 mmol) and 2-(chloromethyl)pyridine (1.9 g, 15 mmol) in THF (50 mL) using the same procedure reported for **7**: 0.73 g (69%). ¹H NMR (200 MHz, CDCl₃): δ = 0.78 (d, 6H, ³J_{HH} = 6.8 Hz, H-1), 0.82 (d, ³J_{HH} = 6.8 Hz, 6H, H-1), 1.67 (m, 2H, H-2), 3.45 (d, ²J_{HH} = 13.6 Hz, 2H, H-7), 3.58 (d, ²J_{HH} = 13.6 Hz, 2H, H-7), 3.73–3.85 (m, 4H, 4-H), 4.06–4.26 (m, 2H, 3-H), 7.06–7.13 (m, 2H, H-11), 7.44–7.64 (m, 4H, H-10/H-12) 8.55–8.51 (m, 2H, H-11). {¹H}¹³C NMR (50 MHz, CDCl₃): δ = 17.7 (C-1), 18.9 (C-1), 32.2 (C-2), 39.8 (C-7), 47.2 (C-6), 69.8 (C-4), 71.8 (C-3), 121.4 (C-10/C-12), 125.4 (C-10/C-12), 135.6 (C-11), 148.9 (C-9), 158.0 (C-8), 166.1 (C-5). MS (FAB+): C₂₅H₃₂N₄O₂ *m/z* (%) = 421 (100.0). Calc. for C₂₅H₃₂N₄O₂: C 71.40, H 7.67, N 13.32. Found: C 71.12, H 7.58, N 13.19%.

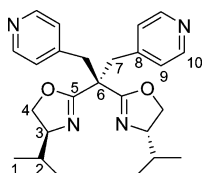


3-(2,2-Bis((*S*)-4,5-dihydro-4-isopropylloxazol-2-yl)-3-(pyridin-3-yl)propyl)pyridine (**8b**). This compound was prepared as a pale yellow solid from (4*S*)-bis-[(1-methylethyl)-4,5-dihydrooxazole] (0.5 g, 2.1 mmol), NaH (0.25 g, 10.5 mmol) and 3-(chloromethyl)pyridine (1.6 g, 12.5 mmol) in THF (50 mL) using the same procedure reported for **7**: yield 0.30 g (34%). ¹H NMR (200 MHz, CDCl₃): δ = 0.82 (d, ³J_{HH} = 6.7 Hz, 6H, H-1), 0.89 (d, ³J_{HH} = 6.7 Hz, 6H, H-1), 1.59 (m, 2H, H-2), 3.14 (d, ²J_{HH} = 14.0 Hz, 2H, H-7), 3.39 (d, ²J_{HH} = 14.0 Hz, 2H, H-7), 3.78–3.95 (m, 4H, 4-H), 4.09–4.22 (m, 2H, 3-H), 7.15–7.21 (m, 2H, H-11), 7.64–7.58 (m, 2H, H-12), 8.47–8.43 (m, 4H, H-9/H-10). {¹H}¹³C NMR (50 MHz, CDCl₃): δ = 18.1 (C-1), 18.7 (C-1), 32.6 (C-2), 37.9 (C-7), 48.1 (C-6), 70.2 (C-4), 72.0 (C-3), 122.8 (C-11), 132.3 (C-12), 137.8 (C-9/C-10), 148.2 (C-8), 151.4 (C-9/C-10), 165.2 (C-5). MS (EI): C₂₅H₃₂N₄O₂ *m/z* (%): 421.3 [M]⁺ (20), 328.2 [M – PyCH₂]⁺ (100), 92.0 [CH₂Py]⁺ (40). Calc. for C₂₅H₃₂N₄O₂: C, 71.40; H, 7.67; N, 13.32; Found C, 70.16; H, 7.78; N, 12.67%.



4-(2,2-Bis((*S*)-4,5-dihydro-4-isopropylloxazol-2-yl)-3-(pyridin-4-yl)propyl)pyridine (**8c**). This compound was prepared as a

pale yellow oil from bis((*S*)-4-isopropyl-4,5-dihydrooxazol-2-yl)-methane² (0.4 g, 1.7 mmol), NaH (0.20 g, 8.3 mmol) and 4-(chloromethyl)-pyridine (1.3 g, 10.0 mmol) in THF (50 mL) using the same procedure reported for **8a**: yield 0.34 g (48%). ¹H NMR (200 MHz, CDCl₃): δ = 0.83 (d, ³J_{HH} = 6.7 Hz, 6H, 1-H), 0.90 (d, ³J_{HH} = 6.7 Hz, 6H, 1-H), 1.64 (m, 2H, 2-H), 3.20 (d, ²J_{HH} = 14 Hz, 2H, H-7), 3.40 (d, ²J_{HH} = 14 Hz, 2H, H-7), 3.94–3.79 (m, 4H, H-4), 4.20–4.14 (m, 2H, H-3), 7.14 (d, ³J_{HH} = 6 Hz, 2H, H-9/H-10), 8.48 (d, ²J_{HH} = 6 Hz, 2H, H-9/H-10). ¹³C NMR (50 MHz, CDCl₃): δ = 18.0 (C-1), 18.7 (C-1), 32.6 (C-2), 37.5 (C-7), 47.2 (C-6), 70.2 (C-4), 72.1 (C-3), 125.5 (C-9), 145.6 (C-8), 149.5 (C-10), 165.1 (C-5). MS (FAB+): C₂₅H₃₂N₄O₂ m/z (%) = 421.5 (100.0) [M⁺ + H]. HRMS (FAB+): 421.2635 (requires 421.2604).



{2-(2,2-Bis((*S*)-4-isopropyl-4,5-dihydrooxazol-2-yl)propyl)pyridine}copper(II) acetate monohydrate (9·H₂O). To a stirred solution of ligand **3a** (50 mg, 0.14 mmol) in methanol (2 mL) a solution of copper(II) acetate monohydrate (56 mg, 0.28 mmol) in methanol (3 mL) was added. After 12 h the solvent was removed *in vacuo*, the residue extracted with toluene (5 mL) and filtered through a Celite pad. Layering of the resulting solution of **9** with *n*-hexane gave blue crystals: Yield 10 mg (14%). IR (KBr) [ν/cm⁻¹]: 2963 (m), 2930 (w), 2873 (w), 1671 (s), 1589 (s), 1400 (m), 1333 (m), 1240 (m), 1104 (m), 1040 (w), 777 (f), 678 (w). MS (FAB): C₂₄H₃₅CuN₃O₆·H₂O m/z (%) = 465 (80.5) [M⁺ – OAc], 406 (100.0) [M⁺ – 2OAc]. Calcd. for C₂₄H₃₅CuN₃O₆·H₂O: C, 53.08; H, 6.87; N, 7.74; Found C, 53.20; H, 6.81; N, 8.07%.

{N-(3,3-Bis((*S*)-4-isopropyl-4,5-dihydrooxazol-2-yl)butyl)-4-methylbenzolsulfonamide}copper(II) acetate (10). This compound was prepared as blue crystals from ligand **5** (50 mg, 0.11 mmol) and copper(II) acetate monohydrate (50 mg, 0.22 mmol) using the same procedure reported for **9**: yield 25 mg (36%). IR (KBr) [ν/cm⁻¹]: 3106 (w), 2960 (m), 2872 (m), 1662 (s), 1595 (m), 1563 (m), 1400 (s), 1329 (m), 1158 (s), 1105 (s), 926 (w), 821 (m). MS (FAB): C₂₇H₄₁CuN₃O₈S m/z (%) = 571 (37.8) [M⁺ – OAc], 512 (100.0) [M⁺ – 2 OAc]. Calcd. for C₂₇H₄₁CuN₃O₈S: C, 51.37; H, 6.55; N, 6.66, S 5.08; Found C, 51.19; H, 6.51; N, 6.48, S 5.37%.

{2-(2,2-Bis((*S*)-4,5-dihydro-4-isopropylloxazol-2-yl)-3-(pyridin-2-yl)propyl)pyridine}copper(II) acetate monohydrate (11). This compound was prepared as blue crystals from ligand **8a** (50 mg, 0.12 mmol) and copper(II) acetate monohydrate (56 mg, 0.28 mmol) using the same procedure reported for **9**: yield 14 mg (20%). MS (FAB): C₂₉H₃₈CuN₄O₆ m/z (%) = 542 (19) [M⁺ – OAc], 483 (100.0) [M⁺ – 2OAc]. Calcd. for C₂₉H₃₈CuN₄O₆: C, 57.84; H, 6.36; N, 9.30; Found C, 57.93; H, 6.55; N, 9.13%.

General procedure for the asymmetric allylic oxidation catalyzed by Cu(II) complexes

A solution of the suitable ligand (0.05 mmol) and Cu salt (0.04 mmol) in distilled acetonitrile (3.0 mL) was stirred at rt for 1 h to ensure the formation of the copper complex. The solution was then cooled to the desired temperature and the cyclohexene (5 mmol) was added. To the stirred mixture a solution of peroxyester (0.85 mmol) in acetonitrile (2 mL) was added dropwise. After the reaction was judged to be complete (TLC disappearance of the peroxyester), which generally was the case after 5–7 days, the solvent was removed *in vacuo*, and the residue was dissolved in CH₂Cl₂ (20 mL), washed successively with an aqueous KHCO₃ solution (10%), brine, and water and dried

Table 3 X-Ray data for **5**, **9·H₂O**, **10** and **11**

	5	9·H₂O	10	11
Empirical formula	C ₂₃ H ₃₅ N ₃ O ₄ S	C ₂₄ H ₃₇ CuN ₃ O ₇	C ₂₇ H ₄₁ CuN ₃ O ₈ S	C ₂₉ H ₃₈ CuN ₄ O ₆
Formula weight	449.60	543.11	631.22	602.17
Crystal size/mm	0.30 × 0.25 × 0.13	0.22 × 0.06 × 0.02	0.25 × 0.25 × 0.10	0.30 × 0.25 × 0.15
Crystal system	Monoclinic	Orthorhombic	Monoclinic	Orthorhombic
Space group	<i>P</i> 2 ₁	<i>P</i> 2 ₁ 2 ₁ 2 ₁	<i>P</i> 2 ₁	<i>P</i> 2 ₁ 2 ₁ 2 ₁
<i>a</i> /Å	6.5200(4)	9.3854(12)	9.3203(6)	9.1940(10)
<i>b</i> /Å	19.3181(11)	14.6399(18)	10.7524(8)	16.122(2)
<i>c</i> /Å	9.6743(6)	19.322(2)	16.0394(11)	19.152(6)
<i>a</i> /°	90	90	90	90
<i>β</i> /°	106.0890(10)	90	104.198(2)	90
<i>γ</i> /°	90	90	90	90
<i>V</i> /Å ³	1170.79(12)	2654.9(6)	1558.30(19)	2838.8(10)
<i>Z</i>	2	4	2	4
<i>D_c</i> /Mg m ⁻³	1.275	1.359	1.345	1.409
<i>μ</i> /mm ⁻¹	0.172	0.869	0.817	0.819
<i>T</i> /K	100(2)	100(2)	100(2)	193(2)
<i>F</i> (000)	484	1148	666	1268
Refl. collected	18426	29150	13654	10824
Refl. indep. [<i>R</i> _{int}]	6926 [0.035]	4693 [0.137]	6927 [0.053]	4819 [0.061]
Data/rest./par.	6926/1/302	4693/0/323	6927/1/367	4819/0/367
Goodness-of-fit on <i>F</i> ²	1.042	1.054	1.057	1.095
Final <i>R</i> indices [<i>I</i> > 2σ(<i>I</i>)]	<i>R</i> ₁ = 0.045, <i>wR</i> ₂ = 0.106	<i>R</i> ₁ = 0.074, <i>wR</i> ₂ = 0.191	<i>R</i> ₁ = 0.053, <i>wR</i> ₂ = 0.129	<i>R</i> = 0.047, <i>wR</i> ₂ = 0.089
<i>R</i> indices (all data)	<i>R</i> ₁ = 0.060, <i>wR</i> ₂ = 0.116	<i>R</i> ₁ = 0.092, <i>wR</i> ₂ = 0.203	<i>R</i> ₁ = 0.072, <i>wR</i> ₂ = 0.138	<i>R</i> = 0.069, <i>wR</i> ₂ = 0.108
Largest residual peak and hole/e Å ⁻³	0.69 and -0.36	0.93 and -0.74	1.47 and -0.88	0.38 and -0.48

over Na₂SO₄. Concentration and chromatography on a silica gel column with a hexane–ethyl acetate mixture (50 : 1) afforded pure allylic benzoate. The yields and ee's are given in Tables 1 and 2. In general, slightly higher yields were obtained upon increasing the reaction times without loss of enantioselectivity

The enantiopurity of the products was determined by chiral HPLC using the following conditions:

2-Cyclohexenyl-1-benzoate. AS–H column [hexane; flow rate 0.5 ml min⁻¹; *t_r* = 18.3 min (R), 19.3 min (S)].

2-Cyclohexenyl-1-nitrobenzoate. AD–H column [hexane–2-propanol 99.5 : 0.5; flow rate 0.5 ml min⁻¹; *t_r* = 30.8 min (R), 34.9 min (S)].

Crystal structure determinations

Suitable crystals of the protioligand **5** and the complexes **9**·H₂O, **10** and **11** were obtained by layering concentrated solutions in dichloromethane with pentane or diethyl ether and allowing slow diffusion at room temperature. Intensity data were collected at low temperature on a Bruker AXS Smart 1000 CCD (**5**, **9**, **10**) and a Nonius Kappa CCD (**11**) diffractometer. A semi-empirical absorption correction was applied. The structures were solved with heavy atom and/or direct methods and refined by full matrix least squares. Hydrogen atoms were input at calculated positions and refined with the riding model, except the amide hydrogens, which were taken from difference Fourier synthesis and refined. In complex **10**, the distance *d*(N4–H4) was restrained to 0.93(2) Å. The positions of the hydrogen atoms of the water of crystallization in **9**·H₂O were inferred by relatively short intermolecular O···O vectors. The calculations were performed using the programs DIRDIF,¹⁵ SHELXS-86¹⁶ and SHELXL-97.¹⁷ Graphical representations were drawn with PLATON.¹⁸ Anisotropic displacement ellipsoids are scaled to 40% probability. Crystal and experimental data are given in Table 3.

CCDC reference numbers 283311–283314.

For crystallographic data in CIF or other electronic format see DOI: 10.1039/b512570g

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