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

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A series of sidearm functionalized bisoxazoline ligands has been synthesized by reaction of the monolithiated methyl{bis(oxazolinyl)}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 $CuN_2O_4$ 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.

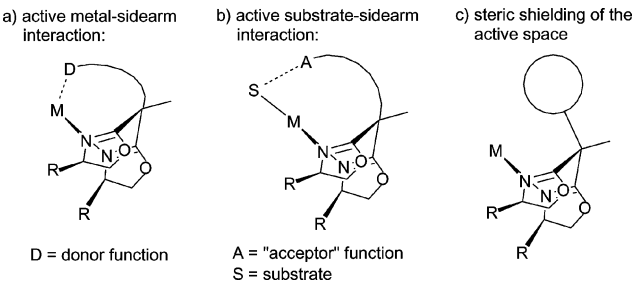


**Fig. 1** Possible roles of ligand sidearms in bisoxazolines.

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) ligands[6] 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

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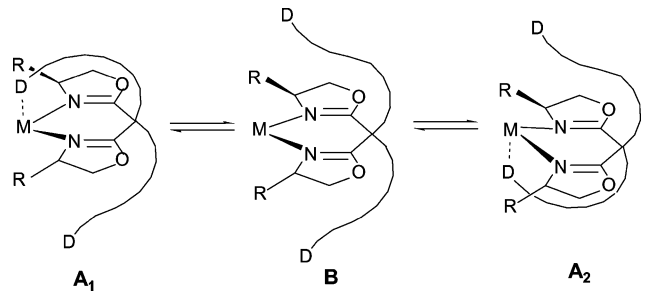


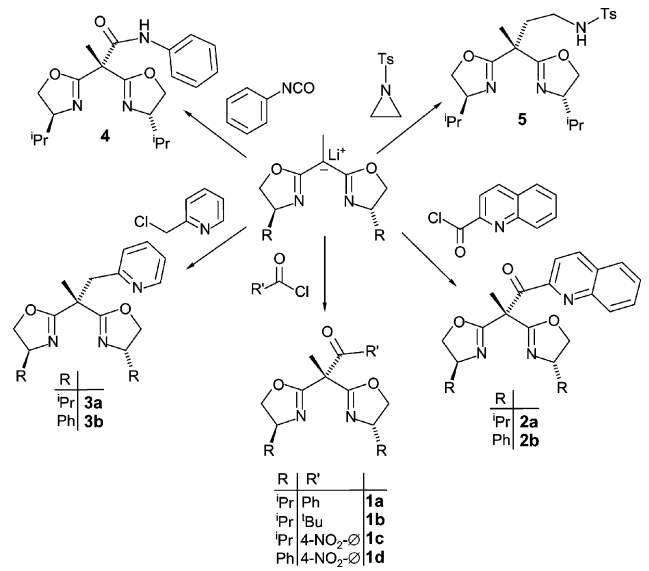

**Fig. 2** "Degenerate" interaction of the ligand sidearms in difunctionized bisoxazolines.

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(oxazolinyl)}methane[10] 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 $^t$BuLi. 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 $\nu(RSO_2N)$-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.

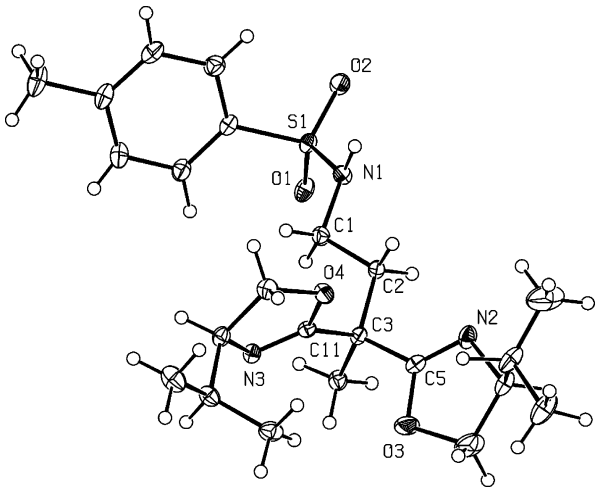



**Fig. 3** Molecular structure of compound **5**. Selected bond lengths (Å) and angles (°): C5–N2, 1.263(3); C11–N3, 1.270(2); N1–S1, 1.6107(16); O1–S1, 1.4376(15); O2–S1, 1.4338(15); C5–C3–C11, 106.21(14); N2–C5–O3, 119.10(19); N2–C5–C3, 127.62(18); N3–C11–O4, 118.57(15); N3–C11–C3, 127.36(16); O1–S1–O2,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

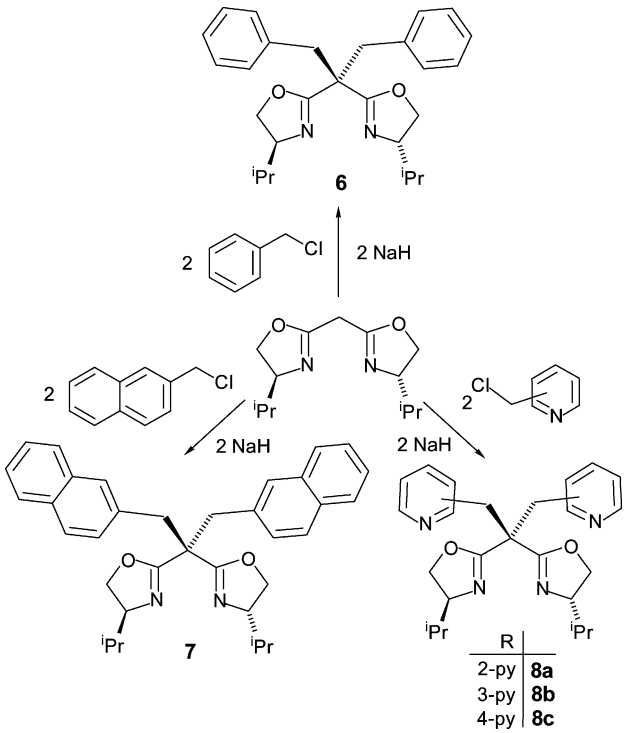
The two oxazoline rings in **5** are twisted relative to one another with the two N-atoms, N2 and N3, adopting opposite orientations. This leads to torsion angles N3–C11–C3–C2 120.3(2)° and C2–C3–C5–N2 8.1(3)°. This particular molecular arrangement is thought to be due to the steric demand of the two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

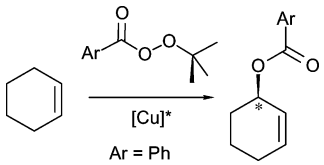
ligands, enantioselectivities of *ca.* 60% ee (with yields of *ca.* 65%) are obtained.

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.

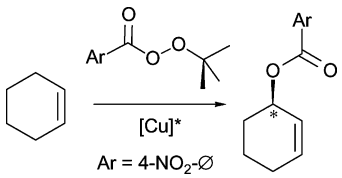
It is worth noting that the copper complexes of ligands **6** and **8a**, both bearing two substituents on the carbon atom bridging the two oxazoline units (**6**: benzyl; **8a**: 2-pyridyl), display higher selectivity. As previously observed, the use of *p*-$NO_2PhCO_3$-*t*-Bu significantly enhances 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 $PhCO_3$-*t*-Bu as oxidant (isolated yields after reaction times of 5–7 days)




| Entry | Ligand | Copper salt | *T*/°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*-$NO_2PhCO_3$-*t*-Bu as oxidant (isolated yields after reaction times of 5–7 days)

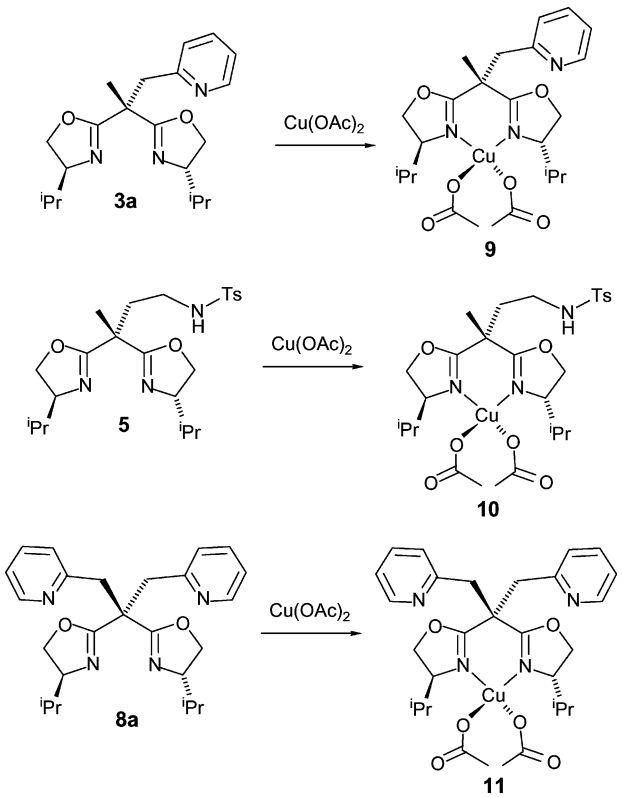



| Entry | Ligand | Copper salt | *T*/°C | Yield (%) | ee (%) |
|---|---|---|---|---|---|
| 1 | **5** | $Cu(OTf)_2$ | 20 | 87 | 77 |
| 2 | **5** | $Cu(OCl_4)_2$ | 20 | 63 | 77 |
| 3 | **5** | $Cu(BF_4)_2$ | 20 | 73 | 72 |
| 4 | **5** | $Cu(OTf)_2$ | −15 | 19 | 79 |
| 5 | **6** | $Cu(OTf)_2$ | 20 | 52 | 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 only 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 $CuN_2O_4$ 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 $\kappa^2$-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 acetato 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 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.

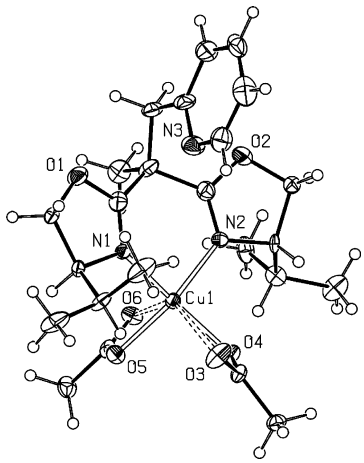



**Fig. 4** Molecular structure of compound **9**. Selected bond lengths (Å) and angles (°): Cu1–N1, 1.946(6); Cu1–N2, 1.973(6); Cu1–O4, 1.954(5); Cu1–O5, 1.977(5); Cu1–O3, 2.687(6); Cu1–O6, 2.540(5); N1–Cu1–N2, 90.1(3); O4–Cu1–N2, 93.9(3); N1–Cu1–O5, 92.4(3); N1–Cu1–O4, 158.2(2); N2–Cu1–O5, 154.1(2);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

## 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)pyridine[5] (**3a**), (4*S*)-2,2′-(1-phenylmethyl-2-phenylethylidene)bis[4-(1-methylethyl)-4,5-dihydroxazole[14] (**6**) and *tert*-butyl *p*-nitrobenzoate[11] were prepared according to literature procedures. The $^1$H and $^{13}$C 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 ($^1$H) or the carbon ($^{13}$C) resonance. IR spectra were recorded as thin films between KBr plates using a FT-IR Merlin Excalibur FT3000

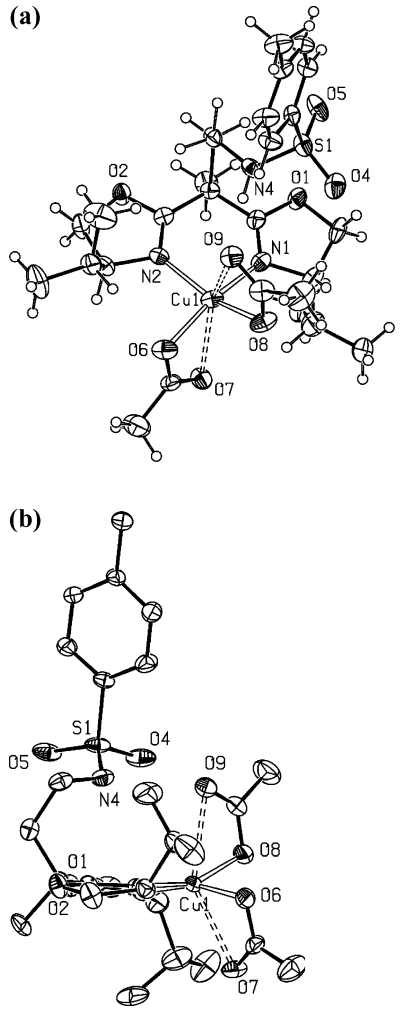



**Fig. 5** a) Molecular structure of compound **10**. Selected bond lengths (Å) and angles (°): Cu1–N1, 1.974(4); Cu1–N2, 1.975(4); Cu1–O6, 1.962(4); Cu1–O8, 1.966(4); N4–S1, 1.603(4); O4–S1, 1.434(4); O5–S1, 1.431(4); Cu1–O7, 2.501(3); Cu1–O9, 2.584(3); N1–Cu1–N2, 89.27(14); O8–Cu1–N1, 91.93(16); O6–Cu1–N2, 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 Surveyer™ 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 °C. The mixture was allowed

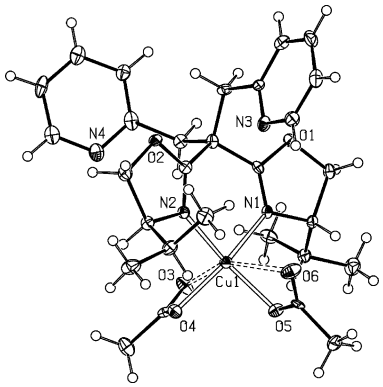
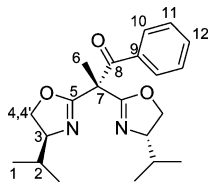


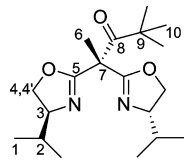

**Fig. 6** Molecular structure of compound **11**. Selected bond lengths (Å) and angles (°): Cu1–N1, 1.991(4); Cu1–N2, 1.976(4); Cu1–O4, 1.986(3); Cu1–O5, 1.948(3); N2–Cu1–N1, 89.72(15); N2–Cu1–O4, 92.80(15); O5–Cu1–N1, 95.75(14); O4–Cu1–N1, 156.45(14); O5–Cu1–N2, 153.24(16); O5–Cu1–O4, 92.48(14).

to warm to −50 °C and stirred for 1 h. This solution was then cooled to −78 °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 °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 × 50 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 (EtOAc–$CH_2Cl_2$, 20 : 80) affording **1a** as a colourless oil (0.17 g, 75% yield). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 0.84 (d, $^3J_{HH}$ = 5.3 Hz, 3H, H-1), 0.87 (d, $^3J_{HH}$ = 5.3 Hz, 3H, H-1), 0.91 (d, $^3J_{HH}$ = 6.9 Hz, 3H, H-1), 0.95 (d, $^3J_{HH}$ = 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, $^3J_{HH}$ = 7.3 Hz, 1H, H-12), 7.91 (d, $^3J_{HH}$ = 7.2 Hz, 2H, H-10). {$^1$H}$^{13}$C NMR (75.5 MHz, $CDCl_3$): $\delta$ = 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+): $C_{21}H_{28}N_2O_3$ *m*/*z* (%) = 358 (23) [M + H]$^+$, 341 (5) [M − $CH_3$]$^+$, 313 (5) [M − $C_3H_7$]$^+$, 285 (4) [M − $C_3H_7$ − CO]$^+$, 253 (30), 251 (19) [M − COPh]$^+$, 246 (4), 244 (5) [M − $C_6H_{10}NO$]$^+$, 210 (5), 209 (33), 207 (4), 202 (4).

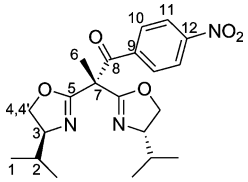



**2,2-Bis((*S*)-4-isopropyl-4,5-dihydrooxazol-2-yl)-4,4-dimethyl-pentan-3-one (1b).** This compound was prepared as a colourless oil from 2,2-bis((*S*)-4-isopropyl-4,5-dihydrooxazol-2-yl)-ethane (0.50 g, 2.0 mmol), *tert*-BuLi in *n*-hexane (1.5 M, 1.5 mL, 2.2 mmol) and pivaloylchloride (0.48 g, 4.0 mmol) in THF (50 mL) using the same procedure reported for **1a**: yield 0.54 g (81%). $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ = 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). {$^1$H}$^{13}$C

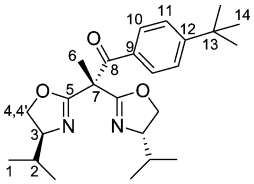
NMR (50 MHz, $CDCl_3$): $\delta$ = 18.06 (C-1), 18.10 (C-1), 18.85 (C-1), 18.90 (C-1), 21.28 (C-6), 28.42 (C-10), 32.11 (C-2), 32.46 (C-2), 46.10 (C-9), 55.69 (C-7), 70.25 (C-4) 70.47 (C-4), 71.90 (C-3), 72.00 (C-3), 164.58 (C-5), 164.68 (C-5), 208.75 (C-8). IR (film) [$\nu$/cm$^{-1}$]: 2964 (s), 2907 (m), 2360 (w), 1704 (m), 1662 (s), 1520 (w), 1469 (m), 1335 (m), 1088 (m), 1039 (w), 978 (m). MS (FAB+): $C_{19}H_{32}N_2O_3$ $m/z$ (%) = 337 (100.0) [$M^+$ + H], 459 (2.7) [$M^+$ + Na], 253 (9.6) [bisoxazoline$^+$ + H]. HRMS (FAB+): 337.2520 ($C_{19}H_{33}N_2O_3$ requires 337.2520). Calc. for $C_{19}H_{32}N_2O_3$ (337.25): C 67.82, H 9.59, N 8.33. Found: C 67.60, H 9.66, N 8.10%.



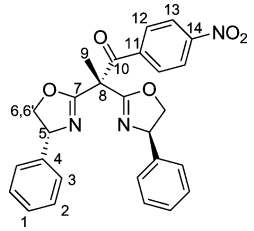
**2,2-Bis((*S*)-4-isopropyl-4,5-dihydrooxazol-2-yl)-1-(4-nitrophenyl)-propan-1-one (1c).** This compound was prepared as a yellow oil from 2,2-bis((*S*)-4-isopropyl-4,5-dihydrooxazol-2-yl)-ethane (0.50 g, 2.0 mmol), *tert*-BuLi in *n*-hexane (1.5 M, 1.5 mL, 2.2 mmol) and *p*-nitrobenzoylchloride (0.41 g, 2.2 mmol) in THF (50 mL) using the same procedure reported for **1a**: yield 0.23 g (29%). $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ = 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). {$^1$H}$^{13}$C NMR (50 MHz, $CDCl_3$): $\delta$ = 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) [$\nu$/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+): $C_{21}H_{27}N_3O_5$ $m/z$ (%) 402 (15.6) [$M^+$ + H], 253 (100.0) [bisoxazoline$^+$ + H]. HRMS (FAB+): 402.2053 ($C_{21}H_{28}N_3O_5$ 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%). $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ = 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).{$^1$H}$^{13}$C NMR (50 MHz, $CDCl_3$): $\delta$ = 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) [$\nu$/cm$^{-1}$]: 3054 (w), 2966 (s), 1728 (m), 1670 (s), 1610 (w), 1518 (m), 1466 (w), 1279 (w), 1188 (w), 1089 (m). MS (FAB+): $C_{25}H_{36}N_2O_3$ $m/z$ (%) = 413 (100.0) [$M^+$ + H], 435 (1.9) [$M^+$ + Na], 253 (21.1) [bisoxazoline$^+$ + H]. HRMS (FAB+): 413.2787 ($C_{25}H_{37}N_2O_3$ requires 413.2804). Calc. for $C_{25}H_{37}N_2O_3 \cdot 0.05CHCl_3$ (412.56): C 71.89, H 8.68, N 6.69. Found: C 71.84, H 8.86, N 6.41%.



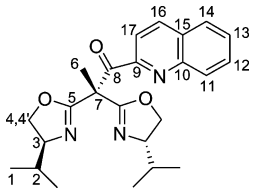
**2,2-Bis((*R*)-4-phenyl-4,5-dihydrooxazol-2-yl)-1-(4-nitrophenyl)-propan-1-one (1e).** This compound was prepared as a yellow solid from 2,2-bis((*S*)-4-phenyl-4,5-dihydrooxazol-2-yl)-ethane (0.50 g, 1.6 mmol), *tert*-BuLi in *n*-hexane (1.5 M, 1.2 mL, 1.7 mmol) and *p*-nitrobenzylchloride (0.44 g, 2.4 mmol) in THF (50 mL) using the same procedure reported for **1a**: yield 0.51 g (68%). $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ = 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, H5), 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). {$^1$H}$^{13}$C NMR (50 MHz, $CDCl_3$): $\delta$ = 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) [$\nu$/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+): $C_{27}H_{23}N_3O_5$ $m/z$ (%) = 470 (10.8) [$M^+$ + H], 321 (100.0) [bisoxazoline$^+$ + H]. HRMS (FAB+): 470.1694 ($C_{27}H_{24}N_3O_5$ requires 470.1716). Calc. for $C_{27}H_{23}N_3O_5 \cdot 0.25CHCl_3$: C 65.55, H 4.69, N 8.42. Found: C 65.34, H 4.95, N 8.43%.



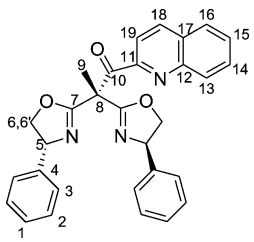
**2,2-Bis((*S*)-4-isopropyl-4,5-dihydrooxazol-2-yl)-1-(quinolin-2-yl)-propan-1-one (2a).** This compound was prepared as a brown oil from 2,2-bis((*S*)-4-isopropyl-4,5-dihydrooxazol-2-yl)-ethane (0.70 g, 2.8 mmol), *tert*-BuLi in *n*-hexane (1.5 M, 2.1 mL, 3.1 mmol) and quinoline-2-carbonyl chloride (0.94 g, 4.9 mmol) in THF (50 mL) using the same procedure reported for **1a**: yield 0.24 g (21%). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 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). {$^1$H}$^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 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

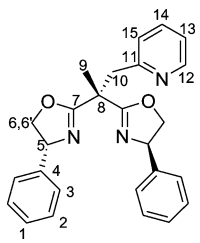
(C-11), 136.78 (C-16), 146.47 (C-10), 151.28 (C-9), 165.13 (C-5), 165.28 (C-5), 194.85 (C-8). IR (film) [$\nu$/cm$^{-1}$]: 3057 (m), 2966 (s), 1743 (m), 1674 (s), 1603 (w), 1525 (m), 1464 (w), 1372 (m), 1275 (w), 1240 (w), 1168 (w). MS (FAB+): $C_{24}H_{29}N_3O_3$ $m/z$ (%) 408 (44.2) [M$^+$ + H], 253 (100.0) [bisoxazoline$^+$ + H]. HRMS (FAB+): 408.2283 ($C_{24}H_{30}N_3O_3$ requires 408.2287).



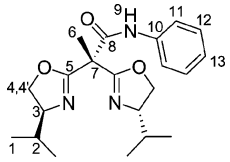
**2,2-Bis((*R*)-4-phenyl-4,5-dihydrooxazol-2-yl)-1-(quinolin-2-yl)-propan-1-one (2b).** This compound was prepared as a white solid from 2,2-bis((*S*)-4-phenyl-4,5-dihydrooxazol-2-yl)-ethane (0.32 g, 1.0 mmol), *tert*-BuLi in *n*-hexane (1.5 M, 0.8 mL, 1.1 mmol) and quinoline-2-carbonyl chloride (0.29 g, 1.5 mmol) in THF (50 mL) using the same procedure reported for **1a**: yield 0.40 g (84%). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 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, H5), 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, $^3J_{HH}$ = 8.5 Hz, 1H, H-19), 8.29 (d, $^3J_{HH}$ = 8.5 Hz, 1H, H-18). {$^1$H}$^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 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) [$\nu$/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+): $C_{30}H_{25}N_3O_3$ $m/z$ (%) = 476 (100.0) [M$^+$ + H], 498 (3.0) [M$^+$ + Na]. HRMS (FAB+): 476.1950 ($C_{30}H_{26}N_3O_3$ requires 476.1974). Calc. for $C_{26}H_{26}N_3O_3 \cdot 0.3CHCl_3$: 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 × 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%). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 1.73 (s, 3H, H-9), 3.66 (d, $^2J_{HH}$ = 13.5 Hz, 1H, H-10), 3.69 (d, $^2J_{HH}$ = 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, H5), 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). {$^1$H}$^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 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) [$\nu$/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+): $C_{26}H_{25}N_3O_2$ $m/z$ (%) = 412 (100.0) [M$^+$ + H]. HRMS (FAB+): 412.2041 ($C_{26}H_{26}N_3O_2$ requires 412.2024). Calc. for $C_{26}H_{25}N_3O_2 \cdot 0.3CHCl_3$: C 74.95, H 6.05, N 10.07. Found: C 74.73, H 6.05, N 10.00%.

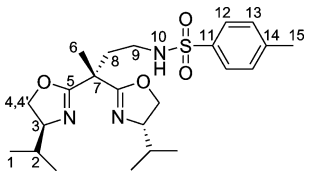


***N*-Phenyl-2,2-bis[(4*S*)-4-isopropyl-1,3-oxazolin-2-yl]propionamide (4).** This compound was prepared as a colourless oil from 2,2-bis((*S*)-4-isopropyl-4,5-dihydrooxazol-2-yl)-ethane (0.16 g, 0.63 mmol), *tert*-BuLi in *n*-hexane (1.7 M, 0.4 mL, 0.68 mmol) and phenyl isocyanate (0.76 mL, 0.70 mmol) 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. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 1.01–0.91 (m, 12H, H-1), 1.83 (sept, $^3J_{HH}$ = 6.8 Hz, 2H, H-3), 1.88 (1, 3H, H-6), 4.05 (m, 2H, H-3), 4.30 (m, 4H, H-4, H4′), 7.10 (t, $^3J_{HH}$ = 7.4 Hz, 1H, H-13), 7.31 (m, 2H, H-12), 7.60 (d, $^3J_{HH}$ = 8.6 Hz, 2H, H-11), 11.85 (s, 1H, 9-H). {$^1$H}$^{13}$C NMR (75.5 MHz, $CDCl_3$) $\delta$ = 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): $C_{21}H_{29}N_3O_3$ $m/z$ (%) 371.4 [M]$^+$ (0.1), 252.3 [M − PhCONH]$^+$ (10), 209.3 [M − (PhCONH + CH(CH$_3$)$_2$)]$^+$ (100). Calcd. for $C_{21}H_{29}N_3O_3$: C, 67.8; H, 7.9; N, 11.3. Found: C, 67.3; H, 7.9; N, 11.2%.

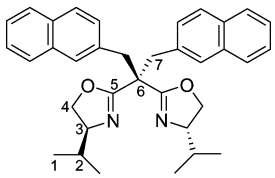


***N*-(3,3-Bis((*S*)-4-isopropyl-4,5-dihydrooxazol-2-yl)butyl)-4-methylbenzolsulfonamide (5).** This compound was prepared as

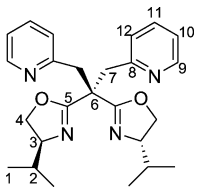
a white solid from 2,2-bis((*S*)-4-isopropyl-4,5-dihydrooxazol-2-yl)-ethane (1.10 g, 4.4 mmol), *tert*-BuLi in *n*-hexane (1.5 M, 3.2 mL, 4.8 mmol) and tosylaziridine (0.65 g, 3.3 mmol) in THF (50 mL) using the same procedure reported for **3b**: yield 0.49 g (25%). $^1$H NMR (400 MHz, $CDCl_3$): $\delta = 0.87$–$0.89$ (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). $\{^1H\}^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta =$ 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) [$\nu$/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+): $C_{23}H_{35}N_3O_4S$ *m*/*z* (%) = 450 (100.0) [M$^+$ + H], 253 (13.2) [bisoxazolin$^+$ + H]. [M$^+$ + H]. HRMS (FAB+): 450.2437 ($C_{23}H_{37}N_3O_4S$ requires 450.2427). Calc. for $C_{23}H_{36}N_3O_4S$: 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%.



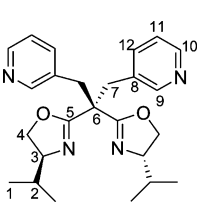
**(*S*)-2-(2-((*S*)-4-*tert*-Butyl-4,5-dihydrooxazol-2-yl)-1,3-di(naphthalen-2-yl)propan-2-yl)-4-isopropyl-4,5-dihydrooxazole (7).** A solution of bis((*S*)-4-isopropyl-4,5-dihydrooxazol-2-yl)-methane (0.6 g, 2.5 mmol), in 10 mL of THF was added dropwise to a stirred suspension of NaH (0.30 g, 12.5 mmol) 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 $NH_4Cl$ (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 $Na_2SO_4$. 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%). $^1$H NMR (200 MHz, $CDCl_3$): $\delta = 0.81$ (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). $^{13}$C NMR (50 MHz, $CDCl_3$): $\delta =$ 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+): $C_{35}H_{38}N_2O_2$ *m*/*z* (%) = 519.5 (100.0) [M$^+$ + H], 577.4 (50) [M − $CH_2$Naph$^+$]. HRMS (FAB+): 519.3008 ($C_{35}H_{39}N_2O_2$ requires 519.3011).



**2-(2,2-Bis((*S*)-4,5-dihydro-4-isopropyloxazol-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-(chlormethyl)-pyridine (1.9 g, 15 mmol) in THF (50 mL) using the same procedure reported for **7**: 0.73 g (69%). $^1$H NMR (200 MHz, $CDCl_3$): $\delta = 0.78$ (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). $\{^1H\}^{13}C$ NMR (50 MHz, $CDCl_3$): $\delta =$ 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+): $C_{25}H_{32}N_4O_2$ *m*/*z* (%) = 421 (100.0). Calc. for $C_{25}H_{32}N_4O_2$: C 71.40, H 7.67, N 13.32. Found: C 71.12, H 7.58, N 13.19%.

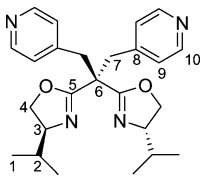


**3-(2,2-Bis((*S*)-4,5-dihydro-4-isopropyloxazol-2-yl)-3-(pyridin-3-yl)propyl)pyridine (8b).** This compound was prepared as a pale yellow solid from (4*S*)-bis-[(1-methylethyl)-4,5-dihydrooxazole] (0.5 g, 2.1 mmol), NaH (0.25 g, 10.5 mmol) and 3-(chlormethyl)-pyridine (1.6 g, 12.5 mmol) in THF (50 mL) using the same procedure reported for **7**: yield 0.30 g (34%). $^1$H NMR (200 MHz, $CDCl_3$): $\delta = 0.82$ (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).). $\{^1H\}^{13}C$ NMR (50 MHz, $CDCl_3$): $\delta =$ 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): $C_{25}H_{32}N_4O_2$ *m*/*z* (%): 421.3 [M]$^+$ (20), 328.2 [M − $PyCH_2$]$^+$ (100), 92.0 [$CH_2$Py]$^+$ (40). Calcd. for $C_{25}H_{32}N_4O_2$: 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-isopropyloxazol-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)-methane[2] (0.4 g, 1.7 mmol), NaH (0.20 g, 8.3 mmol) and 4-(chlormethyl)-pyridine (1.3 g, 10.0 mmol) in THF (50 mL) using the same procedure reported for **8a**: yield 0.34 g (48%). $^1$H NMR (200 MHz, $CDCl_3$): $\delta = 0.83$ (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). $^{13}$C NMR (50 MHz, $CDCl_3$): $\delta$ = 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+): $C_{25}H_{32}N_4O_2$ *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·H$_2$O).** 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) [$\nu$/cm$^{-1}$]: 2963 (m), 2930 (w), 2873 (w), 1671 (s), 1589 (s), 1400 (m), 1333 (m), 1240 (m), 1104 (m), 1040 (w), 777 (w), 678 (w). MS (FAB): $C_{24}H_{35}CuN_3O_6{\cdot}H_2O$ *m*/*z* (%) = 465 (80.5) [M$^+$ − OAc], 406 (100.0) [M$^+$ − 2OAc]. Calcd. for $C_{24}H_{35}CuN_3O_6{\cdot}H_2O$: 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) [$\nu$/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): $C_{27}H_{41}CuN_3O_8S$ *m*/*z* (%) = 571 (37.8) [M$^+$ − OAc], 512 (100.0) [M$^+$ − 2 OAc]. Calcd. for $C_{27}H_{41}CuN_3O_8S$: 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-isopropyloxazol-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): $C_{29}H_{38}CuN_4O_6$ *m*/*z* (%) = 542 (19) [M$^+$ − OAc], 483 (100.0) [M$^+$ − 2OAc]. Calcd. for $C_{29}H_{38}CuN_4O_6$: 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 a 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 $CH_2Cl_2$ (20 mL), washed successively with an aqueous $KHCO_3$ solution (10%), brine, and water and dried

**Table 3** X-Ray data for **5**, **9**·H$_2$O, **10** and **11**

| | **5** | **9**·H$_2$O | **10** | **11** |
|---|---|---|---|---|
| Empirical formula | $C_{23}H_{35}N_3O_4S$ | $C_{24}H_{37}CuN_3O_7$ | $C_{27}H_{41}CuN_3O_8S$ | $C_{29}H_{38}CuN_4O_6$ |
| 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 | $P2_1$ | $P2_12_12_1$ | $P2_1$ | $P2_12_12_1$ |
| *a*/Å | 6.5200(4) | 9.3854(12) | 9.3203(6) | 9.1940(10) |
| *b*/Å | 19.3181(11) | 14.6399(18) | 10.7524(8) | 16.122(2) |
| *c*/Å | 9.6743(6) | 19.322(2) | 16.0394(11) | 19.152(6) |
| $\alpha$/° | 90 | 90 | 90 | 90 |
| $\beta$/° | 106.0890(10 | 90 | 104.198(2 | 90 |
| $\gamma$/° | 90 | 90 | 90 | 90 |
| *V*/Å$^3$ | 1170.79(12) | 2654.9(6) | 1558.30(19) | 2838.8(10) |
| *Z* | 2 | 4 | 2 | 4 |
| $D_c$/Mg m$^{-3}$ | 1.275 | 1.359 | 1.345 | 1.409 |
| $\mu$/mm$^{-1}$ | 0.172 | 0.869 | 0.817 | 0.819 |
| *T*/K | 100(2) | 100(2) | 100(2) | 193(2) |
| *F*(000) | 484 | 1148 | 666 | 1268 |
| Refl. collected | 18426 | 29150 | 13654 | 10824 |
| Refl. indep. [$R_{int}$] | 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 $F^2$ | 1.042 | 1.054 | 1.057 | 1.095 |
| Final *R* indices [$I > 2\sigma(I)$] | $R_1 = 0.045$, $wR_2 = 0.106$ | $R_1 = 0.074$, $wR_2 = 0.191$ | $R_1 = 0.053$, $wR_2 = 0.129$ | $R = 0.047$, $wR2 = 0.089$ |
| *R* indices (all data) | $R_1 = 0.060$, $wR_2 = 0.116$ | $R_1 = 0.092$, $wR_2 = 0.203$ | $R_1 = 0.072$, $wR_2 = 0.138$ | $R = 0.069$, $wR2 = 0.108$ |
| 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 $Na_2SO_4$. 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**·$H_2O$, **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**·$H_2O$ were inferred by relatively short intermolecular O···O vectors. The calculations were performed using the programs DIRDIF,[15] SHELXS-86[16] and SHELXL-97.[17] Graphical representations were drawn with PLATON.[18] Anisotropic displacement elipsoids 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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## References

1 (*a*) R. E. Lowenthal, A. Abiko and S. Masamune, *Tetrahedron Lett.*, 1990, **31**, 6005; (*b*) D. A. Evans, K. A. Woerpel, M. M. Hinman and M. M. Faul, *J. Am. Chem. Soc.*, 1991, **113**, 726; (*c*) E. J. Corey, N. Imai and H. Y. Zhang, *J. Am. Chem. Soc.*, 1991, **113**, 728; (*d*) D. Müller, G. Umbricht, B. Weber and A. Pfaltz, *Helv. Chim. Acta*, 1991, **74**, 232.

2 Selected examples: (*a*) D. A. Evans, D. Seidel, M. Rueping, H. W. Lam, J. T. Shaw and C. W. Downey, *J. Am. Chem. Soc.*, 2003, **125**, 12692; (*b*) D. A. Evans, K. A. Scheidt, J. N. Johnston and M. C. Willis, *J. Am. Chem. Soc.*, 2001, **123**, 4480; (*c*) J. Cong-Dung Le and B. Pagenkopf, *Org. Lett.*, 2004, **6**, 4097; (*d*) J. Thorhauge, M. Johannsen and K. A. Jørgensen, *Angew. Chem., Int. Ed.*, 1998, **37**, 2404; (*e*) D. A. Evans and J. M. Janey, *Org. Lett.*, 2001, **3**, 2125; (*f*) C. Christensen, K. Juhl and K. A. Jørgensen, *Chem. Commun.*, 2001, 2222; (*g*) D. A. Evans, J. S. Johnson and E. J. Olhava, *J. Am. Chem. Soc.*, 2000, **122**, 1635; (*h*) F. Glorius and A. Pfaltz, *Org. Lett.*, 1999, **1**, 141.

3 Reviews: (*a*) F. Fache, E. Schulz, M. Lorraine Tommasino and M. Lemaire, *Chem. Rev.*, 2000, **100**, 2159; (*b*) A. K. Ghosh, P. Mathivanan and J. Cappiello, *Tetrahedron: Asymmetry*, 1998, **9**, 1; (*c*) H. A. McManus and P. J. Guiry, *Chem. Rev.*, 2004, **104**, 4151.

4 (*a*) J. Zhou and Y. Tang, *J. Am. Chem. Soc.*, 2002, **124**, 9030; (*b*) J. Zhou, M.-C. Ye, Z.-Z. Huang and Y. Tang, *J. Org. Chem.*, 2004, **69**, 1309; (*c*) J. Zhou and Y. Tang, *Chem. Commun.*, 2004, 432; (*d*) M.-C. Ye, B. Li, J. Zhou, X.-L. Sun and Y. Tang, *J. Org. Chem.*, 2005, **70**, ASAP.

5 Y. Tang, M. C. Ye and J. Zhou, *J. Comb. Chem.*, 2004, **6**, 301.

6 (*a*) S. Bellemin-Laponnaz and L. H. Gade, *Chem. Commun.*, 2002, 1286; (*b*) C. Dro, S. Bellemin-Laponnaz, R. Welter and L. H. Gade, *Angew. Chem., Int. Ed.*, 2004, **43**, 4479; (*c*) B. D. Ward, S. Bellemin-Laponnaz and L. H. Gade, *Angew. Chem., Int. Ed.*, 2005, **44**, 1668; (*d*) C. Foltz, B. Stecker, G. Marconi, S. Bellemin-Laponnaz, H. Wadepohl and L. H. Gade, *Chem. Commun.*, 2005, 5115.

7 M. S. Kharasch and G. Sosnovsky, *J. Am. Chem. Soc.*, 1958, **80**, 756.

8 (*a*) M. S. Kharasch and G. Sosnovsky, *J. Am. Chem. Soc.*, 1959, **81**, 5819; (*b*) A. L. Beckwith and A. A. Zavistas, *J. Am. Chem. Soc.*, 1986, **108**, 8230.

9 (*a*) A. S. Gokhale, A. B. E. Minindis and A. Pfaltz, *Tetrahedron Lett.*, 1995, **36**, 1831; (*b*) M. B. Andrus, A. B. Agrade, X. Chen and M. G. Pamment, *Tetrahedron Lett.*, 1995, **36**, 2945; (*c*) K. Kawasaki, S. Tsumura and T. Katsuki, *Synlett*, 1995, 1245; (*d*) A. Levina and J. Muzart, *Tetrahedron: Asymmetry*, 1995, **6**, 147. For reviews, see: (*e*) M. B. Andrus and J. C. Lashley, *Tetrahedron*, 2002, **58**, 845 (*f*) J. Eames and M. Watkinson, *Angew. Chem., Int. Ed.*, 2001, **40**, 3567.

10 S. E. Denmark and C. M. Stiff, *J. Org. Chem.*, 2000, **98**, 5875.

11 M. B. Andrus and Z. Zhou, *J. Am. Chem. Soc.*, 2002, **124**, 8806.

12 (*a*) J. Ratilainen, K. Airola, R. Fröhlich, M. Nieger and K. Rissanen, *Polyhedron*, 1999, **18**, 2265; (*b*) A. S. Antsyshkina, M. A. Porai-Koshits, V. N. Ostrikova, M. Pilkington and H. Stoeckli-Evans, *Eur. J. Inorg. Chem.*, 2002, 1985; (*c*) C. P. Raptopoulou, S. Paschalidou, A. A. Pantazaki, A. Terzis, S. P. Perlepes, T. Lialiaris, E. G. Bakalbassis, J. Mrozinski and D. A. Kyriakidis, *J. Inorg. Biochem.*, 1998, **71**, 15; (*d*) P. Molenveld, J. F. J. Engbersen, H. Kooijman, A. L. Spek and D. N. Reinhoudt, *J. Am. Chem. Soc.*, 1998, **120**, 6726; (*e*) S. Youngme, C. Pakawatchai, H.-K. Fun and K. Chinnakali, *Acta Crystallogr., Sect. C: Cryst. Struct. Commun.*, 1998, **54**, 1586; (*f*) B. Kozlevcar, A. Murn, K. Podlipnik, N. Lah, I. Leban and P. Segedin, *Croat. Chem. Acta*, 2004, **77**, 613; (*g*) R. Grobelny, T. Glowiak, J. Mrozinski, L. Brzozka, W. Baran and P. Tomasik, *Pol. J. Chem.*, 1995, **69**, 559; (*h*) M. B. Meder and L. H. Gade, *Eur. J. Inorg. Chem.*, 2004, 2716.

13 S. Bellemin-Laponnaz and L. H. Gade, *Angew. Chem., Int. Ed.*, 2002, **41**, 3473.

14 M. Honma, T. Sawada, Y. Fujisawa, M. Utsugi, H. Watanabe, A. Umino, T. Matsamura, T. Hagihara, M. Takano and M. Nakada, *J. Am. Chem. Soc.*, 2003, **125**, 2860.

15 P. T. Beurskens, G. Beurskens, R. de Gelder, S. G. Granda, R. O. Gould, R. Israel and J. M. M. Smits, *DIRDIF-99*, University of Nijmegen, The Netherlands, 1999.

16 G. M. Sheldrick, *SHELXS-86*, University of Göttingen, Germany, 1986.

17 G. M. Sheldrick, *SHELXL-97*, University of Göttingen, Germany, 1997.

18 A. L. Spek, *J. Appl. Crystallogr.*, 2003, **36**, 7.



 