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Preparation, structure and catalytic activity of copper(II) complexes of novel 4,4′-BOX ligands

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ABSTRACT

This Letter details the synthesis of two new 4,4′-bisoxazoline (BOX) ligands. The copper(II) complex of one of the new ligands is structurally determined. The catalytic performance of the copper(II) complexes of the novel ligands, and that of our recently described phenyl AraBOX ligand in Diels–Alder reactions are reported. We have used the structural information to propose an explanation of a curious variation in the diastereoselectivity obtained in the case of one ligand complex.

Metal complexes of oxazoline-based ligands have proved to be very effective catalysts for asymmetric synthesis.[1,2] Among these ligands the bisoxazolines have been very successful since their introduction in the early 1990s.[3–5] Metal complexes of bisoxazoline ligands are both active and stereoselective catalysts in reactions such as aldol condensations,[6–8] cyclopropanations,[9–11] ene reactions[12–14] and Diels–Alder cycloadditions,[15–18] amongst many others. In all the bisoxazolines reported to date the bulky groups at the chiral centres exert their influence on the reaction outcome from a position external to the metallocycle formed on complexation of the metals via the oxazoline nitrogens. We have prepared ligands where the chiral centres are internal to the metallocycle formed in the catalytic complex (Fig. 1). This arrangement is somewhat reminiscent of the Salen-type complexes.[19] We also hope that ultimately these ligands will address one problem which occurs with standard BOX ligands. Regulating the electron density of the oxazoline rings in standard BOX ligands is difficult because of the potential for migration of the double bonds into conjugation. This factor has traditionally limited the use of methylene-bridged boxes and has led to the use of *gem* dimethyl-substituted bridges. The so called AraBOX and XyliBOX ligands cannot undergo such a migration. This concept will be developed in further publications. Herein we report our initial catalytic results.

The closest related ligands to those reported here are probably the spiroBOX of Sasai[20] (synthesised as the racemate) and the so-called BIOX ligands.[21] These ligands differ quite radically in structure from the 2,2′-BOX which has been so successful in stereoselective synthesis. These spiroBOX and BIOX ligands have, however, to date found limited application in synthesis.

Recently we reported that arabitol could be used as a chiral starting material in the synthesis of a novel C_2-symmetric *O*-silyl bis β-aminoalcohol **7**, that could serve as a precursor for a new class of bisoxazoline, and abbreviated to the 'AraBOX' ligand.[22]

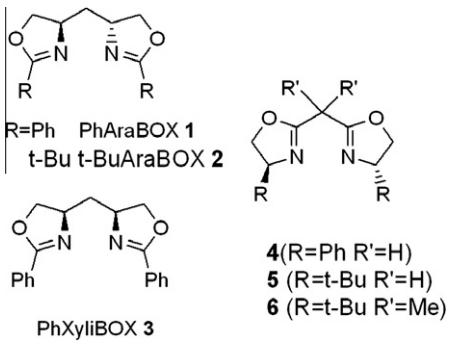

Figure 1. The 4,4′-BOX ligands reported herein (left) and 'traditional' 2,2′-BOX ligands (right).

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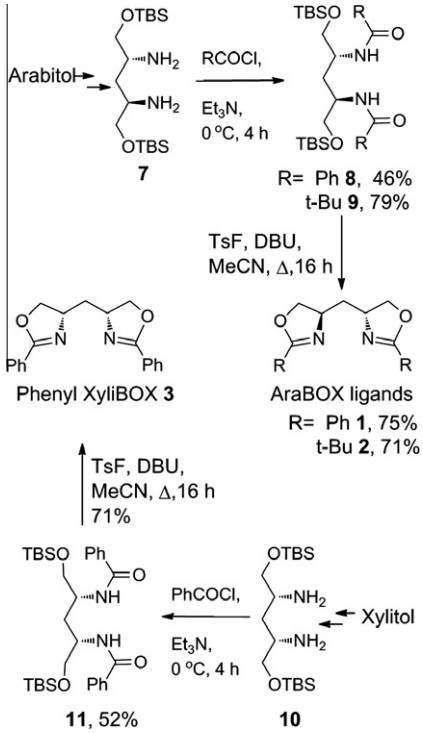


Scheme 1. Synthetic routes for the preparation of AraBOX and XyliBOX Ligands.

We also showed that, via an efficient one-pot tandem deprotection/activation/ring-closure (DARC) reaction, phenyl AraBOX **1** could be prepared from benzyl amide.

This methodology has now been expanded to the first synthesis of the *tert*-butyl-substituted AraBOX ligand **2** (Scheme 1). The previously reported intermediate diamine was treated with the *tert*-butyl-substituted acid chloride giving the diamide **9** in 79% yield.[23] Using a one-pot tandem DARC reaction, the *tert*-butyl-substituted AraBOX ligand **2** was isolated in 71% yield.[24] The DARC reaction involves the use of tosyl fluoride to both deprotect the silyl-protected alcohols and activate them as the tosylates. DBU also plays a dual role by acting as a catalyst for the deprotection step and as a base in the in situ ring closure.

We have also expanded this methodology to synthesise the *meso* phenyl XyliBOX ligand **3** which, using a similar synthesis, is derived from xylitol.

Having synthesised the three ligands, our attention now turned to the metal complexes of the ligands and their catalytic activity and selectivity. Complexation of the phenyl XyliBOX ligand **3** with copper(II) chloride followed by careful crystallisation resulted in the isolation of crystals of the Cu(PhXyliBOX)Cl_2 complex which were suitable for X-ray crystal structure determination (Fig. 2).[25] The X-ray structure shows complexation through the nitrogens and the non-planarity of the BOX due to the chirality of the centres within the metallocycle. The geometry around the copper centre was found to be square planar.

We decided to use the Diels–Alder cycloaddition reaction as the first test of the catalytic performance of complexes derived from our ligands. Copper(II) complexes of both phenyl AraBOX and *tert*-butyl AraBOX were tested as catalysts in the Diels–Alder cycloaddition of cyclopentadiene with 7-crotonoyl-2-oxazolidinone (Table 1).[26] The results where the 2,2′-BOX ligands **4**, **5** and **6** were used under similar conditions, as reported by Takacs et al.,[27] are included for comparison.

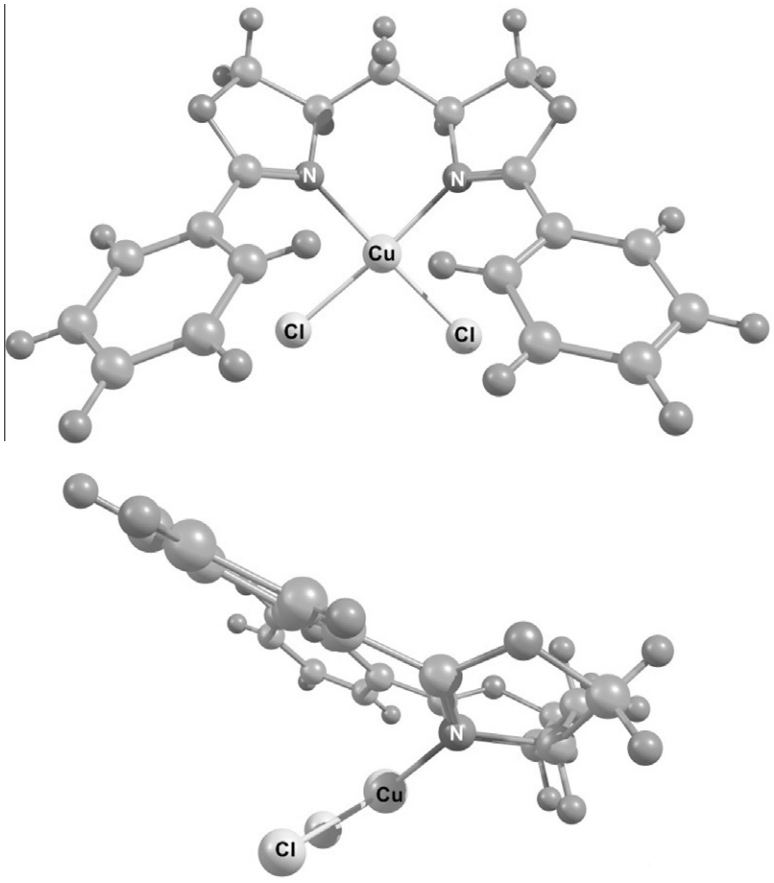
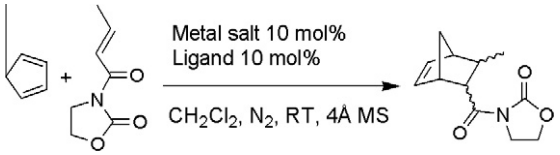


Figure 2. Two comparative views of the X-ray crystal structure of the Cu(PhXyliBOX)Cl_2 complex.

Table 1
Cu(II)AraBOX complex catalysed Diels–Alder reaction



Ligand	Metal source	Conversion %	*Endo*/*exo*	ee *endo*
1 (*R*)	$Cu(OTf)_2$	60	70/30	44 (*S*)
1 (*R*)	$Cu(ClO_4)\cdot 6H_2O$[a]	4	—	—
1 (*R*)	$Cu(ClO_4)\cdot 6H_2O$	90	70/30	53 (*S*)
1 (*R*)	$Cu(SbF_6)_2$	52	70/30	—
1 (*R*)	$Cu(SbF_6)_2$ (40 h)	99	80/20	7 (*S*)
2 (*R*)	$Cu(OTf)_2$	60	77/23	12 (*S*)
2 (*R*)	$Cu(ClO_4)\cdot 6H_2O$			
3	$Cu(OTf)_2$	96	59/41	
4 (*R*)	$Cu(OTf)_2$[a]	99	90/10	22 (*R*)[27]
5 (*S*)	$Cu(OTf)_2$[a]	90	85/15	8 (*S*)[27]
6 (*S*)	$Cu(OTf)_2$[a]	90	87/13	76 (*S*)[27]

[a] No molecular sieves used.

In the case of the phenyl AraBOX ligand **1**, copper(II) complexes with the triflate or perchlorate anion gave encouraging results, with 44% and 53% ee, respectively. The conversion was better when the perchlorate salt was used.

Encouragingly, the first application of these ligands in a catalytic context gave a higher enantioselectivity (with the triflate salt) than those reported with **4** and **5**, which are the two established BOX ligands. The enantioselectivity reported with BOX **6**, possibly the best known and most widely used BOX ligand, is somewhat better, but considering these as first generation ligands, the results certainly indicate promise.

In the case of the *tert*-butyl AraBOX ligand **2** the triflate-based complex showed reduced selectivity giving only 12% ee. Though it is disappointing, this does compare with the performance of the BOX **5** under similar conditions.

Interestingly, we see in the case of both ligands **1** and **2** that the complex derived from the *R* ligand gives the *S* product whereas the complexes derived from the 2,2′-BOX ligands **3, 4** and **5** give the same enantiomer of the product as the ligand was employed.

The results with *meso* **3** were interesting in terms of the diastereoselectivity of the reaction. The selectivity in this case is atypical in the large amount of the *exo* product produced. The copper(II) complexes of AraBOX ligands give diastereoselectivities more typical of those seen with BOX ligands. We propose that the increase in *exo* product formation is due to secondary orbital interactions between the carbonyl of the co-ordinated dienophile and the XyliBOX ligand.[28] This interaction in effect turns off secondary orbital interactions between the same carbonyl and the incoming cyclopentadiene which are, in general, responsible for favouring the kinetically favoured *endo* product over the thermodynamically favoured *exo* product. Apparently such interactions are not present in the AraBOX case possibly due to a change in geometry about the metal. We have tested this hypothesis by calculating the activation energy barrier to the Diels–Alder reaction (semi-empirical PM-3). This was accomplished by modelling the *endo* and *exo* products co-ordinated to the copper(II) ligand (both XyliBOX and AraBOX). The Cu(II)(PhXyliBOX) product complex is closely related to the crystal structure mentioned above with the geometry about the copper being square planar. The Cu(II)(PhAraBOX) product complex shows geometry at the copper intermediate between square planar and tetrahedral. We generated an energy profile as the C–C bonds formed, in the Diels–Alder reaction, lengthened allowing us to estimate the activation energy barrier for the forward reaction.

As expected the Cu(II)(PhAraBOX) energy profiles showed a lower activation energy for the reaction leading to the *endo* product as compared with the *exo* product (difference in activation energies $\sim$30 kJ mol^{-1}). This is consistent with the *endo* product being the kinetically favoured product. In the same study, Cu(II)(PhXyliBOX) energy profiles showed effectively the same activation energy for reactions to give both *endo* and *exo* products confirming a decrease in importance of kinetic factors in this case increasing the amount of thermodynamically favoured *exo* product.

In summary, we have successfully synthesised the first three members of the 4,4′-BOX family. The copper(II) chloride complex of the XyliBOX ligand was characterised. We have employed the copper(II) complexes of the new ligands in Diels–Alder cycloadditions reaction obtaining reasonable enantioselectivities. A curious variation in the diastereoselectivity obtained in the case of the XyliBOX-based catalyst can be explained by reference to the likely structure of an intermediate complex and secondary orbital interactions.

Acknowledgement

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23. To a stirring solution of **7** (270 mg, 0.74 mmol) and triethylamine (400 μL, 2.8 mmol) in CH_2Cl_2 (5 mL) was added a solution of trimethylacetyl chloride (300 μL, 2.5 mmol) in CH_2Cl_2 (2 mL) via syringe pump over 6 h. The reaction was quenched by addition of satd aq $NaHCO_3$. The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 5 mL. The combined organic phase was dried over $MgSO_4$, filtered, concentrated in vacuo and purified by column chromatography on SiO_2 (pet. ether/EtOAc; 75:25) to yield **9** (310 mg, 79%).
24. Procedure for the tandem deprotection/activation/ring closure reaction: 4,4′-methylenebis[(4*R*)-2-*tert*-butyl-2-oxazoline] **2**: To a solution of **9** (300 mg, 0.525 mmol) and *p*-toluenesulfonyl fluoride (200 mg, 1.155 mmol) in dry MeCN (8 mL) was added DBU (185 μL, 1.115 mmol). The mixture was stirred at reflux overnight, cooled and concentrated in vacuo. The residue was purified by flash chromatography on SiO_2 (pet. ether/EtOAc; 75:25) to yield the desired AraBOX **2** (99 mg, 71%); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.74 (2H, t, *J* = 6.9 Hz),

3.89 (2H, app. t, J = 7.8 Hz), 4.17–4.13 (2H, m), 4.34 (2H, app. t, J = 8.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 27.9, 33.2, 43.3, 64.9, 73.5, 174.2; IR 2924, 1720, 1642, 1080, 779 cm^{-1}; Anal. Calcd for $C_{15}H_{26}N_2O_2$: C, 67.63; H, 9.84; N, 10.52. Found: C, 66.79; H, 10.11; N, 9.92; $[\alpha]_D$ +24.1 (*c* 0.7, MeCN, 23 °C).

25. Crystallographic data (excluding structure factors) for the structure reported in this Letter have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 758186. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: (internat.) +44 1223/336-033; e-mail: deposit@ccdc.cam.ac.uk].
26. Typical procedure for the Diels–Alder reaction: To a flame-dried N_2 filled Schlenk tube was added $Cu(OTf)_2$ (0.033 mmol, 10 mol %), phenyl AraBOX ligand **1** (0.033 mmol, 10 mol %), 4 Å powdered molecular sieves (20 mg) and CH_2Cl_2 (2 mL). This mixture was stirred under N_2 for 90 min at rt. To this stirring catalyst was added 1-(*trans*-crotonoyl)-2-oxazolidinone (51 mg, 0.33 mmol) and freshly distilled cyclopentadiene (0.10 mL, 1.21 mmol). The reaction proceeded for 16 h. A mixture of *endo* and *exo* products was isolated as an oil. The reaction resulted in 60% conversion with an *endo*/*exo* ratio of 70:30. The crude mixture was then purified by column chromatography (pet./EtOAc, 3:2) affording a mixture of *endo* and *exo* products as a colourless oil, from which the enantiomeric excess (ee) of the *endo* diastereomer was found to be 44% (*S*), as measured on the purified product using chiral HPLC (CHIRACEL OD, 254 nm, hexane/*iso*-propyl alcohol, 98:2, 1.0 mL/min), t(*S*) 22.5, t(*R*) 28.5.
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