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4,4′BOX based catalysts: Synthesis, structure and catalytic application

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ABSTRACT

The synthesis of two new 4,4′ bisoxazoline ligands is described. The use of copper complexes of these and three other recently described related ligands as catalysts in a cyclopropanation reaction is discussed. The first structural data on one such chiral copper complex is reported herein.

1. Introduction

2,2′ Bisoxazolines are a highly useful ligand class in the area of asymmetric synthesis [1]. They were first reported more than 20 years ago [2,3] and complexes of these ligands with metals such as copper [4], magnesium [5], zinc [5,6], iron [7], palladium [8] and many others have found wide application in organic synthesis. The reactions to which such complexes have been applied are amongst the most useful in the synthetic chemists arsenal; Diels-Alder [9], cyclopropanations [10,11], ene reactions [12], aldol reactions [13], alkylations [8] etc. Though many variations of the BOX ligands have been reported in general the degree of variation has been limited to the pendant groups on the chiral centers or the substituents at the bridgehead. In this paper we will present results in cyclopropanation chemistry. A general review of this area has recently been published by Pellissier [14].

We have for a number of years been working with BOX ligands [15,16] and thus became interested in their design and ultimately their redesign. We became interested in the prospect of preparing the 4,4′BOX ligands (Fig. 1) because the co-ordination complexes of these ligands with metals would have the chiral centers internal to the metallocycle thus introducing a twist into the ligand reminiscent of the salen ligands. We have recently reported the synthesis of the first members of this new class of ligands derived from Arabitol **1** and **2** and xylitol **3** (Fig. 2) [17].

2. Results and discussion

Though Xylitol presents significant advantages over Arabitol in terms of cost as a starting material it leads to a meso ligand and thus will not function as an asymmetric ligand. Using our experience with the XyliBOX ligand we have now prepared two new ligands **4** and **5** incorporating other chiral moieties into the XyliBOX structure giving it potential for use in asymmetric synthesis. The additional chiral elements in these ligands were derived from chiral butyric acids.

2.1. Synthesis

The new ligands were prepared from the TBDMS protected diaminodialcohol **6** which is prepared from xylitol [17]. The amines were reacted with chiral acid chlorides to form the amides. These amides were isolated in good yield. The amides in turn were cyclised in a tandem DARC reaction [17]. Tosyl fluoride was used to deprotect the alcohols and activate them as the tosylates thus facilitating the ring closure. The DBU facilitates the two steps. The new ligands were isolated in exceptional yield (**4** 70%, 5, 80%) considering the tandem DARC reactions involve 6 separate synthetic steps (Scheme 1).

2.2. Complex characterisation

The rational behind this work demanded that these 4,4′BOX ligands would co-ordinate to metals such as copper in a similar manner to the established 2,2′BOX ligands. Before applying complexes of these ligands to the asymmetric cyclopropanation we decided to try to make a copper complex, grow crystals and endeavour to confirm its structure by X-Ray studies. The phenylAraBOX ligand was complexed with copper(II)chloride and crystals grown from THF. The crystals

Abbreviations: BOX, bisoxazoline ligand; XyliBOX, 4,4′Bisoxazoline whose backbone is derived from Xylitol; AraBOX, 4,4′Bisoxazoline whose backbone is derived from Arabitol; DARC, deprotection, activation, ring closure.

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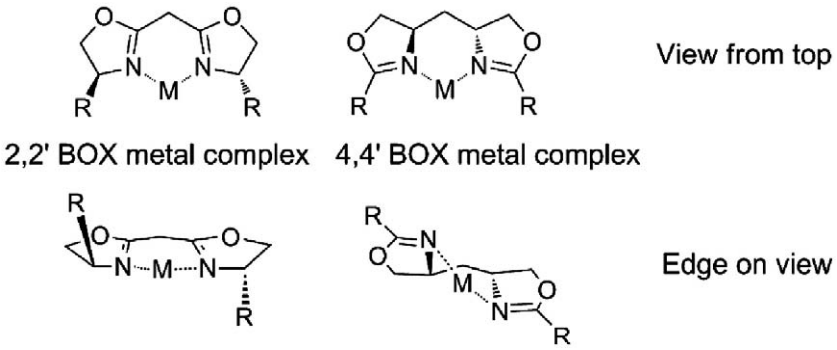


Fig. 1. Views of the metal complexes of standard 2,2′ BOX ligands and those of the 4,4′ BOX ligands which are the subject of this study.

were analysed and the structure solved [18]. Two views **A** and **B** of the structure are shown in Fig. 3 and key data from the crystal structure are outlined in Table 1. It confirms that the co-ordination chemistry of the ligand is as expected and the copper is bound to the two nitrogens. The bond lengths of the co-ordination at 2.0 are slightly longer than those reported by Evans for the 2,2′BOX ligand (1.9).[19] The N–Cu–N angle is ~90° which is slightly less than the same angle in the 2,2′BOX complex (94°). The geometry around the copper is a distorted tetrahedron which is not unexpected given the geometry of similar 2,2′BOX complexes vary between mainly square planar right through to mainly tetrahedral depending on the functionality present. The twist in the complex is also evident showing the effect of having the chiral centers contained within the metallocycle. The twist can be quantified by the torsion angle between the C=N in each planar oxazoline ring. This value of 52° represents a large deviation from the planarity of the 2,2′BOX systems. The unit cell contained six molecules arranged in a spiral the formation of which is probably aided by π stacking. Views of the unit cell **C** and **D** are also shown in Fig. 3.

2.3. Application of copper complexes to the catalysis of the cyclopropanation reaction

The copper complexes of ligands **1**–**5** were utilised as catalysts in the cyclopropanation of styrene using ethyl diazoacetate (Scheme 2). The results obtained are presented in Table 2. The catalyst loading used was 1% relative to the limiting reagent, ethyl diazoacetate.

The conversion was in general >90% except in the case of the MePrXyliBOX where it dropped to 79%. The use of $Cu(OTf)_2$ did not alter the result in this regard. The *trans*:*cis* ratio typically was around 60:40 with only the PhXyliBOX **3** and MePrXyliBOX **4** (entries 3 and 4) showing little or no selectivity. The asymmetric catalysts did give modest enantioselectivities in both the *cis* and *trans* isomers. The highest ee being achieved in the *cis* diasteromer with the PhAraBOX ligand (entry 1) at 32%ee. In the *trans* case the highest ee achieved was with the MePrXyliBOX ligand (entry 5) at 26%ee.

It is interesting to note that ligands (*R*)-PhAraBOX **1** and (*S*)-^{t}BuAraBOX **2** which have opposite configuration at the chiral centers selectively form the same stereoisomers of product. This so-called reversal in selectivity is not unknown in oxazoline ligand chemistry [20,21] and generally is thought to be due to a change in conformation in co-ordination to the metal center [22]. Reversals of this type are seen for Diels-Alder reactions but are much rarer in cyclopropanation reactions [23]. The ee's achieved are undoubtedly modest, particularly when viewed in tandem with entries 7 and 8 in the table which show reported results for the same reaction using the copper complexes of the 2,2′BOX ligands **9** and **10** [24,25]. In these cases superior enantioselectivity was obtained though the diastereoselectivity is far from ideal. It is important to note that this is the first generation of these ligands and they do provide a basis on which to develop structure activity relationships and design the next generation of such catalysts. For instance it is evident from the XyliBOX ligands that chirality on the pendant arms of the ligands does have an effect on the selectivity of the catalysts. A logical step would be the inclusion of such a sidearm on the already chiral AraBOX framework to enhance selectivity. Such a study is in train in our laboratory.

3. Conclusion

We have completed the synthesis of two new 4,4′BOX ligands. In addition we have confirmed the structure of the copper complex of one such ligand by X-ray analysis. We have applied copper complexes of all five reported 4,4′BOX ligands to the asymmetric catalysis of a cyclopropanation. In the case of two ligands we have observed an unusual reversal of selectivity in the cyclopropanation reaction. The ee's achieved in both cases though modest are encouraging for the development of this catalyst class. The two new ligands reported in this communication are synthesised from the cheap and widely available xylitol or 'wood alcohol' and chirality is introduced late on in the synthetic scheme which is a significant development economically on our previous arabitol based ligands. We continue to develop these and related ligands and applications of the ligands already reported and we will report these shortly.

4. Experimental

All chemicals were purchased from Aldrich Chemical Company and generally used without further purification. Melting points were measured on a Stuart Scientific SMP3 apparatus. IR spectra were

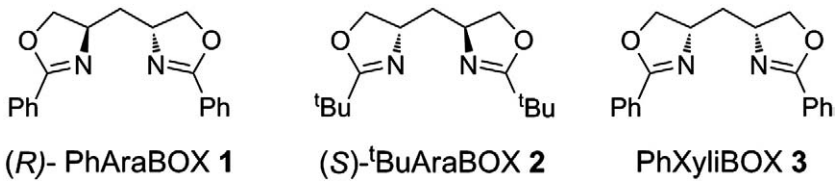
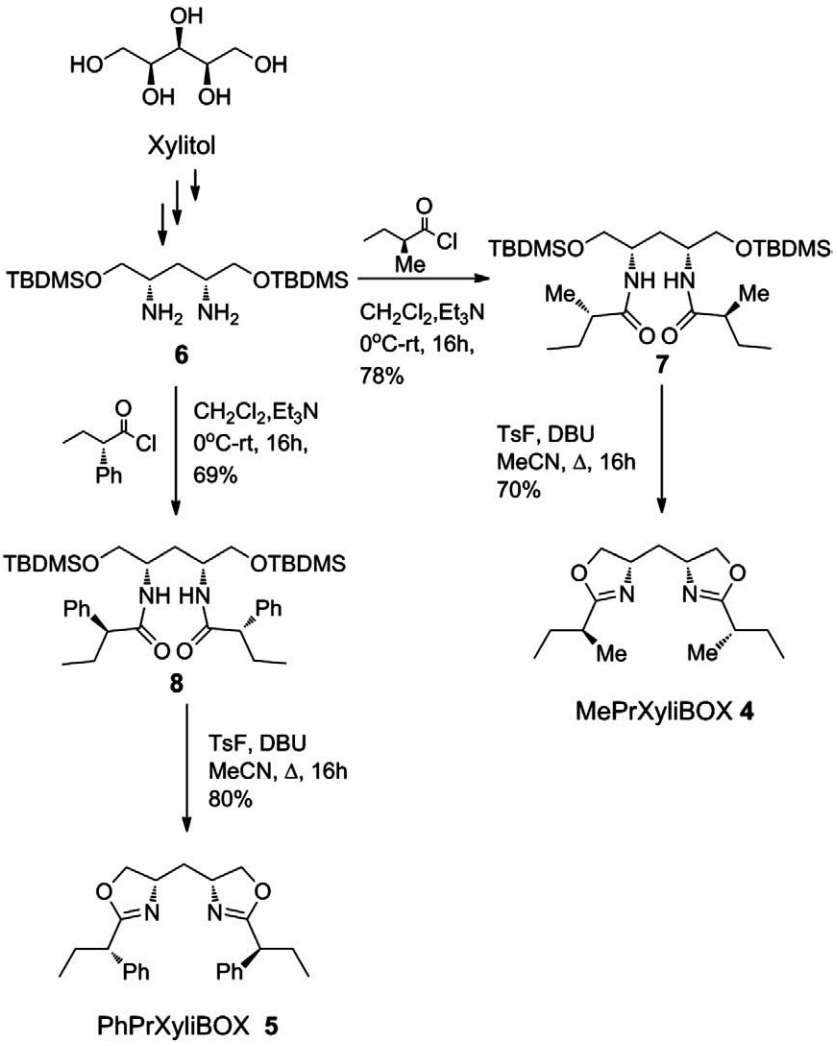


Fig. 2. Previously reported 4,4′ BOX ligands **1–3** which are used in this study.



Scheme 1. Previously reported 4,4′BOX ligands and the synthesis of the two new ligands **4** and **5.**

measured on a Perkin Elmer Spectrum 1000 FT-IR, or a Perkin Elmer Spectrum One FT-IR. Optical rotations were measured on The polarimeter is a UniPOL L1000 polarimeter at 589 nm (Na) in a 10 cm cell. Thin layer chromatography (TLC) was carried out on precoated silica gel plates (Merck 60 F254); column chromatography was conducted using Merck silica gel 60 or Apollo Scientific silica gel 40–63 μ. ^{1}H NMR (400 MHz), ^{13}C NMR (100 MHz), were recorded on a JEOL ECX-400 NMR spectrometer. All spectra were recorded at probe temperatures (~20 °C) using tetramethylsilane as internal standard. All chiral liquid–liquid chromatography (HPLC) was carried out on a Varian instrument, with an UV/Vis detector at the specified wavelength, with a Daicel CHIRALCEL OD 0.46 cm_×25 cm column, under conditions described for each experiment. All chiral GC analysis was carried out on a Varian 3900 instrument, using helium as the mobile phase and a FID (Flame Ionisation Detector), with a CYCLODEX-β 0.25 mmΦ×30 m column under conditions described for each experiment. Acid chlorides were prepared with reference to a previous report [26].

4.1. Synthesis of bis amides 7 and 8

4.1.1. Synthesis of bis amide 7

To a stirring solution of **6** (700 mg, 1.93 mmol) and triethylamine (593 μL, 4.25 mmol) in CH_2Cl_2 (20 mL) at 0 °C was added (S)-(+)-2-methylbutyric acid chloride (513 μL, 4.25 mmol). The mixture was stirred at room temperature overnight, concentrated *in vacuo* and purified by column chromatography on SiO_2 (Pet. Ether-EtOAc; 80:20) to yield **7** (800 mg, 78%) as a white solid. $[\alpha]_D$ −12.3 (*c* 0.007, MeCN, 23 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.13–6.07 (2H, m, 2×N*H*), 3.92–3.89 (2H, m, 2×C*H*N), 3.72–3.66 (2H, m, one of CH_2OSi), 3.57–3.53 (2H, dd, *J* = 10.0, 4.5 Hz, one of CH_2OSi), 2.17–2.09 (2H, m, 2×C*H*CH_3), 1.9–1.83 (1H, m, one of CHCH_2CH), 1.71–1.6 (3H, m, one of CHCH_2CH, CH_2CH_3), 1.49–1.38 (2H, m, CH_2CH_3), 1.15–1.13 (6H, dd, *J* = 6.9, 1.6 Hz, 2×CH_3CH), 0.94–0.88 (24H, m, 2×*t* bu, 2×CH_3CH_2), 0.07–0.05 [12H, m, 2×Si(CH_3)$_2$]; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 176.4,64.4, 64.0, 47.8, 43.3, 32.9, 27.4, 25.9, 18.3, 17.6, 12.0, −5.3; IR 3292, 2959, 2930, 2858, 1638 cm^{-1}. ESI-HRMS calcd for $C_{27}H_{58}N_2O_4Si_2$ 529.3857, found *m*/*z* 529.3897 $(M–H)^-$.

4.1.2. Synthesis of bisamide 8

To a stirring solution of **6** (670 mg, 1.85 mmol) and triethylamine (566 μL, 4.07 mmol) in CH_2Cl_2 (20 mL) at 0 °C was added (S)-(+)-2-phenylbutyric acid chloride (743 μL, 4.07 mmol). The mixture was stirred at room temperature over night, concentrated *in vacuo* and purified by column chromatography on SiO_2 (Pet. Ether-EtOAc; 80:20) to yield **8** (840 mg, 69%) as a white solid.$[\alpha]_D$ −21.7 (*c* 0.002, MeCN, 23 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.3–7.18 (10H, m, 10×Ar*H*), 6.23 (1H, *t*, *J* = 8.6 Hz, N*H*), 6.08–6.07 (1H, m, N*H*), 3.87–3.32 (6H, m, 2×CH_2OSi, 2×C*H*N), 3.27–3.21 (2H, m, 2×C*H*Ar), 2.21–2.11 (2H, m, one of CH_2CH_3), 1.85–1.72 (2H, m, one of CH_2CH_3), 1.7–1.59 (1H, m,

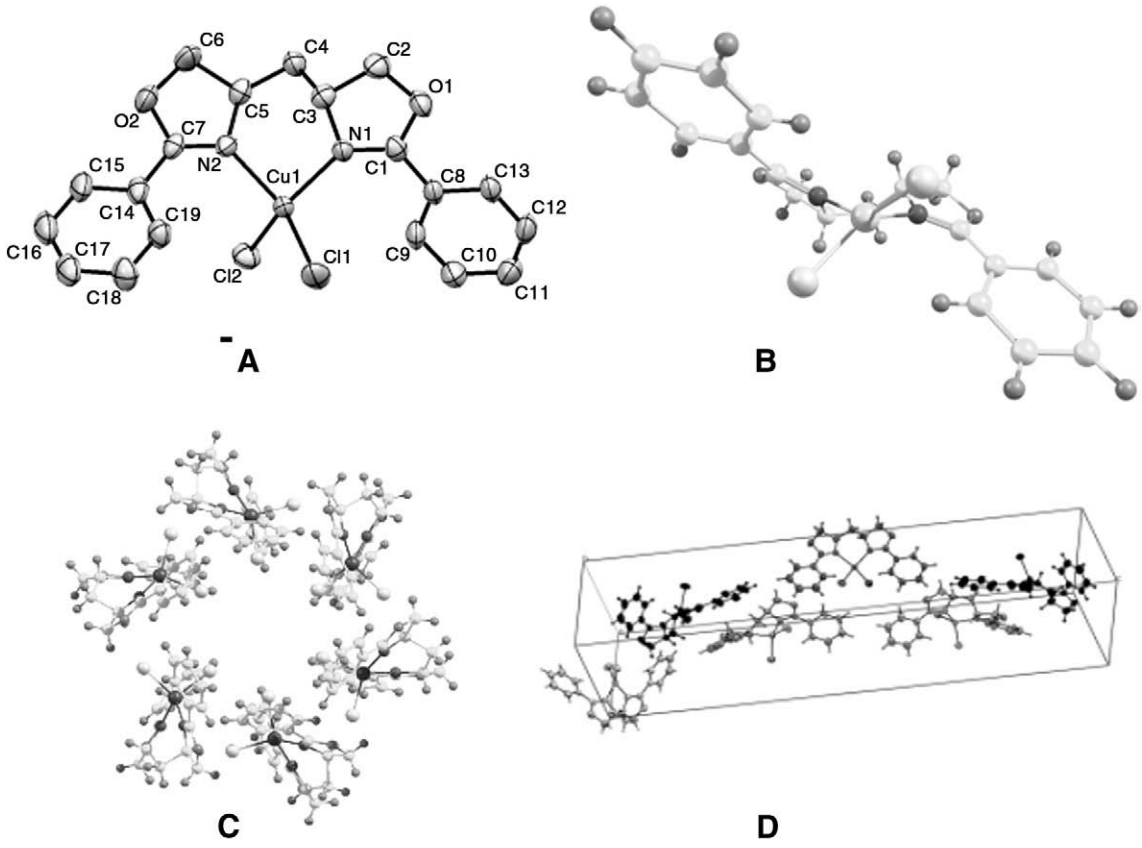


Fig. 3. The X-Ray crystal structure of the PhenylAraBOXCuCl$_2$ complex.

one of CHC*H*$_2$CH), 1.56–1.46 (1H, m, one of CHC*H*$_2$CH), 0.91–0.84 (6H, m, 2×C*H*$_3$CH$_2$), 0.81, 0.79, 0.78, 0.76 (18H, series of singlets due to rotamers, 2×*t*-bu), −0.01–0.17 (12H, series of singlets due to rotamers, 2×Si(C*H*$_3$)$_2$);^{13}C NMR (100 MHz, CDCl$_3$) δ = 173.5, 140.2, 140.0, 128.8, 128.7, 128.1, 64.1, 63.9, 63.7, 55.4, 48.2, 47.9, 32.4, 26.4, 26.2, 25.9, 18.2, 12.5, 12.4, -5.5, −5.6; IR 3305, 2955. 2928, 2857, 1649 cm^{-1}. ESI-HRMS calcd for $C_{37}H_{62}N_2O_4Si_2$ 655.4326 found *m/z* 655.4290 $(M+H)^+$.

4.2. Synthesis of ligands 4 and 5

4.2.1. Synthesis of MePrXyliBOX 4

To a solution of **7** (300 mg, 0.56 mmol) and *p*-toluenesulfonyl fluoride (217 mg, 1.24 mmol) in dry acetonitrile (15 mL) was added DBU (186 μL, 1.24 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; 70:30) to yield desired bis (oxazoline) **4** (105 mg, 70%) as a yellow oil. $[\alpha]_D$ −25.6 (*c* 0.01, MeCN, 23 °C); ^{1}H NMR (400 MHz, CDCl$_3$) δ = 4.3 (2H, m, *J* = 8.8, one of C*H*$_2$O), 4.12–4.23 (2H, m, 2×C*H*N), 3.94 (2H, *t*, *J* = 7.6, one of C*H*$_2$O), 2.34–2.4 (2H, m, 2×C*H*CH$_3$), 1.91–1.98 (1H, m, one of CHC*H*$_2$CH), 1.6–1.68 (3H, m, one of C*H*$_2$CH$_3$, one of CHC*H*$_2$CH), 1.41–1.52 (2H, m, one of C*H*$_2$CH$_3$), 1.14 (6H, d, *J* = 6.9, 2×*CH*CH$_3$), 0.90 (6H, *t*, *J* = 7.5, 2×C*H*$_3$CH$_2$); ^{13}C NMR (100 MHz, CDCl$_3$) δ = 171.4, 72.3, 62.9, 42.2, 35.1, 27.3, 17.4, 11.7; IR 2966, 1663, 976 cm^{-1}. ESI-HRMS calcd for $C_{15}H_{26}N_2O_2$ 267.2072, found *m/z* 267.1971 $(M+H)^+$.

4.2.2. Synthesis of PhPrXyliBOX 5

To a solution of **8** (800 mg, 1.22 mmol) and *p*-toluenesulfonyl fluoride (469 mg, 2.68 mmol) in dry acetonitrile (30 mL) was added DBU (400 μL, 2.68 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; 70:30) to yield desired bis (oxazoline) **5** (380 mg, 80%) as a colourless oil. $[\alpha]_D$ −76.2 (*c* 0.008, MeCN, 23 °C); ^{1}H NMR (400 MHz, CDCl$_3$) δ = 7.29(10H, m, 10×Ar*H*), 4.25 (4H, m, 2×C*H*$_2$O),3.93 (2H, m, 2×C*H*N), 3.44 (2H, m, 2×C*H*Ar) 2.05–2.08 (1.91-2.0, 2H, m, one of CH$_3$C*H*$_2$), (1H, m, one of CHC*H*$_2$CH), 1.82–1.84(2H, m, one of CH$_3$C*H*$_2$), 1.61–1.7 (1H, m, one of CHC*H*$_2$CH), 0.89 (6H, *t*, *J* = 7.3 Hz, 2×C*H*$_3$CH$_2$); ^{13}C NMR (100 MHz, CDCl$_3$) δ = 168.9, 140.2, 128.6, 128, 127.1, 72.5, 62.9, 47.35, 41.8, 27.1, 12.3; IR 2963, 2931, 1658 cm^{-1}. ESI-HRMS calcd for $C_{25}H_{30}N_2O_2$ 389.2229, found *m/z* 389.2218 $(M-H)^-$.

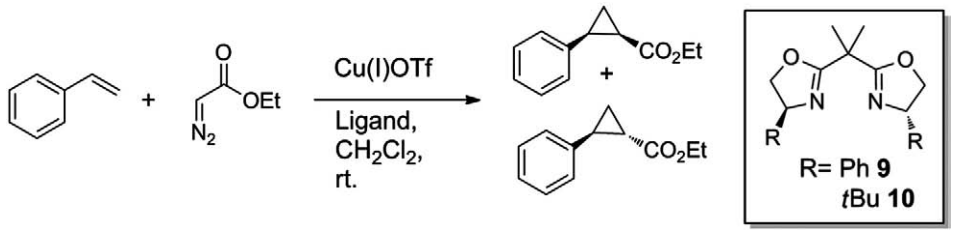
Table 1
Key bond lengths and angles for PhenylAraBOXCuCl$_2$ complex.

Atoms	Bond lengths,
N–Cu	2.004, 2.011
Cl–Cu	2.21, 2.22
Atoms	Bond angle,°
N–Cu–N	89.72
Cl–Cu–Cl	99.68
Atoms	Torsion angles,°
N–Cu–N–Cl	143.50, 98.56
C5 = N1 N2 = C3	52.35 (representing the deviation of the two oxazolines from the one plane)

4.3. Cyclopropanation reaction: general procedure

4.3.1. General procedure for asymmetric cyclopropanation catalyzed by ligand–Cu(I) complexes

A solution of ligand (0.013 mmol) and [Cu(OTf)]$_2 \cdot C_6H_6$ (3 mg, 0.006 mmol) in CH_2Cl_2 (1 mL) was stirred under a nitrogen atmosphere at room temperature for 90 min and transferred through a cotton plug



Scheme 2. Copper catalyzed cyclopropanation of styrene using ethyl diazoacetate.

Table 2
Results for the cyclopropanation of styrene.

	Ligand	Metal salt	Conv %	Trans: *cis*	% ee (*cis*)	% ee (*trans*)
1	(*R*)Ph-AraBOX **1**	Cu(OTf)	99	60:40	32 (1*R*, 2 *S*)	16 (1*R*, 2*R*)
2	(*S*)^{t}Bu-AraBOX **2**	Cu(OTf)	99	62:38	14 (1*R*, 2 *S*)	7 (1*R*, 2*R*)
3	PhXyliBOX **3**	Cu(OTf)	91	48:52	–	–
4	MePrXyliBOX **4**	Cu(OTf)	79	53:47	24 (1 *S*, 2*R*)	24 (1 *S*, 2 *S*)
5	MePrXyliBOX **4**	$Cu(OTf)_2$	80	62:38	31 (1 *S*, 2*R*)	26 (1 *S*, 2 *S*)
6	PhPrXyliBOX **5**	Cu(OTf)	99	59:41	6 (1 *S*, 2*R*)	4 (1 *S*, 2 *S*)
7[24]	Ph-2,2′BOX **9**	Cu(OTf)	98	70:30	54	66
8[25]	*t*-Bu-2,2′BOX **10**	Cu(OTf)	77	77:23	99	99

to flame-dried N_2-filled schlenk. Styrene (690 μL, 5 mmol) was then added. A solution of ethyldiazoacetate (137 μL, 1.2 mmol) in dry CH_2Cl_2 was added over *ca.* 6 h *via* a syringe pump. After the addition was complete, the reaction was stirred for an additional 12 h. The reaction was then concentrated *in vacuo* to afford the crude product. Conversion and *trans*/*cis* ratio were determined by ^{1}H NMR. Flash chromatography of the residue (Petrol-EtOAc; 25:1) provided a mixture of *trans*/*cis* isomers. The enantiomeric excess of each isomer was determined by chiral GC (Cyclodex-B 30 m × 0.252 mm × 0.25 μm).

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References

[1] R. Rasappan, D. Laventine, O. Reiser, Coord. Chem. Rev. 252 (2008) 702–714.
[2] D.A. Evans, K.A. Woerpel, M.M. Hinman, M.M. Faul, J. Am. Chem. Soc. 113 (1991) 726–728.
[3] E.J. Corey, N. Imai, H.Y. Zhang, J. Am. Chem. Soc. 113 (1991) 728–729.
[4] M. Shizuka, M.L. Snapper, Angew. Chem. Int. Ed. (2008) 5049–5051.
[5] J.M. Takacs, D.A. Quincy, W. Shay, B.E. Jones, C.R. Ross, Tetrahedron Asymmetr. 8 (1997) 3079–3087.
[6] M. Schinnerl, M. Seitz, A. Kaiser, O. Reiser, Org. Lett. 3 (2001) 4259–4262.
[7] T. Inagaki, Le.T. Phong, A. Furuta, J.-i. Ito, H. Nishiyama, Chem. - A Eur. J. 16 (2010) 3090–3096.
[8] H. Aït-Haddou, O. Hoarau, D. Cramailére, F. Pezet, J.-C. Daran, G.G.A. Balavoine, Chem. - A Eur. J. 10 (2004) 699–707.
[9] S. Barroso, G. Blay, L. Al-Midfa, M.C. Munìƒoz, J.R. Pedro, J. Org. Chem. 73 (2008) 6389–6392.
[10] E.P. Carreiro, A.J. Burke, J.P.P. Ramalho, A.I. Rodrigues, Tetrahedron Asymmetr. 20 (2009) 1272–1278.
[11] T. Minuth, M. Irmak, A. Groschner, T. Lehnert, M.M.K. Boysen, Eur. J. Org. Chem. (2009) 997–1008.
[12] R. Kolodziuk, C. Goux-Henry, D. Sinou, Tetrahedron Asymmetr. 18 (2007) 2782–2786.
[13] M.J. Fabra, J.M. Fraile, C.I. Herrerias, F.J. Lahoz, J.A. Mayoral, I. Perez, Chem. Commun. (2008) 5402–5404.
[14] H. Pellissier, Tetrahedron 64 (2008) 7041–7095.
[15] C. McDonagh, P. O'Leary, Tetrahedron Lett. 50 (2009) 979–982.
[16] P. O'Leary, N.P. Krosveld, K.P. De Jong, G. Van Koten, R.J.M. Klein Gebbink, Tetrahedron Lett. 45 (2004) 3177–3180.
[17] D. Frain, F. Kirby, P. McArdle, P. O'Leary, Synlett (2009) 1261–1264.
[18] D.A. Evans, D. Seidel, M. Rueping, H.W. Lam, J.T. Shaw, C.W. Downey, J. Am. Chem. Soc. 125 (2003) 12692–12693.
[19] D.A. Evans, G.S. Peterson, J.S. Johnson, D.M. Barnes, K.R. Campos, K.A. Woerpel, J. Org. Chem. 63 (1998) 4541–4544.
[20] P. O'Leary, N.P. Krosveld, K.P. De Jong, G. van Koten, R. Gebbink, Tetrahedron Lett. 45 (2004) 3177–3180.
[21] C. McDonagh, P. O'Leary, Tetrahedron Lett. 50 (2009) 979–982.
[22] J. Thorhauge, M. Roberson, R.G. Hazell, K.A. Jorgensen, Chem. -A Eur. J. 8 (2002) 1888–1898.
[23] M. Bartók, Chem. Rev. 110 (2010) 1663–1705.
[24] T. Portada, M. Roje, Z. Hamersak, M. Zinic, Tetrahedron Lett. 46 (2005) 5957–5959.
[25] J.G. Knight, P.E. Belcher, Tetrahedron Asymmetr. 16 (2005) 1415–1418.
[26] F.L. Weisenborn, J.W. Bolger, D.B. Rosen, L.T. Mann, L. Johnson, H.L. Holmes, J. Am. Chem. Soc. 76 (1954) 1792–1795.