N Ligands

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Chiral Boron-Bridged Bisoxazolines: Readily Available Anionic Ligands for Asymmetric Catalysis**

*Clément Mazet, Valentin Köhler, and Andreas Pfaltz**

Dedicated to Professor Albert Eschenmoser on the occasion of his 80th birthday

The structural motif of the semicorrins **1**[1] has inspired the development of many related chiral ligands for asymmetric catalysis. The closest structural analogues are the bisoxazo-

[*] Dr. C. Mazet, V. Köhler, Prof. A. Pfaltz
Department of Chemistry
University of Basel
St. Johanns Ring 19, 4056 Basel (Switzerland)
Fax: (+41) 61-267-1103
E-mail: andreas.pfaltz@unibas.ch

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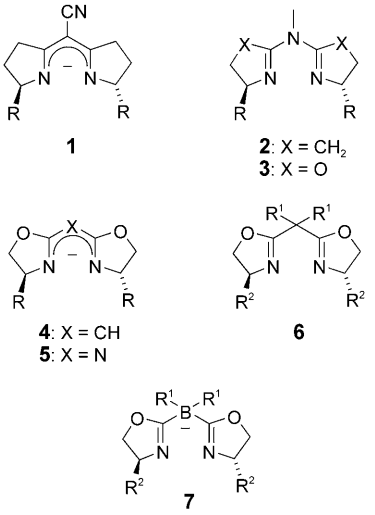
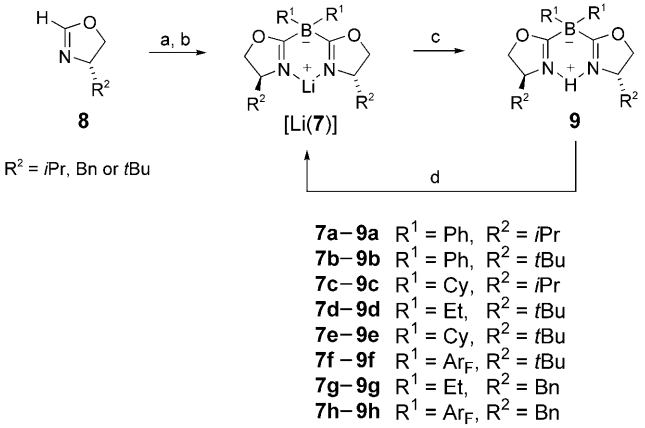
lines **4**[1,2a,b] and the aza bisoxazolines **5**,[3] the backbone of which contains a planar, negatively charged π system. In



addition, neutral variants **2**[1] and **3**,[3] which contain a planar bridging N atom or a neutral dialkylated methylene bridge **6**, have been developed. The ligand charge, the geometry of the bridging atom, and the electronic properties of the coordinating N atoms all influence the reactivity and enantioselectivity of a metal catalyst.[1,3] Among the various semicorrin analogues reported to date, the bisoxazolines (box) **6** stand out as particularly versatile ligands that have been successfully applied in a wide range of metal-catalyzed reactions.[2] As a further variation of this structural motif, we report herein a class of readily available, anionic bisoxazoline ligands (borabox) **7** that contain a tetrasubstitued B atom that bridges the two oxazoline rings. In contrast to the known anionic ligands **1**, **4**, and **5**, the negative charge in the borabox structure is located in the backbone and the geometry of the bridging atom is tetrahedral as in the neutral box ligand **6**. Anionic ligands of this type that can form neutral zwitterionic complexes with metal cations have recently received increased attention, and a number of N, P, and S ligands which contain tetraorganoborate or indenyl anions as structural elements have been reported.[4–6]

The borabox ligand structure can be readily assembled by reaction of a metalated oxazoline with a dialkyl or diaryl haloborane (Scheme 1). This strategy, which differs from known synthetic approaches to bisoxazolines, is attractive because simple and readily accessible oxazolines **8** can be used as precursors. Lithiation of **8** following the procedure of Meyers and Novachek[7] and subsequent treatment with 0.5 equivalents of haloborane at low temperature led to the lithium salts of bora bisoxazolines **7a–f**. These compounds were isolated in analytically pure form as highly hygroscopic white powders in moderate to good yields, depending on the nature of the substituents at the B atom. The lithium salts could be converted into the protonated ligands **9a–f** by chromatographic workup on silica gel using hexanes/ethyl acetate/triethylamine as the eluent. Regeneration of the lithium salts of **7a–f** was readily accomplished by treatment of



Scheme 1. Synthesis of borabox ligands as the lithium salts of **7a–f** (34–98%) or in their protonated form **9a–f** (44–89%). a) *t*BuLi, −78°C, THF; b) $(R^1)_2BX$ (X = Cl, Br), toluene, −78°C; c) hexanes/EtOAc/Et_3N, SiO_2; d) *n*BuLi, THF, 0°C. Ar_F = 3,5-bis(trifluoromethyl)-phenyl, Cy = cyclohexyl, Bn = benzyl.

compounds **9a–f** with one molar equivalent of *n*-butyllithium in diethyl ether at room temperature.

A wide variety of sterically and electronically different ligands can be prepared by structural variation of the haloborane and the oxazoline **8**. The borabox ligands readily form stable complexes with transition-metal ions, such as Cu^{II}, Zn^{II}, Pd^{II}, Rh^{I}, and Ir^{I} ions, starting from the lithium salts [Li(**7**)] or the protonated precursors **9** in the presence of a base such as K_2CO_3. Figure 1 shows the crystal structure of the homoleptic Cu^{II} complex of **7a** alongside a Cu^{II} complex derived from the analogous diphenylmethyl-bridged box derivative **6a**.[8,9]

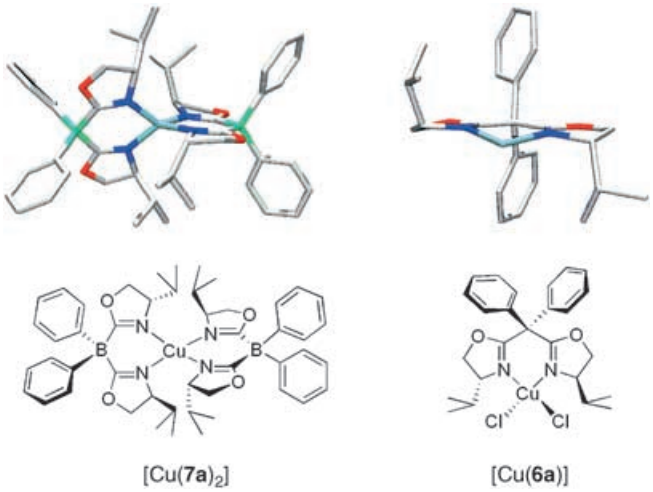


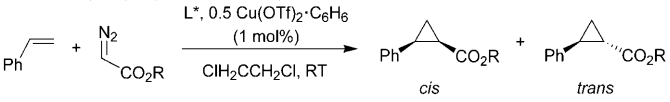
Figure 1. Crystal structures of complexes [Cu(**7a**)$_2$] and [$CuCl_2$(**6a**)]. Hydrogen and chlorine atoms have been omitted for clarity.

In contrast to the slightly distorted boatlike conformation of **6a**, the borabox ligand **7a** adopts an almost flat conformation. The average bond lengths between the bridging atom and the oxazoline rings, as well as the bite angle, are

larger in complex [Cu(**7a**)$_2$] than in complex [CuCl$_2$(**6a**)] (B–C$_{oxa}$ = 1.61 Å versus C–C$_{oxa}$ = 1.50 Å (oxa = oxazoline), and N-Cu-N = 94.5° versus N-Cu-N = 89.9°). As a consequence, the substituents at the stereogenic centers in [Cu(**7a**)$_2$] are farther away from the metal ion than in [CuCl$_2$(**6a**)].

As a first test of the borabox ligands, we carried out a comparative study of the cyclopropanation of styrene with Cu^I catalysts prepared in situ from CuOTf (Tf = trifluoromethanesulfonyl), lithium salts of **7a–f**, and analogous box ligands **6a–b**, and **6d** (Table 1).[1,10] In this reaction, which

Table 1: Cyclopropanation of styrene.



Entry	Ligand	R^1	R^2	Diazo ester (R)	*cis*/*trans*	*cis*[a] *ee* [%]	*trans*[a] *ee* [%]	Yield [%][b] (*cis*+*trans*)
1	**6a**[c]	Ph	*i*Pr	Et	36:64	54	51	85
2	**6b**[d]	Ph	*t*Bu	Et	33:67	91	89	72
3	**6d**[d]	Me	*t*Bu	Et	27:73	97	99	77
4	**7a**	Ph	*i*Pr	Et	29:71	58	65	77
5	**7b**	Ph	*t*Bu	Et	30:70	66	70	84
6	**7c**	Cy	*i*Pr	Et	32:68	24	33	68
7	**7d**	Et	*t*Bu	Et	28:72	59	72	75
8	**7e**	Cy	*t*Bu	Et	28:72	78	66	79
9	**7f**	Ar$_F$	*t*Bu	Et	32:68	68	77	89
10	**6b**	Ph	*t*Bu	*t*Bu	21:79	93	90	70
11	**6d**[e]	Me	*t*Bu	*t*Bu	19:81	93	96	75
12	**7b**	Ph	*t*Bu	*t*Bu	15:85	77	67	77
13	**7d**	Et	*t*Bu	*t*Bu	13:87	76	73	65
14	**7e**	Cy	*t*Bu	*t*Bu	9:91	82	73	63
15	**7f**	Ar$_F$	*t*Bu	*t*Bu	17:83	86	92	65
16	**6d**[d]	Me	*t*Bu	BHT	4:96[f]	–	99	85
17	**7f**	Ar$_F$	*t*Bu	BHT	1:99[f]	–	98	89

[a] Determined by GC or HPLC analysis (see the Supporting Information). [b] After chromatography. [c] Ligands **6a**, **b** were prepared from 2,2-diphenylmalonyl chloride (see the Supporting Information for detailed procedures). [d] In good agreement with reference [11b]. [e] Taken from reference [11b]. [f] Determined by ^{1}H NMR spectroscopic analysis. L* = ligand.

often serves as a benchmark for new ligands, the borabox complexes showed similar reactivities to the corresponding box complexes.[11] As observed for the box ligands, bulkier *tert*-butyl substituents at the stereogenic centers of the borabox ligands induced higher *ee* values than isopropyl groups. However, this effect was less pronounced than in the box series. In the reaction with ethyl diazoacetate, the borabox catalysts gave only moderate enantioselectivities. On the other hand, with *tert*-butyl diazoacetate and 2,6-di-*tert*-butyl-4-methylphenyl (BHT) diazoacetate, the performance of the borabox ligands was much better, with ligand **7f** rivaling the most efficient box derivative **6d**. Consistent with previous studies, the more bulky esters gave much higher ratios of *trans*/*cis* isomers. The best result, 98% *ee* and almost perfect diastereoselectivity, was obtained in the reaction of the BHT ester with borabox derivative **7f** (entry 17).

The borabox catalyst [Cu(**7f**)] also performed well with other alkenes (Table 2). Overall, the enantioselectivities were

Table 2: Cyclopropanation of different alkenes.

Entry	Ligand	R^1	R^2	R^3	*cis*/*trans*[a]	*trans*[b] *ee* [%]	Yield[c] [%] (*cis*+*trans*)
1	**6d**	Me	*t*Bu	Ph	4:96	99	85
2	**7f**	Ar$_F$	*t*Bu	Ph	1:99	98	89
3	**6d**	Me	*t*Bu	*p*-MeOC$_6$H$_4$	4:96	96	35[d]
4	**7f**	Ar$_F$	*t*Bu	*p*-MeOC$_6$H$_4$	4:96	97	65[d]
5	**6d**	Me	*t*Bu	*p*-FC$_6$H$_4$	4:96	99.4	89
6	**7f**	Ar$_F$	*t*Bu	*p*-FC$_6$H$_4$	1:99	99.5	91
7	**6d**	Me	*t*Bu	PhCH$_2$	7:93	99	ng[e]
8	**7f**	Ar$_F$	*t*Bu	PhCH$_2$	8:92	97	66
9	**6d**	Me	*t*Bu	*n*-hexyl	2:98	99	51[d]
10	**7f**	Ar$_F$	*t*Bu	*n*-hexyl	1:99	95	68[d]

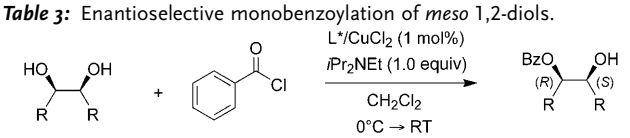
[a] Determined by ^{1}H NMR spectroscopic analysis. [b] Determined by HPLC (see the Supporting Information). [c] After chromatography; average of two runs. [d] Reaction time not optimized. [e] ng = not given; results taken from reference [11a].

similar to those obtained with box derivative **6d**, but in several cases the *trans* selectivitiy of the borabox catalyst was higher (compare entries 1, 5, and 9 with 2, 6, and 10, respectively).

To explore further the potential of the borabox ligands, we studied the Cu-catalyzed enantioselective monobenzoylation of *meso* 1,2-diols, a reaction recently reported by Matsumura et al. (Table 3).[12]

The monobenzoylated products were obtained in good yields (62–83%) under the optimized conditions. The borabox derivative **9h** proved to be the most effective ligand for all three substrates with *ee* values of 76, 90, and 94% being obtained. The corresponding benzyl-substituted bisoxazoline

Table 3: Enantioselective monobenzoylation of *meso* 1,2-diols.



Entry	Ligand	R^1	R^2	*meso* 1,2-diol	Yield [%][a]	*ee* [%][b]
1	**6c**	Me	Bn		70	33[c]
2	**6e**	Me	Ph		58	13
3	**9g**	Et	Bn		79	40
4	**9h**	Ar$_F$	Bn		73	76
5	**6c**	Me	Bn		74	85[c]
6	**6e**	Me	Ph		62	22
7	**9g**	Et	Bn		75	47
8	**9h**	Ar$_F$	Bn		83	90
9	**6c**	Me	Bn		68	84[c]
10	**6e**	Me	Ph		58	86
11	**9g**	Et	Bn		62	92
12	**9h**	Ar$_F$	Bn		65	94

[a] Average of two runs. [b] *ee* and absolute configuration values were determined by HPLC according to the literature data (see the Supporting Information). [c] The enantiomer of **6c** was used in this case and, therefore, a product of opposite configuration was obtained.

6c and the diphenyl analogue **6e**, which in the study of Matsumura et al.[12a] had given the best results, induced distinctly lower enantioselectivities.

In summary, we have developed a new class of anionic, boron-bridged analogues of the box ligands. These ligands are of interest because they are anionic with the negative charge located in the backbone, but otherwise closely resemble the netural box ligands **6**. The results obtained in the asymmetric cyclopropanation and, especially, in the desymmetrization of *meso* diols point to a considerable potential for borabox ligands in asymmetric catalysis.

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[8] X-ray crystal-structure analysis of [Cu(**7a**)$_2$]: crystallized from CH_2Cl_2/Et_2O/hexane, $C_{48}H_{60}B_2Cu_1N_4O_4$, $M_r = 842.20$, $F(000) = 2684.448$, blue–green plates, $0.06 \times 0.28 \times 0.30$ mm^3, hexagonal, space group $P6_122$, $Z = 6$, $a = 10.9216(17)$, $b = 10.9216(17)$, $c = 65.042(9)$ Å, $\alpha = 90$, $\beta = 90$, $\gamma = 120°$, $V = 6718.9$ Å^3, $\rho_{calcd} = 1.249$ Mg m^{-3}. The crystal structure was measured on a Enraf Nonius Kappa CCD diffractometer at 173 K using graphite monochromated $Mo_{K\alpha}$ radiation with $\lambda = 0.71073$ Å, $\Theta_{max} = 27.47°$. Minimal/maximal transmission = 0.86/0.97, $\mu = 0.535$ mm^{-1}. The COLLECT suite has been used for data collection and integration. From a total of 28085 reflections, 5088 were independent (merging $r = 0.18$). From these, 2731 were considered as observed ($I > 2.00\sigma(I)$) and were used to refine 268 parameters. The structure was solved by direct methods by using the program SIR92. Least-squares refinement against F was carried out on all non-hydrogen atoms by using the program CRYSTALS. $R = 0.0469$ (observed data), $wR = 0.0413$ (all data), GOF = 1.0429. Minimal/maximal residual electron density = −0.62/0.58 e Å^{-3}. Chebychev polynomial weights were used to complete the refinement. Plots were produced using CAMERON.
[9] X-ray crystal-structure analysis of [$CuCl_2$(**6a**)]: crystallized from CH_2Cl_2/hexane, $C_{26}H_{32}Cl_4Cu_1N_2O_2$, $M_r = 609.91$, $F(000) = 1260$, blue blocks, $0.18 \times 0.21 \times 0.23$ mm^3, orthorhombic, space group $P2_12_12_1$, $Z = 4$, $a = 10.3143(6)$, $b = 15.0541(15)$, $c = 17.8386(11)$ Å, $\alpha = 90$, $\beta = 90$, $\gamma = 90°$, $V = 2769.8(4)$ Å^3, $\rho_{calcd} = 1.462$ Mg m^{-3}. The crystal was measured on a Nonius Kappa CCD diffractometer at 173 K using graphite monochromated $Mo_{K\alpha}$ radiation with $\lambda = 0.71073$ Å, $\Theta_{max} = 31.505°$. Minimal/maximal transmission = 0.78/0.81, $\mu = 1.201$ mm^{-1}. The COLLECT suite has been used for data collection and integration. From a total of 102125 reflections, 9224 were independent (merging $r = 0.07$). From these, 5664 were considered as observed ($I > 3.00\sigma(I)$) and were used to refine 446 parameters. The structure was solved by direct methods using the program SIR92. Least-squares refinement against F was carried out on all non-hydrogen atoms using the program CRYSTALS. $R = 0.0241$ (observed data), $wR = 0.0451$ (all data), GOF = 1.0959. Minimal/maximal residual electron density = −0.53/1.07 e Å^{-3}. Chebychev polynomial weights were used to complete the refinement. Plots were produced using ORTEP III for Windows. CCDC-267175 and -267176 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. Programs used: structure solution: SIR92 A. Almatore, G. Cascarano, G. Giacovazzo, A. Guagliardi, M. C. Burla, G. Polidori, M. Camalli, *J. Appl. Crystallogr.* **1994**, *27*, 435 – 435; collect software: Nonius BV **1997–2001**; structure refinement: D. J. Watkin, C. K. Prout, J. R. Carruthers, P. W. Betteridge, R. I. Cooper, CRYSTALS *Issue 11.*, Chemical Crystallography Laboratory, Oxford, UK, **2001**.
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