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Synthesis of Boron-Bridged Anionic C_2-Symmetric Bisoxazolines and Their Application in Asymmetric Catalysis

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Abstract: Anionic boron-based chiral bisoxazoline ligands, the borabox ligands, are readily prepared from amino alcohols and haloboranes. The highly modular nature of these ligands allows both for electronic and steric tuning of the structure. The high enantioselectivities obtained in various Cu-catalyzed asymmetric reactions and especially in the kinetic resolution of pyridyl alcohols where bisoxazoline ligands exhibit almost no selectivity, point to a considerable potential of borabox ligands in asymmetric catalysis.

Keywords: Asymmetric catalysis · Combinatorial synthesis · Ligand design · N ligand

In 1970, Schrock and Osborn introduced the first neutral zwitterionic metal complex **1** [1]. It was later on shown by Alper and coworkers that this rhodium complex is an effective catalyst both in hydroformylation and silylformylation reactions [2]. More recently, such metal complexes have found increasing attention and a number of structures containing either an indenyl anion **2** [3] or a tetra-organoborate unit **3**-**4** [4] as structural elements have been described in the literature. Some of these systems have been shown to be efficient catalysts or catalyst precursors in reactions such as hydroboration, copolymerization, dehydrogenative silylation or hydrogenation of olefins (Fig. 1) [3–5].

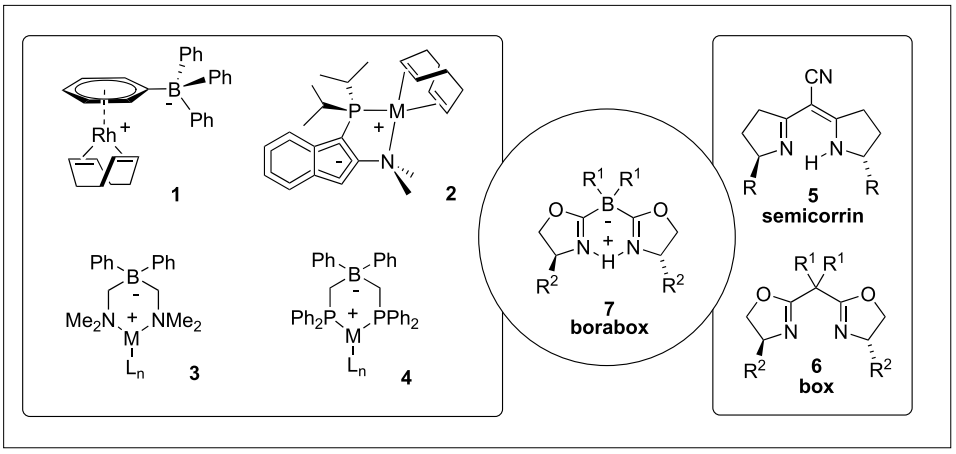

Fig. 1. Historical and conceptual background leading to the design of the borabox ligands

C_2-Symmetric semicorrins **5** were introduced by our group in 1986 and were shown to induce high enantioselectivity levels in the Cu-catalyzed asymmetric cyclopropanation [6] of olefins and Co-catalyzed conjugate reduction of α,β-unsaturated carboxylic acid derivatives [7]. Variation of this structure led to the bisoxazolines **6** (box). These ligands were independently reported by several research groups in the early 1990s [8] and, since then, have established themselves as one of the most versatile ligand classes in asymmetric catalysis [9]. The substituents at the stereogenic centers of ligands **5** and **6** are in close proximity to the coordination sites and shield the metal center from two opposite directions. Therefore, these substituents are expected to exert a strong directing effect on a reaction taking place in the coordination sphere of the metal ion.

We recently became interested in the development of a new anionic bisoxazoline analogue where the two oxazoline rings are bridged by a tetrasubstituted boron atom [10]. Ultimately, these borabox ligands **7** are expected to combine the best features of both bisoxazoline chiral ligands and tetra-organoborate anions for asymmetric catalysis.

It is not realistic to expect one particular ligand to exert perfect enantiocontrol for many substrates in a given reaction or in different reactions. Consequently, it is crucial that the synthesis of any new chiral ligand is flexible and allows straightforward

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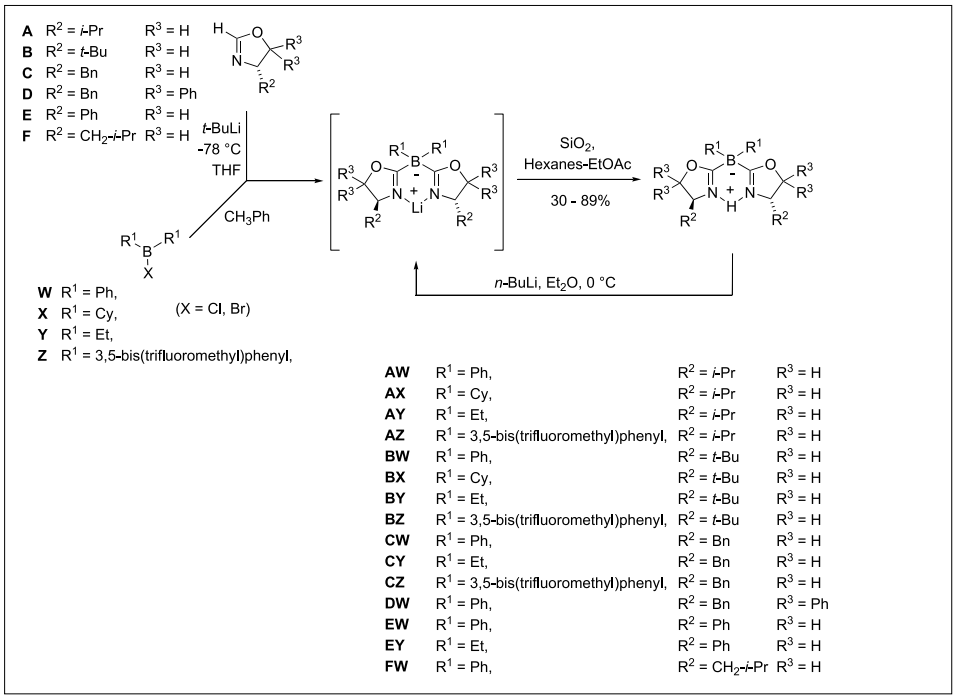

Fig. 2. Synthetic protocol for the synthesis of borabox ligands

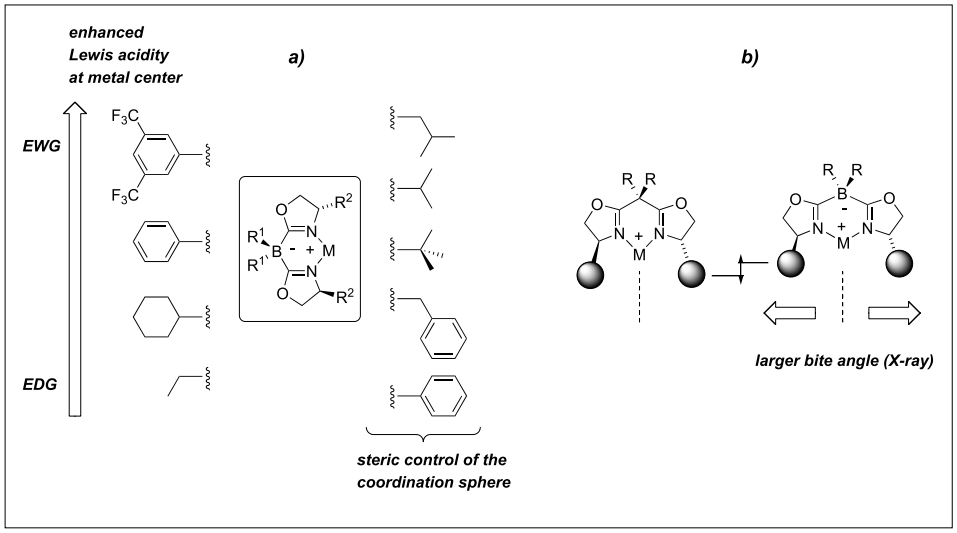

Fig. 3. a) Electronic and steric tuning of the parent borabox structure; b) structural properties

structural optimization. The synthesis of the borabox ligands fits these criteria: lithiation of the H-oxazoline (**A**–**F**) following Meyers' procedure [11] and subsequent quenching with 0.5 equiv. of the appropriate haloborane (**W**–**Z**) led to the lithium salts of the anionic ligands. These salts were usually converted to their protonated analogues by standard chromatographic work-up on silica gel. Regeneration of the Li-salts could be accomplished by reaction of the H-ligands with 1.0 equivalent of *n*-BuLi at 0 °C. Starting from two relatively small libraries of building blocks, a library of 15 different chiral ligands has been built following this procedure (Fig. 2).

Variation of the substituents both at the boron atom and the stereogenic centers of the oxazoline units allows for electronic and steric tuning of the ligand structure. DFT calculations (B3LYP, 6-31G*, LALN2DZ) showed that the Lewis acidic character of the metal center could be varied by changing the nature of the substituent at the central B atom [12]. Introduction of different substituents at the stereogenic center of the oxazoline rings allowed steric tuning of the coordination sphere (Fig. 3a). A series of comparative X-ray analyses allowed us to conclude that the bite angle is larger in borabox transition metal complexes than in analogous box species (Fig. 3b) [10][12].

As an initial evaluation of the potential of the borabox ligands in asymmetric catalysis, we performed a comparative study of the cyclopropanation of alkenes with Cu(i) catalysts derived from borabox and analogous box ligands. Both systems exhibited similar reactivity and furnished the cyclopropanes in good yields. When a diazo-ester having a small substituent was used, the enantioselectivities obtained with the borabox ligands were only moderate. When the bulkier BHT-diazoacetate (BHT = 2,6-di-*tert*-butyl-4-methylphenyl) was used, the enantioselectivities were significantly improved and the ligand possessing perfluorinated aryl groups at the boron atom (**BZ**) compared well with the best box derivative (**6a**) giving comparable yields, diastereo- and enantioselectivities for all the products depicted in Fig. 4. Interestingly, higher *cis*/*trans* ratios were obtained in some cases with borabox ligands. The larger bite angle of the borabox ligand might explain the increased selectivity observed in cyclopropanation reactions when going from ethyl diazoacetate as substrate to bulkier *tert*-butyl and BHT esters whereas box ligands are less sensitive to the size of the diazo-ester employed.

To further investigate the potential of the borabox ligand, we next turned our attention to the Cu-catalyzed benzoylation of racemic alcohols. This method was recently reported by Matsumura *et al.* [13]. After screening and optimization of the reaction conditions, a comparative study between the best box (**6b**) and borabox (**CY**, **CZ**) ligands was carried out for two different substrate classes (Fig. 5). In the case of 1,2-diols **8**, both ligand classes exhibited similar potential, with selectivity factors *S* greater than 200 [14] for 1,2-diphenylethane-1,2-diol **8a**. In the case of pyridyl alcohol derivatives **9**, the borabox ligands clearly outperformed the best box derivative. For all substrates examined the copper box complex exhibited poor selectivities; the selectivities obtained with the borabox ligands were generally higher, although highly dependent on the structure of the substrate. The selectivities obtained for both diols and pyridyl alcohols suggests that interactions between the substituents at the stereogenic centers of the ligand and the substituents α to the donor atoms are important in attaining very high selectivity factors *S* [15].

Another Cu-catalyzed asymmetric transformation we have been interested in is the asymmetric variant of the Kharasch-Sosnovsky allylic oxidation of alkenes [16][17]. The most representative results obtained after screening of the reaction conditions are given in Fig. 6a. With a catalyst loading of 5 mol% Cu and 7.5 mol% ligand and in the presence of 15 mol% of K_2CO_3 as external base, cyclopentene could be se-

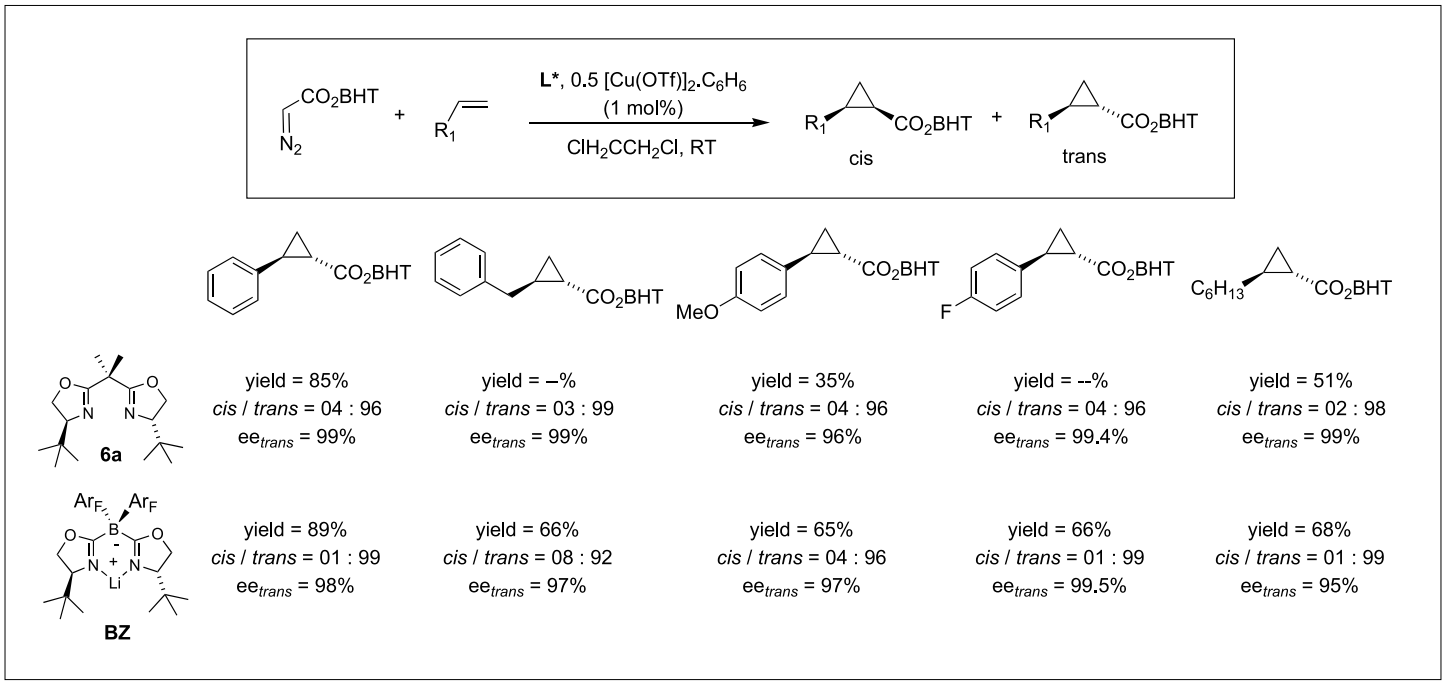

Fig. 4. Comparative study for the asymmetric cyclopropanation of olefins

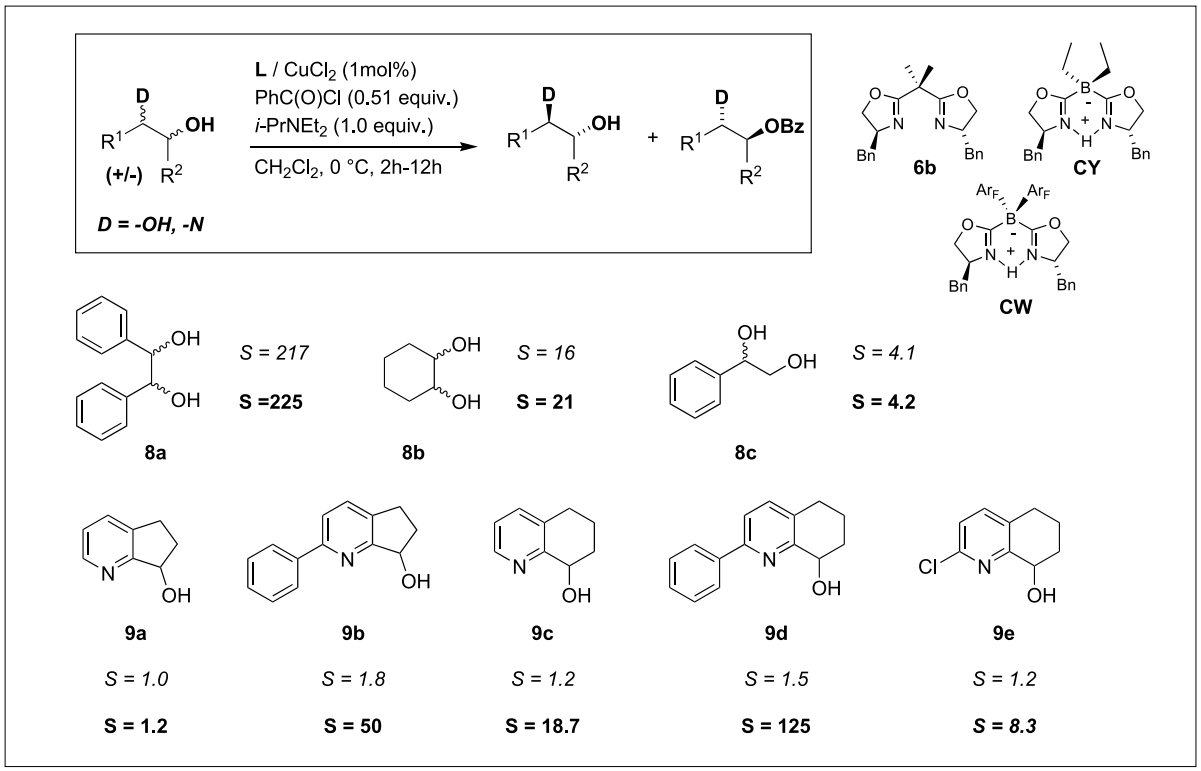

Fig. 5. Kinetic resolution of alcohols. In italic: results obtained with ligand **6b**. In bold: results obtained with borabox ligands **CY** or **CW**.

lectively oxidized in 87% yield and 86% ee after three days. Cyclohexene, a more challenging substrate, furnished the corresponding benzoate in 69% yield and 79% ee after ten days. Aside from the selectivity, the long reaction time is one of the main problems of this catalytic transformation. Interestingly, we have found that increasing the reaction temperature to 80 °C significantly shortens the reaction time with only a small decrease of enantioselectivity. Thus, at 40 °C (*S*)-cyclopent-2-enyl benzoate could be isolated in 79% yield and 81% ee after only eight hours (Fig. 6b) [12]. This is in contrast with carbon-based bisoxazoline ligands that do not exhibit similar stability at elevated temperatures.

The results presented herein show that the borabox ligands are a valuable addition to the bisoxazoline ligand family. Borabox ligands compete well with neutral bisoxazoline ligands in the Cu-catalyzed asymmetric cyclopropanation of olefins, Cu-catalyzed

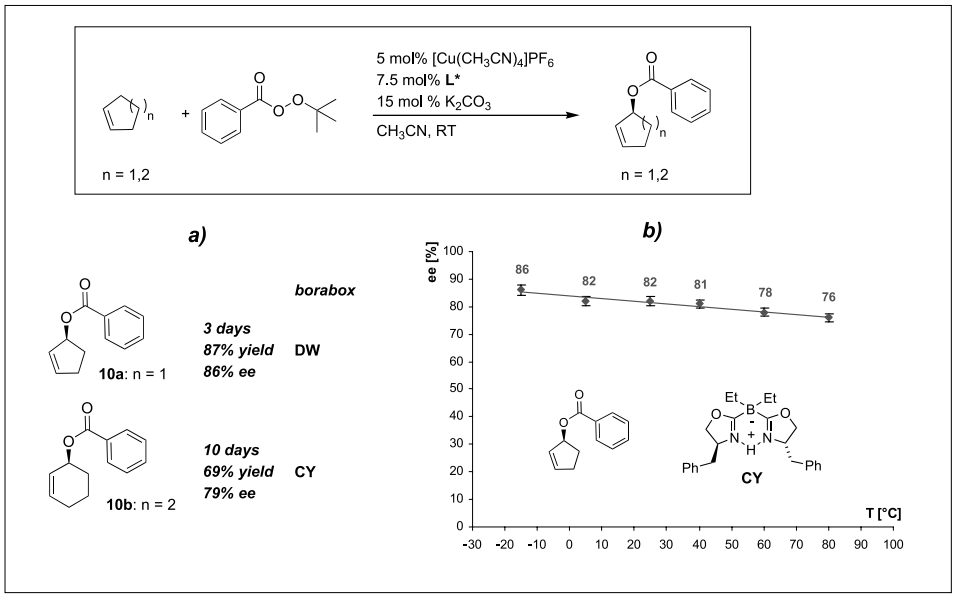

Fig. 6. Asymmetric allylic oxidation. a) Optimized results; b) temperature dependence of the enantioselectivity.

kinetic resolution of racemic 1,2-diols and allylic oxidation. They clearly outperform the box analogues in the kinetic resolution of pyridyl alcohols, a class of substrate that has been used in the synthesis of chiral PN ligands in our laboratory [18].

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