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Design of boron bis-oxazolinate (B-BOXate) complexes: a new class of stable organometallic catalysts

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A new class of remarkably stable B-BOXate complexes has been synthesised, isolated and employed as chiral catalysts for asymmetric reduction of variously substituted prochiral ketones.

Enantioselective catalytic processes have emerged as among the most powerful of methodologies for the preparation of enantiomerically enriched compounds.[1] Of all the catalytic asymmetric procedures, the use of metal complexes bearing chiral ligands is receiving a great deal of attention from the chemical community.[2] In the class of the 'privileged ligands' reported in literature, chiral bis-oxazoline (BOX) ligations have been demonstrated to be effective motifs in many stereocontrolled reactions.[3] Normally, bis-oxazoline metal complexes are designed to behave as chiral Lewis acids, and free coordination sites are available for the incoming electrophile. Our attention was addressed towards the design of stable and coordinatively saturated BOX complexes where simultaneous binding of electrophiles and nucleophiles is possible.[4] With this in mind our interest was drawn to the preparation of coordinatively saturated boron bis-oxazolinate complexes. We discovered that the achiral BOX[5] **1** reacted smoothly with catecholborane (CATBH) in CH_2Cl_2 affording, after removal of the solvent, the boron bis-oxazolinate adduct **3** (B-BOXate) as a white solid stable to moisture in 85% yield.† The ^{1}H NMR, ^{13}C NMR and ^{11}B NMR spectroscopy investigations supported the formation of a single symmetric complex derived from the reaction between the CATBH and the BOX **1** (Scheme 1). To the best of our knowledge, B-BOXate complexes have not been reported until now. As a matter of fact, although the BOX ligands are easily deprotonated, only a few cases of BOXate–metal complexes have been described.[6] Diagnostic signals for **3** are the singlet for the proton bridge at δ = 4.45 ppm, the ^{13}C signal at δ = 57.8 ppm for the methine carbon of the ligand and the ^{11}B signal at δ = 8.87 ppm typical for a tetrahedral coordination of the boron atom.[7] These findings were also confirmed by an X-ray crystallographic analysis of **3**.‡ The structure reported in Fig. 1 shows that the BOX and the catechol motifs lie in two perpendicular planes, whereas the boron atom adopts a tetrahedral coordination slightly deviating from the idealised geometry as a consequence of the ring constraints. The molecule would conform to an idealised C_{2v} symmetry, but

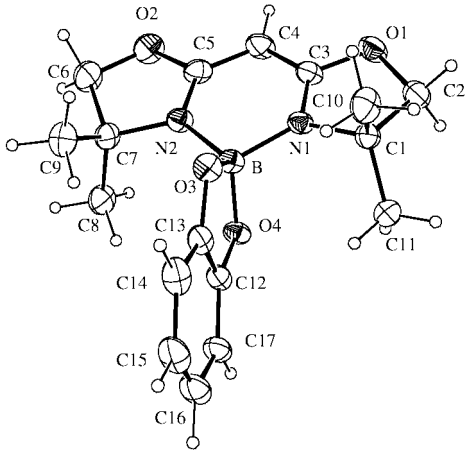
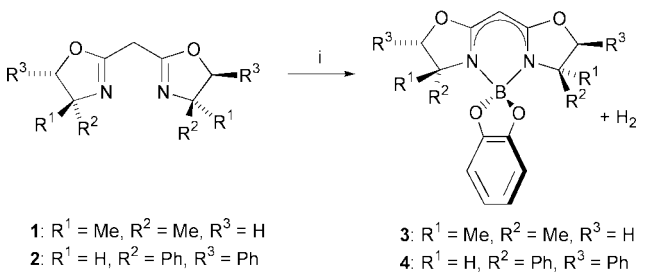


Fig. 1 An ORTEP plot of the molecular structure of **3**. Thermal ellipsoids are drawn at the 30% probability level. Selected bond lengths (Å) and angles (°): B–N(1) 1.541(2), B–N(2) 1.548(2), B–O(3) 1.479(2), B–O(4) 1.481(2), N(1)–C(1) 1.494(2), N(1)–C(3) 1.316(2), N(2)–C(5) 1.319(2), N(2)–C(7) 1.493(2), C(3)–C(4) 1.375(2), C(4)–C(5) 1.370(2); O(3)–B–O(4) 104.5(1), N(1)–B–N(2) 105.8(1), O(3)–B–N(1) 111.8(1), O(4)–B–N(1) 111.3(1), O(3)–B–N(2) 111.6(1), O(4)–B-N(2) 111.9(1). Dihedral angle between plane N(1)–B–N(2) and O(3)–B–O(4) is 89.69(8).

C(2) and C(6) atoms lie out the plane of their oxazoline rings [±0.223(5) Å] therefore the actual idealised symmetry is only C_2.

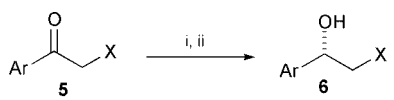
Employing chiral BOX ligands, the corresponding B-BOXate complexes can be isolated as stable solids. For instance, starting from the 2,2′-methylenebis[(4*R*,5*S*)-4,5-diphenyl-2-oxazoline] **2** and CATBH following the synthetic protocol employed for **3** the chiral B-BOXate **4** is isolated (diagnostic signals for **4** are as follows: ^{1}H NMR δ = 5.03 ppm and ^{13}C NMR δ = 57.8 ppm). In the course of our studies on the enantioselective reduction of prochiral ketones in the presence of M-BOX complexes,[6a,8] we found that the complex **3** was able to catalyse effectively the reduction of acetophenone with CATBH yielding the corresponding 1-phenylethanol in 86% yield after 18 h (Scheme 2). The use of **4** in catalytic amount (8 mol%) gave the desired (*R*)-1-phenylethanol (**6a**) in 80% yield and 44% enantiomeric excess. With the aim of searching for the optimal reaction protocol we screened, in the asymmetric



1: R^1 = Me, R^2 = Me, R^3 = H
2: R^1 = H, R^2 = Ph, R^3 = Ph

3: R^1 = Me, R^2 = Me, R^3 = H
4: R^1 = H, R^2 = Ph, R^3 = Ph

Scheme 1 *Reagents and conditions*: (i) BOX (1 eq.), CATBH (1.5 eq.), CH_2Cl_2, rt, 4 h.



5 **6**

a: Ar = Ph, X = H;
b: Ar = Ph, X = Et;
c: Ar = Ph, X = Cl;
d: Ar = Ph, X = Br;
e: Ar = α-Naphthyl, X = H

Scheme 2 *Reagents and conditions*: (i) **5** (1 eq.), B-BOX (8 mol%), CATBH (2 eq.), CH_2Cl_2, 0 °C. (ii) NaOH (2 M).

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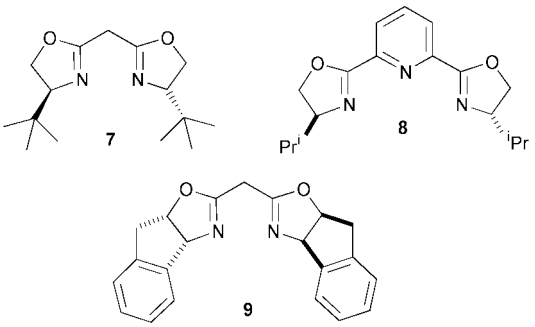

Fig. 2 BOX ligands.

reduction, other chiral C_2 bis-oxazoline ligands (BOX **7**–**9**, Fig. 2) preparing the catalytic precursors *in situ*, in order to simplify the procedure.[9]

The best result was obtained using 8 mol% of the BOX **9** that furnished the enantioenriched alcohol in 76% ee (Table 1, entry 4),§ while the use of non-enolizable BOXs such as the PyBOX **8**, significantly decreased the enantioselectivity (ee = 18%, entry 3). Moreover, the catalytic protocol can be successfully applied in the reduction of branched aromatic ketones and α-halo ketones[10] (Table 1, entries 5–8). Although the mechanism of the present reduction is still unclear, a cooperative action in which ketones and CATBH simultaneously bind to the chiral catalyst (chemzyme) could be invoked. In summary, the design of a new class of B-BOXate complexes and their use in the catalytic asymmetric reduction of ketones is presented. The fine-tuning of the stereo-electronical features (both the bis-oxazoline and the catechol motifs can be opportunely matched), makes these systems promising catalysts for a variety of stereocontrolled organic transformations.

Table 1 Enantioselective reduction of ketones in the presence of boron BOX complexes as catalysts

Entry[a]	BOX	Ketone	Yield (%)[b]	Ee (%)[c]	Config.[d]
1	**2**	**5a**	80	67	*S*
2	**7**	**5a**	40	30	*S*
3	**8**	**5a**	52	18	*S*
4	**9**	**5a**	78	76	*R*
5	**9**	**5b**	65	76	*R*
6	**9**	**5c**	85	84	*S*
7	**9**	**5d**	56[e]	86	*S*
8	**9**	**5e**	78	72	*R*

[a] The reactions were carried out as described in the note §. [b] Isolated yields after flash chromatography. [c] Evaluated by chiral GC analysis with a chiral cyclodextrin Megadex-5 column. [d] The absolute configuration was assigned by comparison of the $[\alpha]_D$ value reported in the literature (see: ref. 6*a*, 8). [e] The corresponding epoxide was isolated in 24% yield (ee = 86%) as a by-product of the reaction.

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Notes and references

† *Synthesis of the B-BOXate* **3***:* A 25 mL round-bottom flask containing a stirring bar was charged with dry CH_2Cl_2 (4 mL), BOX **1** (105 mg, 0.5 mmol) and CATBH (80 μL, 0.75 mmol) at 0 °C. The resulting solution was stirred 4 h, then the solvent was evaporated under reduced pressure. The crude white product obtained was washed with dry Et_2O (5 mL), collected by filtration and dried under vacuum. Yield = 85%. δ_H ($CDCl_3$, 300 MHz) 6.71 (m, 4H), 4.46 (s, 1H), 4.10 (s, 4H), 1.30 (s, 12H); δ_C ($CDCl_3$, 50 MHz) 150.7, 119.1, 109.3, 109.0, 81.7, 62.8, 57.8, 26.3; δ_B (Ref. $BF_3{\cdot}OEt_2$): 8.87; diagnostic chemical shifts for **1** and CATBH: δ_H (**1**) 3.95 (s, 4H), 3.29 (s, 2H), 1.26 (s, 12H); δ_C (**3**) 160.2, 79.5, 67.3, 28.6, 28.2; δ_B (CATBH) 29.92 (d, $J_{B\text{-}H}$ = 554.1 Hz).

‡ *Crystal data* for **3**: $C_{17}H_{21}O_4BN_2$, M = 328.17, triclinic, a = 8.9871(3), b = 9.4340(4), c = 11.1411(4) Å, α = 67.378(2), β = 75.067(2), γ = 77.487(2)°, U = 835.12(5) Å^3, T = 293 K, space group $P\bar{1}$ (No. 2), Z = 2, μ(Mo-Kα) = 0.092 mm^{-1}, 11678 reflections measured by Bruker AXS SMART 2000 diffractometer with a CCD detector, 4866 unique (R_{int} = 0.0293) which were used in all calculations. Final $R1(F)$ = 0.0455 [$I > 2\sigma(I)$] and $wR2(F^2)$ = 0.1260 (all data). Software contained in the SHELXTL (5.1) library (G. M. Sheldrick, Bruker AXS, Madison, WI). CCDC 163357. See http://www.rsc.org/suppdata/cc/b1/b103571c/ for crystallographic files in .cif format.

§ *Catalytic reduction reaction*: To a stirring solution of **9** (13.2 mg, 0.04 mmol) in dry CH_2Cl_2 (2 mL) at 0 °C was added CATBH (100 μL, 1 mmol). The clear mixture was stirred for 2–3 h at the same temperature then acetophenone (58 μL, 0.5 mmol) was added by syringe. The reaction was kept without stirring for 48–72 h at 0 °C, quenched with NaOH (2 mL, 2 M) and then stirred for 10 min. After the usual workup (Et_2O, Na_2SO_4) the crude product was purified by flash chromatography (cyclohexane–Et_2O 85 : 15) to afford the (*R*)-(+)-phenylethanol as a pale yellow oil in 78% yield and 76% ee (Chiral GC analysis, Megadex-5 column).

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9 Other boron reducing agents were tested in the asymmetric reduction (*i.e.* $BH_3{\cdot}S(Me)_2$, $BH_3{\cdot}$2,6-lutidine and $BH_3{\cdot}$4-phenylmorpholine). However the enantiomeric excesses were significantly lower.
10 Aliphatic carbonyl substrates afforded the secondary alcohol in low chemical and optical yields (2-methylheptan-3-one: yield = 31%, ee = 26%).

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