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Zinc triflate–bis-oxazoline complexes as chiral catalysts: enantioselective reduction of α-alkoxy-ketones with catecholborane

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Abstract

A new methodology for the catalytic enantioselective reduction of α-alkoxy-ketones is described. The procedure employes $Zn(OTf)_2$–bis-oxazoline complexes (8–10 mol%) as catalysts and catecholborane as the reducing agent. The reaction, carried out in CH_2Cl_2 at 0°C, affords the α-alkoxy-alcohols in high yields and with good enantioselectivity.

Keywords: asymmetric reactions; catalysis; ketones; reduction.

Enantioselective reduction of ketones represents one of the most important methodologies for obtaining enantiomerically pure compounds which are used as key intermediates in the preparation of fine chemicals and biologically active compounds.[1] The asymmetric borane reductions of α-substituted prochiral ketones such as α-halo ketones,[2a] α-ketophosphonates[2b] and other prochiral ketones containing heteroatoms,[2c] have been recently reported to give optically active 1,2-diols. Moreover, BINAP–ruthenium complexes have been found to be highly effective in the enantioselective reduction of chelating substrates such as β-ketoesters and β-alkoxy-ketones.[3] As a part of our program devoted to the application of the bis-oxazoline (box) ligands in asymmetric catalytic processes,[4] we describe herein a new simple and convenient method for the enantioselective reduction of α-alkoxy-ketones employing chiral catalysts derived from $Zn(OTf)_2$ and optically pure bis-oxazolines. The Lewis acidity of these box–$M(OTf)_n$ complexes is well established, and highly enantioselective Diels–Alder,[5a] aldol condensation,[5b] hetero Diels–Alder,[5a] Michael addition[5c] and carbonyl ene[5a] reactions based on such catalysts, have been reported.

In almost all of these reports, two-point catalyst–substrate binding, is involved.† However, to the best of our knowledge, the same strategy has never been applied to the catalytic enantioselective reduction

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† In fact, *N*-acyl-oxazolidinones, α-benzyloxy-aldehydes and piruvates are the substrates which give higher ees in the catalytic box-Lewis acid mediated reactions.

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of ketones. Moreover, a recent report pointed out that α-chelating ketones are not suitable substrates for enantioselective transfer hydrogenation reductions promoted by chiral ruthenium catalysts.[6] Initially, the box ligands **1**–**6** (Fig. 1)[7] were chosen as ligands for the reduction of the α-methoxy-acetophenone **7**[8] with different reducing agents: catecholborane (CATBH), $BH_3 \cdot SMe_2$, $NaBH_4$, $(EtO)_3SiH$. The catecholborane reductant afforded both higher yields and enantioselectivity.‡ The asymmetric reductions were carried out at 0°C in the presence of a catalytic amount of a box–$Zn(OTf)_2$ complex (simply prepared by stirring a solution of box and $Zn(OTf)_2$ in CH_2Cl_2 for 1 h) (Scheme 1).

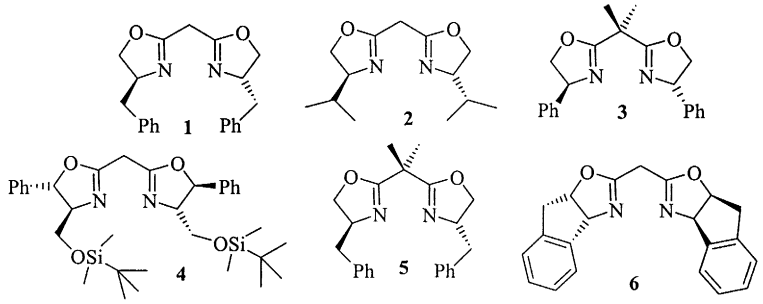
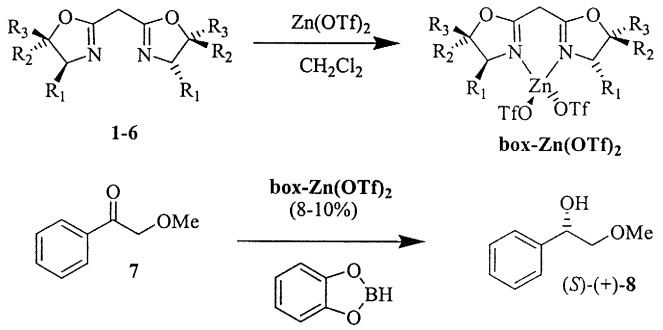


Fig. 1.



Scheme 1.

The results obtained using the box-ligands **1**–**6** and 1.2 eq. of CATBH as reductant, are shown in Table 1.

On the basis of these results, it is important to point out that, while the box-ligands **2** and **4** (excellent ligands for several asymmetric reactions)[10] afforded (*S*)-(+)-2-methoxy-1-phenylethanol (**8**) with a modest enantioselection (entries 2 and 4, Table 1), the box bearing the benzylic substitution (**1**) gave the highest enantioselectivity (ee=82%).

This methodology has been extended to several aliphatic and aromatic α-benzyloxy-[11] and α-methoxy-ketones[12] synthesised following the procedures known in literature. The results obtained using box **1** as a ligand for $Zn(OTf)_2$, are summarised in Table 2.

The data in Table 2 provide evidence that in order to obtain a high level of enantioselection (ee>80%), the α-methoxy substitution of the ketone is necessary. In fact, a different protecting group, such as benzyloxy, gave lower enantioselectivity probably due to steric reasons (Table 2, entries 5–6). A second trend is evident from the illustrated data: aromatic ketones displayed higher enantiomeric excesses in this reaction with respect to the aliphatic analogues, probably due to π-polar interaction with the

‡ Other reducting agents catalysed the asymmetric reduction of **7** in low yield and with poor enantioselectivity.

Table 1
Catalytic enantioselective reduction of α-methoxy-acetophenone promoted by Zn–box complexes in the presence of catecholborane as reductant

Entry[a]	Box	Cat. (%)	Time (h)	Yield (%)[b]	Ee (%)[c]	Config.[d]
1	**1**	10	72	78	82	*S*
2	**2**	8	48	70	15	*S*
3	**3**	8	48	62	42	*S*
4	**4**	10	48	98	0	-
5	**5**	8	48	52	46	*S*
6	**6**	8	48	40	49	*S*

a) All reactions were carried out at 0°C in CH_2Cl_2. b) Isolated yields after chromatography. c) The enantiomeric excess was evaluated by chiral GC analysis, using a Megadex 5 capillary column. d) The absolute configuration of the product was assigned by comparison of the $[\alpha]_D$ value reported in the literature.[9]

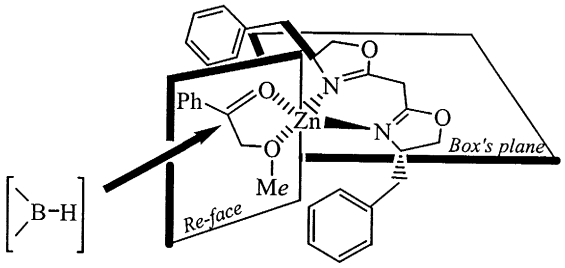


Fig. 2.

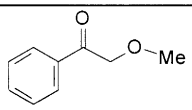
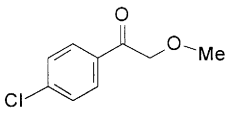
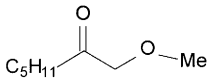
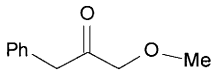
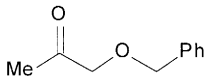
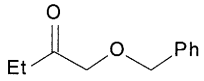
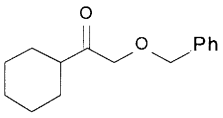
benzyl substituent of the ligand. A remarkable feature of this protocol is the necessary two-point catalyst–substrate binding. In fact, while a high level of enantioselectivity is recorded with chelating substrates, unsubstituted ketones afforded only racemic alcohols.

At the present time, we can only speculate about the mechanism of the reaction. However, the absolute configuration observed for the alcohol **8** appears to be in agreement with the hypothetical chelating model proposed in Fig. 2.

In conclusion, we have developed a new methodology for the enantioselective reduction of α-alkoxy-ketones based on chiral $Zn(OTf)_2$–bis-oxazoline complexes. Analogous studies using other α-hetero substituted ketones (-SR, $-NR_2$), are now under investigation in our laboratories.

The typical procedure for the catalytic enantioselective reduction is as follows: A flame-dried flask was charged with the bis-oxazoline **1** (26 mg, 0.078 mmol), $Zn(OTf)_2$ (28 mg, 0.078 mmol) and anhydrous CH_2Cl_2 (2 mL) under nitrogen. The solution was stirred during 1 h, cooled at 0°C and then **7** (107 μL, 0.78 mmol) was added. The mixture was then stirred for 5 minutes and CATBH (100 μL, 0.94 mmol) was added. The solution was kept without stirring for 72 h at 0°C then diluted with Et_2O (5 mL) and quenched

Table 2
Enantioselective reduction of aliphatic and aromatic α-benzyloxy- and α-methoxy-ketones promoted by the **1**–$Zn(OTf)_2$ catalyst

Entry	Ketone	Yield (%)[a]	Ee (%)[b]	$[\alpha]_D^{25}$
1		78	82	+39.6 (c1, $CHCl_3$)[c]
2		69	81	+31.7 (c0.5, $CHCl_3$)[d]
3		78	67	+0.9 (c1, $CHCl_3$)[e]
4		65	65	+3.0 (c1, $CHCl_3$)[e]
5		91	40	+21.0 (c1, $CHCl_3$)[f]
6		82	45	+6.4 (c1, $CHCl_3$)[f]
7		70	21	-0.5 (c1, $CHCl_3$)[g]

a) Isolated yields after flash chromatography. b) The enantiomeric excess was evaluated by chiral GC analysis, using a Megadex 5 capillary column. c) The absolute configuration was assigned as *S* by comparison of the $[\alpha]_D$ value reported in the literature.[9] d) The absolute configuration was assigned as *S*.[13] e) The absolute configuration is not known but is probably *S* based on the sign of the $[\alpha]_D$ and the elution order of the (*S*)-(+)-2-methoxy-1-phenylethanol and (*S*)-(+)-1,2-butandiol-1-benzyl ether. f) The absolute configuration was assigned as *S* by comparison of the $[\alpha]_D$ value reported in the literature.[14] g) The absolute configuration was not assigned.

with NaOH 2N (5 mL). The organic phase was separated and the aqueous phase extracted with Et_2O (3×5 mL). The combined organic phases were dried over anhydrous Na_2SO_4 and evaporated in vacuo. Finally, the crude product was purified by flash chromatography (cyclohexane:Et_2O, 9:1), affording the (*S*)-(+)-2-methoxy-1-phenylethanol as a colourless oil in 78% yield and with 82% ee.

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