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Enantioselective reduction of ketones with triethoxysilane catalyzed by chiral bis-oxazoline titanium complexes

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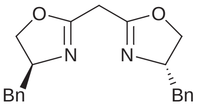
Chiral bis-oxazoline titanium complexes [Ti(BOX)$_2$X$_2$] prepared from C_2 chiral bis-oxazolines, BuLi and titanium salts, catalyze the enantiosective reduction of ketones in the presence of triethoxysilane.

Enantioselective reduction of ketones is an important and widely utilized methodology for the preparation of key intermediates for the synthesis of drugs and biologically active compounds.[1] Corey's oxazaborolidine and related compounds play a decisive role in these chirotechnologies.[2] Recently, Buchwald has demonstrated that chiral titanium metallocenes are able to catalyze the enantioselective hydrosilylation of ketones and imines with high ees.[3] For these reactions enantiomerically pure titanocene complexes should be available. Although a new methodology to prepare the chiral C_2 metallocene complexes in high diastereomeric ratios was recently reported,[4] a resolution process is still needed to access the enantiomerically pure metal complex.[5] Based on a different strategy, *i.e.* replacing chiral metallocene with more accessible, easily prepared, chiral metal complexes, we have explored the possibility of using chiral bis-oxazolines[6] as ligands in coordinating group 4 metals and to employ the corresponding complexes in asymmetric catalysis (Fig. 1). To the best of our knowledge, until now the use of early transition metals with C_2 chiral bis-oxazolines in asymmetric catalysis has never been reported.[7]

Herein, we present a novel method for the enantioselective titanium-catalyzed hydrosilylation of ketones and α-halo ketones. The procedure involves the treatment of C_2 chiral bis-oxazolines (BOX **1–7**) with BuLi followed by the addition of a titanium salt.[8] Since the titanium complex was prepared *in situ* using a 2:1 molar ratio between the methylene bis-oxazoline and a titanium salt, we suggest that the BOX–titanium complex could have an octahedral structure (Fig. 1, M = Ti; X = Cl, F, OPr^i).[9] These new BOX–titanium complexes were treated with (EtO)$_3$SiH leading to a catalytic system for the hydrosilylation of ketones and α-halo ketones. It is noteworthy that no particular activation is necessary for the preparation of the active catalytic species. Various silyl hydrides such as Cl$_3$SiH, (EtO)$_3$SiH, Ph$_3$SiH, PhSiH$_3$ and poly(methylhydrosiloxane) were tested for asymmetric reduction catalyzed by the BOX–titanium complex. However, in general, (EtO)$_3$SiH gave better results. Initially we investigated the reaction of acetophenone with (EtO)$_3$SiH using various titanium salts and oxazolines (Scheme 1). As reported in Table 1 the best results were obtained using 3–5 mol% of the catalyst prepared from commercially available TiF$_4$ and oxazoline **4** as ligand. The hydrosilylation proceeded at room temperature, affording in 48 h the (*S*)-1-phenylethan-1-ol[3a] in 86% yield and 61% ee. The ee obtained in the asymmetric reaction seems to depend on the steric hindrance of the BOX ligand (entries 4,9 and 10). THF was the most suitable solvent with respect to both enantioselectivities and chemical yields. In the process of optimizing catalytic conditions with a variety of titanium salts, we found that TiF$_4$ was more effective in preparing the soluble orange–yellow BOX–titanium complexes. On the other hand, TiCl$_4$(THF)$_2$ gave insoluble complexes and we occasionally observed a definite change in the color of the reaction to blue, indicative of the presence of a Ti^{III} species.[10]



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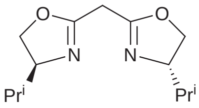

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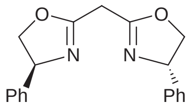

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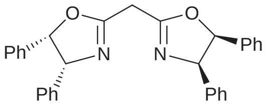

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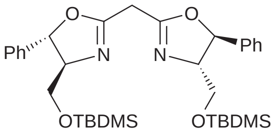

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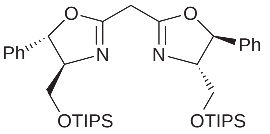

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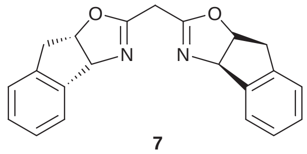

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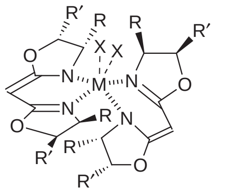
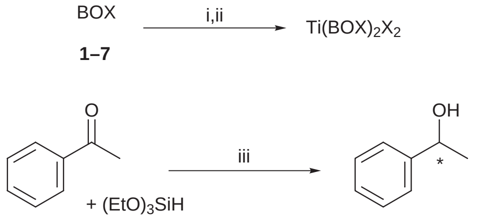
Since TiF$_4$, bis(oxazoline) **4** and (EtO)$_3$SiH afforded the best results,† the catalyst system reported in Scheme 2 was successfully applied to the asymmetric reduction of branched aromatic ketones and α-halo ketones.[11] From the data in Table 2, it is evident that the enantioselectivity is independent of the



M = Ti, Zr, Hf ; X = F, Cl, Br, OR, NR$_2$

Fig. 1 Hypothetic structure of M(BOX)$_2$X$_2$.

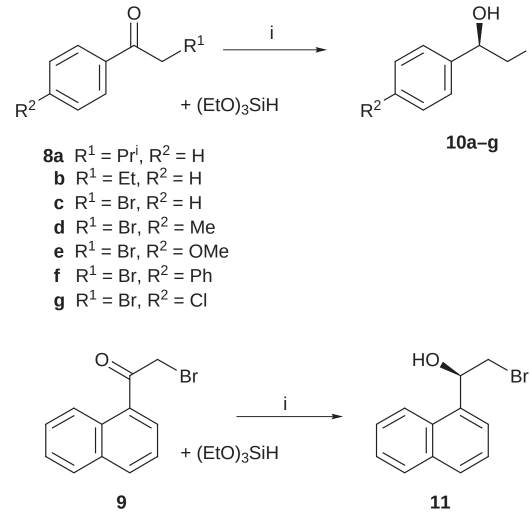


Scheme 1 *Reagents and conditions*: i, BuLi, THF; ii, TiX$_4$, THF; iii, Ti(BOX)$_2$X$_2$ (3-8 mol%), room temp.

Table 1 Enantioselective reduction of acetophenone catalyzed by Titanium-BOX complex[a]

Entry	BOX	TiX_4 (mol%)	Yield (%)	Ee[b] (%)
1	**1**	$TiCl_4(THF)_2$ (4)	60	30 (*R*)
2[c]	**1**	$TiCl_4(THF)_2$ (3)	60	50 (*R*)
3[c]	**3**	$TiCl_4(THF)_2$ (4)	20	23 (*R*)
4	**1**	$TiCl_2(OPr^i)_2$ (15)	87	18 (*S*)
5	**4**	$TiCl_2(OPr^i)_2$ (4)	85	51 (*S*)
6	**7**	$TiCl_2(OPr^i)_2$ (3)	13	64 (*S*)
7	**4**	TiF_4 (5)	86	61 (*S*)
8[d]	**4**	TiF_4 (4)	28	72 (*S*)
9	**5**	TiF_4 (5)	30	56 (*S*)
10	**6**	TiF_4 (5)	18	51 (*S*)

[a] Reaction conditions as in Scheme 1. All the reactions were performed by employing 4 equiv. of $(EtO)_3SiH$ as the reducing agent. The reactions were stirred at room temperature for 2–3 d. [b] The ee was evaluated by GC analysis with a chiral cyclodextrin Megadex column. [c] The reaction was effected in the presence of molecular sieves 4 Å (1 g. for 1 mol of ketone). [d] The reaction was performed in Et_2O.



Scheme 2 *Reagents and conditions*: i, **4** (8 mol%), room temp., 80–120 h.

Table **2** Enantioselective reduction of ketones and α-halo ketones catalyzed by titanium–BOX complexes[a]

Entry	Ligand	Ketone	Alcohol	Yield (%)[b]	Ee (%)[c]
1	**4**	**8a**	**10a**	61	85 (*S*)
2	**4**	**8c**	**10c**	60	84 (*R*)
3	**4**	**8d**	**10d**	61	83 (*R*)
4	**4**	**9**	**11**	64	84 (*R*)
5	**4**	**8e**	**10e**	53	80 (*R*)
6	**4**	**8f**	**10f**	50	78 (*R*)
7	**4**	**8b**	**10b**	58	75 (*S*)[d]
8	**4**	**8g**	**10g**	50	65 (*R*)

[a] All the reactions were performed as reported in the experimental procedure. [b] Isolated yield after chromatographic purification. [c] The ee was determined by GC analysis on Megadex cyclodextrin chiral column. The configurations of **10a**,**c** were assigned by comparison of the $[\alpha]_D$ values reported in the literature. In the other cases, the absolute configuration was assigned by analogy. [d] The ee was determined on the silylated alcohol.

nature of the ketone, showing generality from aromatic substituted ketones to α-halo ketones.[12] The excellent enantioselectivity and the satisfactory yields observed in these reactions, accompanied by the simple protocol and the commercial availability of the ligands and reagents, make this procedure useful for the preparation of optically active epoxides and α-amino alcohols.[1]

Bis(oxazoline) ligands are able to replace Britzinger's C_2 metallocenes in these reductions, suggesting that other early transition metal-mediated reactions can be successfully catalyzed by early transition metals and appropriate BOX ligands. At the present time we can only speculate about the mechanism of this reaction. In particular, we are unable to definitively demonstrate that the reduction is due to the formation of an active titanium(III)[3a,b] or titanium(IV) species,[14] or if other mechanisms are involved.[15] In conclusion, we have developed a new methodology for the enantioselective reduction of ketones based on chiral titanium bis(oxazoline) complexes.

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Notes and references

† Typical experimental procedure: A solution of **4** (0.044 g, 0.097 mmol) in anhydrous THF (1.5 ml) was cooled to −78 °C and then BuLi (0.064 ml, 1.5 M in hexane) was added under nitrogen. The resulting pale yellow solution was stirred for 5 min at −78 °C and then warmed to 0 °C for 15 min. To this yellow solution TiF_4 was added (0.006 g, 0.048 mmol) all at once and the mixture was vigorously stirred until complete dissolution of the salt. The resulting solution was stirred for 60 min at room temperature and then $(EtO)_3SiH$ (0.240 ml, 1.2 mmol) and **8e** (0.14 ml, 0.605 mmol) were added. The mixture was stirred for 96 h at room temperature. The reaction mixture was diluted with AcOEt (5 ml) and then carefully made basic (pH 12) by the addition of aq. NaOH (1 M). The solution was stirred at room temperature until a white precipitate was formed. The solid was separated by filtration and the organic phase was collected. The aqueous phase was then extracted with AcOEt (2 × 3 ml). The organic layers were combined, dried over anhydrous Na_2SO_4, then concentrated under reduced pressure to give a yellow oil which was purified by column chromatography on silica gel (pentane–Et_2O, 9:1) (53%).

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10. In these cases, only racemic alcohol was obtained. Reduction of titanium depending on the ligand is well known problem in metallocene chemistry.
11. Aliphatic, non-branched aromatic and cyclic ketones were reduced with our titanium catalyst in lower ees. For example, the reduction of octan-2-one and indan-2-one afforded the corresponding alcohols in 65% yield, 20% ee and 70% yield, 29% ee, respectively.
12. The absolute configurations of **10a** [ref. 3(*a*)] and **10c** (ref. 13) were determined by comparison with the $[\alpha]_D$ values reported in the literature. The absolute configurations of **10b** and the other halo ketones were assigned by analogy.
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