



## Enantioselective Borane Reduction of Ketones Catalyzed by Chiral Lanthanum Alkoxides

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**Abstract:** The reaction of lanthanum triisopropoxide with chiral diols gave a highly active catalyst system for the asymmetric borane reduction of prochiral ketones.  
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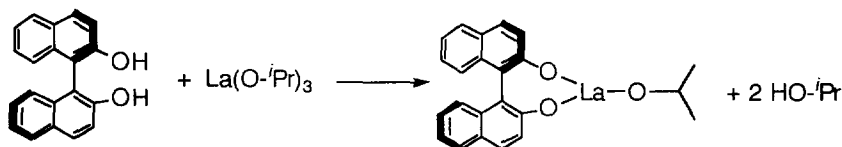
### Introduction

The development of novel chiral catalysts is one of the most actively pursued areas of chemical research in recent years.<sup>1</sup> Among the many interesting asymmetric catalytic reactions studied, the chiral borane reduction of ketones is one of those which are convenient to handle and potentially useful for the preparation of a variety of chiral alcohols.<sup>2</sup> Itsuno *et al* achieved an important breakthrough in the use of mixtures of borane and chiral amino alcohols to catalyze the asymmetric reduction of ketones in the early 1980's.<sup>3</sup> Corey *et al* developed a highly enantioselective system based on the use of chiral oxazaborolidine catalysts.<sup>4</sup> More recently, Giffels *et al* reported moderate to good e.e.'s in the borane reduction of acetophenone using chiral titanium alkoxides as catalyst.<sup>5</sup> In this communication we wish to report a highly active catalyst system based on the use of chiral lanthanide alkoxides for the borane reduction of prochiral ketones. The use of lanthanide complexes in organic synthesis and homogeneous catalysis has attracted much attention in the past two decades.<sup>6</sup> Recently the application of chiral rare earth complexes in asymmetric catalysis produced remarkable results.<sup>7</sup>

In 1989 Okawa *et al* reported the use of tris{4-(*l*-menthyloxy)-1-(*p*-tolyl)butane-1,3-dionato}lanthanoid(III) as catalyst for the asymmetric reduction of ketones with NaBH<sub>4</sub>.<sup>8</sup> Unfortunately the extremely slow rate of reaction (less than one turnover in 5 days at ambient temperature) made this reaction unattractive. (The reaction was considered to be stoichiometric because of the low turnover rate.<sup>8</sup>) In our recent study of the use of chiral lanthanum alkoxide complexes as catalysts in the borane reduction of prochiral ketones, we observed a very fast catalytic reaction.

### Results and Discussion

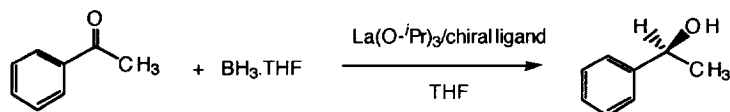
When lanthanum triisopropoxide was allowed to react with a chiral chelating diol (e.g. *S*- or *R*-binaphthol) in THF, chiral dialkoxylanthanum complexes were obtained:



I

[NMR data of I: <sup>1</sup>H NMR in CDCl<sub>3</sub>: δ7.146 - 7.982 (m, 12 H, binaphthyl H's); 4.03 (s, 1 H, OCH); 1.20 (s, 6 H, CH<sub>3</sub>'s). <sup>13</sup>C NMR in CDCl<sub>3</sub>: δ159.32, 133.47, 130.48, 129.29, 128.47, 127.33, 125.84, 123.78, 121.58, 118.95 (binaphthyl C's); 81.44 (O-CH); 25.84 (CH<sub>3</sub>'s).] I and other similar complexes were found to be very reactive in the catalytic asymmetric reduction of ketones with borane. In a

preliminary screening study we tested a variety of chiral bidentate ligands for the borane reduction of acetophenone.



In most cases using 10 mol% lanthanum chiral alkoxide catalyst, 100% conversion of the ketone substrate was obtained in less than 5 minutes. Some typical results are summarized in Table 1.

**Table 1.** The borane reduction of acetophenone with chiral lanthanide catalysts<sup>a,b,c</sup>

entry	chiral ligand	temp. (°C)	reaction time (min.)	conversion (%) <sup>d</sup>	e.e. (%) <sup>d</sup>
1	<i>R</i> -binaphthol	- 80	10	100	41.7 ( <i>S</i> )
2	<i>R</i> -binaphthol	- 30	10	100	41.7 ( <i>S</i> )
3	<i>R</i> -binaphthol	0	10	100	40.2 ( <i>S</i> )
4	<i>R</i> -binaphthol	20	3	100	38.8 ( <i>S</i> )
5	2 <i>S</i> , 4 <i>S</i> -butanediol	- 30	10	92.7	0
6	1 <i>S</i> , 2 <i>R</i> -2- <i>amino</i> - 1,2-diphenylethanol	- 80	5	100	10.7 ( <i>S</i> )
7	<i>R</i> -pantolactone	20	5	100	0
8	$\beta$ -cyclodextrin	20	10	20.1	0

a) The catalyst was prepared *in situ* by reacting lanthanum triisopropoxide with the 1.1 equivalent of the corresponding chiral ligand in THF at reflux temperature for two hours.

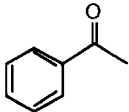
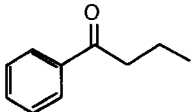
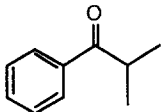
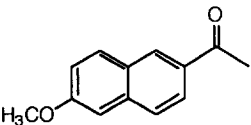
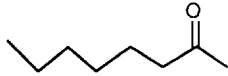
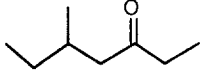
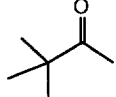
b) The reactions were carried in THF solvent with BH<sub>3</sub>·THF as reducing agent. Borane/substrate = 1.1/1 (mol/mol). c) Substrate/catalyst = 10/1 (mol/mol). d) Based on GLC analysis.

It can be easily seen from Table 1 that the nature of the chiral ligand has a substantial influence on the enantioselectivity of the lanthanide catalyst. It should be noted that this new catalyst system is significantly faster than the corresponding titanium catalyst system recently reported. For example, under similar conditions as in entry 2, the borane reduction of acetophenone with a titanium *R*-binaphthol catalyst gave only 77% conversion in 15 hours.<sup>5</sup> The fast reaction rates of the lanthanide catalyst system clearly indicate a good opportunity for further exploration of this interesting area.

It is of interest to note that while borane-tetrahydrofuran complex was a good reducing agent in this catalyst system, the system was inactive when catecholborane was used as a reducing agent. When borane-dimethylamine was used as a reducing agent, the reaction was much slower. For example, for the reaction in entry 4 of Table 1, if the borane-tetrahydrofuran was replaced by borane-dimethylamine as reducing agent, only 7.9% conversion was observed in 2 hours.

Further study of the *R*-binaphthoxylanthanum catalyst system revealed that the enantiomeric excesses of the ketone reduction are sensitive to the prochiral ketone substrates used. So far in the preliminary study, the best enantiomeric excess obtained was in the reduction of 2-acetyl-6-methoxynaphthalene which gave 61.8% e.e. at ambient temperature. More detailed results of the substrate study are summarized in Table 2.

**Table 2.** Borane reduction of ketones with *R*-binaphthoxylanthanum catalyst<sup>a</sup>

entry	substrate	% conversion <sup>b</sup>	% e.e. <sup>b</sup>
1		100	38.8 ( <i>S</i> )
2		100	23.6 ( <i>S</i> )
3		100	48.6 ( <i>S</i> )
4		100	61.8 ( <i>S</i> )
5		73.2	24.1 ( <i>S</i> )
6		60.7	19.6 ( <i>S</i> )
7		70.5	23.4 ( <i>S</i> )

a) Substrate/catalyst (mol/mol) = 10; BH<sub>3</sub>.THF/substrate = 1.1; solvent = THF; reaction temperature = 20 °C; reaction time = 10 minutes; the catalyst was prepared *in situ* by reacting lanthanum triisopropoxide with the 1.1 equivalent of *R*-binaphthol in THF at reflux temperature for two hours. b) Based on GLC analysis.

It should be pointed out that *R*-binaphthol alone is not a catalyst. In the absence of lanthanum complex, the combination of *R*-binaphthol and borane-tetrahydrofuran for the reduction of 2-acetyl-6-methoxynaphthalene under otherwise similar conditions as in entry 4 of Table 2 gave only 10% conversion with no enantioselectivity. (Same result was obtained when both *R*-binaphthol and lanthanum triisopropoxide were absent from the system.) On the other hand, lanthanum triisopropoxide was an active catalyst for this reaction but obviously was totally non-enantioselective. These results clearly showed the effect of a new class of chiral catalyst for the borane reduction of ketones. Since there is much room for the modification of the lanthanide catalyst, these findings offer an excellent opportunity for the further development of this class of chiral catalyst.

## Experimental Section

All experiments were carried out under nitrogen atmosphere. The THF solvent was distilled from sodium benzophenone and the lanthanum triisopropoxide was prepared according to a method reported by Mehrotra and Batwara.<sup>9</sup>

### A typical procedure for the borane reduction of acetophenone

A solution of 24 mg *R*-binaphthol (0.083 mmol) in 5 mL THF was mixed with a solution of 23 mg lanthanum triisopropoxide (0.075 mmol) in 10 mL THF under nitrogen atmosphere in a 50-mL round bottom flask which was equipped with a magnetic stirring bar and a condenser. The mixture was allowed to stir with a magnetic stirrer at reflux temperature for two hours to give a yellow solution. The solvent was removed under vacuum until a dry residue was obtained. The residue was re-dissolved in 7.5 mL THF and 0.09 mL of acetophenone (0.75 mmol) and 0.82 mL of 1 M BH<sub>3</sub>.THF solution (0.82 mmol) were added to the catalyst solution. The mixture was allowed to stir at ambient temperature for a period of three to ten minutes. The conversion and enantioselectivity of the reaction were followed by GLC with a Chrompack CP-Chirasil-DEX CB capillary column. The experiments of the reduction of other ketones and/or catalyzed by other catalysts were carried out in a similar manner.

### Acknowledgment

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