Pergamon

Tetrahedron: Asymmetry, Vol. 7, No. 11, pp. 3135-3140, 1996

0957-4166/96 $15.00 + 0.00

PII: S0957-4166(96)00414-4

The Acceleration of the Catalytic Asymmetric Borane Reduction of Ketones by Organoaluminum Compounds

Fu-Yao Zhang, Chiu-Wing Yip, Albert S. C. Chan*

Department of Applied Biology and Chemical Technology, The Hong Kong Polytechnic University, Hong Kong

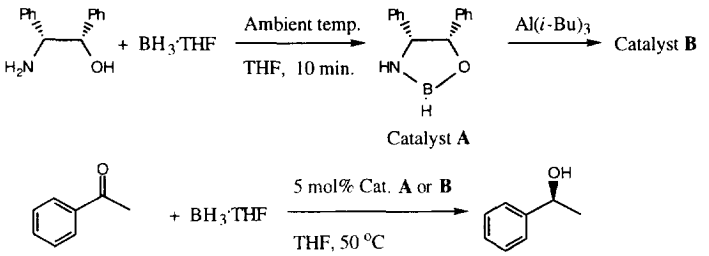
Abstract: The rates of the asymmetric borane reduction of prochiral ketones catalyzed by oxazaborolidines were found to substantially accelerate in the presence of organoaluminum compounds. The enantioselectivities of the reactions were relatively unaffected.

Introduction

The catalytic asymmetric reduction of prochiral ketones is a useful method for the preparation of chiral alcohols.[1] In recent years the use of chiral oxazaborolidines as catalysts for the enantioselective borane reductions of ketones has attracted much attention. In the early 1980's Itsuno *et al* achieved an important breakthrough in the use of mixtures of borane and chiral amino alcohols to catalyzed the asymmetric reduction of ketones and obtained high enantiomeric excesses.[2] This chemistry was further developed by Corey *et al* and a highly active and enantioselective system based on the use of chiral oxazaborolidine catalysts was reported.[3] The application of this method in the preparation of a variety of chiral alcohols has been extensively studied.[4] In many cases very high enantioselectivity has been achieved. The mechanism of the reaction has been explored and the active catalyst has also been characterized.[5] In contrast, to our knowledge, so far there is no study on the acceleration of the rates of these catalytic reactions. In our recent investigation of the effect of promoters for this reaction, we found that organoaluminum compounds in all cases significantly increased the rate and in some cases slightly increased the enantioselectivity of the reaction. This finding offers a simple modification of the reaction system to make the asymmetric catalytic reduction of prochiral ketones a truly convenient synthetic method.

Results and discussion.

In most previous studies the oxazaborolidine catalysts were usually prepared by reacting the corresponding amino alcohol with excess of borane for several hours. The catalysts thus prepared were isolated via sublimation or were used *in situ*. Recently Willems *et al* found that the formation of the oxazaborolidine was very fast and 10 minutes was sufficient for the catalyst to be formed.[6] In this study we also found that the reaction of the amino alcohols with borane was very fast and all the catalysts were prepared in less than 10 minutes. (Extending the catalyst preparation time did not make any difference to rate or selectivity.) More interestingly, the addition of one equivalent of an organoaluminum compound to the catalyst solution resulted with a substantially more active catalyst. For example, when 5 mol% of an oxazaborolidine catalyst (which was prepared from the reaction of (1S, 2R)-1,2-diphenyl-2-aminoethanol with borane) was used in the borane reduction of acetophenone, the complete conversion required over two hours. However, if one equivalent (as compared to the catalyst) of triisobutylaluminum was added to the system, the same reaction under identical reaction conditions was completed in less than 5 minutes. The enantioselectivity was also slightly higher in the latter case.

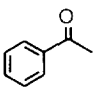
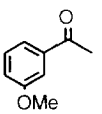
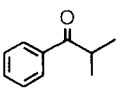
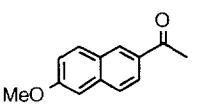
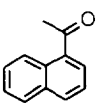
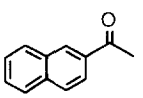


time required for 100% conversion

Cat. **A**: 2 hours; Cat. **B**: 5 minutes.

The rate enhancement effect of triisobutylaluminum in the oxazaborolidine-catalyzed borane reduction of ketones was found to be significant for all of the ketone substrates we have tested. In most cases the enantioselectivity of the reaction was relatively unaffected by the addition of the organoaluminum compound. A detailed comparison of the catalyst systems with and without the added organoaluminum co-catalyst for the borane reduction of prochiral ketones is shown in Table 1.

Table 1. The effect of triisobutylaluminum on the rate of borane reduction of ketones

Entry	Substrate	Al(i-Bu)$_3$	Conversion (%)	e.e. (%)	Configuration
1		No	77	75	S
2		Yes	100	80	S
3		No	26	69	S
4		Yes	96	69	S
5		No	34	65	R
6		Yes	78	65	R
7		No	68	89	S
8		Yes	100	88	S
9		No	41	19	S
10		Yes	77	20	S
11		No	46	82	S
12		Yes	100	81	S

Substrate : ligand [(1S, 2R)-1,2-diphenyl-2-aminoethanol] = 20; triisobutylaluminum : ligand = 1; BH_3·THF : substrate = 1.1; reaction temperature = 50 °C; reaction time = 5 minutes.

It is of interest to note that while fast rates were observed in a variety of organic solvents for the triisobutylaluminum promoted, oxazaborolidine-catalyzed borane reduction of ketones, the enantioselectivity was found to be quite sensitive to the solvents employed. The results of a preliminary comparison study are summarized in Table 2.

Table 2. Solvent effect of the triisobutylaluminum promoted borane reduction of acetophenone.

Entry	Solvent	Conversion (%)	e.e. (%)	Configuration
1	THF	100	80	S
2	CCl_4	100	71	S
3	CH_2Cl_2	100	62	S

Substrate : ligand [(1S, 2R)-1,2-diphenyl-2-aminoethanol] = 20; Al(i-Bu)$_3$: ligand = 1; BH_3•THF : substrate = 1.1; reaction temperature = 50 ^oC; reaction time = 5 minutes.

Unlike many enantioselective reactions which gave higher enantioselectivity at lower reaction temperature, the enantioselectivity of the triisobutylaluminum promoted, oxazaborolidine-catalyzed borane reduction of prochiral ketones was found to be significantly lower at lower reaction temperature. At -80 ^oC, the borane reduction of acetophenone catalyzed by Catalyst **B** gave a racemic *sec*-phenethyl alcohol product. More detailed data of the temperature effect are summarized in Table 3.

Table 3. The temperature effect of the Al(i-Bu)$_3$ promoted borane reduction of acetophenone.

Entry	Temperature (^oC)	Conversion (%)	e.e. (%)	Configuration
1	-80	10	0	--
2	0	32	23	S
3	20	80	49	S
4	50	100	80	S

Substrate : ligand [(1S, 2R)-1,2-diphenyl-2-aminoethanol] = 20; Al(i-Bu)$_3$: ligand = 1; BH_3•THF : substrate = 1.1; reaction time = 5 minutes.

The level of alkylaluminum compounds used in the promotion of the borane reduction was important. When the alkylaluminum to amino alcohol ratio was kept below one, the rate of reduction increased along with the increase of the alkylaluminum compounds used without significant adverse effect on the enantioselectivity of the reaction. Excess of alkylaluminum reagent significantly lowered the enantioselectivity. More detailed experimental results are shown in Table 4.

Table 4. The effect of $Al(i\text{-}Bu)_3$: L ratio in the reduction of 2-acetyl-6-methoxynaphthalene

entry	$Al(i\text{-}Bu)_3$: L	Conversion (%)	e.e. (%)	Configuration
1	0	68	89	S
2	0.5	79	88	S
3	1.0	100	88	S
4	2.0	100	70	S

Substrate : ligand = 20; BH_3•THF : substrate = 1.1; T = 50 °C; reaction time = 5 minutes.

The promoting effect of organoaluminum compounds was unique. Other Lewis acid type compounds tested in a preliminary screening were found to be either ineffective for rate enhancement or significantly detrimental in terms of enantioselectivity. For example, when tributyltin hydride or tributyltin chloride was used to replace the organoaluminum promoter in the catalyst system, the rate of borane reduction was found to be even slower than that without the Lewis acid. On the other hand, while titanium tetraisopropoxide and titanium tetrachloride were found to accelerate the rate of borane reduction, the oxazaborolidine catalyst system was found to completely lose enantioselectivity. More detailed results are shown in Table 5.

Table 5. The effect of different Lewis acids in the borane reduction of acetophenone

entry	Lewis acid added	Conversion (%)	e.e. (%)	Configuration
1	None	77	76	S
2	$AlEt_3$	100	74	S
3	$Al(i\text{-}Bu)_3$	100	80	S
4	$AlH(i\text{-}Bu)_2$	100	80	S
5	$HSnBu_3$	27	76	S
6	$ClSnBu_3$	36	77	S
7	$Ti(O\text{-}^iPr)_4$	100	0	--
8	$TiCl_4$	90	0	--

Lewis acid : chiral ligand = 1; substrate : chiral ligand = 20; BH_3•THF : substrate = 1.1; reaction temperature = 50 °C; reaction time = 5 minutes.

From these results, it can be clearly seen that alkylaluminum compounds can significantly accelerate the rate of the oxazaborolidine-catalyzed borane reduction of ketones. It can also be observed from Table 5 that the promoting effect of the alkylaluminum compounds in the borane reduction is not a simple Lewis acid effect. These findings add a new dimension to the chemistry of borane reduction and it is believed that further development of the promoter system may result with more effective catalyst systems.

Experimental

All experiments were carried out under nitrogen atmosphere. The commercial reagents were used as received without further purification. All solvents used were dried by using standard, published methods and were distilled before use.

A typical procedure for the oxazaborolidine-catalyzed borane reduction of acetophenone.

A solution of (1S, 2R)-1,2-diphenyl-2-aminoethanol (19 mg, 0.09 mmol) in 5 mL THF and a THF solution of BH_3•THF (180 μL of a 1M solution, 0.18 mmol) were mixed well in a 25 mL 2-necked round bottom flask with a magnetic stirrer at ambient temperature for 10 minutes. After the addition of 210 μL of acetophenone (1.8 mmol), a THF solution of BH_3•THF (2.0 mL of a 1M solution, 2.0 mmol) was added and the mixture was allowed to stir at 50 °C for 5 minutes. The conversion and enantioselectivity of the reaction were determined by GLC with a Chrompack CD-Chirasil-DEX CB Capillary column.

A typical procedure for the triisobutylaluminum-promoted, oxazaborolidine-catalyzed borane reduction of acetophenone.

A solution of (1S, 2R)-1,2-diphenyl-2-aminoethanol (19 mg, 0.09 mmol) in 5 mL THF and a THF solution of BH_3•THF (180 μL of a 1M solution, 0.18 mmol) were mixed well in a 25 mL 2-necked round bottom flask with a magnetic stirrer at ambient temperature for 10 minutes. A 15% triisobutylaluminum in toluene solution (120 μL, 0.09 mmol) was added and the mixture was stirred for another 10 minutes. After the addition of 210 μL of acetophenone (1.8 mmol), a THF solution of BH_3•THF (2.0 mL of a 1M solution, 2.0 mmol) was added and the mixture was allowed to stir at 50 °C for 5 minutes. The conversion and enantioselectivity of the reaction were determined by GLC with a Chrompack CD-Chirasil-DEX CB Capillary column.

Acknowledgment

We thank the Hong Kong Research Grant Council for financial support of this study.

References

1. For recent reviews, see a) Nishizawa, M.; Noyori, R. in Trost, B. M.; Fleming, I. Ed. *Comprehensive Organic Synthesis,* Vol. 8, p. 159; Pergamon Press: Oxford, 1991. b) Midland, M. M. in Morrison, J. D. *Asymmetric Synthesis,* Vol. 2, p. 45; Academic Press: New York, 1983. c) Singh, V. K. *Synthesis,* **1992,** 605
2. a) Itsuno, S.; Ito, K.; Hirao, A.; Nakahama, S. *J. Chem. Soc. Chem. Commun.* **1983,** 469. b) Itsuno, S.; Nakano, M.; Miyazaki, K.; Masuda, H.; Ito, K.; Hirao, A.; Nakahama, S. *J. Chem. Soc. Perkin Trans. I.* **1985,** 2039.
3. a) Corey, E. J.; Bakshi, R. K.; Shibata, S. *J. Am. Chem. Soc.* **1987,** *109,* 5551. b) Corey, E. J.; Link, J. O. *Tetrahedron Lett.* **1992,** *33,* 4141.
4. a) Quallich, G. J.; Woodall, J. M. *Tetrahedron Lett.* **1993,** *34,* 785. b) Bringman, G.; Hartung, T. *Angew. Chem. Int. Ed. Engl.* **1992,** *31,* 761. c) Rao, A. V. R.; Gurjar, M. K.; Kalwar, V. *Tetrahedron: Asymmetry* **1992,** *3,* 859. d) Tanaka, K.; Matsui, J.; Sujuki, H. *J. Chem. Soc.*

Chem. Commun. **1991,** 1311. e) Jiang, Y.; Qin, Y.; Mi, A. *Tetrahedron: Asymmetry* **1994,** *5,* 1211

5. Corey, E. J.; Azimioara, M.; Sarshar, S. *Tetrahedron Lett.* **1992,** *33,* 3429.
6. Willems, J. G. H.; Dommerholt, F, J.; Hammink, J. B.; Vaarhorst, A. M.; Thijs, Lambertus, Zwaneburg, B. *Tetrahedron Lett.* **1995,** *36,* 603.

(*Received in Japan* 29 *July* 1996; *accepted* 9 *September* 1996)