



RESEARCH ARTICLE

Application of *In Situ* Generated Chiral Oxazaborolidine Catalyst for the
Enantioselective Reduction of Prochiral Ketones

Inamdar Murad Ismail^{1*}, Mohan Prasad¹, Lalita S. Kumar²

¹Sun Pharmaceutical Industries Limited, Sarhaul, Sector 18, Gurugram, Haryana, 122015, India.

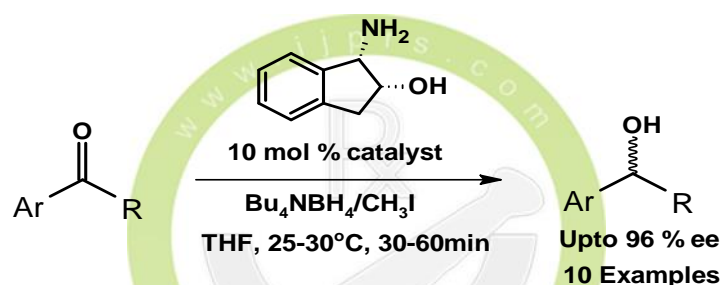
²Discipline of Chemistry, School of Sciences, IGNOU, New Delhi, 110068, India.

Manuscript No: IJPRS/V7/I4/00008, Received On: 08/12/2018, Accepted On: 20/12/2018

ABSTRACT

In situ synthesis of chiral oxazaborolidine catalyst by using (1*S*, 2*R*)-(-)-*cis*-1-amino-2-indanol, tetrabutylammonium borohydride and methyl iodide is described. Various borane reduction systems have been studied. Application of (1*S*, 2*R*)-(-)-*cis*-1-amino-2-indanol along with tetrabutylammonium borohydride and methyl iodide to reduce prochiral ketones to the corresponding alcohols with enantiomeric excess up to 96 % is reported.

Graphical Abstract



KEYWORDS

Enantioselective ketone reduction, *In situ* oxazaborolidine catalyst

INTRODUCTION

Asymmetric reduction of prochiral ketones to give enantiopure alcohols is an essential transformation with diverse applications in pharmaceutical as well as chemical industry. Although an extensive study has already been done in this area of asymmetric conversion, there remains always a need to explore more

ecofriendly, stable, cheaper and easily available catalyst systems.

Undoubtedly, biocatalysis, metal catalysis and organocatalysis are regarded as three major pillars of modern asymmetric chemistry. Organocatalysis fascinates the synthetic organic chemist due to its easy availability, less toxicity and cost effectiveness.

The oxazaborolidine catalyst systems prepared from chiral amino alcohols and borane source have been extensively studied for the asymmetric reduction¹⁻³. The parent catalyst H-CBZ (**1**) *in situ* synthesized from α,α -diphenylpyrrolidine methanol and BH₃-THF

*Address for Correspondence:

Mr. Inamdar Murad Ismail,
Sun Pharmaceutical Industries Limited,
Sarhaul, Sector 18, Gurugram,
Haryana, 122015, India.
E mail ID: murad.inamdar@gmail.com

has been found effective to furnish the asymmetric transformation, however due to its relatively less stability to air and moisture its corresponding B-methyl derivative (**2**) is favored.

Several other amino alcohols derived from natural and unnatural sources were then synthesized and applied as catalysts for various asymmetric transformations⁴. Chirally pure *cis*-1-amino-2-indanols have also been reported for asymmetric transformation.^{5,6}

Didier and coworkers reported (1*S*, 2*R*)-(-)-*cis*-1-amino-2-indanol (**3**) as a chiral catalyst for asymmetric reduction of acetophenone using stoichiometric amounts of 1,3,2-oxazaborolidine B-H compounds. However the authors concluded that no system was found to be efficient with catalytic amounts of ligand (studied)⁶.

In order to achieve high enantioselectivity the essential requirement for chiral catalyst is, it must possess substituent at one face of transition state which can block attack from that side. Considering the structural advantages of indanyl moiety during the chiral transition state Gao Yun and coworkers studied and reported *cis*-1-amino-2-indanol for asymmetric reduction of aromatic prochiral ketones using BH₃-THF System.⁷

The use of borane reagents has limitations due to difficulties in their handling, transportation and storage during commercial applications despite of their commercial availability. Periasamy and coworkers reported tetraalkylammonium borohydride, methyl iodide along with (*S*)- α,α -diphenylpyrrolidine methanol as an efficient catalyst system for asymmetric reduction of prochiral ketones by *in situ* formation of oxazaborolidine catalyst at 25°C in THF to their corresponding alcohols with up to 99 % *ee*⁸. In the past, Periasamy and coworkers also reported that BH₃-THF can be prepared *in situ* using sodium borohydride and iodine in THF. However the combination of α,α -diphenylpyrrolidine methanol, sodium borohydride and iodine gave poor results in asymmetric reduction of acetophenone. The

primary reason for this fact was thought to be sparing solubility of sodium borohydride in THF⁹. Accordingly we have undertaken a study to employ (1*S*, 2*R*)-(-)-*cis*-1-amino-2-indanol as a chiral catalyst along with various borohydride reagents like sodium borohydride (**4**) tetramethylammonium borohydride (**5**) tetraethylammonium borohydride (**6**) and tetrabutylammonium borohydride (**7**).

Here in we report, *in situ* synthesis of chiral oxazaborolidine organocatalyst by using (1*S*, 2*R*)-(-)-*cis*-1-amino-2-indanol, tetrabutylammonium borohydride and methyl iodide to reduce prochiral ketones to the corresponding alcohols with enantiomeric excess up to 96 %.

MATERIALS AND METHOD

General Information

All reactions were carried out under inert atmosphere. Thin layer chromatography (TLC) was performed on precoated aluminium TLC plates, with detection by ninhydrin stain. Products were purified by column chromatography (Ethyl acetate and Hexane solvent system). The products were identified by spectral data (¹H NMR, ¹³C NMR, IR and physical constants) and compared with literature values.

Enantiomeric excess was determined by HPLC using chiral column, Chiralcel-OD-H. Absolute configuration was assigned by comparison of sign of the specific rotation with that of a literature value.

The physical constants were determined using digital melting point apparatus and were observed to be uncorrected. Spectral analysis was performed by ¹H-NMR spectra recorded in DMSO-d₆ and CDCl₃ on a Bruker Avance III, 400 MHz and Bruker Avance 300 MHz. Chemical shifts were reported as δ (ppm) scale using TMS as internal standard with multiplicities and number of protons. Infrared spectra were recorded on a Perkin Elmer IR Spectrometer with ν_{max} value reported in cm⁻¹.

All the products obtained and discussed in this work have been reported and characterized by suitable technique such as ¹H NMR, ¹³C NMR,

IR and were compared with previously reported data.

General experimental procedure for asymmetric reduction of ketones using (1*S*, 2*R*)-(-)-*cis*-1-amino-2-indanol, tetrabutylammonium borohydride and methyl iodide

Tetrabutylammonium borohydride (**7**) (5 mmol) and (1*S*, 2*R*)-(-)-*cis*-1-amino-2-indanol (10 mol %) in THF (5 times) were taken in a three neck RB flask. The contents were stirred at 25 -30°C for about 10 min under nitrogen atmosphere. Methyl iodide (5 mmol) was added using a syringe and the reaction mixture was stirred for about 30 min. Acetophenone derivative (**8a-8k**) (5 mmol) in THF (5 times) was added drop wisely for about 30 min under nitrogen atmosphere. The reaction mixture was stirred till reaction completion. The mixture was carefully quenched with HCl to get pH 5.0-6.0, the organic layer was extracted with Dichloromethane (10 times). The combined organic extract was washed with brine (3 Times), dried over anhydrous Na₂SO₄, and the solvent was evaporated to give residue. The residue was purified on a silica gel column using hexane/ethyl acetate as eluent to furnish desired chirally pure alcohol (**9a-9k**).

RESULTS AND DISCUSSION

Initially various borohydride reagents like sodium borohydride (**4**) tetramethylammonium borohydride (**5**) tetraethylammonium borohydride (**6**) and tetrabutylammonium borohydride (**7**) were examined (Figure 2) by employing these reagents for the asymmetric reduction of acetophenone using (1*S*, 2*R*)-(-)-*cis*-1-amino-2-indanol **3** as a chiral catalyst as per the reported process, **Scheme 1**.

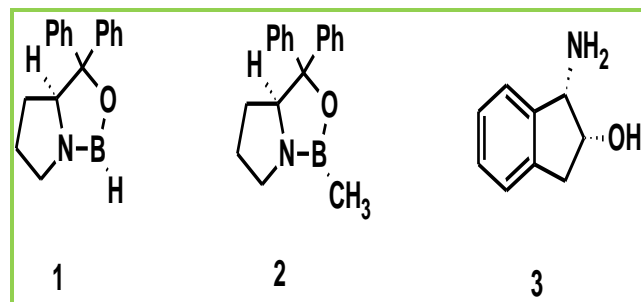


Figure 1: Chiral organocatalysts

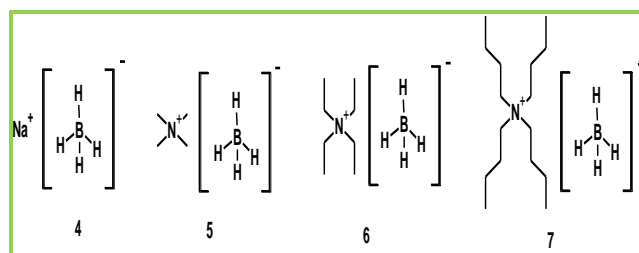
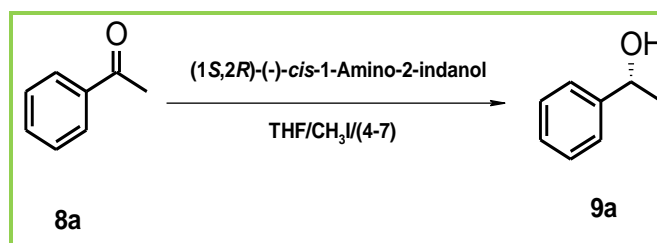


Figure 2: Borohydride reagents examined for reduction



Scheme 1: Reduction of acetophenone using in situ generated oxazaborolidine catalyst

It was observed that acetophenone when subjected for asymmetric reduction by using (1*S*, 2*R*)-(-)-*cis*-1-amino-2-indanol (**3**) as a chiral catalyst with sodium borohydride and methyl iodide gave very poor enantioselectivity. Comparatively better enantioselectivity (67-73%) was obtained with tetramethylammonium borohydride (**5**) tetraethylammonium borohydride (**6**) however longer reaction time required. Employment of tetrabutylammonium borohydride (**7**) and methyl iodide with chiral organocatalyst (**3**) resulted in even better enantioselectivity (91%) with 89 % yield. The improved enantioselectivity for reagent (**7**) attributed to better solubility of tetrabutyl ammonium borohydride (**7**) in THF.

It was also observed that replacing the reaction solvent from THF to DCM or employing iodine instead of methyl iodide lowers the enantioselectivity. Initially we carried out reactions with 5 mol % of catalyst (**3**). When catalyst loading was increased to 10 mol %, enantiomeric excess increased upto 93 %. However further increase in catalyst loading (20 mol %) could not enhance enantioselectivity. The enantioselective reduction of acetophenone under different conditions is given in Table 1.

Table 1: Enantioselective reduction of acetophenone under different conditions^a

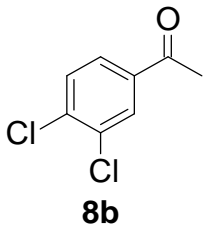
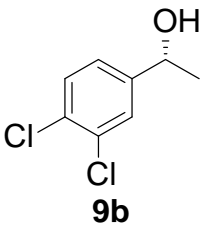
S. No.	Catalyst Loading (mol %)	Reagents	Solvent	Yield (%) ^b	Enantiomeric Excess ^c	Absolute Configuration ^d
1	5	4 / CH ₃ I	THF	85	63	(R)
2	5	5 / CH ₃ I	THF	81	67	(R)
3	5	6 / CH ₃ I	THF	85	73	(R)
4	5	7 / CH ₃ I	THF	89	91	(R)
5	5	7 / Iodine	THF	87	85	(R)
6	5	7 / CH ₃ I	DCM	86	84	(R)
7	10	7 / CH ₃ I	THF	92	93	(R)
8	20	7 / CH ₃ I	THF	89	93	(R)

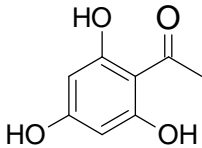
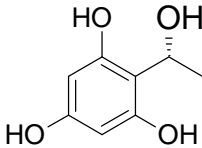
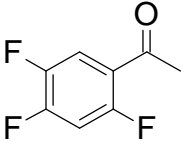
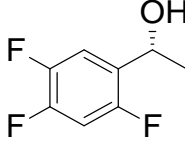
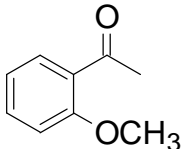
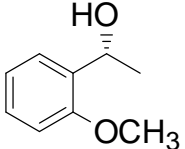
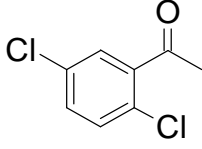
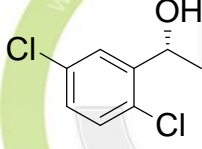
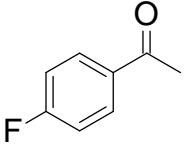
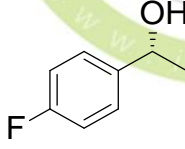
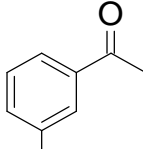
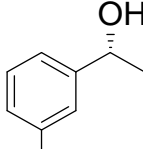
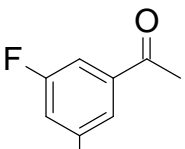
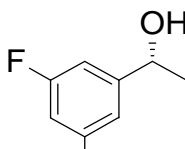
- a. All reactions were carried out using 5 mmol of borohydride reagent, 5 mmol of methyl iodide, 5 mmol of acetophenone, 5 - 20 mol % of (1*S*, 2*R*)-(-)-*cis*-1-amino-2-indanol in 5 times of solvent.
- b. The yields are of isolated product after purification by column chromatography. The products were identified by spectral data (¹H NMR, ¹³C NMR, IR and physical constants) and compared with literature values.
- c. Enantiomeric excess was determined by HPLC using chiral column, Chiralcel-OD-H
- d. Absolute configuration was assigned by comparison of sign of the specific rotation with that of a literature value.

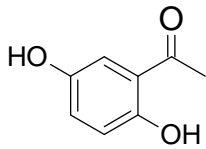
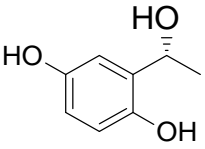
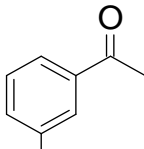
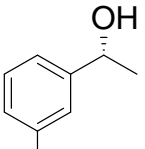
The substrate scope of this protocol is studied by varying substituent on aromatic ring of acetophenone, Table 2. Better enantioselectivity

was obtained with acetophenone derivatives bearing electron withdrawing groups compared to electron donating substituents.

Table 2: Substrate scope for asymmetric reduction of ketones^a

S No.	Starting Material	Product	Yield ^b (%)	Enantiomeric Excess (%) ^c	Absolute Configuration ^d
1	 8b	 9b	93	95	(R)

2	 <p>8c</p>	 <p>8c</p>	88	90	(R)
3	 <p>8d</p>	 <p>9d</p>	94	96	(R)
4	 <p>8e</p>	 <p>9e</p>	89	90	(R)
5	 <p>8f</p>	 <p>9f</p>	93	95	(R)
6	 <p>8g</p>	 <p>9g</p>	92	94	(R)
7	 <p>8h</p>	 <p>9h</p>	90	92	(R)
8	 <p>8i</p>	 <p>9i</p>	93	95	(R)

9	 8j	 9j	89	91	(<i>R</i>)
10	 8k	 9k	92	94	(<i>R</i>)

- All reactions were carried out using 5 mmol of tetrabutylammonium borohydride, 5 mmol of methyl iodide, 5 mmol of acetophenone and 10 mol % of (1*S*,2*R*)-(-)-*cis*-1-amino-2-indanol in 5 times THF.
- The yields are of isolated product after purification by column chromatography. The products were identified by spectral data (¹H NMR, ¹³C NMR, IR, and physical constants) and compared with literature values.
- Enantiomeric excess was determined by HPLC using chiral column, Chiralcel-OD-H
- Absolute configuration was assigned by comparison of sign of the specific rotation with that of a literature value.

CONCLUSION

In conclusion, we have explored *in situ* synthesis of chiral oxazaborolidine catalyst by using (1*S*, 2*R*)-(-)-*cis*-1-amino-2-indanol, tetrabutylammonium borohydride and methyl iodide. Various borane reduction systems have been studied and reported in this work. The chiral organocatalyst (1*S*,2*R*)-(-)-*cis*-1-amino-2-indanol along with tetrabutylammonium bromide, methyl iodide was employed for the reduction of a number of *ortho*, *meta* and *para* substituted acetophenones. It was inferred that acetophenone derivatives bearing electron withdrawing groups depicted better enantioselectivity compared to electron donating substituents.

ACKNOWLEDGEMENT

We are thankful to the analytical department of Sun Pharmaceutical Industries Limited, Gurgaon, India for their characterization

analysis support.

REFERENCES

- (a) Singh, V. K. (1992). Practical and useful methods for the enantioselective reduction of unsymmetrical ketones. *Synthesis*, 1992(7), 605-617. <https://doi.org/10.1055/s-1992-26174>
- (b) Corey, E. J., & Helal, C. J. (1998). Reduction of carbonyl compounds with chiral oxazaborolidine catalysts: a new paradigm for enantioselective catalysis and a powerful new synthetic method. *Angewandte Chemie International Edition*, 37(15), 1986-2012. [https://doi.org/10.1002/\(SICI\)1521-3773\(19980817\)37:15<1986::AID-ANIE1986>3.0.CO;2-Z](https://doi.org/10.1002/(SICI)1521-3773(19980817)37:15<1986::AID-ANIE1986>3.0.CO;2-Z)
- (c) Mathre, D. J., Thompson, A. S., Douglas, A. W., Hoogsteen, K., Carroll, J. D., Corley, E. G., & Grabowski, E. J.

- (1993). A practical process for the preparation of tetrahydro-1-methyl-3, 3-diphenyl-1H, 3H-pyrrolo [1, 2-c][1, 3, 2] oxazaborole-borane. A highly enantioselective stoichiometric and catalytic reducing agent. *The Journal of Organic Chemistry*, 58(10), 2880-2888. <https://doi.org/10.1021/jo00062a037>
2. (a) Corey, E. J., Bakshi, R. K., & Shibata, S. (1987). Highly enantioselective borane reduction of ketones catalyzed by chiral oxazaborolidines. Mechanism and synthetic implications. *Journal of the American Chemical Society*, 109(18), 5551-5553. <https://doi.org/10.1021/ja00252a056>
- (b) Corey, E. J., Bakshi, R. K., Shibata, S., Chen, C. P., & Singh, V. K. (1987). A stable and easily prepared catalyst for the enantioselective reduction of ketones. Applications to multistep syntheses. *Journal of the American Chemical Society*, 109(25), 7925-7926. <https://doi.org/10.1021/ja00259a075>
3. (a) Itsuno, S., Ito, K., Hirao, A., & Nakahama, S. (1983). Asymmetric reduction of aromatic ketones with the reagent prepared from (S)-(-)-2-amino-3-methyl-1, 1-diphenylbutan-1-ol and borane. *Journal of the Chemical Society, Chemical Communications*, (8), 469-470. <https://doi.org/10.1039/C39830000469>
- (b) Corey, E. J. (1990). New enantioselective routes to biologically interesting compounds. *Pure and applied chemistry*, 62(7), 1209-1216. <https://doi.org/10.1351/pac199062071209>
4. Reddy, U. V. S., Chennapuram, M., Seki, C., Kwon, E., Okuyama, Y., & Nakano, H. (2016). Catalytic Efficiency of Primary β -Amino Alcohols and Their Derivatives in Organocatalysis. *European Journal of Organic Chemistry*, 2016(24), 4124-4143. <https://doi.org/10.1002/ejoc.201600164>
5. Thompson, W. J., Fitzgerald, P. M., Holloway, M. K., Emini, E. A., Darke, P. L., McKeever, B. M., ... & Zugay, J. A. (1992). Synthesis and antiviral activity of a series of HIV-1 protease inhibitors with functionality tethered to the P1 or P1'phenyl design. *Journal of medicinal chemistry*, 35(10), 1685-1701. <https://doi.org/10.1021/jm00088a003>, PMID:1588551
6. Didier, E., Loubinoux, B., Tombo, G. H. R., & Rihs, G. (1991). Chemo-enzymatic synthesis of 1, 2-and 1, 3-amino-alcohols and their use in the enantioselective reduction of acetophenone and anti-acetophenone oxime methyl ether with borane. *Tetrahedron*, 47(27), 4941-4958. [https://doi.org/10.1016/S0040-4020\(01\)80959-5](https://doi.org/10.1016/S0040-4020(01)80959-5)
7. Hong, Y., Gao, Y., Nie, X., & Zepp, C. M. (1994). cis-1-amino-2-indanol in asymmetric synthesis. Part I. A practical catalyst system for the enantioselective borane reduction of aromatic ketones. *Tetrahedron letters*, 35(36), 6631-6634. [https://doi.org/10.1016/S0040-4039\(00\)73453-8](https://doi.org/10.1016/S0040-4039(00)73453-8)
8. Anwar, S., & Periasamy, M. (2006). A convenient method for the preparation of oxazaborolidine catalyst in situ using (S)- α , α -diphenylpyrrolidinemethanol, tetrabutylammonium borohydride, and methyl iodide for the asymmetric reduction of prochiral ketones. *Tetrahedron: Asymmetry*, 17(23), 3244-3247. <https://doi.org/10.1016/j.tetasy.2006.11.032>
9. Periasamy, M., Kanth, J. B., & Prasad, A. B. (1994). Convenient procedures for the asymmetric reductions utilizing α , α -diphenyl-pyrrolidinemethanol and borane complexes generated using the I2/NaBH4 system. *Tetrahedron*, 50(21), 6411-6416. [https://doi.org/10.1016/S0040-4020\(01\)80657-8](https://doi.org/10.1016/S0040-4020(01)80657-8)

HOW TO CITE THIS ARTICLE

Ismail, I. M., Prasad, M., Kumar, L. S. (2018). Application of In Situ Generated Chiral Oxazaborolidine Catalyst for the Enantioselective Reduction of Prochiral Ketones. *International Journal for Pharmaceutical Research Scholars*, 7(4), 31-39. <http://dx.doi.org/10.31638/IJPRS.V7.I4.00008>

THIS PAGE IS INTENTIONALLY LEFT BLANK.

