A New Method for the Preparation of Oxazaborolidine Catalyst In Situ Using 1,2-Aminoalcohol, Sodium Borohydride, and Diiodomethane for the Asymmetric Reduction of Prochiral Ketones and N-Substituted Imines

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Abstract: An oxazaborolidine catalyst is readily prepared in situ at room temperature in THF using 1,2-aminoalcohols and borane generated from sodium borohydride/CH₂I₂ reagent system. The oxazaborolidine/BH₃ reagent system prepared in this way is useful for the reduction of prochiral ketones and N-substituted imines to the corresponding alcohols and amines with moderate to good enantiomeric excesses.

Keywords: Asymmetric reduction, oxazaborolidine, borane, ketone, imine.

1. INTRODUCTION

Chiral organoborane reagents, in particular 1,3,2-oxazaborolidines, have been extensively studied and applied as efficient Lewis acid catalysts to a wide range of asymmetric transformations [1,2]. B-H oxazaborolidines are commonly used as convenient catalysts for the enantioselective borane reduction of prochiral ketones, imines, and oximes [1a,c-f,3]. The most used method described in the literature for the preparation of B-H oxazaborolidines is by the in situ reaction of chiral aminoalcohols with an excess of borane without isolation and characterization of the catalyst [1-3]. We have reported from this laboratory that borane –THF prepared in situ using NaBH₄ and I₂ in THF is useful for several synthetic applications that require borane-THF (Table 1). Unfortunately, the α,α-diphenylpyrrolidinemethanol and NaBH₄/I₂ combination gave poor results in the asymmetric reduction of acetophenone [4]. Herein we report that the NaBH₄, CH₂I₂ and 1,2-aminoalcohols combination is useful for the asymmetric reduction of ketones and imines to obtain the corresponding alcohols and amines with moderate to good enantiomeric excess.

2. RESULTS AND DISCUSSION

The NaBH₄ species has been reported to have good reactivity as a reducing agent [5]. This reagent has been used for the reduction of a wide large number of representative carbonyl functionalities. However, it has been widely employed in the reduction with ZrCl₄ [3C,6], Me₂SiCl [7, 8], BF₃·OEt₂ [8], ZnCl₂ [9], I₂ [4,10,17], Lanthanoid [11], (PhCO₂H, H₂BO₂) [12], SnCl₄ [13a], CoCl₂ [13b], H₂SO₄ [14], etc, in THF solution instead of BH₃ reagents. Also chiral 1,2-aminoalcohol, such as valinol and leucinol [3c,6], 2-(α-hydroxybenzyl)benzimidazole [15], α,α-diphenylpyrrolidinemethanol [4,7b], 12-sulfonamide [8], azacrownethers [16], ferrocenylaminoalcohol [17] has been used in the asymmetric reduction with NaBH₄.

It has been reported that NaBH₄ could not reduce diiodomethane to methyl iodide [18]. We have observed that the sodium borohydride (NaBH₄)/CH₂I₂ reagent system in the presence of 1,2-aminoalcohols affords a very easy and simple preparation of the oxazaborolidines catalyst (Fig. 1, Scheme 1). As well as the BH₃ species, which effectively reduces acetophenone within about 30 min at 25 °C and Phenyl(1-phenylethylidene)amine (6) within about 2 h at 25°C (Scheme 2, Table 1).

Initially, we examined the reduction of acetophenone (5) using the sodium borohydride (NaBH₄)/CH₂I₂ combination under the influence of (R)-leucinol (1) (10 mol%) in THF at 25 °C. In this case, the desired alcohol (7) was obtained in 84% yield and 72% ee. Stereoselectivities up to 87% ee in the presence of (R)-valinol (2) were reached with acetophenone (5). We observed that the NaBH₄/CH₂I₂ reagent system in the presence of catalyst (R)-prolinol (4) (10 mol%) yielded the desired alcohol 7 in 88% yield and 49% ee. The poor results were obtained with (R)-methioninol (3) (23%
In each case the (S)-enantiomer of the secondary alcohol \((7)\) was formed preferentially.

The use of \(I_2\) in place of \(CH_2I_2\) led to a decreased ee and yield. In the absence of additive (\(CH_2I_2\) and \(I_2\)), the acetophenone \((5)\) and phenyl (1-phenylethylidene)amine \((6)\) remained uninfected. Upon the addition of \(CH_2I_2\), evolution of \(CH_4\) was noticed, indicating that the formation of \(BH_3\cdot THF\) in situ from sodium borohydride is essential for the reduction. Chiral aminoalcohol \((R)\)-valinol \((3)\) with 10 mol% or 100 mol% in THF gave maximum selectivity (Table 1).

Table 1. Oxazaborolidine-Mediated Reduction of Acetophenone and Phenyl-(1-Phenylethylidene)Amine

<table>
<thead>
<tr>
<th>Substrat</th>
<th>Additive</th>
<th>Catalyst (mol %)</th>
<th>Yield (%)</th>
<th>Configuration</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetophenone</td>
<td>CH2I2</td>
<td>None</td>
<td>45</td>
<td>-</td>
<td>0°</td>
</tr>
<tr>
<td></td>
<td>CH2I2</td>
<td>1 (10)</td>
<td>84</td>
<td>S</td>
<td>72°</td>
</tr>
<tr>
<td></td>
<td>I2</td>
<td>1(10)</td>
<td>73</td>
<td>S</td>
<td>68°</td>
</tr>
<tr>
<td></td>
<td>CH2I2</td>
<td>2 (10)</td>
<td>94</td>
<td>S</td>
<td>87°</td>
</tr>
<tr>
<td></td>
<td>I2</td>
<td>2 (10)</td>
<td>85</td>
<td>S</td>
<td>76°</td>
</tr>
<tr>
<td></td>
<td>CH2I2</td>
<td>3 (10)</td>
<td>51</td>
<td>S</td>
<td>23°</td>
</tr>
<tr>
<td></td>
<td>CH2I2</td>
<td>4 (10)</td>
<td>88</td>
<td>S</td>
<td>49°</td>
</tr>
<tr>
<td>Phenyl (1-phenylethylidene)amine</td>
<td>CH2I2</td>
<td>None</td>
<td>92</td>
<td>-</td>
<td>0°</td>
</tr>
<tr>
<td></td>
<td>CH2I2</td>
<td>1 (100)</td>
<td>65</td>
<td>S</td>
<td>70°</td>
</tr>
<tr>
<td></td>
<td>I2</td>
<td>1(100)</td>
<td>53</td>
<td>S</td>
<td>66°</td>
</tr>
<tr>
<td></td>
<td>CH2I2</td>
<td>2(100)</td>
<td>72</td>
<td>S</td>
<td>74°</td>
</tr>
<tr>
<td></td>
<td>I2</td>
<td>2 (100)</td>
<td>64</td>
<td>S</td>
<td>67°</td>
</tr>
<tr>
<td></td>
<td>CH2I2</td>
<td>3 (100)</td>
<td>49</td>
<td>S</td>
<td>32°</td>
</tr>
<tr>
<td></td>
<td>CH2I2</td>
<td>4 (100)</td>
<td>58</td>
<td>S</td>
<td>64°</td>
</tr>
</tbody>
</table>

1. All reactions were carried out using 4 mmol of NaBH4, 2 mmol of CH2I2, 5 mmol of ketone or imine in 25 mL of solvent at 25 °C.
2. Isolated yields of the corresponding secondary alcohol and amine.
3. Absolute configurations were assigned by comparison of the sign of the specific rotation with that of a literature value.
4. Based on reported maximum \([20] \alpha_d^2 = -45.2 (c 2, MeOH)\) for (S)-isomer.
5. Based on reported maximum \([21] \alpha_d^2 = +17 (c 1, MeOH)\) for (S)-isomer.
The reduction of Ketone (5) with NaBH₄/CH₂I₂ in the absence of oxazaborolidines catalysts was sluggish. In contrast the uncatalysed reduction of imine (6) with this reducing agent was essentially complete within 10 min.

To verify the rationale, a coordination between a sulfur atom which is a softer Lewis base in the (R)-methioninol, and borane provides low selectivity and yield. The results support our rationale.

In the reduction of N-substituted imine (6) the best enantioselectivity with up to 74% ee was achieved when (R) valinol (2) with 100 mol% was utilized as catalyst whereas, the (R)-prolinol (4) gave the amine (8) in 64% ee (58% yield) and with (R)-methioninol (3) in 32% ee (49% yield). We observed that the NaBH₄/CH₂I₂ reagent system in the presence of catalyst (R)-leucinol (1) (100 mol%) yielded the desired amine (8) in 70% ee and 65% yield, reduction of imine (6) with NaBH₄/CH₂I₂ and 1,2 amino alcohol did indeed give rise predominantly to the (S)-amine (8).

Based on the rationale, the limited success shown in the reduction of N-substituted imine (6) due to the low electrophilicity of the imine carbon and the rapid equilibration between the E and Z isomer [19].

3. MECHANISTIC CONSIDERATION

In 1987, Corey et al. [3b] Reported ¹H NMR, ¹¹BNMR and infrared spectroscopic evidence of the structure of valinol chiral 3. The oxazaborolidine 3 is unable to reduce ketones and imines [1a,c-f,3]. The addition of second equivalent of borane at the opposite site of the iso-propyl group gives the effective chiral reducing agent 3'. The complex is sterically unfavorable 3''.

Our adaptation of the mechanism for the reduction of ketones and imines to alcohols and amines agrees with high enantioselectivity observed. The nitrogen or oxygen of the the anti-geometric isomer is complexed by the endocyclic borane allowing the chiral hydrogen transfer via a six-membered cyclic transition state 9.

At this stage, the stereogenic centre is formed, benzylic amines or alcohols and (R)-Valinol are obtained after work-up. This hypothetical mechanism illustrates a general feature of the reaction.

4. CONCLUSION

In conclusion, the asymmetric reduction of prochiral ketones and N-substituted imines using NaBH₄/CH₂I₂ reagent system gave the corresponding chiral secondary alcohol and amine in moderate to good selectivity. This method offers a relatively simple and inexpensive approach to this widely used transformation in syntheses.

5. EXPERIMENTAL

5.1. General

IR spectra were determined using a Shimadzu IR-435 spectrometer. ¹H NMR and ¹³C NMR spectra were recorded at 400 and 100MHz using JNM-A400 spectrometer respectively. Mass spectra were recorded on a JEOL JMS-SX102A mass spectrometer. Optical rotations were taken with a JASCO p-1010 polarimeter. Tetrahydrofurane (THF) was distilled from sodium benzophenone ketyl before use. TLC was carried out on Merck glass plates precoated with silica gel 60F-254 (0.25mm) and column chromatography was performed using Merck 23-400 mesh silica gel. All aminoal-
5.2. General Procedure for the Asymmetric Reduction of Acetophenone Utilizing the NaBH₄/CH₂I₂ Reagent System

Sodium borohydride (0.19 g, 4 mmol) and (R)-valinol (0.052 g, 0.5 mmol) in THF (12 mL) were taken in a two neck RB flask. The contents were stirred at 25 °C for 15 min under an argon atmosphere. Methylene iodide (0.54 g, 2 mmol) was added as a syringe and the reaction mixture was stirred for about 30 min. Acetophenone (5) (0.60 g, 5 mmol) in THF (12 mL) was added dropwise through a pressure equalizer for about 30 min under an argon atmosphere. The reaction mixture was stirred until the ketone had disappeared. The mixture was carefully quenched with 3 M HCl (30 mL). The combined organic extract was washed with brine (30 mL), dried over anhydrous Na₂SO₄, and the solvent was evaporated to give a yellow residue. The residue was purified on a silica gel column chromatography to obtain the (S)-1-phenylethanol (7) using hexane/ethyl acetate (973) as eluent, identified by comparison (GC, ¹H NMR) with an authentic sample. Conditions of GC analyses: β-DEX 120, 120column, 30m length, 0.25 mm internal diameter, isothermal temperature program, He as carrier gas (2.4 mL/min). tᵣ R isomer 52.1 min, tᵣ S isomer 55.7 min.

5.3. General Procedure for the Asymmetric Reduction of Acetophenone Utilizing the NaBH₄/I₂ Reagent System

Sodium borohydride (0.19 g, 4 mmol) and (R)-leucinol (0.059 g, 0.5 mmol) in THF (12 mL) were taken in a two neck RB flask. The contents were stirred at 25 °C for 5 min under an argon atmosphere. I₂ (0.50 g, 2 mmol) dissolved in THF (12 mL) was added slowly for about 15-20 min through a pressure equalizer at 0 °C under an argon atmosphere and the reaction mixture was allowed to stir at 0 °C for about 30 min. The reaction mixture was then slowly brought to 25 °C and was stirred for about 10 min under an argon atmosphere. Phenyl-(1-phenylethylidene)amine (6) (0.98 g, 5 mmol) in THF (3 mL) was slowly added through a pressure equalizer for about 30 min at 0 °C under an argon atmosphere. After 2 h, a 3 M sodium hydroxide (5 mL) was added dropwise, and stirring was continued for 1 h. layers were separated and the aqueous layer was extracted with diethyl ether (3×5 mL). The extracts were combined and dried with magnesium sulphate. Evaporation of the solvents and flash column chromatography on silica gel (petroleum ether/ethyl acetate, 8:2) afforded (S)-phenyl-(1-phenylethylidene)amine (8), identified by comparison (GC, ¹H NMR) with an authentic sample. Elemental analysis, Calcd C, 85.24; H, 7.66; N, 7.10. for S isomer [α]D = +17 ° (C, CH₃OH); lit. [21] [α]D = +18.5° (C, CH₃OH). for R isomer [α]D = -16° (C, CH₃OH); lit. [21] [α]D = -17.7° (C, CH₃OH).

REFERENCES


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