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Highly enantioselective reduction of achiral ketones with $NaBH_4/Me_3SiCl$ catalyzed by (*S*)-α,α-diphenylpyrrolidinemethanol

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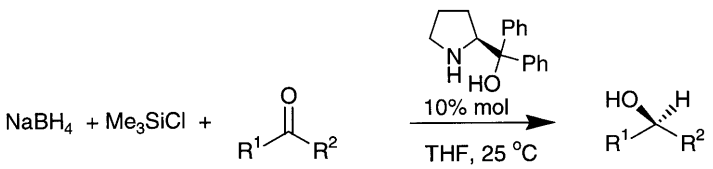
Abstract

The reducing agent prepared from sodium borohydride, trimethylsilyl chloride and a catalytic amount of (*S*)-α,α-diphenylpyrrolidinemethanol has been successfully applied to the enantioselective reduction of ketones. The optically active secondary alcohols were obtained in excellent enantiomeric excess and almost quantitative chemical yield.

Keywords: asymmetric reduction; enantioselective catalysis; $NaBH_4/Me_3SiCl$ combination.

Much attention has been devoted to the enantioselective synthesis of optically active alcohols which are important starting materials for many biologically active compounds.[1] The chiral oxazaborolidine-catalyzed reduction (CBS reduction) of prochiral ketones developed by Corey and co-workers is one of the most important methods for generation of chiral secondary alcohols.[2] However, the CBS reduction commonly requires expensive borane–dimethyl sulfide complex, borane–tetrahydrofuran, borane–1,4-thioxane[3] or catecholborane,[2f,4] which are toxic and rather expensive. Moreover, due to the air and moisture sensitivity of the B–H oxazaborolidine, the method for generation of the oxazaborolidine using α,α-diphenylpyrrolidine methanol and borane suffers from a complicated preparation procedure.[2a] The expanding utility of the CBS reduction in the pharmaceutical industries has created a need for development of more convenient processes for reduction of prochiral ketones to chiral secondary alcohols. Herein we report an enantioselective reduction of ketones with the combined reagent of $NaBH_4/Me_3SiCl$ and a catalytic amount of (*S*)-α,α-diphenylpyrrolidinemethanol.



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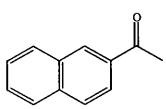
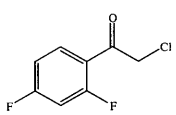
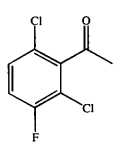
Sodium borohydride has become one of the most widely used reagents for both laboratory and industrial scale application in chemistry.[5] It was reported that the combination reagent of $LiBH_4(NaBH_4)$ and Me_3SiCl was used for the reduction of the carboxyl group of amino acids. The reaction mechanism proposed that a borane–tetrahydrofuran complex was formed when $LiBH_4(NaBH_4)$ was treated with Me_3SiCl in THF,[6] and this inspired us to investigate the possibility of carrying out the CBS asymmetric reductions of ketones by formation of the oxazaborolidine in situ from $NaBH_4/Me_3SiCl$ and (*S*)-α,α-diphenylpyrrolidinemethanol.

Typically a mixture of 1.2 equivalents of $NaBH_4$ and Me_3SiCl in THF was allowed to react at 70°C for one hour, then 0.1 equivalents of (*S*)-α,α-diphenylpyrrolidinemethanol was added to give a reducing mixture to which the ketone was slowly added for reduction at room temperature. We have found that the reduction of ketones using the combined reagent of $NaBH_4/Me_3SiCl$ catalyzed by (*S*)-α,α-diphenylpyrrolidinemethanol yielded the corresponding alcohols almost quantitatively with excellent enantiomeric excess. The reduction of several ketones was examined by using the new reduction conditions (Table 1). In each case, the enantioselective reduction gave almost the same result as a CBS reduction.[2a] Reduction of acetophenone (entry 1) offered (*R*)-1-phenylethanol in 96% ee (97% in CBS reduction). In the

Table 1
Asymmetric reduction of prochiral ketones using the combination of $NaBH_4$ and Me_3SiCl catalyzed by (*S*)-α,α-diphenylpyrrolidinemethanol[a]

Entry	Ketone	Yield (%) [b]	E.e (%) [c]	Config.[d]
1	$C_6H_5COCH_3$	98	96	*R*
2	$C_6H_5COC_2H_5$	96	90	*R*
3	$C_6H_5COCH_2Cl$	96	96	*S*
4	$C_6H_5COCH_2Br$	95	98	*S*
5	*p*-F-$C_6H_4COCH_2CH_2Cl$	96	93	*S*
6		97	98	*R*
7		93	92	*S*
8		95	96	*R*

[a] All reactions were carried out using 1.2 mmol of $NaBH_4$, 1.2 mmol of Me_3SiCl, 1.0 mmol ketone and 0.1 mmol of (*S*)-α,α-diphenylpyrrolidinemethanol; [b] Isolated yields; [c] Ee determined by HPLC on chiralcel OD column with 5% isopropanol in hexane as solvent; [d] Absolute configurations were determined by the comparison of optical rotation with literature values.

reduction of α-bromoacetophenone and 2-acetonaphthenone (entries 4 and 6), the highest enantiomeric excesses (98%) were observed. After reaction, the chiral auxiliary (*S*)-α,α-diphenylpyrrolidinemethanol was easily recovered in 86% yield by extraction into aqueous acid and precipitation with ammonium hydroxide. The results suggest that the catalyst, the B–H oxazaborolidine, is generated in situ on treatment of (*S*)-α,α-diphenylpyrrolidinemethanol with the combined reagent of $NaBH_4/Me_3SiCl$.

The following procedure for the asymmetric reduction of acetophenone is representative. Freshly distilled trimethylsilyl chloride (130 mg, 1.2 mmol) was added to a suspension of $NaBH_4$ (45 mg, 1.2 mmol) in dry THF (5 mL). After the mixture was heated at 70°C for 1 h and allowed to cool to room temperature, a solution of (*S*)-α,α-diphenylpyrrolidinemethanol (25 mg, 0.1 mmol) in THF (2 mL) was added. When there was no gas emitted, a solution of acetophenone (120 mg, 1 mmol) in THF (2 mL) was added slowly with a gas-tight syringe controlled by a syringe pump to the reductive system at a rate of 0.6 mL/h. After the addition was complete, the mixture was hydrolyzed with 2N HCl (5 mL) and extracted with ether (3×10 mL). The combined organic layers were washed with brine, and dried with sodium sulfate. After removal of the solvent by distillation, the residue was distilled under vacuum to afford (*R*)-1-phenylethanol (120 mg) in 98% yield. The optical purity of (*R*)-1-phenylethanol was checked by HPLC on a Chiralcel OD column to be 96% ee.

In summary, a highly practical enantioselective reduction of prochiral ketones with $NaBH_4/Me_3SiCl$ catalyzed by (*S*)-α,α-diphenylpyrrolidinemethanol is demonstrated. The results of our research of asymmetric reduction are favorably comparable to the reported CBS reduction. This in situ procedure eliminates to use of toxic borane complexes and the necessity of isolating unstable air and moisture sensitive B–H oxazaborolidines, providing a cost-effective and simple manipulation method for enantioselective reduction of prochiral ketones.

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