

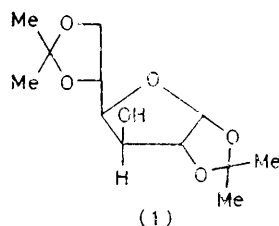
Asymmetric Reduction of Prochiral Aromatic Ketones with Reagents prepared from Sodium Borohydride and Lewis Acids in the presence of 1,2:5,6-Di-O-isopropylidene- α -D-glucofuranose

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Summary Asymmetric reduction of aromatic ketones with reagents formed from sodium borohydride and various Lewis acids in the presence of 1,2:5,6-di-O-isopropylidene- α -D-glucofuranose afforded the corresponding phenyl carbinols in reasonably good optical yields (up to 88%).

THE asymmetric reduction of prochiral ketones with chirally modified metal hydrides continues to be studied actively.¹ Many studies, mostly based on the use of lithium aluminium hydride derivatives modified by chiral alcohols,² aminoalcohols,³ and amines⁴ have been conducted with both the reagents and the experimental conditions being varied in order to obtain optimum results and to gain an insight into the mechanism of reduction.

In contrast, little attention has been paid to the use of sodium borohydride in this type of asymmetric reduction.[†] We have recently found that prochiral ketones are asymmetrically reduced by NaBH₄⁵ and its derivatives⁶ in the presence of hydroxymonosaccharide derivatives. Carbinols produced from the reduction of propiophenone with NaBH₄ in the presence of 1,2:5,6-di-O-isopropylidene- α -D-glucofuranose (**1**) have been obtained in as much as 39% enantiomeric excess.⁵ When NaBH₃(RCO₂), prepared from NaBH₄ and carboxylic acids, was used instead of NaBH₄ for this reduction optical yields of 45–91% were obtained.⁶



We here describe the additive effect of Lewis acids on the asymmetric reduction of prochiral aromatic ketones with NaBH₄ in the presence of (**1**). This system gave the *R* enantiomer in excess in each case, while the *S* stereoisomer was only produced in one case using ZnCl₂ (0.5 mol equiv.) and NaBH₄ (1 mol equiv.) as the reducing agent. The optical yield was enhanced by ageing the reagent before introducing the ketone and by increasing the proportion of (**1**) used.

The procedure is illustrated by the asymmetric reduction of propiophenone with NaBH₄ and ZnCl₂ in the presence of (**1**) under nitrogen. A solution containing ZnCl₂ (5 mmol) in tetrahydrofuran (THF) (10 ml) was added to a mixture of NaBH₄ (10 mmol) and THF (5 ml) over 5 min, while the temperature was maintained at 30 °C. The resulting suspension was stirred at 25 °C for 3 h and then a solution of (**1**) (20 mmol) in THF (10 ml) was added. 1 h after mixing, propiophenone (10 mmol) was introduced and the mixture was stirred at 25 °C for 48 h. Since a precipitate of NaCl was produced it was not possible to determine whether or not the reaction was homogeneous. The usual work-up gave a pale yellow oil which was purified by distillation to give *S*-(-)-3-phenylpropanol, [α]_D²⁰ -18.6° (*c* 6.60, Et₂O). This represents a 53% excess of the *S*-(-)-enantiomer based upon the known maximum rotation, [α]_D²⁰ -34.8° (*c* 8, Et₂O).⁷

The action of a metal chloride on NaBH₄ may possibly lead to the corresponding metal borohydride as the dominant species.^{8,9} However, both MgCl₂ and BaCl₂ seemed to react with NaBH₄ only sluggishly and incompletely under the conditions employed here. The Table reveals that the addition of either AlCl₃ or ZnCl₂ produced a significant improvement in the extent of the asymmetric reduction, whereas satisfactory results could not be obtained by the addition of (PhCH₂)Me₃N⁺Cl⁻, MgCl₂, or BaCl₂. Thus, up

† Several studies have recently been reported on asymmetric reductions using NaBH₄ in aqueous solution in the presence of chiral phase-transfer catalysts (J. P. Massé and E. R. Parayre, *J.C.S. Chem. Comm.*, 1976, 438; S. Colonna and R. Fornasier, *J.C.S. Perkin I*, 1978, 371) or bovine serum albumin (T. Sugimoto, Y. Matsumura, S. Tanimoto, and M. Okano, *J.C.S. Chem. Comm.*, 1978, 926).

TABLE. Asymmetric reduction of aromatic ketones with reagents prepared from NaBH₄ and Lewis acids in the presence of (1) in THF at 25 °C for 48 h.^a

Reagent	Ketone	Yield/% ^b	Alcohols produced [α] _D ²⁰ /°	Optical yield/%	Absolute configuration
NaBH ₄	EtCOPh	100	+ 8.72 ^c	25	R
NaBH ₄ + (PhCH ₂)Me ₃ N ⁺ Cl ⁻	EtCOPh	100	+ 1.17	3.3	R
NaBH ₄ + 1/2 MgCl ₂	EtCOPh	100	+ 7.83	23	R
NaBH ₄ + 1/2 BaCl ₂	EtCOPh	100	+ 10.2	29	R
NaBH ₄ + 1/3 AlCl ₃	EtCOPh	55	+ 18.9	54	R
NaBH ₄ + 1/2 ZnCl ₂	EtCOPh	77	- 18.6	53	S
NaBH ₄ + 1/2 ZnCl ₂ ^d	EtCOPh	79	- 24.9	72	S
NaBH ₄ + 1/2 ZnCl ₂ ^e	EtCOPh	66	- 30.6	88	S
NaBH ₄ + 1/2 ZnCl ₂	MeCOPh	99	- 21.4 ^f	41	S
NaBH ₄ + 1/2 ZnCl ₂	Pr ⁿ COPh	100	- 19.5 ^g	45	S
NaBH ₄ + 1/2 ZnCl ₂	Pr ⁱ COPh	99	- 2.43 ^h	5.1	S
NaBH ₄ + 1/2 ZnCl ₂	β-Naphthyl methyl ketone	100	- 10.6 ⁱ	25	S

^a Conditions: NaBH₄, 10 mmol; (PhCH₂)Me₃N⁺Cl⁻, 10 mmol (MgCl₂, BaCl₂, and ZnCl₂, 5 mmol; AlCl₃, 3.33 mmol); ketone, 10 mmol; (1), 20 mmol; total volume of THF, 25 ml. The ratio of [reagent]:[ketone]:[(1)] was 1:1:2 unless otherwise stated. ^b Based on relative peak areas of carbinol and unchanged ketone in g.l.c. ^c Optical yield was calculated from optical rotation. Maximum value for 3-phenylpropanol [α]_D²⁰ + 34.8° (c 8, Et₂O) (see ref. 7). ^d The ratio of [reagent]:[ketone]:[(1)] was 1:1:4. ^e Reagent and (1) were allowed to stand for 48 h. ^f Maximum value for [α]_D²³ - 52.5° (c 2.27, CH₂Cl₂) (see U. Nagai, T. Shishido, R. Chiba, and H. Mitsuhashi, *Tetrahedron*, 1965, **23**, 1201). ^g Maximum value for [α]_D²⁰ + 43.6° (c 4.18, C₆H₆) (see J. Kenyon and S. M. Partridge, *J. Chem. Soc.*, 1936, 128). ^h Maximum value for [α]_D²⁰ + 47.7° (c 6.8, Et₂O) (see D. J. Cram and J. E. McCarty, *J. Amer. Chem. Soc.*, 1957, **79**, 2866). ⁱ Maximum value for [α]_D²⁰ - 41.9° (c 5, EtOH) (see S. R. Lander, B. J. Miller, and A. R. Tatchell, *J. Chem. Soc.*, 1966, 2282).

to 50% selectivities were readily obtained in the reduction of propiophenone with reagents formed from NaBH₄ and AlCl₃ or ZnCl₂ in the presence of (1). Interestingly, the reagent from NaBH₄ and ZnCl₂ in the presence of (1) is the only one which gives the S enantiomer in excess, while phenyl carbinols possessing the R configuration are obtained with other reagents and NaBH₄ alone.

The use of 4 mol equiv. of (1) to the reagent formed from NaBH₄ and ZnCl₂ proved to be more effective, giving the carbinol in 72% optical yield. Unfortunately, further investigation of the dependence of selectivity on the amount of (1) used was hindered by its limited solubility in THF.

The reduction of four additional aromatic ketones with NaBH₄ and ZnCl₂ in the presence of (1) afforded relatively good selectivities (25—45%) except for isopropyl phenyl ketone. All the alcohols thus obtained possessed the S-configuration.

Finally, it was found that changing the time that the reagent had been allowed to stand with (1) from 1 to 48 h before use increased the optical yield to 88%. A similar ageing effect was reported by Yamaguchi and Mosher³ for the reduction of ketones with chiral reagents from LiAlH₄ and Darvon alcohols.

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