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Amino Acid Mediated Borane Reduction of Ketones

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Summary. Acetophenone, 2,2-dimethylcyclopentanone, 3,3-dimethyl-2-butanone, 3-methyl-2-butanone, and 2-pentanone were reduced with (*S*)-proline- and (*S*)-phenylalanine-mediated borane in good to very good yields giving predominantly (32–86% *ee*) alcohols of (*R*)-configuration.

Keywords. Acetophenone; Asymmetric induction; Modified borane reduction; Proline.

Durch Aminosäuren vermittelte Reduktion von Ketonen mit Boran

Zusammenfassung. Acetophenon, 2,2-Dimethylcyclopentanon, 3,3-Dimethyl-2-butanon, 3-Methyl-2-butanon und 2-Pentanon wurden mit Hilfe von Boran in Gegenwart von (*S*)-Prolin und (*S*)-Phenylalanin in guten bis sehr guten Ausbeuten reduziert, wobei vornehmlich (32–86% *ee*) die (*R*)-konfigurierten Alkohole erhalten wurden.

Introduction

Amino acids are versatile materials and can be used as enantioselective auxiliaries [1]. It has been shown that sodium salts of amino acid borane complexes [2] produced from an equimolar amount of sodium borohydride and optically active α-amino acids in tetrahydrofurane (*THF*) at room temperature reduce various ketones (reduction time: 10 days) to the corresponding optically active alcohols (2–62% *ee*). The results of the asymmetric reduction of acetophenone with the reagent prepared from (*S*)-(−)-proline and $NaBH_4$ or with that synthesized from sodium (*S*)-(−)-prolinate and B_2H_6 were very similar (∼33% *ee*). Various alkyl phenyl ketones were examined [3] using a 2:1 ratio of borane/(*S*)-valinol: an increase in the length of the alkyl chains in the series led to higher enantioselectivities.

Corey et al. have found that a fast reaction occurs between (*S*)-2-amino-3-methyl-1,1-diphenylbutan-1-ol and 2 equivalents of B_2H_6 to give rise to the corresponding oxazaborolidine [4]. A solution of this oxazaborolidine in *THF* did not reduce ketones [4]. However, mixtures of oxazaborolidine and $BH_3 \cdot THF$

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(6.6 mol equiv.) cause a complete reduction of acetophenone in less than a minute to give 97% of (*R*)-1-phenylethanol.

The borane reduction of ketones applying catalytic amounts of (*S*)-proline or (*S*)-(+)-prolinol in refluxing toluene gave the alcohols in good enantiomeric excess (81–95%) [5], whereby (*R*)-1-phenylethanol was isolated with 59% and >95% *ee* when 2 and 10 mol% of (*S*)-(−)-proline were used, respectively. However, at room temperature the reaction yields (*R*)-1-phenylethanol in only low enantiomeric excess (8%) with 2 mol% of (*S*)-(−)-proline.

Here we wish to describe our preliminary research on borane reductions of ketones employing (*S*)-(−)-proline or (*S*)-(−)-phenylalanine as chiral auxiliaries.

Results and Discussion

In order to explore the influence of the reaction conditions on reduction of acetophenone by means of proline-mediated borane (1) we varied (*i*) the source of borane and (*ii*) the proline/BH_3/$PhCOCH_3$ molar ratio as summarized in Table 1.

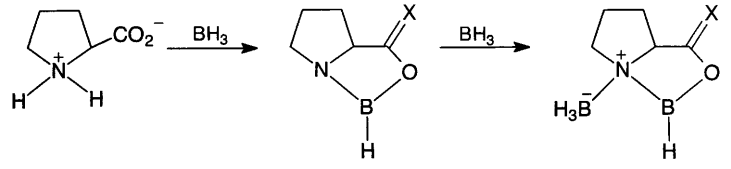
$$R^1COR^2 + (S)\text{-Amino acid} + BH_3 \cdot THF \rightarrow R^1CH(OH)R^2 \qquad (1)$$

The source of borane was either the borane-tetrahydrofurane complex ($BH_3 \cdot THF$; entries: 1–3, 5, and 6 in Table 1) or the borane-dimethyl sulfide complex ($BH_3 \cdot SMe_2$ entries 4 and 7 in Table 1). Two sets of parallel experiments (3/4 and 6/7, Table 1) clearly indicate that there is no difference between $BH_3 \cdot THF$ and $BH_3 \cdot SMe_2$ regarding the chemical or optical yield of the alcohol. When the molar ratio of proline, borane, and acetophenone was 1:2:1, the conversion of the ketone to the corresponding alcohol was small (entry 2, Table 1). Total conversion of the ketone was accomplished with 1:3:1; 1:5:1, and 1:7:10 proline/borane/acetophenone ratios (entries 3–7 in Table 1), but optical yields were 72, 27, and 85%. The best molar ratio of proline/borane/acetophenone was estimated to be ∼1:7:10 (entries 6 and 7 in Table 1). This corresponds to earlier results [4] for the case of ketone reduction by borane in the presence of diphenyl-3-oxa-1-aza-2-borabicyclo-

Table 1. Influence of reaction conditions[a] on the reduction of acetophenone by means of proline-mediated borane

Entry	Source of borane	Proline/BH_3/$PhCOCH_3$ (molar ratio)	Reagent time preparation	Reduction time	% *ee*	Conversion of ketone (%)
1	$BH_3 \cdot THF$	1:2:1	1.5 h	1 h[b]	–	37
2	$BH_3 \cdot THF$	1:2:1	1.5 h	5 h[b]	34	39
3	$BH_3 \cdot THF$	1:3:1	1.5 h	10 min[c]	72	100
4	$BH_3 \cdot SMe_2$	1:3:1	1.5 h	10 min[c]	72	100
5	$BH_3 \cdot THF$	1:5:1	1.5 h	10 min[c]	27	100
6	$BH_3 \cdot THF$	1:7:10	5 min	10 min[d]	85	100
7	$BH_3 \cdot SMe_2$	1:7:10	5 min	10 min[d]	85	100

[a] All reactions were carried out in *THF* solution at room temperature; [b] 7 mmol of ketones in *THF* (1.4 *M*) were added in portions of 0.5 ml every 5 min; [c] 7 mmol of ketones in *THF* (1.4 *M*) were added during a 5 min period; [d] 11.5 mmol of ketone in *THF* (2.3 *M*) were added during a 10 min period



X = O (**2** or **5**), H_2 (**4** or **7**), H, O—B< (**3** or **6**)

Scheme 1

Table 2. Reduction of some ketones with amino acid-mediated borane

Ketone	Type of reagent	
	(*S*)-proline-mediated	(*S*)-phenylalanine-mediated
	Yield isolated (%) and % *ee* of alcohols[a]	
2-Pentanone	79 (32)	83 (47)
3-Methyl-2-butanone	84 (86)	81 (69)
3,3-Dimethyl-2-butanone	86 (35)	87 (51)
2,2-Dimethylcyclopentanone	78 (43)	76 (56)
Acetophenone	90 (85)	94 (74)

[a] In all cases, the (*R*)-configuration of the alcohols is predominant according to the sign of $[\alpha]_D$

[3.3.0]octane. Therefore, the role of (*S*)-(−)-proline in borane reduction might be accounted for by formation of the corresponding oxaza-borolidine **4** (Scheme 1). Because of stoichiometric reasons, three moles of borane are needed for the formation of the oxazaborolidine-borane adduct **7** ($X = H_2$) which is responsible for enantioselective hydride transfer. Thus, reactions with a 1:2:1 proline/borane/acetophenone ratio did not produce satisfactory reduction results (entries 1 and 2 in Table 1).

We reduced several ketones more reactive than acetophenone (Table 2). Asymmetric induction with this reagent was within the range of 32 to 85% *ee*. When phenylalanine was used as a mediator for the similar type of borane reduction of the same ketones, the enantiomeric excess of the corresponding alcohols was in the range from 47 to 74% (Table 2). A range from 36% *ee* for 2-pentanol to 80% *ee* for 1-phenylethanol was observed for the valine-mediated borane reduction of the ketones [6]. In this research we found that 2-pentanone, 3,3-dimethyl-2-butanone and 2,2-dimethylcyclopentanone were reduced with better asymmetric induction in the case of phenylalanine-mediated borane reagents; on the other hand, the proline-type reagent was better suited for 2-methyl-2-butanone and acetophenone (Table 2). It is know that selectivity decreases in the case of reactive ketones [1d]. This could be overcome to some extent by changing the mode of addition.

For a better understanding of the obtained reduction results it will be necessary to investigate the complete catalytic cycle, including all transition structures. To our knowledge, that kind of calculation has been done so far only for the catalytic reduction of propanone to propan-2-ol by the borane adduct of 4,4-diphenyl-type oxazaborolidine [7].

Experimental

All operations concerning air sensitive materials were carried out under Ar [8]. Tetrahydrofurane (*THF*) was dried over 4 Å molecular sieve and distilled from sodium benzophenone ketyl prior to use. 2-Pentanone, 3-methyl-2-butanone, 3,3-dimethyl-2-butanone, 2,2-dimethylcyclopentanone, acetophenone, 10 *M* borane-methyl sulfide complex, 1.0 *M* borane-tetrahydrofurane complex, and (*R*)-(+)-α-methoxy-α-(trifluoromethyl)-phenylacetic acid (*MPTA*) were obtained from Aldrich. Specific rotations were determined on a Perkin-Elmer 241 polarimeter. Analytical gas chromatography (GC) was carried out on a Hewlett-Packard 5890A gas chromatograph using SPB-5 capillary columns. The alcohols were purified by preparative GC on a Carbowax 20 M column. The optical purities of alcohols were determined by GC analysis of *MTPA* esters of the corresponding alcohols [9]. In general terms the chiral reagents were prepared as follows and used *in situ* for reduction.

(S)-Proline-mediated reduction

To 0.133 g (1.15 mmol) of (*S*)-proline in a dried flask, 7 cm^3 of 1 *M* $BH_3 \cdot THF$ (7 mmol) was added dropwise from a syringe. When the acid was dissolved ($\approx$3 min), 8 cm^3 of *THF* were added. After stirring of the resulting solution for 5 min, a solution of the ketone (11.5 mmol) in 4.7 cm^3 of *THF* was added dropwise over 10 min. The resulting mixture was stirred for additional 10 min, and *THF* was removed. After hydrolysis with 5 cm^3 3 *M* NaOH, the resulting solution was extracted with 2 *M* HCl and then with saturated $NaHCO_3$. After drying (Na_2SO_4) and distillation, the obtained alcohol was further purified by preparative GC on Carbowax 20 M columns. The chemical yields and enantiomeric excess of alcohols are listed in Table 2.

(S)-Phenylalanine-mediated reduction

The method is analogous to previous one. The chemical yields and % *ee* of alcohols are shown in Table 2.

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