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Amino Acid Mediated Borane Reduction of Ketones II[a]

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Summary. Acetophenone, 2,2-dimethylcyclopentanone, 3,3-dimethyl-2-butanone, 3-methyl-2-butanone, and 2-pentanone were reduced with borane mediated by (*S*)-alanine, (*S*)-methionine, (*S*)-leucine, (*S*)-valine, and (*S*)-isoleucine in very good yields giving predominantly alcohols of (*R*)-configuration (*ee* = 23–89%). A molecular topology based model was developed for describing the influence of the substituents, both in the oxazaborolidine type reagent and in the ketone, on the observed chiral induction.

Keywords. (*S*)-Amino acids; Ketones; Alcohols; Chiral induction; Molecular topology based model.

Introduction

Among the catalytic enantioselective borane reductions, the oxazaborolidine mediated reaction, introduced by *Corey* [1] who followed the pioneering work by *Itsuno* [2], stands as a well-established methodology for the synthesis of chiral secondary alcohols [3]. The active species for hydride transfer is an oxazaborolidine-borane adduct [1] which can be employed either stoichiometrically or catalytically [4].

Borane reductions of prochiral ketones with catalytic amounts of (*S*)-proline in refluxing toluene gave the corresponding alcohols in good enantiomeric excess (*ee* = 81–95%) [5]:

$$R^1\mathrm{CO}R^2 + (S)\text{-amino acid } (R-\mathrm{CH}(\mathrm{NH_2})\mathrm{COOH}) + \mathrm{BH_3}\cdot THF \rightarrow R^1\mathrm{CH}(\mathrm{OH})R^2 \quad (1)$$

In continuation of the investigation of the reaction of Eq. (1) we have performed borane reductions of the same or similar ketones using (*S*)-proline, (*S*)-phenylalanine, and (*S*)-valine in *THF* at room temperature [6]. The results obtained [6] were of limited preparative value, *i.e.* had small *ee*-values. We now report on further borane reductions of ketones involving (*S*)-alanine, (*S*)-methionine, (*S*)-leucine, (*S*)-valine, and (*S*)-isoleucine which, at least in some cases, exhibit a higher degree of chiral induction.

[a] For part I, see Ref. [6a]

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In addition, we put forward a simple topological model capable of predicting the influence of the structure of both the reducing agent (*i.e.* of the group R in the amino acid in Eq. (1)) and the ketone (*i.e.* of the groups R^1 and R^2 in Eq. (1)) on the observed chiral inductions.

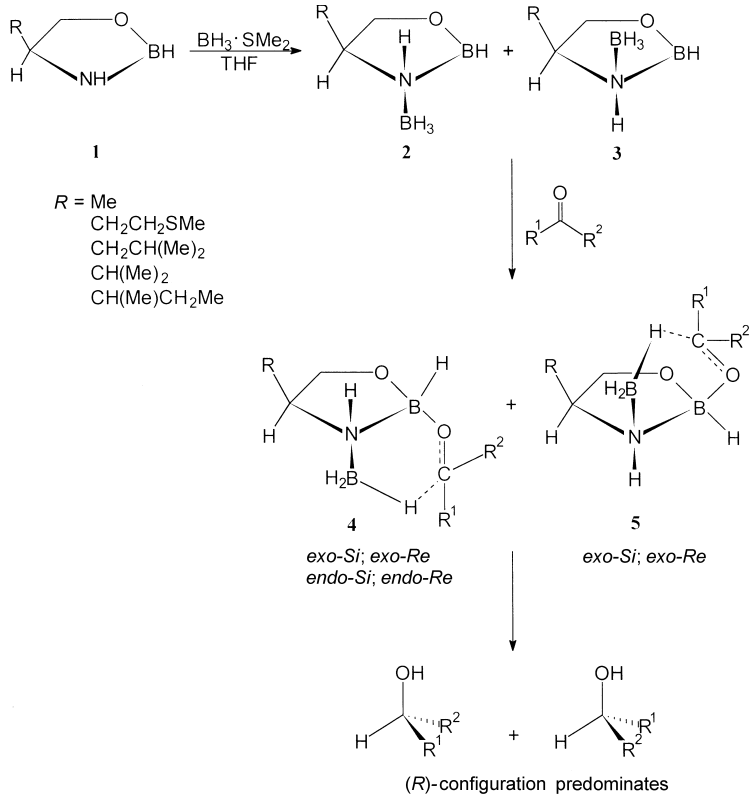
Results and Discussion

When we used proline as a chiral modifier in the reduction of acetophenone [6a], the best molar proline:borane:acetophenone ratio was estimated to be 1:7:10 (85% *ee* of 1-phenylethan-1-ol; other conditions: (*i*) $BH_3{\cdot}THF$ or $BH_3{\cdot}SMe_2$ as the source of borane; (*ii*) *THF* as solvent; (*iii*) 10 min of preparation of the reagent at room temperature; (*iv*) 10 min of reduction of ketone at room temperature). This ratio is in agreement with two earlier results obtained by *Corey et al.* [1a] in the reduction performed in presence of diphenyl-3-oxa-1-aza-2-borabicyclo [3.3.0]-octane. Surprisingly, in the variant with slower addition of ketone (80% *ee*; reaction time: 2.5 h) [6b], the optimal valine:borane:acetophenone ratio was found to be 1:2:1. The reaction was still catalytic, because as much as 89% of (*S*)-valine could be recovered; consequently, only 4% of valinole was isolated. The other amino acids applied in this work have showed a similar behaviour towards the *THF*/borane system. The reaction mixture prevails in the form of suspension. It should be stressed that the reagent prepared directly from valinol [7] is completely soluble in *THF*. In order to obtain mutually comparable results, the same reaction conditions were applied for all amino acids used in this work. The obtained results are given in Table 1.

The role of the amino acids in the borane reduction of prochiral ketones (R^1COR^2, $R^1 \neq R^2$) might be accounted for by formation of the corresponding oxazaborolidine (**1**; Scheme 1). Through the adjacent boron and nitrogen atoms of **1**, one ketone and one borane molecule can react by the double docking mechanism

Table 1. Enantiomeric excess (*ee*/%) of the alcohols obtained by reduction of ketones with borane modified with (*S*)-amino acids; molar amino acid:$BH_3 \cdot SMe_2$:ketone ratio = 1:2:1; reagent preparation time: 2.5 h; conversion of the ketones: ~100%; chemical purities of the alcohols after distillation: >99%; in all cases, the (*R*)-configuration of the alcohols was predominant, as inferred by the sign of rotation; the reagent prepared from phenylalanine gave, under same conditions, 1-phenylethan-1-ol of 73% *ee*; a 1:7:10 phenylalanine:borane:acetophenone mole ratio gave, in 10 min of reaction time, 1-phenylethan-1-ol in 74% *ee* [6a]; % of amino acid recovered: 87 (*Ala*), 82 (*Met*), 88 (*Leu*), 89 (*Val*), 87 (*Ile*); % of aminols recovered: 2 (*Ala*), 7 (*Met*), 3 (*Leu*), 4 (*Val*), 3 (*Ile*); the yield of isolated alcohol (%) is given in parentheses

Ketone	(*S*)-Amino acid employed				
	Alanine	Methionine	Leucine	Valine	Isoleucine
2-Pentanone	23 (86)	34 (87)	33 (81)	36 (86)	45 (82)
3-Methyl-2-butanone	31 (80)	42 (86)	50 (80)	55 (82)	59 (85)
3,3-Dimethyl-2-butanone	36 (81)	55 (87)	57 (82)	64 (83)	68 (82)
2,2-Dimethylcyclopentanone	36 (87)	57 (90)	56 (91)	59 (81)	73 (87)
Acetophenone	57 (90)	64 (92)	71 (92)	80 (91)	89 (95)



Scheme 1

[1a]. The favorable six-membered cyclic arrangements (**4** and **5**; Scheme 1) depend on the oxygen lone-pair involved in the complexation and the enantiotopic face of the carbonyl compound exposed to the NBH_3^- unit. The primary requirement for obtaining a good oxazaborolidine catalyst capable of achieving high enantiomeric excess in prochiral ketone reductions is to completely block one face of the oxazaborolidine [8, 9]. In our study, we varied the alkyl group in structure **1** from a small one as methyl to a moderately bulky group as *sec*-butyl. The results in Table 1 show that the bulkiness of the alkyl group in the reagent significantly affects the enantiomeric excesses of the reaction product. A substituent in the supposed oxazaborolidine–borane adduct type reagent (which originates from the corresponding amino acid) affects the ratio of the adducts **2** and **3**, thus influencing the formation of **4** and **5** by ketone complexation (Scheme 1).

Modeling the structure dependence of the enantiomeric excess

One serious limitation of molecular graph based structure models of organic compounds and reactions is that they do not distinguish between stereoisomers. Recently, efforts have been undertaken to overcome this shortcoming (see Ref. [10] and references cited therein). In order to describe the influence of the bulkiness of the alkyl group *R* in the supposed active form (as above described) of the reducing

agent as well as of the groups R^1 and R^2 of the ketone (cf. Eq. (1)) on the resulting enantiomeric excess, we developed a topological model upon which the following requirements were imposed:

(a) If $R^1 = R^2$ then the predicted *ee*-value must be zero, irrespective of the nature of the group R (*i.e.* irrespective of the amino acid employed)
(b) The predicted *ee*-value must not change if R^1 and R^2 exchange place
(c) The effect of the groups R^1 and R^2 is modeled by the same topological index denoted by T
(d) The effect of the group R is modeled by a topological index denoted by T^* whose structure dependence is identical or as similar as possible to that of T
(e) The topological indices T and T^* depend on the rooted molecular graphs of the groups R, R^1, and R^2, with the root corresponding to the position at which R, R^1, and R^2 are connected to the remainder of the molecule (cf. Eq. (1))

Conditions (a) and (b) reflect obvious stereochemical features, whereas (c) and (e) are just mathematical reformulations of elementary chemical facts. Condition (d) is based on the intention to make our approach as simple as possible. Bearing in mind (a)–(e) we constructed and examined several mathematical models, of which that of Eq. (2) proved to be the most efficient.

$$ee = |T(R^1) - T(R^2)|(a \cdot T^*(R) + b) \tag{2}$$

In Eq. (2), a and b are least-squares fitting parameters, and the topological indices T and T^* are defined as $T(G) = \sum_v \mathrm{d}(v, r|G)^{-x}$ and $T^*(G) = \sum_v \mathrm{d}(v, r|G)^{-y}$.

Both summations go over all vertices of the rooted graph G, whose root is r. The topological distance between the vertex v and the root r (= number of edges in the shortest path connecting v and r) is denoted by $\mathrm{d}(v, r|G)$; for details, see Ref. [11]. The parameters x and y measure the speed by which the influence of structural details on the examined property (in this case, on *ee*) diminishes with increasing distance from the reaction center. These parameters were adjusted so that Eq. (2) gave optimal agreement with experimentally determined *ee*-values.

We examined the model of Eq. (2) using hydrogen-filled and hydrogen-depleted moleculars [10a]; the latter gave slightly better results.

In the case of 2,2-dimethylcyclopentanone it is not self-evident what R^1 and R^2 should be. Following *Raychaudury* [12], we associated the carbon atoms closer to one side of the keto group with R^1 and those closer to its other side with R^2.

By using all 25 experimental *ee*-values we obtained $a = 252.1$, $b = -209.5$, $x = 1.5$, and $y = 4.0$ for the parameters of Eq. (2). With these parameters, the correlation coefficient was 0.898, and *ee* was reproduced with an average error of 7.2%.

Analyzing the results obtained (see Fig. 1) we found that one experimental result (that for the reduction of 2,2-dimethylcyclopentanone with (*S*)-isoleucine) is an outlier. Without this single point (indicated in Fig. 1 by an arrow), the correlation coefficient increases to 0.926, whereas the average error remains essentially the same. By checking the respective experiment it was found that the *ee*-value reported above is correct.

As already mentioned, the treatment of 2,2-dimethylcyclopentanone (and, in general, of any cycloalkanone) by means of our model is somewhat ambiguous. When avoiding the five experimental data for 2,2-dimethylcyclopentanone we

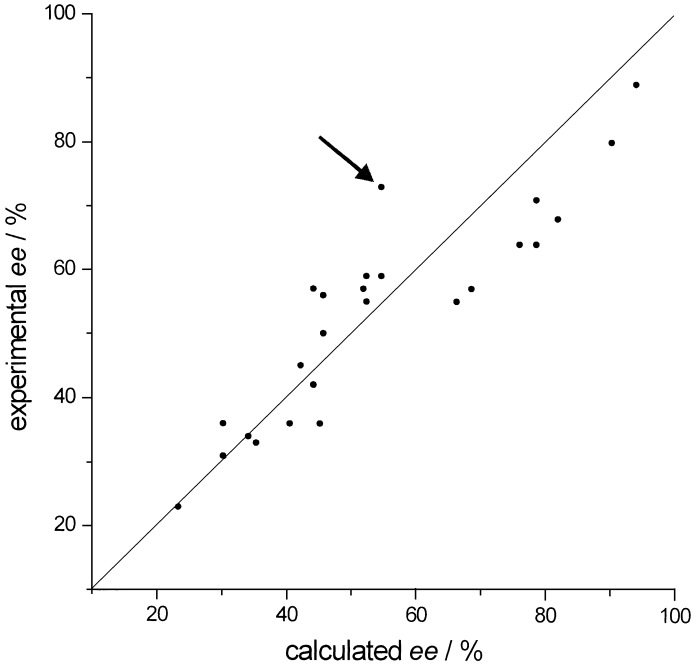


Fig. 1. Experimental *vs.* calculated *ee*-values; for details, see text

obtained $a = 263.1$, $b = -230.9$, $x = 1.2$, $y = 4.5$, and the model became significantly more accurate (average error 5.1%, correlation coefficient 0.962).

Anyway, the model of Eq. (2) is capable of reproducing the *ee*-values within less than 10%, which for usual purposes (in particular for the prediction of which reactions are valuable from a preparative point of view) may be considered as satisfactory. On the other hand, the model is quite simple and requires a minute amount of numerical work.

It is interesting to note that we found that the exponent y is significantly larger (about three times) than the exponent x. This implies that, at least within our model, only those structural features of the amino acid which are located near the amino group (*i.e.* local structural details) have a pronounced effect on the chiral induction. In other words, the bulkiness of the group R of the amino acid is much less decisive for the observed degree of chiral induction (measured as *ee*) than the bulkiness of the groups R^1 and R^2 attached to the keto group.

Experimental

All operations concerning air sensitive materials were carried out under Ar [13]. *THF* was dried over 4 Å molecular sieves and distilled from sodium benzophenone ketyl prior to use. Acetophenone, 2,2-dimethylcyclopentanone, 3,3-dimethyl-2-butanone, 3-methyl-2-butanone, 10 *M* borane-methyl sulfide complex, and (*R*)-(+)-α-methoxy-α-(trifluoromethyl)-phenylacetic acid (*MTPA*) were obtained from Aldrich. Amino acids were obtained from Fluka and used without purification. 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 purity of the alcohols was determined by analysis of the corresponding *MTPA* esters. The chiral regents were prepared as given below and used *in situ* for reduction.

Typical experimental procedure

An oven-dried 100 cm^3 round-bottomed flask equipped with a magnetic stirring bar and a septum was cooled to room temperature in a stream of Ar. (*S*)-Isoleucine (0.918 g, 7 mmol) was transferred to the flask in a glove bag, and 15 cm^3 of *THF* were added. Then, 1.4 cm^3 of 10 *M* borane-methyl sulfide complex was added dropwise *via* a syringe at a rate of 1 cm^3/min. After stirring for additional 2.5 h, 0.84 g acetophenone (7 mmol) in 4.1 cm^3 *THF* was added in portions of 0.5 cm^3 every 5 min, and the resulting reaction mixture was stirred for 1 h at room temperature. The solvent was evaporated under reduced pressure, and the residue was treated with 10 cm^3 of aqueous 3 *M* NaOH. When the evolution of H_2 was complete, the solution was extracted with ether (2×10 cm^3), and the combined organic phase was washed with 2 *M* HCl, saturated aqueous $NaHCO_3$, and H_2O. The etheral solution was dried over Na_2SO_4 and distilled. 1-Phenylethan-1-ol, b.p.: 98°C (20 mm Hg), was obtained (0.81 g, 95% yield, 99% GC purity). The optical rotation (neat), after further purification by preparative GC, was determined to be $[\alpha]_D = +38.13$ Ref. [14]: $[\alpha]_D = +42.85$ (neat) and revealed an excess of the (*R*)-enantiomer of 1-phenylethan-1-ol. The obtained alcohol was converted to its *MTPA* ester using a literature procedure [15] and analyzed by GC to reveal an *ee* of 89% in the (*R*)-isomer. The other ketones were reduced in an analogous manner using (*S*)-isoleucine, (*S*)-alanine, (*S*)-methionine, (*S*)-leucine, or (*S*)-valine (Table 1).

(*S*)-Isoleucine (0.809 g, 88%) was recovered by adjusting the basic aqueous solution (before extraction with ether) to *pH* 5.74, filtering off, washing with ethanol and ether, and drying. The filtrate was combined with the acidic aqueous solution (obtained after washing of the etheral phase with 2 *M* HCl) and treated with 2 *M* NaOH up to $pH \sim 11$, followed by continuous extraction with ether. After evaporation of the solvent, 3% of (*S*)-2-amino-3-methylpentan-1-ol (isoleucinol) were obtained. The other amino acids were treated in a similar manner (Table 1).

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