Pergamon

*Tetrahedron: Asymmetry* Vol. 6, No. 8, pp. 1881-1884, 1995
Elsevier Science Ltd
Printed in Great Britain
0957-4166/95 $9.50+0.00

0957-4166(95)00242-1

# NONLINEAR EFFECTS IN THE REDUCTION OF ACETOPHENONE BY DIISOPINOCAMPHEYL CHLOROBORANE: INFLUENCE OF THE REAGENT PREPARATION

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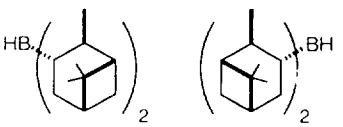
**Abstract**: A nonlinear effect (NLE) in the relation between the *e.e.*'s of diisopinocampheyl chloroborane ($EE_{aux}$) and the *e.e.*'s of 1-phenylethanol ($EE_{prod}$) was found during the reduction of acetophenone using this chloroborane derived from mixtures of α-pinenes. Furthermore, this effect was a function of the preparation method of the borane precursor.

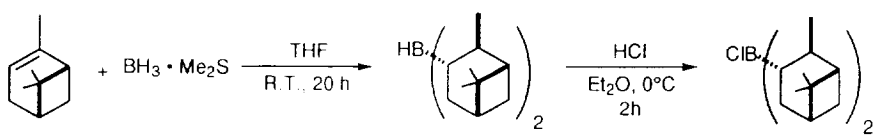
Initially prepared by Brown and coworkers[1], diisopinocampheylboranes **1** were the first stereoselective reagents used in preparative asymmetric synthesis. The homochiral boranes, noted here as "*ll*"-**1** ("*ll*"$Ipc_2BH$) and "*dd*"-**1** ("*dd*"$Ipc_2BH$), are obtained by simple hydroboration of (-) and (+)-α-pinene (**2**) respectively[2].




"*ll*"-**1** "*dd*"-**1**

When used as chiral hydroborating reagents on alkenes, they can give access after oxidation to the corresponding enantiomerically enriched alcohols with high enantioselectivities[3]. The boranes "*ll*"-**1** and "*dd*"-**1** were later used to prepare other borane derivatives of different reactivity but now well proven utility[4]. Amongst them, the chloroboranes corresponding to "*ll*"-**1** and "*dd*"-**1** were found to perform highly enantioselective reduction of a number of prochiral ketones[5]. A Merck group recently reported that the use of "*ll*"$Ipc_2BCl$, prepared from 70% *e.e.* (-)-α-pinene and chloroborane-dimethylsulfide complex, in the reduction of a complex ketone was giving a product of 95% *e.e.*, indicating a nonlinear effect in the process[6].

Owing our interest in the nonlinear behaviors in asymmetric synthesis[7], this communication prompted us to describe our own findings regarding the exploration of the reaction between acetophenone and diisopinocampheyl chloroboranes of different enantiomeric purities. They were prepared according to the Brown procedure passing through the formation of the borane derivative and its subsequent reaction with hydrogen chloride in diethyl ether, as illustrated for the *l*-enantiomer of α-pinene **2** (*Scheme 1*)[2,5]. Differences in the preparation methods will be described in detail in each section.

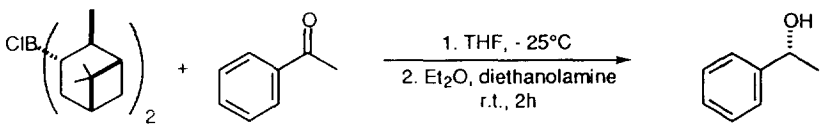



*l*-**2** "*ll*"-**1** "*ll*"-**3**

Scheme 1

*Synthesis of the chloroboranes by mixing α-pinenes before the formation of $Ipc_2BH$*

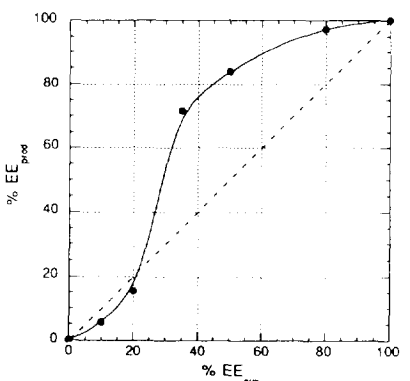
In a first serie of experiments, the *e.e.* of the chiral auxiliary (α-pinene) was adjusted by mixing calculated amounts of *l*-α-pinene (*l*-**2**) and *d*-α-pinene (*d*-**2**) before reacting them with borane-dimethylsulfide complex[8]. The diisopinocampheyl boranes (**1**) formed were used as such in the treatment with hydrogen chloride as in *Scheme 1*. Reductions of acetophenone **4** by the chloroborane **3** of various *e.e.* were conducted in deficit of the ketone (4 time excess of the reductant) at -25°C (*Scheme 2*)[9].




**3** (*from l-2*) **4** *R*-**5**

Scheme 2

The enantiomeric purity of the resulting (*R*)-1-phenylethanol (*R*-**5**) was determined by the use of chiral HPLC and *Graphic 1* is displaying the results obtained in these cases.

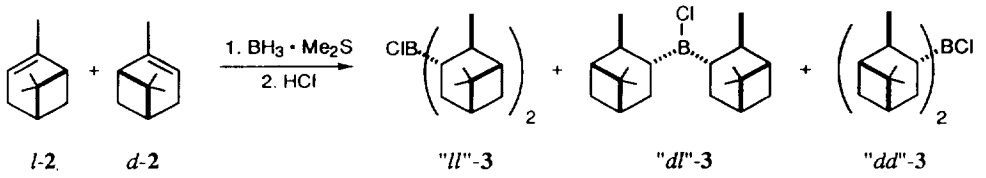



Graphic 1

| % $EE_{aux}$ | % $EE_{prod}$ |
|---|---|
| 10 | 6 |
| 20 | 15 |
| 35 | 72 |
| 50 | 84 |
| 80 | 97 |

The relation existing between the *e.e.*'s of 1-phenylethanol ($EE_{prod}$) and the *e.e.*'s of *l*-α-pinene used to prepare diisopinocampheyl chloroborane mixtures ($EE_{aux}$) is nonlinear, displaying a strong positive deviation. For example, starting with a mixture of α-pinenes with an *e.e.* as low as 50% in the preparation of the chloroborane, an enantiomeric excess of 84% for the 1-phenylethanol (*R*-**5**) can be reached. Below $EE_{aux}$ = 20% a slight negative NLE can however be observed.

These findings indicate that there should be a strong difference in the nature of the reagent prepared by mixing α-pinenes for its generation. To our belief, this preparation method can produce such a reagent that its formation is removing from the reaction the minor enantiomer, thus preventing it to react and to decrease the observed *e.e.*. The exclusive formation of homochiral chloroboranes "*ll*"-**3** and "*dd*"-**3** ("*ll*"$Ipc_2BCl$ and "*dd*"$Ipc_2BCl$) should not influence the outcome of the reaction since they will produce alcohols of opposite configuration at the same rate (*Scheme 3*).



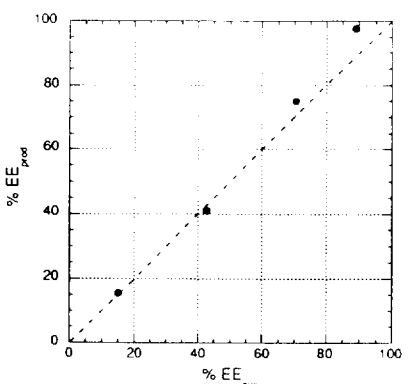

*l*-2 *d*-2 "*ll*"-3 "*dl*"-3 "*dd*"-3

Scheme 3

The nonlinear effect encountered in these cases may be explained by the generation of an heterochiral chloroborane "*dl*"-3 in which the minor enantiomer is trapped. Moreover, this reagent has to be less reactive than the homochiral chloroborane in order to observe any effect, since it precludes to the formation of a racemic mixture of alcohol. We then decided to repeat the experiments on acetophenone using a different preparation procedure of **3** to test this hypothesis.

*Preparation of the chloroboranes by mixing separately synthesized "ll" Ipc2BH and "dd" Ipc2BH*

We first conducted the independent preparation of "*ll*"Ipc$_2$BH ("*ll*"-**1**) and "*dd*"Ipc$_2$BH ("*dd*"-**1**) accordingly to Brown's work[2]. The needed amounts of "*ll*"-**1** and "*dd*"-**1** were then mixed to reach determined *e.e.*'s before the HCl treatment to produce the chloroborane **3**. The resulting 1-phenylethanol (**5**) was analyzed using the previously described technique. The relation existing between the measured *e.e.*'s of 1-phenylethanol ($EE_{prod}$) and the *e.e.*'s of (-)-α-pinene ($EE_{aux}$), regenerated from Ipc$_2$BH used to prepare Ipc$_2$BCl samples[10], is perfectly linear, as illustrated in *Graphic 2*.




Graphic 2

| % $EE_{aux}$ | % $EE_{prod}$ |
|---|---|
| -4 | -8 |
| 15 | 15 |
| 43 | 41 |
| 71 | 75 |
| 89 | 98 |

The linear relationship observed in the present method indicates that each of the enantiomeric reagents is acting independently in the reduction process. The formation of a mixed reagent is thus a consideration to be set aside in the experimental conditions of the reduction of acetophenone, $EE_{aux}$ fitting here with the *e.e.*'s of the homochiral species "*ll*"-**3** and "*dd*"-**3**.

*Conclusions*

In this letter, we reported that when the borane precursors were prepared independently from each enantiomers of α-pinene, and then mixed to reach the desired $EE_{aux}$, no deviation to the linearity was observed. However, when (-) and (+)-α-pinene mixtures of wanted *e.e.* were used as starting material for the formation of the borane reagent , a strong positive NLE was observed. This amplification was explained on the basis of the formation of a less reactive heterochiral reagent incorporating the minor enantiomer, thus preventing it to react in the reduction of acetophenone[11]. Experiments are in progress for measuring the distribution of the chiral chloroboranes **3** in solution as a function of *e.e.* of α-pinene, in order to give a quantitative basis to the above interpretation and to explain the origin of the two domains diplayed by the curve of *Graphic 1*.

*Acknowledgments*

This work was realized under a grant from CNRS (URA 1497). C. Girard is grateful to the Ministère des Affaires Extérieures de France for the North-American Chateaubriand post-doctoral fellowship.

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8. The commercially available α-pinenes (Janssen Chemicals) used in this preparation were analyzed by chiral GPC on a Cyclodex-B® (200°C Injection, 40°C Isothermal, 0.5 $^{kg}/_{cm2}$ $H_2$, 0.8 $^{kg}/_{cm2}$ air): (*l*-**2**)-$R_t$= 22 min., (*d*-**2**)-$R_t$= 25 min.. Values of *e.e.*'s of 81% for *l*-**2** and 88% for *d*-**2** were obtained.
9. *Typical procedure:* To a solution of $Ipc_2BCl$ (3 mmol) in anhydrous THF (2 mL) cooled to -25°C is added acetophenone (90 µL, 93 mg, 0.8 mmol). The yellow reaction mixture was allowed to stir over-night (20 h) at this temperature before being evaporated under vacuum. The residue was dissolved in diethyl ether (10 mL) and diethanolamine (694 mg, 6.6 mmol, 2.2 eq) was added. After 2 h stirring at room temperature, the mixture was filtered and the solids washed with pentane (2 x 2 mL). After evaporation of the solvents, **5** was obtained and analyzed by chiral HPLC on a Chiralcel®-OD-H (hexane:isopropanol (9:1), 0.5 $^{mL}/_{min.}$, UV detection at 254 nm): (*R*-**5**)-$R_t$= 10 min., (*S*-**5**)-$R_t$= 11 min..
10. The *e.e.*'s of the pinene issued from each borane reagents was then estimated by liberation of the terpene by a published procedure[2] and its analysis by chiral GPC. They were found to be of 89% from "*ll*"$Ipc_2BH$ ("*ll*"-**1**) and 96% *e.e.* from "*dd*"$Ipc_2BH$ ("*dd*"-**1**). These values are superior to the *e.e.*'s of the initial α-pinene[8] used for the preparation of $Ipc_2BCl$ due to the heterogeneous conditions as noticed by Brown.
11. A similar interpretation has been given for $Ipc_2BCl$ reduction of the ketone in ref. 6.

(*Received in UK* 22 *June* 1995)