Nonlinear effects in the reduction of acetophenone by diisopincampheyl chloroborane: influence of the stoichiometry of the reagent [†]

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Abstract: A nonlinear effect (NLE) between the *ees* of diisopincampheyl chloroborane (ee_{aux}) and the *ees* of 1-phenylethanol (ee_{prod}) has previously been observed during the reduction of acetophenone. The size of this asymmetric amplification is related to the amount of Ipc_2BCl used to perform the reduction, as we report in this communication. © 1997 Published by Elsevier Science Ltd. All rights reserved.

Since the seminal work by Brown *et al.* on the hydroboration of α-pinene (*l*- and *d*-1),[1] several reagents derived from this terpene have been synthesized to be used as stereoselective reagents in various reactions.[2] The diisopincampheylboranes were first reacted with alkenes, to give access to enantiomerically enriched alcohols with high enantioselectivities after the usual oxidation of the intermediate borane.[3] The diisopincampheylboranes were also used as precursors for a number of reagents derived from this structure.

A very useful reagent from this series is diisopincampheylchloroborane, abbreviated as Ipc_2BCl or DIP-Cl©, easily prepared from the borane by simple treatment with hydrogen chloride in ether. It was found to perform the highly enantioselective and efficient reduction of prochiral ketones.[4]

During the course of our investigation on nonlinear effects (NLEs)[5] in asymmetric synthesis, we previously reported a study on the influence of the method of preparation of Ipc_2BCl **2** of various *ees* on the reduction of acetophenone **3**.[6] When the borane precursors were prepared independently from each enantiomer of α-pinene (*l*- and *d*-1), and then mixed to reach the desired ee_{aux}, no deviation of the linearity was observed. However, when (−) and (+)-α-pinene (*l*- and *d*-1) mixtures of the desired *ee* were used as the starting material for the formation of the borane reagent (Scheme 1), a strong positive NLE was observed. A similar effect was reported by a Merck group in which the use of 70% *ee* α-pinene for the preparation of Ipc_2BCl and its use in the reduction of a ketone precursor to an LTD$_4$ antagonist led to the corresponding alcohol in 95% *ee*.[7] The nonlinear effect encountered in these cases was explained by the formation of a less reactive heterochiral chloroborane '*dl*'-**2** in which the minor enantiomer is trapped, thus increasing the effective ee_{aux}. This heterochiral species also gives the racemic 1-phenylethanol **4**.[6,7]

l-1   *d*-1   "*ll*"-2   "*dl*"-2   "*dd*"-2

Scheme 1.

[†] Dedicated to Professor Herbert C. Brown on the occasion of his 85th birthday.
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In our previous study, we mentioned that an excess of Ipc$_2$BCl was needed to obtain good conversions over a fair amount of time (20 h at −25°C) in the acetophenone reduction. In fact, up to 4 equivalents of the reductant were used in order to overcome completely the lower reactivities of the reagent containing larger amounts of '*dl*'-2; i.e. the ones prepared from low *ee* pinene mixtures.

We became interested in studying the influence of the stoichiometry of the reagent on the outcome of the reaction. The reduction of acetophenone 3 was thus studied for a given set of reaction conditions, allowing the mixtures to react for the same time.[8] Ipc$_2$BCl was prepared from *l*-α-pinene 1 in various *ees* before using it in different stoichiometries for the reduction of acetophenone 3 in (*R*)-1-phenylethanol (*R*)-4. The results obtained from these reactions are presented in Scheme 2.
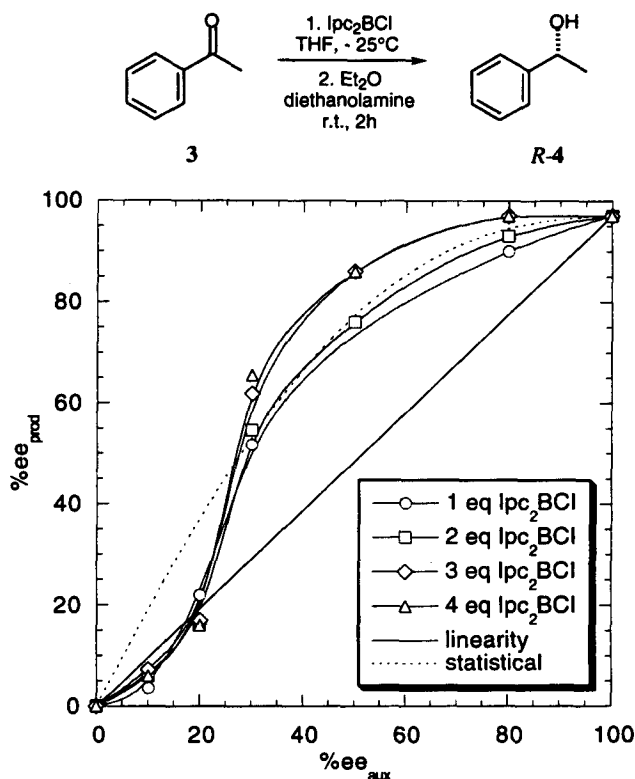
Scheme 2.

It appears from the curves depicted in the graph that the amplitude of the awaited (+)-NLE is increasing when the amount of Ipc$_2$BCl varies from 1 to 4 equivalents with respect to acetophenone 3. The curves, however, remain similarly shaped. As an example, the use of *l*-α-pinene (*l*-1) of 30% *ee* for the preparation of Ipc$_2$BCl and its subsequent use in the reduction afforded (*R*)-1-phenylethanol (*R*)-4 in 52, 55, 62 and 66% *ee* when 1, 2, 3 and 4 equivalents, respectively, were used.

These curves suggest that larger amounts of Ipc$_2$BCl give a better NLE because the more reactive '*ll*'-2 and '*dd*'-2 are present in sufficient amounts to prevent the non-enantioselective heterochiral '*dl*'-2 to participate significantly (curves for 3 and 4 equivalents) in the reaction. When the amount of reductant is reduced to 1 and 2 equivalents, the NLE is less pronounced as a result of smaller amounts of homochiral reagents leaving some unreacted ketone to be the substrate for the less reactive and achiral '*dl*'-Ipc$_2$BCl ('*dl*'-2). As added proof, the yields of the reductions are reduced with the decrease of both quantity and *ee* of Ipc$_2$BCl.[9]

A Merck group recently reported a detailed study of the NLE they encountered during the reduction

of a ketone synthetic intermediate by Ipc$_2$BCl.[10] Using a new efficient method for the preparation of the chloroborane, the relation between ee_{aux} and ee_{prod} was investigated. A nice (+)-NLE was observed and was found to fit a calculated curve based on a statistical distribution of the enantiomers of α-pinene (*l*- and *d*-1) on the boron reagent (1 equivalent). Lowering the ee of the terpene used was deleterious on the yield of the reduction. The reaction with the reagent prepared from racemic α-pinene stops at ~50% conversion. The observations are in agreement with the quasi-statistical distribution between homo and heterochiral species, as well as with the lower reactivity of the latter. Nevertheless, in several experiments in the ee range between 0 and 20% for α-pinene, the curves never diverted from linearity. The use of up to 10 equivalents of the reagent prepared from 20% ee *l*-α-pinene (*l*-1) did not influence the ee of the resulting alcohol. The shape of the curves obtained in our studies are different from the reported ones[10] but this can be due to differences in the preparation methods as to the nature of the substrate. The chemists at Merck also found that the ees of the resulting alcohol varied with the conversion. The initial values at low conversions were higher than the final and calculated values.

Our results also suggest that there are factors other than the sole lack of reactivity of the heterochiral '*dl*'-Ipc$_2$Bcl ('*dl*'-2) that are important. Since the preparations of diisopinocampheylboranes usually use an excess of α-pinene, this can introduce a process of stereoselection of the second molecule of terpene on the boron atom. An increase of the enantiomeric excess of α-pinene borne by the boron was previously noted.[6] A second factor can also have some influence. Since complexation of the ketone by the boron reagent precedes its reduction, the equilibria implicated can have an effect on the outcome of the reaction at a given time with regard to the relative stability of the two types of complexes (homo or hetero reagent) with the ketone.[11] Our procedure also implicated working at a constant concentration of the reductant while that of acetophenone 3 was varying depending on the amount added to the reaction mixture.[8]

Conclusion

We have presented in this paper our additional information regarding the nonlinear effect observed during the reduction of acetophenone by diisopinocampheylchloroborane. The use of larger amounts of the reducing agent of various ees was found to increase the size of the asymmetric amplification. Other factors, still to be uncovered, can be of some influence on the formation and reaction of diisopinocampheylchloroborane. Further investigation of the nonlinear effects of Ipc$_2$BCl will help to gain a better understanding of the behavior of this useful reducing reagent when enantiomerically impure.

Acknowledgements

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8. *Typical procedure*: To a solution of Ipc$_2$BCl (**2**, 3 mmol) in anhydrous THF (2 ml) cooled to −25°C was added acetophenone (**3**, 0.8 to 3.0 mmol in order to adjust the number of equivalents of Ipc$_2$BCl). The yellow reaction mixture was allowed to stir for 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 equivalents) was added. After 2 h stirring at room temperature, the mixture was filtered and the solids washed with pentane (2×2 mL). After evaporation of the solvents, 1-phenylethanol **4** was obtained and analyzed by chiral HPLC on a Chiralcel®-OD-H column [hexane:isopropanol=9:1, 0.5 mL/min., UV detection at 254 nm]: (*R*-**4**) R_t=10 min., (*S*-**4**) R_t=11 min.

9. In general, the yields of the reductions follow this rule. However, inacuraccies of measurement of some conversions prevent curves being drawn.

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11. If one assumes the statistical formation of the three boron reagents and complete inactivity of the *meso* reagent, the *ee* of (*R*)-**4** must be independent of the amount of reagent and is easily calculated. It gives the statistical curve depicted in Scheme 2. This curve is very different from the experimental ones. This is additional confirmation of the complexity of the system.