Pergamon

Tetrahedron: *Asymmetry* 10 (1999) 1413–1418

TETRAHEDRON: *ASYMMETRY*

Asymmetric borane reduction using mixtures of homochiral amino alcohol ligands

Bernard Kaptein,[a,*] Henk Elsenberg,[a] Adriaan J. Minnaard,[a] Quirinus B. Broxterman,[a,*] Lumbertus A. Hulshof,[b] Jan Koek [c] and Ton R. Vries [c]

[a] *DSM Research, Organic Chemistry and Biotechnology Section, P.O. Box 18, 6160 MD Geleen, The Netherlands*
[b] *DSM Fine Chemicals, P.O. Box 81, 5900 AB Venlo, The Netherlands*
[c] *SYNCOM, Nijenborgh 4, 9747 AG Groningen, The Netherlands*

Received 22 March 1999; accepted 2 April 1999

Abstract

The asymmetric borane reduction of acetophenone is investigated using mixtures of homochiral β-amino alcohol ligands. With stoichiometric amounts of a mixture of two- or three-amino alcohols, the e.e. remains at the level of the best amino alcohol for a wide composition range. A small but statistically significant enhancement in e.e. is observed when 10 mol% of an amino alcohol mixture of (1*S*,2*R*)-1-amino-2-indanol and (*S*)-phenylglycinol is used as chiral ligand.

1. Introduction

We have recently described the use of mixtures of resolving agents in classical resolutions.[1,2] We have coined the name 'Dutch Resolution' for this technology. Use of this classical resolution technology improves the success rate for finding a suitable resolution for most racemates tested.

In order to investigate this combinatorial approach in different chiral technologies, we tested the use of a family of related ligands in a catalytic asymmetric reaction. In the literature, only a few examples are reported showing the use of mixtures of chiral catalysts, varying either in the metal ion or in the chiral ligand.[3–10] In general, the catalytic species or the chiral ligands in these cases do have a different role. In our study we clearly intended to test a mixture of catalysts with the same catalytic function.[11] For this approach we chose the thoroughly studied asymmetric borane reduction of acetophenone. Over the years, highly efficient amino alcohol ligands have been described for this model substrate of which the Corey ligand α,α-diphenylprolinol is one of the best.[12]

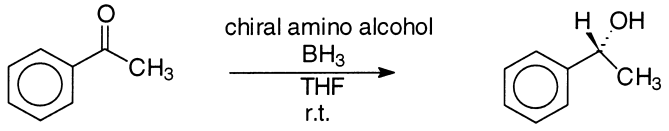
* Corresponding authors. E-mail: bernard.kaptein@dsm-group.com and rinus.broxterman@dsm-group.com

0957-4166/99/$ - see front matter
PII: S0957-4166(99)00129-9

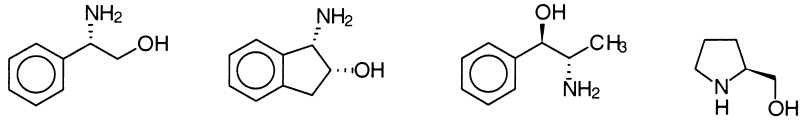
We chose to investigate the asymmetric borane reduction of acetophenone with less enantioselective amino alcohol ligands, like those initially studied by Itsuno et al.[13,14] and Dieder et al.[15] In the lower enantiomeric excess (e.e.) regions, small deviations in stereoselectivity will have a larger effect on the e.e.s. This offers the advantage of establishing how mixtures of homochiral amino alcohol ligands may affect the e.e. of (*R*)-1-phenylethanol.

2. Results and discussion

Initially, we investigated stoichiometric binary mixtures of amino alcohols in different compositions varying from 100:0 to 0:100. Thus, 28 different combinations of homochiral β-amino alcohols were tested,[16] of which the four most extensively investigated are shown in Scheme 1. For most of the binary mixtures tested we observed that the e.e. remains at the level of the best member of the ligand mixture. Only at high mol. fractions of the poorer ligands does the stereoselectivity decrease. Typical examples are shown in Fig. 1 for the binary ligand systems (1*S*,2*R*)-1-amino-2-indanol/(1*R*,2*S*)-norephedrine, (1*S*,2*R*)-1-amino-2-indanol/(*S*)-prolinol and (1*S*,2*R*)-1-amino-2-indanol/(*S*)-phenylglycinol.



chiral amino alcohols:



Scheme 1.

Identical results are obtained for the ternary ligand system (*S*)-phenylglycinol/(*S*)-prolinol/(1*S*,2*R*)-1-amino-2-indanol (see Fig. 2). Also, for this combination the e.e. remains at a high level of approximately 80% for (1*S*,2*R*)-1-amino-2-indanol over a wide range of molar ratios. Only high mol. fractions of (*S*)-prolinol and/or (*S*)-phenylglycinol decrease the e.e. to 56 and 53%, respectively.

In order to investigate if the effects observed are not caused by a higher reactivity of the best ligand in the mixture, we estimated the reactivity order of the four amino alcohols in Scheme 1. Since direct measurement of the reaction rate at ambient temperature is not possible,[17] the relative reactivity of each ligand was compared with the competing uncatalyzed reaction by borane. From the course of the e.e. as a function of the amino alcohol concentration, the reactivity order for the four ligands has been determined to be (*S*)-phenylglycinol>(1*S*,2*R*)-1-amino-2-indanol>(*S*)-prolinol≈(1*R*,2*S*)-norephedrine. However, the difference in reactivity between the fastest and slowest amino alcohol was only a factor of 2. As can be seen in Figs. 1 and 2, this reactivity order does not explain the constant level of the e.e. of the best ligand when mixtures of amino alcohols are used. It is still unknown whether the reactivity of the ligand mixtures is in line with the individual amino alcohols or not.

When using catalytic amounts of amino alcohols as ligands, regeneration of the chiral oxazaborolidine catalysts plays a major role in the asymmetric borane reduction.[18,19] Therefore, we investigated the use

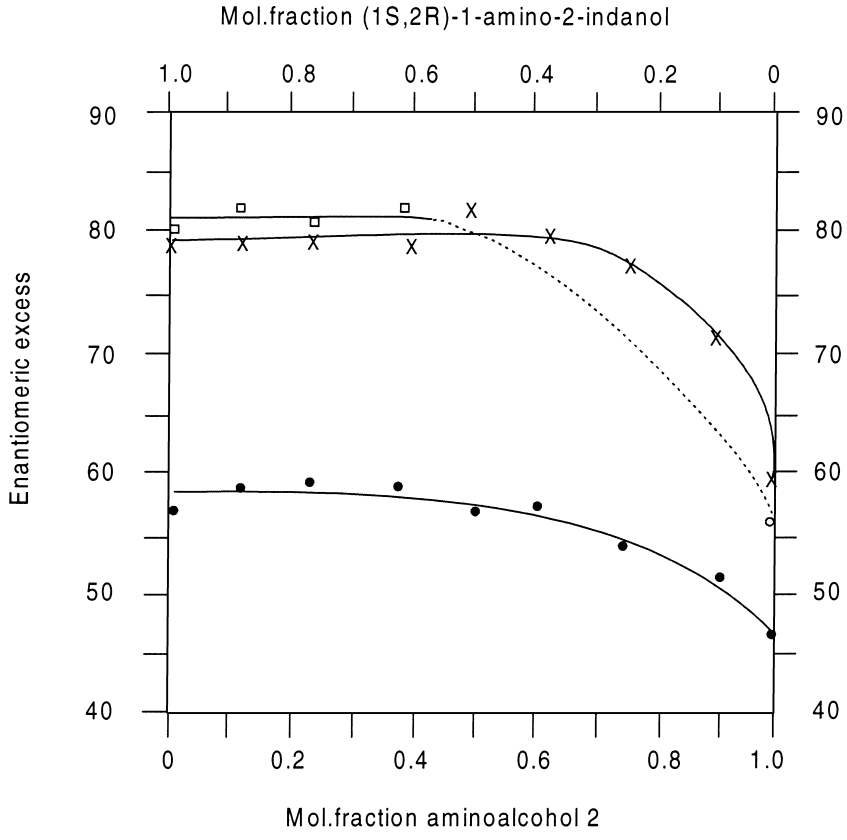


Figure 1. Enantiomeric excess for (*R*)-phenylethanol as a function of the composition of two amino alcohols. Amino alcohol **2**: × (*S*)-phenylglycinol, □ (*S*)-prolinol, ● (1*R*,2*S*)-norephedrine (with fast addition of acetophenone)

of 10 mol% of mixtures of oxazaborolidines derived from (*S*)-phenylglycinol and (1*S*,2*R*)-1-amino-2-indanol. Although the asymmetric induction under these conditions is rather low due to the uncatalyzed reaction, a small but significant increase of the e.e. is observed by using mixtures of both oxazaborolidines (see Fig. 3).

With this oxazaborolidine mixture, the highest e.e. values are observed for a 1:1 composition (i.e. approximately 25% e.e.), while the separate oxazaborolidines from (*S*)-phenylglycinol and (1*S*,2*R*)-1-amino-2-indanol both give an e.e. of 20%. Although the intrinsic asymmetric induction with (1*S*,2*R*)-1-amino-2-indanol is higher than for (*S*)-phenylglycinol, the higher reactivity of the latter results in the identical e.e. of 20% for both catalysts.

The results can be described mathematically by the quadratic equation:

$$\text{e.e.}\% = -18.4x^2 + 17.9x + 20.3 \quad (x = \text{mol. fraction } (1S, 2R)\text{-1-amino-2-indanol})$$

For a 95% accuracy of this equation the square term has a variance of -18.4 ± 5.3, and always remains negative (i.e. a maximum in the curve in Fig. 3). Additional proof that this increase of the e.e. is not caused by the relative reactivity of the oxazaborolidines is obtained by testing the mismatch couple of amino alcohols with the inverse stereochemistry [i.e. (*R*)-phenylglycinol and (1*S*,2*R*)-1-amino-2-indanol]. With 10 mol% of this binary system a linear relation between the e.e. and the composition is observed (see Fig. 3).

Although we are not certain about the origin of the observed effects at the moment, some types of

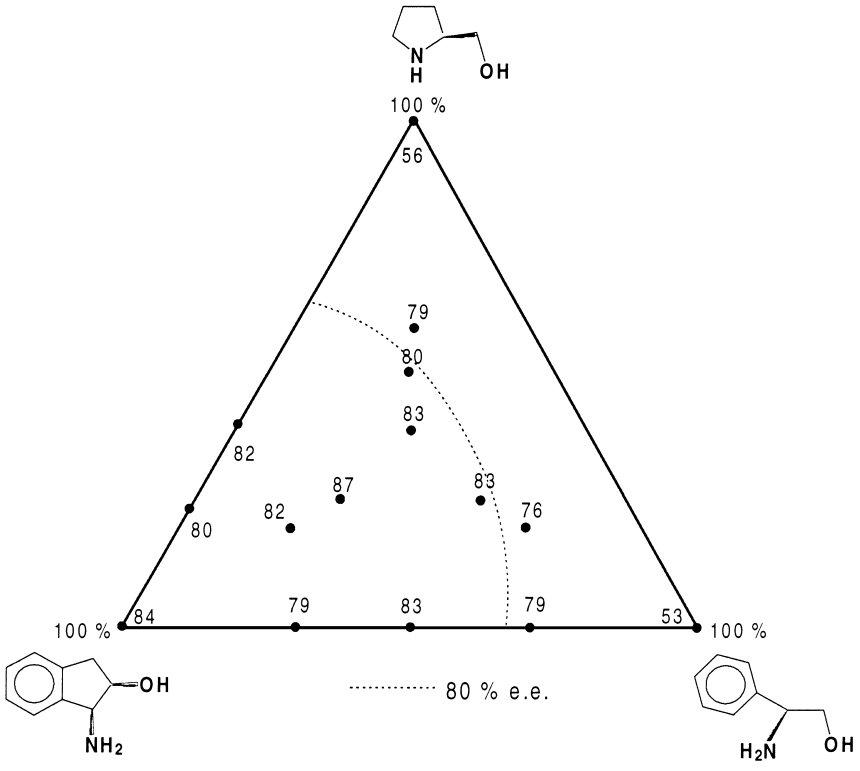


Figure 2. Enantiomeric excess for (*R*)-phenylethanol as a function of the composition of (*S*)-phenylglycinol, (*S*)-prolinol and (1*S*,2*R*)-1-amino-2-indanol

aggregation of the catalyst must be responsible for the (small) improvement of the e.e. when using mixtures of catalyst. Aggregation of oxazaborolidines at lower temperatures has been previously proposed as an explanation for the decrease in the e.e.s of asymmetric borane reductions at lower temperatures.[18,20] Identical effects are observed in asymmetric amplification reactions of similar asymmetric reductions of ketones using Ipc_2BCl and in the diethylzinc addition to benzaldehyde.[21] Further research is necessary to find evidence for this theory.

The fact that the e.e. in the asymmetric borane reduction using mixtures of chiral ligands is almost equal to the e.e. of the best ligand in the mixture offers the opportunity for a fast and efficient screening method in catalytic asymmetric synthesis. Similar effects, as described above, have already been observed in other asymmetric reactions. These results will be published in the near future.

3. Experimental

3.1. Preparation of the oxazaborolidine–borane stock solutions

An oxazaborolidine–BH_3 stock solution for each chiral amino alcohol in THF was prepared independently, using the following procedure: to a solution of 10 mmol of amino alcohol in dry THF (5 ml) was added 1 M borane solution in THF (25 ml). The solution was stirred overnight at ambient temperature before use. For each series of experiments a fresh flask of borane solution was used since re-use of

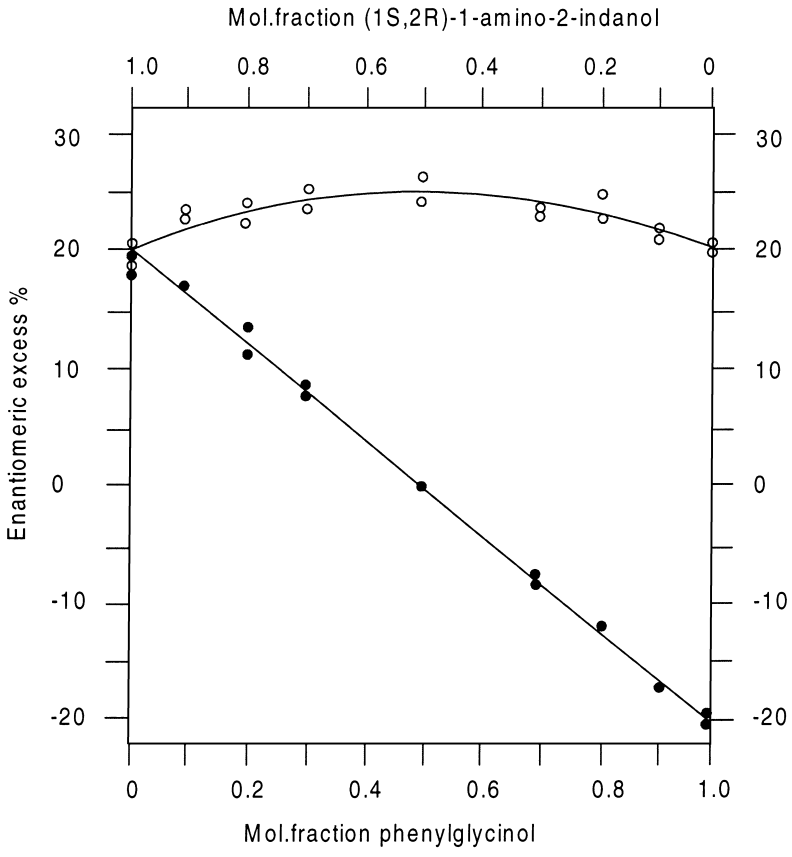


Figure 3. Enantiomeric excess in the asymmetric borane reduction of acetophenone with 10 mol% of a ligand mixture of (1*S*,2*R*)-1-amino-2-indanol with (*S*)-phenylglycinol (— ∘ — ∘ —) or (*R*)-phenylglycinol (— ● — ● —)

opened bottles of borane solutions gave erroneous results. For the reduction experiments with 10 mol% of oxazaborolidines, stock solutions were prepared, starting from 1 mmol of amino alcohol.

3.2. Reduction of acetophenone with mixtures of amino alcohols

Of the independently prepared stock solutions, the appropriate mixtures of two or three oxazaborolidine–BH_3 solutions were prepared by pipetting the correct amounts of each stock solution to a total volume of 3.0 ml. To this stirred solution at ambient temperature, 2.0 ml of a stock solution of 40 mmol of acetophenone in dry THF (25 ml) was added over a period of 60 min (addition times of <5 min resulted in lower e.e.s and a low reproducibility). Although all the borane reductions of acetophenone were quantitative after the addition, the reaction mixtures were stirred overnight at ambient temperature. Samples of the reaction mixtures were analyzed on e.e.s of 1-phenylethanol by HPLC [column: Chiracel OB, eluent hexane:*i*-propanol 90:10, flow: 0.5 ml/min, detection: polarimeter or UV-detector (254 nm)] after dilution with *i*-propanol or acidic extraction with ethyl acetate/4 N sulfuric acid.

References

1. Vries, T. R.; Wynberg, H.; van Echten, E.; Koek, J.; ten Hoeve, W.; Kellogg, R. M.; Broxterman, Q. B.; Minnaard, A. J.; Kaptein, B.; van der Sluis, S.; Hulshof, L. A.; Kooistra, J. *Angew. Chem*. **1998**, *37*, 2349.
2. Broxterman, Q. B.; van Echten, E.; Hulshof, L. A.; Kaptein, B.; Kellogg, R. M.; Minnaard, A. J.; Vries, T.; Wynberg, H. *Chim. Oggi/Chem. Today* **1998**, *16*, 34.
3. Zang, E.-L.; Choy, C. H. *Chin. Chem. Lett.* **1991**, *2*, 169.
4. Sawamura, M.; Sudoh, M.; Ito, Y. *J. Am. Chem. Soc*. **1996**, *118*, 3309.
5. Brunner, H.; Wagenhuber, L. *J. Organomet. Chem*. **1996**, *525*, 259.
6. Broene, R. D.; Buchwald, S. L.; Lee, N. E. US Patent 5491233, 1996 (to Massachusetts Inst. Technology).
7. Mikami, K.; Matsukawa, S. *Nature* **1997**, *385*, 613.
8. Mikami, K.; Matsukawa, S.; Volk, T.; Terada, M. *Angew. Chem*. **1997**, *36*, 2768.
9. Zondervan, C. PhD Thesis, University of Groningen, 1997; pp. 35–39.
10. Ishitani, H.; Komiyama, S.; Kobayashi, S. *Angew. Chem*. **1998**, *37*, 3186.
11. Dutch Pat. Appl., 1997, to DSM N.V. (to be published).
12. Corey, E. J.; Helal, C. J. *Angew. Chem*. **1998**, *37*, 1986 and references cited therein.
13. Hirao, A.; Itsuno, S.; Nakahama, S.; Yamazaki, N. *J. Chem. Soc., Chem. Commun*. **1981**, 315.
14. Itsuno, S.; Hirao, A.; Nakahama, S.; Yamazaki, N. *J. Chem. Soc., Perkin Trans. 1* **1981**, 315.
15. Didier, E.; Loubbinoux, B.; Ramos Tombo, G. M.; Rihs, G. *Tetrahedron* **1991**, *47*, 4941.
16. In addition to the four amino alcohols depicted in Scheme 1, combinations with the following amino alcohols were also tested: (*R*)-aminobutanol, (*S*)-leucinol, (*S*)-phenylalaninol and (1*R*,2*R*)-2-amino-1-phenylpropane-1,3-diol.
17. At ambient temperature the borane reduction of acetophenone (catalyzed as well as uncatalyzed) is almost simultaneous.
18. Douglas, A. W.; Tschaen, D. M.; Reamer, R. A.; Shi, Y.-J. *Tetrahedron: Asymmetry* **1996**, *7*, 1303.
19. Schmidt, R.; Jockel, H.; Schmalz, H.-G.; Jope, H. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2725.
20. Prasad, K. R. K.; Joshi, N. N. *Tetrahedron: Asymmetry* **1996**, *7*, 3147.
21. For a recent review on asymmetric amplification see: Girard, C.; Kagan, H. B. *Angew. Chem*. **1998**, *37*, 2922.