

Asymmetric Aggregative Activation. A New Useful Concept  
for Asymmetric Reduction

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Reduction of arylketones with a Complex Reducing Agent containing 2 equivalents of  $\text{Zn}^0$  and 4 equivalents of sodium chiraldate in a mixture of THF and methylcyclohexane for 1 equivalent of arylketone took place with a chiral induction from 56 to 89% of enantiomeric excess.

In a previous short communication, we showed that reduction of ketones with a complex reducing agent (CRA) and Chirald® or (2S,3R)-(+)-4-dimethylamino-1,2-diphenyl-3-methyl-2-butanol ( $\text{ZnCRA}^*$ ) took place with asymmetric induction.<sup>1)</sup>

According to the basic principle of "Aggregative Activation" (AA)<sup>2)</sup> applied to CRA,<sup>3)</sup> these reductions were interpreted as electron transfers to the complexed ketone in  $\text{Zn}^0$  containing aggregates.

Thus, the chiral induction should be due to an asymmetric complexation of the carbonyl substrate inside some asymmetric sites of the aggregates.

We think that it could be possible to improve the chiral inductions by changing the physical structure of the asymmetric sites of the aggregates and increasing the extent of complexation of the prochiral ketone in the appropriate site. So, we have simply changed the ratio of the components of CRA and the substrate/CRA ratio.

From a number of experiments not presently reported, it appeared that the best  $\text{NaH-Na chiraldate-ZnCl}_2$  ratio was 2/2/1 : in other words, after the reduction of  $\text{ZnCl}_2$  by NaH, there is no NaH left.

We had previously showed that CRAs without NaH are able to reduce carbonyl substrates slowly, but the reduction was not complete and was much slower than with CRAs containing NaH.<sup>4)</sup>

We determined that the best ratio chiraldate/ $\text{Zn}^0$ /substrate is 4/2/1 for a high enantiomeric excess.

Finally, as expected, the preparation conditions of the reagent play an important role. We have empirically adopted the following experimental procedure : Under nitrogen, 40 mM of NaH were washed with 3 times 10 ml of THF in order to degrease it; 2 ml were left. 10 mM of dried  $\text{ZnCl}_2$  (or  $\text{ZnBr}_2$ ) were added, then 2 ml of THF, then 20 mM of chiral d and 2 ml of THF. The mixture is refluxed under stirring and under nitrogen for 2 h with an oil bath at 80-85 °C. Then, a maximum of THF is distilled at this temperature and under nitrogen current (4.5 ml are obtained if recovered in approximately 20 to 30 mn). 6 ml of methylcyclohexane are then added before the cooling of the reactor in a room temperature bath. Finally, the ketone is added without solvent with a Pasteur pipette. After 17 h of reaction, the mixture is hydrolyzed with 5% HCl and then extracted with ether. The crude product is chromatographed over silicagel (generally with  $\text{Et}_2\text{O}$ /P.E. 20%).

The results are collected in Table 1.

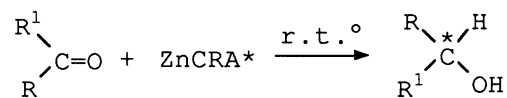
These data deserve some comments : we have verified that during the preparation of the reagent, the amount of evolved hydrogen corresponds to the formation of the sodium salt of chiral and to the reduction of  $\text{ZnCl}_2$  into  $\text{Zn}^0$ . In other words, the reagent is formally constituted by  $\text{Zn}^0$  included in a matrix of chiraldate, chloride and sodium ions. In spite of this simplicity, the enantiomeric excesses vary from high to moderate when compared with much more complicated and expensive reagents.<sup>5)</sup>

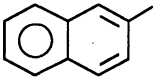
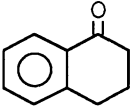
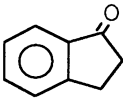
It is noteworthy that the addition of the ketone is accompanied by a rapid increase of the temperature by about 13°. Moreover, most of the reduction (often more than 90%) takes place very rapidly (several minutes). Curiously lowering the temperature (0 °C) does not lead to a significantly better chiral induction, even if the reactional mixture does not freeze.

It must be emphasized that after hydrolysis the (reutilisable) chiral d is easily recovered in 90% yield.

A very intriguing question is : where does the hydrogen come from ? Hydrolysis with  $\text{D}_2\text{O}$  led to no deuterium incorporation in the formed alcohol. Reductions performed in the presence of deuterated THF or  $\text{C}_6\text{D}_{12}$  led to incorporation of some deuterium on one of the benzene rings of the chiral d but not on the produced alcohol. Although we were unable to show any deuterium incorporation in the benzylic position, an hypothesis is that inside the asymmetric aggregates, the benzylic hydrogens could be transferred to the ketone, leading to a radical which is trapped by abstracting a hydrogen from the solvent (Scheme 1).

Table 1.



| R                               | R <sup>1</sup>                                                                      | Alcohol isolated<br>Yields/% | $\alpha_D$                        | % ee |
|---------------------------------|-------------------------------------------------------------------------------------|------------------------------|-----------------------------------|------|
| Me                              | Ph                                                                                  | 73                           |                                   | 73a) |
| Et                              | Ph                                                                                  | 88                           |                                   | 84a) |
| Pr                              | Ph                                                                                  | 75                           |                                   | 88a) |
| iPr                             | Ph                                                                                  | 84                           |                                   | 79a) |
| nBu                             | Ph                                                                                  | 79                           |                                   | 75a) |
| nC <sub>9</sub> H <sub>19</sub> | Ph                                                                                  | 75                           |                                   | 89a) |
| Me                              |    | 70                           | -22 (1/MeOH) c)                   | 57b) |
|                                 |   | 83                           | +18.4 (2.5/CHCl <sub>3</sub> ) d) | 56b) |
|                                 |  | 70                           | +19.5 (2/CHCl <sub>3</sub> ) e)   | 65b) |
| Me                              |  | 95                           |                                   | 54a) |

a) Enantiomeric excess determined by HPLC (Chiracel OB).

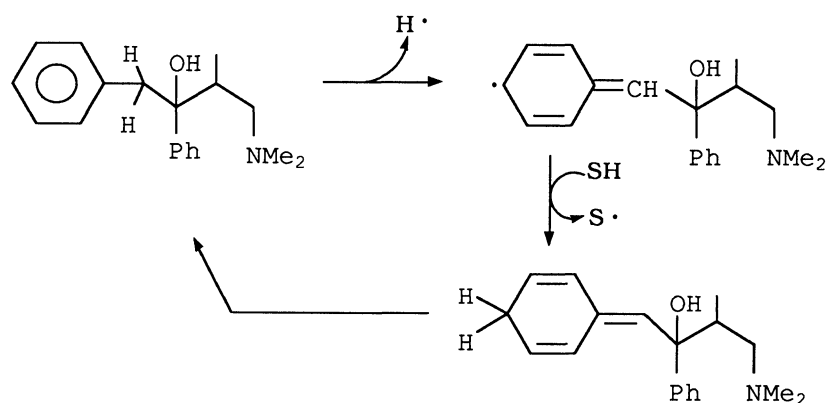
b) Enantiomeric excess determined by polarimetry.

c) Based on  $[\alpha]_D^{20}$  -38 (c 1/CH<sub>3</sub>OH) determined from (S) authentic sample (Fluka).

d) Based on  $[\alpha]_D^{20}$  +33 (c 2.5/CHCl<sub>3</sub>) determined from (S) authentic sample (Fluka).

e) Based on  $[\alpha]_D^{20}$  +30 (c 2/CHCl<sub>3</sub>) determined from (S) authentic sample (Aldrich).

Although a large number of questions remain to be answered, it appears that the concept of "asymmetric aggregative activation" is very fruitful and its study is actively continued in our laboratory.



Finally, we thought that the replacement of sodium chiraldate by an achiral sodium alkoxide or aminoalkoxide should modify the asymmetry of the reduction sites of the aggregates without complete destruction of this asymmetry. The modifications must be a function of the nature of the achiral alkoxide. Thus, we must continue to observe chiral reductions, but the enantiomeric excess must vary with the added alkoxide. This expectation was verified. Thus, reduction of PhCOEt (1 equiv.) with reagents containing 3 equivalents of sodium chiraldate without added alkoxide and with 1 equivalent of PhONa, tAmONa or EtONa led respectively to the following enantiomeric excesses : 80%, 76%, 66%, and 47%. Besides the fact that this result seems to be in agreement with the aggregates hypothesis, it also shows that it would be possible to replace some of the sodium chiraldate by an appropriate achiral sodium alkoxide.

#### References

- 1) A. Feghouli, R. Vanderesse, Y. Fort, and P. Caubère, J. Chem. Soc., Chem. Commun., **1989**, 224 : in this communication, notice the following errors : read 44 and 42% of enantiomeric excess instead of 64 and 61 in Table 1.
- 2) Aggregative activation covers all the phenomena occurring in complex bases and complex reducing agents and was introduced by Caubère P. : Complex reducing agents and their applications, 8th FECHEM on Organometallics Veszprem, Hungary 8/1989; P. Caubère, Reviews on Heteroatom Chemistry, **4**, 79 (1991).
- 3) R. Vanderesse, G. Feghouli, Y. Fort, and P. Caubère, J. Org. Chem., **55**, 5916 (1990).
- 4) D. Besozzi, Thesis, Université de Nancy I, 1982.
- 5) M.M. Midland, A. Kazuleski, and R.E. Woodling, J. Org. Chem., **56**, 1068 (1991) and ref. cited therein; H.C. Brown, B.T. Cho, and W.S. Park, J. Org. Chem., **53**, 1231 (1988).

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