# Asymmetric Reduction of Ketones with Asymmetric Complex Reducing Agents: [ZnCRA*]

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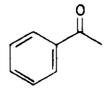
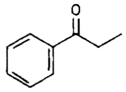
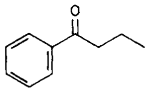
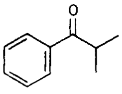
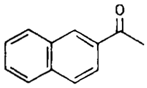
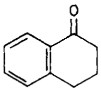
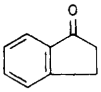
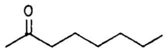
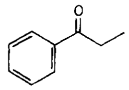
The reduction of selected ketones has been achieved using asymmetric zinc-containing complex reducing agents (ZnCRA*) prepared from (2*S*,3*R*)-(+)-4-dimethylamino-1,2-diphenyl-3-methyl-butan-2-ol (Chirald).

One field of investigation which has received considerable attention in asymmetric synthesis is the reduction of prochiral ketones into optically pure alcohols.[1—3] In a recent publication,[1] Brown and his collaborators have shown that among the numerous reagents described in the literature, only 20 are promising. Interestingly, it appears that these reagents are either borane or complex hydride derivatives and the authors have shown that 'no one particular reagent is effective for all of the different classes of ketones.' Moreover most of them are not easily prepared on large scale and are rather expensive. Thus, new families of reducing agents could be of use for the asymmetric reduction of prochiral ketones. The results obtained in our laboratory with the inexpensive complex reducing agents NaH–RONa–$MX_n$ (MCRA, where M is a metal) easily prepared by simple mixing of a metal salt, NaH and an alcohol, led us to consider that these curious reagents could be of interest in this area.[4—6]

Among the numerous MCRA's developed, ZnCRA reagents were found particularly efficient in reducing ketones.[6] Moreover, a study of the nature of these reagents

**Table 1.** Asymmetric reduction of ketones using Chirald-[ZnCRA*].[a]

| Run | Ketone | % Yield[b] | $[\alpha]_D^{22}$ | Enantiomeric excess/%[c] |
|---|---|---|---|---|
| 1 |  | 70 | −9.2 (*c* 0.50, MeOH) | 21 |
| 2 | | 98[d] | −20.0 (*c* 0.98, MeOH) | 46 |
| 3 |  | 82 | −20.7 (*c* 0.55, $CHCl_3$) | 64 |
| 4 |  | 70 | −22.2 (*c* 3.5, $CHCl_3$] | 49 |
| 5 |  | 55 | −8.2 (*c* 1.39, $CHCl_3$) | 34 |
| 6 | | 90[d] | −9.7 (*c* 1.39, $CHCl_3$) | 40 |
| 7 |  | 92 | −14.3 (*c* 1.39, EtOH) | 35 |
| 8 |  | 80 | +7.7 (*c* 2.07, $CHCl_3$) | 24 |
| 9 |  | 87 | +15.6 (*c* 0.64, $CHCl_3$) | 46 |
| 10 |  | 94 | −0.5 (*c* 1.10, $CHCl_3$) | 5 |
| 11 |  | 80[e] | −19.8 (*c* 0.50, $CHCl_3$) | 61 |

[a] Reactions were carried out at 25 °C for 17 h in tetrahydrofuran (THF) (40 ml) in a system: ketone (10 mmol) and Chirald-[ZnCRA*] [prepared from NaH (50 mmol), Chirald (10 mmol), and $ZnCl_2$ (10 mmol)]. [b] Yield after isolation by flash chromatography. [c] Determined by comparison of maximum rotation reported in the literature. [d] Reactions performed on 5 mmol scale. [e] Reaction performed with recycled Chirald.

*Note added in proof:* We must mention that Chirald has been successfully used with $LiAlH_4$ for the chiral reduction of acetophenone (S. Yamaguchi, H. S. Mosher, and A. Pohland, *J. Am. Chem. Soc.*, 1972, **94**, 9254). For recent publication of chiral reduction of ketones see also E. J. Corey, R. K. Bakshi, and S. Shibata, *ibid.*, 1987, **109**, 5551 and E. J. Corey, R. K. Bakshi, S. Shibata, C.-P. Chen, and V. K. Singh, *ibid.*, 1987, **109**, 7925. The authors express thanks to the referees for help and suggestions.

led us to propose that the reactive part of ZnCRA could have the general formula $[(RONa)_xH_yZnNa_{x+y}]_n$ in which the alkoxide, hydride, and metal are associated. It was expected that replacement of achiral alcohols by chiral ones during the preparation of MCRA would lead to asymmetric reagents [MCRA*] efficient in performing asymmetric reductions. In a general experiment, a suspension of dry $ZnCl_2$ (10 mmol) and degreased NaH (50 mmol) in tetrahydrofuran (THF) (20 ml) under nitrogen at 63 °C was added a solution of Chirald (available from Aldrich) (10 mmol) in THF (10 ml). After stirring for 2 h at 63 °C, the mixture was allowed to cool at 25 °C over 3 h. The ketone (10 mmol) in THF (10 ml) was then added over a period of 2—3 min. After 17 h, the excess NaH was carefully destroyed by addition of water. The alcohol was isolated by flash chromatography after acidic extraction from ether. The Chirald was recovered by extraction of the aqueous phase after basification by NaOH (25%).

From Table 1 it appears that very interesting results were obtained with [ZnCRA*] prepared from the commercially available and inexpensive Chirald.

[ZnCRA*] was as easily prepared by the same method as ZnCRA.[4—6] Moreover Chirald was easily removed and recovered at the end of the reaction. For example in run 3, 95% of Chirald {[α] +8.17°, $[\alpha]_D$ of starting material +8.2°} was recovered. This Chirald was re-used in the reduction reported in run 11 showing that the asymmetric inducing agent can be recycled.

Taking into account the easy obtention of CRA's from inexpensive commercial materials this work appears as very encouraging. It must be underlined that it is shown, for the first time, that reagents looking like 'ate' complexes of zero valent metal species in which the asymmetric inducing alkoxides are not simply bonded to the central metal, are able to efficiently induce asymmetric reduction. Extension of these first results to the numerous CRA's developed in our laboratory is actively being studied in order to obtain a palette of selective effective asymmetric reagents.

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## References

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6 A. Feghouli, Y. Fort, R. Vanderesse, and P. Caubère, *Tetrahedron Lett.*, 1988, **29**, 1379.