

# On the So-called 'Surprising Observation Concerning Sodium Hydride Based Complex Reducing Agents'

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Nordahl and Carlson in their published article [*Acta Chem. Scand.* 44 (1990) 274] questioned results obtained by us involving ZnCRASi [a Zn- and Me<sub>3</sub>SiCl-containing complex reducing agent (CRA) prepared from NaH, *tert*-amyl alcohol, ZnCl<sub>2</sub> and Me<sub>3</sub>SiCl]. In the present publication it is shown that, in fact, their assertions are wrong. Moreover, it is shown that the main factors governing CRAs cannot be determined by the multivariate method used by Nordahl and Carlson. Finally, the reductions performed with the reagent proposed by Nordahl and Carlson are shown to be strongly dependent on the experimental procedure, contrary to their assertion, and less selective than those performed with CRAs.

In a recent publication<sup>1,2</sup> Nordahl and Carlson, by means of an ingenious multivariate experimental design, studied the behavior of one of our reagents, namely ZnCRASi<sup>3,4</sup> [a Zn- and Me<sub>3</sub>SiCl-containing complex reducing agent (CRA) prepared from NaH, *tert*-amyl alcohol, ZnCl<sub>2</sub> and Me<sub>3</sub>SiCl]. Using 2-methylcyclohexanone as a model substrate, they attempted to show that the constituent ratios of ZnCRASi had an effect on the stereochemical outcome of the reduction of cyclic ketones.

Nordahl and Carlson drew the following conclusions. (i) The stereochemistry of the reduction of ketones depends (albeit to a small extent) on the composition of the CRA. (ii) The reduction is very sensitive to the composition of the reagent. (iii) A new reagent combination, from which the alkoxide was excluded, was found to be more efficient than ZnCRASi.

This last result led Nordahl and Carlson to conclude that organic chemists ought to use their multivariate experimental design to allow for all factors to be considered simultaneously and to avoid the publication of erroneous results. Finally the authors concluded that our work was incomplete.

In the present publication we wish to show: (i) that some of Nordahl and Carlson's results on CRAs are in complete agreement with results already published by us; (ii) that their studies concerning the stereochemistry of reduction of ketones were incomplete and that the use of a multivariate experimental design does not mean that some basic chemical properties of ketones can be neglected; (iii) that some of their assertions concerning their new reagent, from which alkoxide was excluded, are inconsistent with their

experimental observations and with our own published results. In fact, we report here a number of reactions performed according to the different experimental conditions given by these authors, and, as will be seen we disagree completely with Nordahl and Carlson. Moreover, we attempt to explain the reasons for not having published results we obtained a long time ago with the reagent in which alkoxide was excluded.

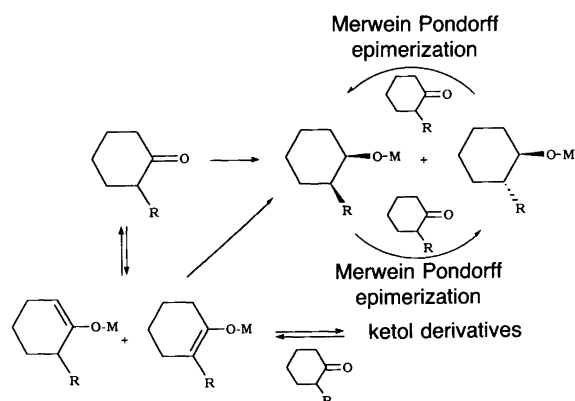
## On the stereoselectivity of ZnCRASi

Carlson and Nordahl showed that the variation of the constituent ratios of ZnCRASi led to variation in the stereochemistry of ketone reductions. This result is a particular characteristic of the general behavior of CRAs we studied several years ago.<sup>3,5</sup>

For a valid discussion of the stereochemistry of reduction of ketones, two types of data must be given: overall yields and, above all, the variation of isomer ratios during the reduction. Indeed a number of side-reactions may take place with non-transition metal containing CRAs. They are summarized in Scheme 1.<sup>4c</sup> According to this scheme, epimerization of the alkoxides formed may take place, therefore it must be determined whether such isomerization must be taken into account or whether it may be neglected.<sup>4b,c</sup> Moreover, under certain conditions, enolization of the ketone may also take place. In addition to the formation of ketol derivatives, the possible reduction of the enolate must also be considered.<sup>4,6</sup>

Unfortunately this information is absent from the work of Nordahl and Carlson. Thus it is impossible to know whether the *cis/trans* ratios they determined with ZnCRASi in which constituent ratios are different from those we determined to be optimal<sup>3b,4</sup> are due to the simple reduc-

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Scheme 1.

tion of 2-methylcyclohexanone or to a combination of reduction, epimerization and enolization–reduction.

Finally, although we did not use a multivariate experimental design, we found that variation in the nature of the metal and, in some cases, in the nature of the alkoxide, led to considerable changes in the stereochemistry of the reductions.<sup>4c</sup> Moreover, these results led us to discover new alcohol-epimerizing agents.<sup>5</sup>

Thus, without denying the usefulness of multivariate experimental design we are convinced that traditional ‘one factor at a time’ method of experimental design also has its place in synthetic organic chemistry.

#### About the ‘new’ reagent NaH–ZnCl<sub>2</sub>–Me<sub>3</sub>SiCl

Nordahl and Carlson seemingly did not understand the goal of the studies we have been performing for many years and now grouped under the basic principle of aggregative activation.<sup>7</sup> We can briefly summarize this principle as follows. It is possible to activate or modulate the properties of a given reagent by aggregate formation with another reagent. For example, we showed that activation of NaNH<sub>2</sub> with sodium alkoxides led to new bases (complex bases) with properties completely different from those of the individual constituents.<sup>8</sup> Two of these complex bases are now commercially available.<sup>9</sup>

With CRAs the same basic principles were applied. So far as our studies on ZnCRASi are concerned, they were conducted in order to find a mild, very selective hydrosilylating agent for carbonyl groups able to give reproducible results.<sup>3b,10a</sup> We were not so much interested in fast reactions as in selectives ones.

During this work we, of course, investigated the kinds of reagent proposed by Nordahl and Carlson, but abandoned them for the following reasons. (i) Instead of the expected silyl ethers these reagents led to mixtures of alcohols and silyl ethers, the ratio of which depended on the experimental conditions. (ii) The reactivity of these reagents was strongly dependent on the preparation procedure. (iii) Since the pioneering works of Ashby,<sup>11</sup> it is well known that 2 equiv. of NaH react with 1 equiv. of ZnCl<sub>2</sub> (the ratio used by Nordahl and Carlson) to give ZnH<sub>2</sub>, a well known

reducing agent for ketones.<sup>11a</sup> Moreover, it is also well known that ZnH<sub>2</sub> is not very stable and decomposes into Zn and H<sub>2</sub>.<sup>11b</sup> Note that we previously showed that Zn was formed during the preparation of ZnCRA,<sup>10b</sup> so, under certain conditions NaH–ZnCl<sub>2</sub>–Me<sub>3</sub>SiCl actually becomes Zn–Me<sub>3</sub>SiCl, a well known and established reducing agent.<sup>12</sup> The lack of reproducibility observed is easily explained by the fact that the reducing agent is a non-reproducible mixture of ZnH<sub>2</sub>, Zn and Me<sub>3</sub>SiCl.

Thus we were very surprised to read that under these conditions, Nordahl and Carlson observed that ‘no significant differences in reactivity or yield could be detected when different procedures were used’. These results contradicted our own experiments. Moreover, in their Experimental section these authors made the recommendation to ‘add as rapidly as possible’ the carbonyl compound after preparation of their reagent. We thought that this observation could be related to one of the procedures we described for the reduction of unsaturated substrates.<sup>13</sup> Indeed we found that simultaneous addition of a mixture of the substrate with Me<sub>3</sub>SiCl or better, with H<sub>2</sub>O to a CRA led to very efficient reductions.

We decided to clarify this situation and performed the reactions presented in Table 1 in which  $\Delta t$  represents the time between the mixing of the constituents of the reagent and the ketone addition. From these data it appears that, contrary to Nordahl and Carlson’s assertions, but in accordance with our previous results, the reducing properties of their reagent strongly depend on the experimental procedure.

Thus, a decrease in the reactivity of the reagent and a decrease of the silyl ether yield corresponded to an increase in  $\Delta t$ . On the other hand, since the silylation of the alcohol formed continues after complete disappearance of the starting ketone, it is possible to obtain good yields of silylated ether. However, it took about 3 h (runs 1 and 7) which is somewhat longer than the 15 min observed with ZnCRASi (run 9)!<sup>3b</sup>

Curiously, we observed that if, under the conditions of run 1, stream of nitrogen is maintained throughout the preparation of Nordahl and Carlson’s reagent in order to remove the hydrogen formed, the reduction of the ketone required a much longer reaction time and the yield of silylated ethers was decreased (run 7). Interestingly the above authors used a ratio of substrate)NaH:RONa:ZnCl<sub>2</sub>:Me<sub>3</sub>SiCl = 1:4:0:2:3 while with ZnCRASi we used the ratio 1:4:1:1:3. A control experiment with Carlson and Nordahl’s reagent using the 1:4:0:1:3 led to 51 % reduced product after 1.5 h (instead of 6 min with the published ratio). In other words, with ZnCRASi, 1 equiv. of RONa advantageously replaced 1 equiv. of ZnCl<sub>2</sub> since our reagent is much more reactive, efficient and reproducible as far as hydrosilylation is concerned.

In passing it must be emphasized that reduction of ketones to alcohols may be very easily performed with numerous CRAs<sup>4,6</sup> and that a number of them are catalytic or semicatalytic relative to the metal.<sup>6,10</sup>

Table 1. Reduction of 2-methylcyclohexanone.<sup>a</sup>

Run	System <sup>b</sup>	$\Delta t$ /h	Reaction time/h	Starting ketone (%) <sup>d</sup>	Yield of alcohol (%) <sup>d</sup>	Silylated ethers (%) <sup>d</sup>	Total reduction (%) <sup>d</sup>
1	A <sup>e</sup> [1:4:0:2:3]	0	0.1	–	22 (30:70)	76 (30:70)	98
			3	–	10 (27:73)	89 (30:70)	99
2	A [1:4:0:2:3]	0.25	0.5	–	61 (25:75)	33 (28:72)	94
3	A [1:4:0:2:3]	0.5	1.5	29.5	63 (24:76)	–	63
			16	25	67 (23:77)	–	67
4	A [1:4:0:2:3]	1	1.5	45	50 (23:77)	–	50
			16	17	78 (23:77)	–	78
5	A [1:4:0:2:3]	2	1.5	45	48 (32:68)	–	48
			16	30	63 (26:74)	–	63
6	A [1:4:0:2:3]	16	4.5	55	39 (34:66)	–	39
			48	36	49 (36:64)	–	49
7	A [1:4:0:2:3]	0 <sup>f</sup>	0.5	42	46 (30:70)	7 (35:65)	53
			2.75	0	6 (30:70)	91 (34:66)	97
8	A [1:4:0:1:3]	0	1.5	43	51 (23:77)	–	51
9	B [1:4:1:1:3]	0	0.25	–	<3 (40:60)	>97 (40:60)	99
10	B [1:4:1:1:3]	2	1.25	–	18 (30:70)	78 (35:65)	96

<sup>a</sup>Reaction performed on a 10 mmol (1 equiv.) of 2-methylcyclohexanone. <sup>b</sup>System A = Substrate:NaH:RONa:ZnCl<sub>2</sub>:Me<sub>3</sub>SiCl [1:x:0:z:f] (Nordahl and Carlson's system); System B = Substrate:NaH:RONa:ZnCl<sub>2</sub>:Me<sub>3</sub>SiCl [1:x:y:z:f] (ZnCRASi). <sup>c</sup> $\Delta t$  represents the time between the end of cooling and the addition of the ketone. <sup>d</sup>Determined by GC analysis. In parentheses, *cis/trans* ratio determined by GC analysis. <sup>e</sup>Nordahl and Carlson's experiment checked by ourselves. <sup>f</sup>A nitrogen stream was maintained over the reagent during its preparation.

Finally we would like to comment on three further points. (i) The above authors performed control experiments in order to determine whether an alkoxide would be formed initially, leading to an *in-situ* formed CRA responsible for the reductions observed. If this was the case an autocatalysed reaction had to have taken place. No such effect was observed. However, their experiments were performed in the presence of Me<sub>3</sub>SiCl which, under their conditions, may partially trap the alkoxide formed. Thus, nothing may be concluded since the concentration of free alkoxide is not known. Furthermore, it may be of interest to note that we observed some autocatalysis with a number ketones during control experiments with NaH–ZnCl<sub>2</sub>.<sup>6,10</sup>

(ii) Nordahl and Carlson described the preparation of our reagents as tedious. This is a matter of opinion and our students have routinely performed such reactions. In contrast the evolution of hydrogen during the rapid addition of the constituents and substrate of Nordahl and Carlson's reagent renders the reaction difficult to control. Moreover the tedious purification of solvents and substrates described in the Experimental section of the authors' paper is not necessary with CRAs.

(iii) Last, but not least, besides the fact that alkoxides confer high reactivity and selectivity to CRAs, they also permit the preparation of chiral reducing agents,<sup>14</sup> a difficult task with Nordahl and Carlson's reagent.

## Conclusions

We continue to believe that alkoxides are useful constituents of CRAs. Moreover, although the multivariate experimental design of Nordahl and Carlson should be considered with interest, the 'one factor at a time' method also has its advantages which must not be neglected, especially during the study of reactions in which the main factors are unknown.

## Experimental

**General.** GC analyses were carried out on a Girdel 330 equipped with FID. A 15 m Supelcowax 10 0.54 mm capillary column was used. Peak areas were calculated with a Merck D 2500 integrator. <sup>1</sup>H NMR spectra were recorded on a JEOL PWX 60 instrument in CDCl<sub>3</sub> solution with Me<sub>4</sub>Si or C<sub>6</sub>H<sub>6</sub> as an internal shift standard. All spectra of products were as expected and in accordance with published spectra.

**Chemicals and solvent.** The chemicals were purchased from Aldrich or Merck. *tert*-Amyl alcohol was distilled from sodium. ZnCl<sub>2</sub> was dried *in vacuo* for 16 h at 100°C. Me<sub>3</sub>SiCl (TMSCl) was distilled under argon from calcium hydride before use. Tetrahydrofuran (THF) was freshly

distilled from a sodium–benzophenone couple. The absence of peroxides was verified before each run.<sup>15</sup> Sodium hydride (50–60 % in oil; Fluka) was used after three washings with the reaction solvent under nitrogen. The exact grade of sodium hydride was carefully determined by a standard technique<sup>16</sup> (measurement of hydrogen evolution after the dropwise addition of water) just after opening the flask and twice more, after 33 and 67 % consumption. All ketones were distilled just before use (it is essential that all reagents be anhydrous). All reactions were carried out under nitrogen (*air liquide*). Silyl ethers were obtained as previously described.<sup>3b</sup>

*Reductive silylation of carbonyl compounds by ZnCRASi.* A mixture of sodium hydride (50 mmol) and zinc chloride (10 mmol) in tetrahydrofuran (20 ml) was warmed under a nitrogen atmosphere. *tert*-Amyl alcohol (10 mmol), diluted with tetrahydrofuran (10 ml) was then added dropwise. After 2 h of stirring at 63 °C, the reaction medium was allowed to cool to room temperature and trimethylchlorosilane (30 mmol) in tetrahydrofuran (10 ml), was added dropwise. After the reaction mixture had been stirred at room temperature for 15 min, the carbonyl compound (10 mmol) in tetrahydrofuran (10 ml) was added dropwise over a 10 min period. The reaction was easily monitored by GC analysis of small aliquots. Upon completion, the reaction flask was cooled in an ice bath. The excess hydride was then destroyed by the careful, very slow, dropwise addition of water until cessation of hydrogen evolution. The liquid phase was collected and the grey curdy mass was washed with anhydrous diethyl ether (3×100 ml). All the ethereal fractions were dried with potassium carbonate. After removal of the solvents, the silyl ethers were distilled (under argon) under reduced pressure (79 °C, 20 mmHg).

*Reduction of carbonyl compounds by Nordahl and Carlson's procedure.* Sodium hydride (40 mmol) was washed with tetrahydrofuran (3×20 ml) and zinc chloride (20 mmol) in THF (30 ml) was immediately added. TMSCl (30 mmol) in THF (10 ml) was then introduced. The reaction mixture was cooled to room temperature and the ketone was added after  $\Delta t$  (see Table 1). The reaction was monitored and quenched as described above.

## References

1. Nordahl, Å. and Carlson, R. *Acta Chem. Scand.* **44** (1990) 274.
2. These authors symbolized metal-containing complex reducing agents as MeCRA which is not as we defined them. Indeed, our definition of our reagents is MCRA, it being possible to confuse Me with CH<sub>3</sub>.
3. (a) Caubère, P. *Angew. Chem., Int. Ed. Engl.* **22** (1983) 599; (b) Brunet, J. J., Besozzi, D. and Caubère, P. *Synthesis* (1982) 721.
4. (a) Feghouli, A., Fort, Y., Vanderesse, R. and Caubère, P. *Tetrahedron Lett.* **29** (1988) 1379; (b) Feghouli, A. *Thèse d'Université 1989*, Nancy, France; (c) Fort, Y., Feghouli, A., Vanderesse, R. and Caubère, P. *J. Org. Chem.* **55** (1990) 5911 and references cited therein.
5. (a) Feghouli, G. *Thèse d'Université*, 1989, Nancy, France; (b) Vanderesse, R., Feghouli, G., Fort, Y. and Caubère, P. *J. Org. Chem.* **55** (1990) 5916 and references cited therein.
6. (a) Mordenti, L. *Thèse d'Etat 1979*, Nancy, France; (b) Brunet, J. J., Mordenti, L. and Caubère, P. *J. Org. Chem.* **43** (1978) 4804; (c) Mordenti, L., Brunet, J. J. and Caubère, P. *J. Org. Chem.* **44** (1979) 2203.
7. (a) Caubère, P. *8th FECHM on Organometallics*, Veszprem, Hungary, 8/1989; (b) A survey on aggregative activation will be soon published.
8. (a) Caubère, P. *Acc. Chem. Res.* **7** (1974) 301; (b) Caubère, P. *Top. Curr. Chem.* **73** (1978) 50.
9. Complex bases are commercially available from Merck-Schuchardt.
10. (a) Besozzi, D. *Thèse de 3ème cycle 1983*, Nancy, France; (b) Brunet, J. J., Besozzi, D., Courtois, A. and Caubère, P. *J. Am. Chem. Soc.* **104** (1982) 7130.
11. (a) Watkins, J. J. and Ashby, E. C. *Inorg. Chem.* **13** (1974) 2350; (b) Ashby, E. C. and Watkins, J. J. *Inorg. Chem.* **12** (1973) 2493.
12. See for example: (a) Schmidt, A. H. and Russ, M. *Chem. Ber.* **114** (1981) 822; (b) Vankar, Y. D., Arya, P. S. and Rao, C. T. *Synth. Commun.* **13** (1983) 869; (c) Banerjee, A. K., Sulbaran de Carrasco, M. C., Frydrych-Houge, C. S. V. and Motherwell, W. B. *J. Chem. Soc., Chem. Commun.* (1986) 1803; (d) Boudjouk, P. and So, J. H. *Synth. Commun.* **16** (1986) 775; (e) Vankar, Y. D., Chaudhury, N. C. and Rao, C. T. *Tetrahedron Lett.* **28** (1987) 551.
13. Fort, Y., Vanderesse, R. and Caubère, P. *Chem. Lett.* (1988) 757.
14. Feghouli, A., Vanderesse, R., Fort, Y. and Caubère, P. *J. Chem. Soc., Chem. Commun.* (1989) 224.
15. Vogel, A. I. *Vogel's Textbook of Practical Organic Chemistry*, 4th ed., Longmans, London 1978, p. 270.
16. Plešek, I. and Hermanek, S. *Sodium Hydride*, Iliffe, London 1968, p. 9.

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