Activation of Reducing Agents. Sodium Hydride Containing Complex Reducing Agents. 36. Stereoselective Reduction of Alkylcyclohexanones and Rigid Ketones by MCRA's

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The stereoselectivity of reduction of selected ketones by a variety of Complex Reducing Agents (resulting from the Aggregative Activation of NaH and symbolized MCRA's) has been investigated. The stereochemistry of reduction is shown to be dependent on the nature of the metal. Steric hindrance plays an important role and the apparent size of the reagents follows the trend MnCRA's > ZnCRA's, CdCRA's > NiCRA's, CoCRA's. On the other hand NiCRA's and CoCRA's have been found as very strong isomerizing reagents. Insertion of the metal species into the C-O bond with formation of metallacycles appears as one of the possible mechanisms intervening during the reduction of ketones by MCRA's.

Introduction

In preceding publications we established that complex reducing agents [NaH–RONa–MX_n symbolized MCRA,[1] or in the presence of $MgBr_2$, MCRA–$MgBr_2$, or in the presence of Me_3SiCl, MCRASi] easily reduced aldehydes and ketones.[2] Among the very interesting points concerning the reduction of ketones, the stereoselectivity is the cornerstone.[3-7] So, we decided to undertake a study on the possible stereoselective reductions of ketones with MCRA's. This work would be of interest for synthetic purposes as well as for improving the knowledge of the phenomena occurring in what we now call aggregative activation (AA).[8] In the present paper we will report the results obtained in this area and show that the stereoselectivity of MCRA reductions strongly depends upon the nature of the metal and may be reversed by a simple change of their constitution.

Scheme I

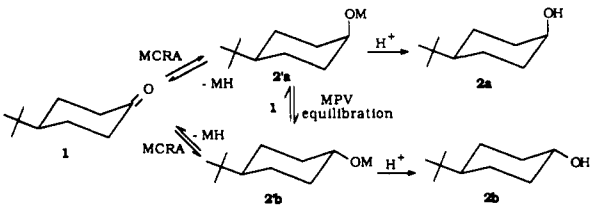


Table I. Reduction of 4-*tert*-Butylcyclohexanone (1) by MCRA in THF[a]

	t (h)	red. (%)[b]	OH_{ax}/OH_{eq}[b]	res. ketone[b]
ZnCRA (4/1/1)	18	70	35/65	20
ZnCRASi (4/1/1/3)	0.25	99	20/80	
ZnCRA–$MgBr_2$ (4/1/1/1)	2	99	36/64	
CdCRA (4/1/1)	18	20	64/36	75
CdCRASi (4/1/1/3)	3	90	63/37	10
CdCRA–$MgBr_2$ (4/1/1/1)	3	56	61/39	32
MnCRA (4/1/1)	18	18	72/28	60
MnCRASi (5/1/1/3)	18	52	74/26	25
TPMNa–MnCRASi (5/1/1/3)	18	78	80/20	12
MnCRA–$MgBr_2$ (4/1/1/1)	1	48	64/36	30
NiCRA (4/1/1)	3	90	42/58	7
NiCRASi (5/1/1/1)	2	96	38/62	
NiCRA–$MgBr_2$ (4/1/1/1)	1	98	21/79	
DMHDNa–NiCRA (4/0.5/1)	18	99	3/97	
CoCRA (4/1/1)	3	45	70/30	52
CoCRASi (5/1/1/1)	3	82	68/32	15
CoCRA–$MgBr_2$ (4/1/1/1)	2	95	63/37	5

[a] Reaction performed on a 10-mmol scale in 40 mL of THF at 45 °C for Ni- and ZnCRA's and at 65 °C for Cd-, Co-, and MnCRA's. [b] Yields and ratios determined by GC analysis.

Results and Discussion

Exploratory Experiments. Exploration of stereoselective reductions may be conveniently performed with 4-*tert*-butylcyclohexanone (1).[3-7] With MCRA's, the ex-

(1) Caubère, P. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 599. In this paper we have adopted the following convention: a MCRA (metal atom specified) prepared from NaH, RONa, and MX_n will be abbreviated MCRA ($x/y/z$). In the same way a MCRASi or a MCRA–$MgBr_2$ prepared from NaH, RONa, MX_n, and Me_3SiCl or $MgBr_2$ will be abbreviated MCRASi ($x/y/z/t$) or MCRA–$MgBr_2$ ($x/y/z/t$) where the molar ratio NaH/RONa/MX_n/Me_3SiCl or $MgBr_2$ (in that order) is equal to $x/y/z/t$.

(2) (a) Brunet, J. J.; Mordenti, L.; Caubère, P. *J. Org. Chem.* **1978**, *43*, 4804. (b) Feghouli, A.; Fort, Y.; Vanderesse, R.; Caubère, P. *Tetrahedron Lett.* **1988**, *29*, 1379.

(3) See, for example: (a) Marshall, J. A.; Caroll, R. O. *J. Org. Chem.* **1965**, *30*, 2748. (b) Brown, H. C.; Muzzio, J. *J. Am. Chem. Soc.* **1966**, *88*, 2811. (c) Brown, H. C.; Varma, V. *J. Am. Chem. Soc.* **1974**, *39*, 1631. (d) Ashby, E. C.; Boone, J. R. *J. Org. Chem.* **1976**, *41*, 2890. (e) Handel, H.; Pierre, J. L. *Tetrahedron Lett.* **1976**, 741. (f) Wigfield, D. C.; Phelps, D. *J. Am. Chem. Soc.* **1974**, *96*, 543; *J. Org. Chem.* **1976**, *41*, 2396. (g) Ashby, E. C.; Lin, J. J.; Goel, A. B. *J. Org. Chem.* **1978**, *43*, 1557, 1560, and 1564. (h) Caro, B.; Boyer, B.; Lamaty, G.; Jaouen, G. *Bull. Soc. Chim. Fr.* **1983**, II-281.

(4) See, for example: (a) Krishnamurthy, S.; Brown, H. C. *J. Am. Chem. Soc.* **1972**, *94*, 715. (b) Brown, C. A. *J. Am. Chem. Soc.* **1973**, *95*, 4100. (c) Brown, H. C.; Krishnamurthy, S. *J. Am. Chem. Soc.* **1973**, *98*, 3383. (d) Brown, C. A.; Krishnamurthy, S. *J. Organomet. Chem.* **1978**, *156*, 111.

(5) See, for example: (a) Hooz, J.; Akiyama, F. J.; Cedar, F. J.; Bennett, M. J.; Tuggle, R. M. *J. Am. Chem. Soc.* **1974**, *96*, 274. (b) Yoon, N. M.; Kim, K. E.; Kang, J. *J. Org. Chem.* **1986**, *51*, 226. (c) Yoon, N. M.; Kim, K. E. *J. Org. Chem.* **1987**, *52*, 5564.

(6) See, for example: (a) Brown, H. C.; Deck, H. E. *J. Am. Chem. Soc.* **1965**, *87*, 5620. (b) Eliel, E.; Senda, Y. *Tetrahedron* **1970**, *26*, 2411. (c) Haubenstock, H. *J. Org. Chem.* **1975**, *40*, 926. (d) Brown, H. C.; Cha, J. S.; Nazer, B.; Kim, S. C.; Krishnamurthy, S.; Brown, C. A. *J. Org. Chem.* **1984**, *49*, 885. (e) Brown, H. C.; Cha, J. S.; Nazer, B. *Synthesis* **1984**, 494. (f) Brown, H. C.; Won, S. P.; Jin, S. C.; Byang, S. C. *J. Org. Chem.* **1986**, *51*, 337.

(7) (a) Eliel, E. L.; Rerick, M. N. *J. Am. Chem. Soc.* **1960**, *82*, 1367. (b) Eliel, E. L.; Senda, Y. *Tetrahedron* **1970**, *26*, 2411. (c) Ashby, E. C.; Lin, J. J.; Goel, A. B. *J. Org. Chem.* **1978**, *43*, 1557, 1560, and 1564.

(8) Aggregative activation covers all the phenomena occurring in complex bases and complex reducing agents and was introduced by P. Caubère, Complex Reducing Agents and their applications, 8th FECHEM on Organometallics, VESZPREM, Hungary, 8/1989.

0022-3263/90/1955-5911$02.50/0

Table II. Reduction of 2-Norbornanone (3), (±)-Camphor (4), and (−)-1,3,3-Trimethyl-2-norbornanone (5) by MCRA in THF[a]

	ketone											
	3				4				5			
	t (h)	red.,[b] %	endo/exo[b]	rec.,[b] %	t (h)	red.,[b] %	endo/exo[b]	rec.,[b] %	t (h)	red.,[b] %	endo/exo[b]	rec.,[b] %
ZnCRA (4/1/1)	18	93	82/18	3	2	89	4/96	10	2	88	97/3	2
ZnCRASi (4/1/1/3)	0.25	99	87/13		1	96	6/94	4	3	90	99/1	9
ZnCRA-$MgBr_2$ (4/1/1/1)	3	98	95/5		1	92	9/91		2	92	98/2	
CdCRASi (4/1/1/3)	18	50	98/2	43	4	90	8/92	8	2	89	98/2	10
NiCRA (4/1/1)	1	97	48/52	2	2	91	9/91		18	98	72/28	
					18	87	23/77					
NiCRASi (5/1/1/1)	1	97	33/67	2	1	96	11/89		3	98	72/28	
					18	82	68/32	11				
NiCRA-$MgBr_2$ (4/1/1/1)	0.25	99	67/33		2	98	16/84		3	96	70/30	
DMHDNa-NiCRA (4/0.5/1)	2	90	18/82	7	1	98	17/83		1	98	67/33	
	48		10/90		18		75/25					
CoCRA (4/1/1)	1	90	74/26		2	88	18/22	7	18	95	61/39	
	18	85	57/43		18	90	34/66	5				
CoCRASi (5/1/1/1)	1	96	57/43		1	63	35/65	20	18	91	65/35	
	18	96	18/82		18	70	38/62					
MnCRASi (5/1/1/3)	18	63	97/3		18	15		75	18	traces		85

[a] Reaction performed on a 10-mmol scale in 40 mL of THF at 45 °C for Ni- and ZnCRA's and at 65 °C for Cd-, Co-, and MnCRA's. [b] Yields and ratios determined by GC analysis.

pected reactions are given in Scheme I.

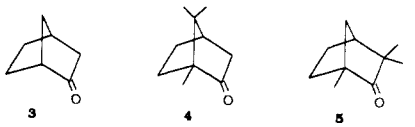
β-Elimination of metal hydride from the formed alkoxides may take place with reagents containing transition-metal species.[9] The result of such an oxidation followed by the reduction of the back-formed ketone is a true equilibration of the alkoxides. This equilibration may also take place in the presence of nonreduced 1 by the usual Meerwein–Pondorff–Verley (MPV) pathway.

In the present work we consider that a reagent cannot be classified as isomerizing if the ratio of the alcohols formed remains constant after 20% of the ketone has been reduced *and* after complete disappearance of the starting material. Under these conditions the ratio of the alcohols formed reflected the stereoselectivity of the reagents.

Exploratory experiments[10,11] led to the following conclusions: (i) Among all the CRA's examined only Zn, Cd, Mn, Ni, and Co-containing reagents appeared of sufficient general interest for the ketone reduction. (ii) Sodium *tert*-amyloxide was determined as a very convenient activating agent and was used throughout this work with, however, two notable exceptions: DMHDNa–NiCRA and TPMNa–MnCRASi prepared from the sodium salts of 2,5-dimethyl-2,5-hexanediol (DMHDNa) and of triphenylmethanol (TPMNa), respectively. (iii) THF was found to be a good solvent and the best reaction temperatures to be 45 °C with Zn- and NiCRA's and 63 °C with other MCRA's. In fact the temperature just affects the rate of the reaction but never the isomer ratios.[10] (iv) Our reagents belong to two different families: Zn, Cd, and MnCRA's with non or very weak isomerizing propensity and Ni- and CoCRA's with a strong propensity to isomerize.[10]

The main results obtained are gathered in Table I. It immediately appears that the presence of additives such as $MgBr_2$ and above all Me_3SiCl considerably increases the efficiency of the corresponding CRA's. These additives of course modify the ratios of the alcohols formed but never to a significant extent. On the contrary the nature of the metal plays an important role in the stereochemistry. With non or very weak isomerizing agents the following trend of axial attack was found: ZnCRA's > CdCRA's > MnCRA's. Passing from ZnCRA's to MnCRA's corresponds to a reversal of the isomer ratio values and allows one to obtain at will the equatorial or axial alcohol as the main product. Obviously this result is due to the intrinsic properties of MCRA's, in other words, to the structure of the aggregates surrounding the metal centers. With Co- and NiCRA's a strong propensity to isomerize reinforces the stereochemistry leading, with DMHDNa–NiCRA, to very high selective formation of equatorial alcohol. Curiously, easy isomerizations were observed with Ni- and CoCRASi. In fact, we expected, as observed with ZnCRA,[12] the formation of silyl ethers instead of metal alkoxides. Thus the back-formation of the ketone would have been suppressed as well as the corresponding isomerization. However we never found evidence of the formation of silyl ethers under these conditions. Moreover, control experiments showed that Ni- and CoCRASi only very slowly isomerized silyl ethers. So it was concluded that silyl ethers were not formed under these conditions and that the behavior of Ni- and CoCRASi was completely different from that of ZnCRASi. Comparison of our best results with those of the literature shows that the stereoselectivity of CRA's may be characterized as good, although less powerful reducing agents than classical ones. However their properties may be much more easily modulated.

Stereoselective Reduction of Rigid Bicyclic Ketones. With these results in hand we tried to determine the factors responsible for the stereoselectivity of MCRA's and first their sensitivity to steric hindrance. The best substrates for obtaining such an information appear to be the ketones **3** to **5**.[3d,4a,c,5b,c,6a]

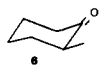
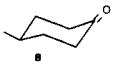
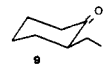
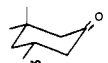


3 **4** **5**

From Table II, some interesting features emerge: (i) Zn, Cd, and MnCRA's (weak isomerizing reagents) appear to be bulkier than $NaBH_4$[3b] and look like $LiAlH(OR)_3$.[6a] We note one exception with ZnCRA, which appeared to be smaller than $LiAlH_4$[3d] against norbornanone. (ii) The low reactivity of MnCRASi against camphor and fenchone may be attributed to large steric requirements of this reagent. This point will be confirmed later. (iii) The influence of

(9) Vanderesse, R.; Feghouli, G.; Fort, Y.; Caubère, P. To be published.
(10) See supplementary material.
(11) Feghouli, A. Thèse de l'Université de Nancy I, 1989, France.
(12) Brunet, J. J.; Besozzi, D.; Caubère, P. *Synthesis* **1982**, 721.

Table III. Reduction of Alkylcyclohexanones by MCRA in THF[a]

ketone	reducing agent	t (h)	T, °C	yield,[b] %	less stable/more stable[c]	rec.,[d] %
 6	ZnCRASi (4/1/1/3)	0,25	45	100	39/61	
	CdCRASi (4/1/1/3)	3	63	91	67/33	
	TPMNa-MnCRASi (5/1/1/3)	18	63	75	65/35	10
	DMHDNa-NiCRA (4/0.5/1)	18	45	96	7/93	
 7	ZnCRASi (4/1/1/3)	0,25	45	99	27/73	
	CdCRASi (4/1/1/3)	3	63	90	49/51	9
	TPMNa-MnCRASi (5/1/1/3)	18	63	80	33/37	14
	DMHDNa-NiCRA (4/0.5/1)	3	45	98	7/93	
 8	ZnCRASi (4/1/1/3)	0,25	45	99	30/70	
	CdCRASi (4/1/1/3)	3	63	91	58/42	7
	MnCRASi (5/1/1/3)	18	63	72	66/34	10
	DMHDNa-NiCRA (4/0.5/1)	18	45	94	5/95	
 9	ZnCRASi (4/1/1/3)	1	45	99	43/57	
	CdCRASi (4/1/1/3)	18	63	70	65/35	23
	MnCRASi (5/1/1/3)	18	63	30	77/23	50
	DMHDNa-NiCRA (4/0.5/1)	48	45	80	15/85	22
 10	ZnCRASi (4/1/1/3)	1	45	98	87/13	
	CdCRASi (4/1/1/3)	18	63	91	89/11	3
	MnCRASi (5/1/1/3)	18	63	75	90/10	24
	DMHDNa-NiCRA (4/0.5/1)	18	45	92	1/99	
 11	ZnCRASi (4/1/1/3)	2	45	97	70/30	2
	CdCRASi (4/1/1/3)	18	63	53	79/21	43
	TPMNa-MnCRASi (5/1/1/3)	18	63	30	92/8	62
	DMHDNa-NiCRA (4/0.5/1)	48	45	72	66/34	25

[a] All reactions were performed on a 10-mmol scale in 40 mL of THF. [b] Yield determined by GC analysis. [c] Ratio of less stable/more stable alcohols determined by GC analysis. [d] Yield of recovered ketone determined by GC analysis.

Table IV. Reduction of *cis*-4-*tert*-Butyl-2-methylcyclohexanone (12) by MCRA in THF[a]

	t (h)	total yield of Me_{eq} alcohol (%)[b]	OH_{ax}/OH_{eq}[b]	res. ketone (%)[b]	total yield of Me_{ax} alcohol (%)[b]	OH_{ax}/OH_{eq}	trans ketone (%)[b]	total red. (%)[b]
ZnCRASi (4/1/1/3)	0.25	96	27/73					96
CdCRASi (4/1/1/3)	3	33	86/14	37	2	43/57	6	35
DMHDNaNiCRA (4/0.5/1)	2	76	38/62	7	12	39/61	3	88
CoCRASi (5/1/1/1)	2	32	82/18	52	10	55/45	4	42
TPMNa-MnCRASi (5/1/1/3)	18	14	90/10	50	5	73/27	14	19

[a] Reaction performed on a 10-mmol scale in 50 mL of THF. [b] Yields and ratio determined by GC analysis.

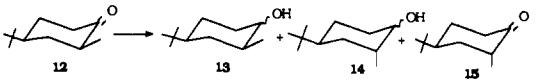
additives such as Me_3SiCl or $MgBr_2$ cannot be predicted or explained. The same is true with the usual mixed complex hydrides in which the influence of the counter cation can rarely be predicted.[3e]

With DMHDNa-NiCRA, the most stable alcohol is obtained as the main product of reduction–epimerization. With other NiCRA's, we were unable to detect any apparent isomerization. This could be due to the fact that isomerization is faster than reduction. However the smaller size of NiCRA's, compared to Zn, Cd, or MnCRA's, may also partially explain the higher propensity of Ni-containing reagents to attack the ketones on the more hindered side of the carbonyl group. In fact, both phenomena may intervene simultaneously.

In conclusion selective reduction of rigid ketones on the less hindered side of the carbonyl group may be performed with appropriately chosen Zn, Cd, or MnCRA's. Ni- or CoCRA's and mainly DMHDNa-NiCRA will lead to the other isomer. Comparison with the literature data[3-7] shows that MCRA's may be classified among the best stereoselective reduction agents. Thermodynamically stable or unstable alcohols may be obtained at will by just changing the nature of the metal.

Reduction of Alkylcyclohexanones 6–12 and 16. The validity of the above conclusions were checked with study the reduction of representative alkylcyclohexanones. The literature shows that the reduction of such ketones lead to the less thermodynamically stable isomer only with hindered reducing agents.

Scheme II



For ketones 6–10 (Table III), MCRA's behavior resembles the one found with 4-*tert*-butylcyclohexanone. The selective formation of the less stable alcohol follows the trend MnCRASi > CdCRASi > ZnCRASi ≫ DMHDNa-NiCRA. The highly isomerizing NiCRA led very selectively to the thermodynamically stable alcohols. On the contrary the less stable isomers were predominantly obtained with MnCRASi and to some extent CdCRASi.

The twisted conformation of ketone 11[13] accounts for the weak marked difference between the two faces of the carbonyl group. Thus cis/trans ratios of the alcohols vary from 50/50 with $NaBH_4$ to 64/36,[3f] with $LiAlH(OMe)_3$ a particularly hindered reagent.[6a] Table III shows that MCRA's are much more selective, the presumed more stable alcohol being predominantly formed. Isomerization took place only with DMHDNa-NiCRA. The low reduction yield and the high stereoselectivity with MnCRASi support the particular bulkness of this reagent.

Some interesting clues on the MCRA's reduction mechanisms were obtained with 12 (Table IV) to the mechanisms that take place during the reduction of ke-

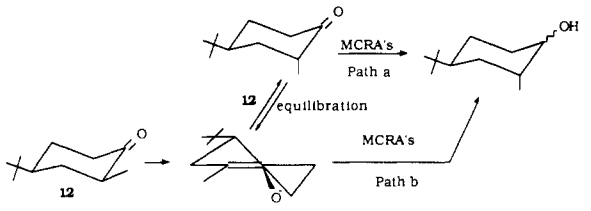
(13) (a) Boone, J. R.; Ashby, E. C. *Top. Stereochem.* **1979**, II-53-95. (b) Rickborn, B.; Wuesthoff, M. T. **1970**, *92*, 6894.

Table V. Reduction of *cis*-2,6-Dimethylcyclohexanone (16) by MCRA (*x*/*y*/*z*/*t*) in THF[a]

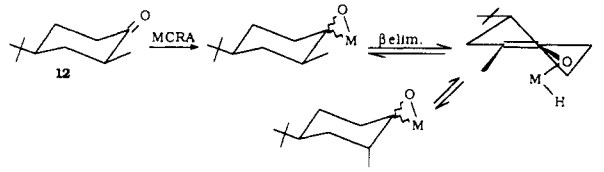
	t (h)	*T*, °C	17,[b] %	17 ax/eq,[c] %	16[d] rec., %	18,[e] %	19,[f] %	18 + 19,[g] %
ZnCRA (4/1/1)	18	45	76	72/28	2	8	1	9
ZnCRASi (4/1/1/3)	18	45	99	62/38				
CdCRASi (4/1/1/3)	1	63	80	76/24	16	2	2	4
DMHDNa-NiCRA (4/1/1)	18	45	45	9/91	2	30	2	32
CoCRASi (5/1/1/1)	1	63	32	74/26	10	49	7	56
MnCRASi (5/1/1/3)	18	63	54	83/17	11	4	6	10
TPMNa-MnCRASi (5/1/1/3)	18	63	57	88/12	21	3	5	8

[a] All reactions were performed on a 10-mmol scale in 40 mL of THF. [b] Total yield in alcohols 17 determined by GC analysis. [c] Ratio of *cis*,*cis*-2,6-dimethylcyclohexanol/*trans*,*trans*-2,6-dimethylcyclohexanol determined by GC analysis. [d] Yield of recovered *cis*-2,6-dimethylcyclohexanone (16) determined by GC analysis. [e] Yield of *cis*,*trans*-2,6-dimethylcyclohexanol (18) determined by GC analysis. [f] Yield of *trans*-2,6-dimethylcyclohexanone (19) determined by GC analysis. [g] Total yield of methyl epimerization determined by GC analysis.

Scheme III



Scheme IV



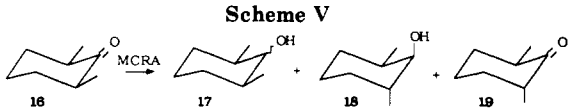
tones with MCRA's. Scheme II summarized the most general reaction.

The obtained results support our previous conclusions as far as apparent sizes are concerned. Moreover, DMHDNa-NiCRA may be definitively considered as the strongest isomerizing reagent, although CoCRA's may be of some use in this way.

From the mechanistic point of view formation of **15** and subsequently of 14 is of interest. Obviously these compounds are due to the epimerization of the methyl group. Such isomerization could be attributed to the basicity of MCRA's and two mechanisms can be proposed (Scheme III).

Previous works[2] and control experiments[10,11] exclude the reduction of enolates. So with Zn- and CdCRA's path A must be invoqued for which methyl isomerization never exceeded 8%. Although the amount of NaH and RONa was the same, methyl epimerization were more important (13 to 19%) with NiCRA's, CoCRA's and MnCRA's. Taking into account of the β-hydride elimination propensity of transition-metal complexes, the mechanism given in Scheme IV must be considered. Note that in MCRA's, the metals are under zero oxidation state degree[1] and that formation of such metallacycles is by insertion of M(O) species into a C–O bond looking like usual carbon–halogen or carbon–sulfur insertions.[14] Moreover such metallacycles have recently been evidenced.[16] In fact it is possible that the reduction of ketones with MCRA's, whatever the nature of the metal, begins with the formation of such metallacycles. Of course β-hydride eliminations can easily take place only with transition-metal species. Concerning the reduction themselves, we do not presently have sufficient experimental data to describe with certainty the evolution of such metallacycles toward the reduced products.

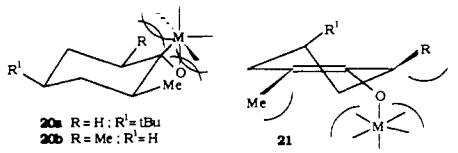
Scheme V



Finally, reactions observed with **16** (Scheme V, Table V) confirm all the above conclusions.

Thus, MnCRASi was the most selective in obtaining the less stable isomer and DMHDNa–NiCRA the best reagent for the very selective obtention of the stable alcohol. According to the results obtained with **12**, the methyl group's isomerization was generally observed. Interestingly with **12** and **16** the amount of epimerization with Zn-, Cd-, and MnCRA was nearly identical. On the contrary this isomerization was much more significant with the transition-metal-containing Ni- and CoCRA's.

Comparison of **12** and **16** shows that the epimerization due to the basicity of CRA's, which may be considered as rather hindered reagents, will be easier with **12** than with **16**. Moreover with **12**, the attack on the C6 position must be easier than on the C2 position but, of course, no apparent isomerization corresponds to such a deprotonation. The most important epimerization of **16** compared to **12** may be explained by Scheme IV. Indeed Dreiding models show that insertion of M(O), a species belonging to sterically hindered aggregates into the C=O π bond of the carbonyl group (Scheme IV) would lead to an intermediate (**20b**) more hindered than **20a**. So **20b** would have much



more propensity than **20a** to reveal its steric interactions and to give **21** in which the metal-containing aggregate may be removed from the methyl group.

Conclusion

In conclusion, as far as the reduction of ketone is concerned, MCRA's resulting from the aggregative activation of NaH, appear as good stereoselective reducing agents, the properties of which may be easily modulated by just changing the nature of the metal. Steric hindrance plays an important role and the apparent size of the reagents presently studied follows the trend MnCRA's > ZnCRA's, CdCRA's > CoCRA's, NiCRA's.

CoCRA's and NiCRA's have a strong propensity to isomerize alkoxides. The efficiency of the reagents depends on the nature of the substrate except for DMHDNa–NiCRA, which appeared as a very strong isomerizing reagent whatever the structure of the substrate.

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Insertion of the metal species into the C–O bond with formation of metallacycles appears as one of the possible mechanisms intervening during the reduction of ketones by MCRA's.

Experimental Section

The following instruments were used. For GC analyses, Girdel 330 FID (150-ft Carbowax 20M capillary, 9 ft × 0.25 in. 10% SE30 or 3% UCON Polar 6% KOH columns); for IR, Perkin-Elmer Model 580B; for NMR, Bruker AW80 (80MHz) and Bruker AM 400 (400 MHz); for preparative HPLC, Waters 500A. Melting points were determined on a Tottoli capillary apparatus.

Reagents. *tert*-Amyl alcohol (Aldrich) was distilled from sodium. Triphenylmethanol (Aldrich) or 2,5-dimethyl-2,5-hexanediol (Aldrich) were used without further purification. $Ni(OAc)_2$, $ZnCl_2$, $CdCl_2$, $CoCl_2$, and $MnCl_2$ were dried in vacuo for 16 h at 120–130 °C. NaH (55–60% in oil, Fluka) was used after three washings with anhydrous THF under N_2. Me_3SiCl (Aldrich) was distilled over CaH_2 under N_2 before use. Anhydrous $MgBr_2$ was prepared by using a reported procedure.[2a]

Ketones. 4-*tert*-Butylcyclohexanone, 2-norbornanone (norcamphor), (±)-camphor, (−)-1,3,3-trimethyl-2-norbornanone (1*R*)-(−)-fenchone, 3,3,5-trimethylcyclohexanone, 2-*tert*-butylcyclohexanone, 2-methylcyclohexanone, 3-methylcyclohexanone, and 4-methylcyclohexanone (Aldrich) were used after classical purification. 2-Ethylcyclohexanone was prepared by oxidation from 2-ethylcyclohexanols.[16] *cis*-4-*tert*-Butyl-2-methylcyclohexanone[17] was prepared by Conia's procedure[17a] and separated by flash chromatography. *cis*-2,6-Dimethylcyclohexanone[17b] was obtained from a commercial mixture by preparative HPLC.

Alcohols. Alcohols of reductions were identified by GC analyses in comparison with authentic samples. In each separation and by analogy with the literature,[18] the order of elution was ketone, axial alcohol, and equatorial alcohol. The identification was confirmed by NMR analysis of the chemical shifts of the methine proton adjacent to hydroxyl.[19] The axial protons appeared in the range δ = 2.45–3.45 and the equatorial protons in the range δ = 3.45–4.45. Integration of the signals due to these protons gave corroborating product ratios in each case. Authentic samples of *cis*- and *trans*-4-*tert*-butylcyclohexanol[3c,19b,20] were prepared by reduction of 4-*tert*-butylcyclohexanone with $LiAlH_4$[3c] and separated by flash chromatography. *endo*- and *exo*-norborneol, borneol, and isoborneol were commercially available (Aldrich). Authentic samples of *endo*- and *exo*-1,3,3-trimethyl-2-norbornanol (*endo*- and *exo*-fenchyl alcohol) and *cis*- and *trans*-2-*tert*-butylcyclohexanol[6a,21] were prepared by reduction with $LiAlH(OMe)_3$ of the corresponding ketones[6a] and separated by flash chromatography. *cis*- and *trans*-2-methyl, 3-methyl-, and -4-methylcyclohexanols[19b] were separated by flash chromatography. *cis*- and *trans*-2-ethylcyclohexanols[19b,22] and *cis*- and *trans*-3,3,5-trimethylcyclohexanols[19b] were prepared by reduction of the corresponding ketones with $LiAlH_4$[3b,4,20] and separated by preparative HPLC. *trans,trans*-, *cis,cis*-, and *trans,cis*-2,6-dimethylcyclohexanols were obtained by reduction of *cis*- and *trans*-2,6-dimethylcyclohexanone with $NaBH_4$.[3f] Trans,trans and cis,cis isomers[19b] were separated by flash chromatography. The four isomers obtained in the reduction of 4-*tert*-butyl-2-methylcyclohexanone[6a,18] were identified by direct comparison of authentic samples prepared by Doyle's and Cherest's procedures.[18]

General Procedures. Preparation of MCRA (4/1/1). Under N_2, a solution of *t*-AmOH (10 mmol) in 10 mL of THF was added dropwise to a suspension of degreased NaH (50 mmol) and anhydrous metal salt (10 mmol; $Ni(OAc)_2$, $ZnCl_2$, $CdCl_2$, $CoCl_2$, $MnCl_2$) in refluxing THF (30 mL). After 2 h of stirring for Ni, Zn, Cd, and Co salt or 4 h for Mn salt, the reagent was ready for use and the substrate could be added in THF (10 mL). NiCRA and ZnCRA were used at 45 °C and CdCRA, CoCRA, and MnCRA were used at 63 °C.

Preparation of MCRASi (5/1/1/1) (M = Ni, Co). The above procedure for the preparation of MCRA was employed by using 50 mmol of NaH. After 2 h, the temperature was adjusted to 45 °C and 10 mmol of Me_3SiCl in 10 mL of THF was added. The temperature of reaction was adjusted at 65 °C for CoCRASi.

Preparation of MnCRASi (5/1/1/3) (M = Zn, Cd, Mn). The above procedure for MCRASi was used with 30 mmol of Me_3SiCl. The reaction temperature was adjusted to 65 °C for CdCRASi and MnCRASi.

Preparation of MCRA–$MgBr_2$ (4/1/1/1). MgBr2 (10 mmol) was added to the MCRA (4/1/1) 0.5 h before the substrate at the reaction temperature.

Preparation of DMHDNa–NiCRA (4/0.5/1). In the above procedure *t*-AmOH was replaced by 5 mmol of 2,5-dimethyl-2,5-hexanediol.

Preparation of TPMNa–MnCRASi (5/1/1/3). In the above procedure *t*-AmOH was replaced by 10 mmol of triphenylmethanol.

The reactions were monitored by GC analysis of small aliquots. After completion of the reaction, the excess of hydride was carefully destroyed by dropwise addition of EtOH at 25 °C. After usual workup, products were separated by flash chromatography. The isolated yields of alcohols were in accordance with those of GC analyses (±5%). Spectral and physical data (^1H NMR, IR, bp, mp) of the alcohols were the same as those of authentic samples.

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Supplementary Material Available: Tables of reduction stereochemistry and influence of the nature of activating agent for exploratory experiments in this study (19 pages). Ordering information is given on any current masthead page.

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