Activation of Reducing Agents. Sodium Hydride Containing Complex Reducing Agents. 9.[1] Ketone and Aldehyde Reductions[2]

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The reduction of carbonyl compounds by complex reducing agent "NaH–*t*-AmONa–Ni(OAc)$_2$" (NiCRA) is described. The intrinsic properties of this reagent were pointed out by control experiments performed with the different combinations of NiCRA's components. It was also demonstrated that secondary alcohols, or their sodium alkoxides, may be partially oxidized to ketones by NiCRA; a β elimination of nickel hydride species is proposed in order to explain these reactions. Addition of alkaline or alkaline earth metal salts improves the reducing ability of NiCRA and dramatically postpones the reoxidation process. Finally, *catalytic reductions* of ketones were easily achieved by NiCRA–MgBr$_2$ systems. This work strengthens the idea that CRA's are very promising reducing agents in organic chemistry.

Reducing agents prepared by reacting complex metal hydrides with metallic salts or organometallic compounds have attracted considerable interest in recent years.[3,4] While definite structures have been demonstrated for a few such reagents,[5] the majority remain undefined or, at best, only partially identified.[6] Among this latter class are groups of alkali metal hydrides activated toward reduction with alkoxides (i.e., NaH–RONa)[7] or combinations of alkoxides and metal salts (i.e., NaH –RONa–MX$_n$, where MX$_n$ is a metallic salt).[8] For convenience these latter reagents are referred to as "complex reducing agents" (CRA).

We have previously reported some preliminary results pointing out the usefulness of CRA in reductions,[8-10] oligomerizations,[11] coupling,[11] and carbonylation reactions[12] and as a new source of heterogeneous hydrogenation catalysts.[13] Moreover, we recently demonstrated that the properties of such reagents may be modified by varying the alkoxide or the metallic salt.[14]

This article presents extensive studies of the scope and limitations of CRA with respect to ketone and aldehyde reductions.

Results and Discussion

Reductions of Saturated Ketones. Previous work[8] suggested that excess NaH and RONa is required for useful CRA systems. A serious limitation would therefore be anticipated with base-sensitive substrates, including enolizable carbonyl compounds, if the basic properties of these components were preserved in the reagent. We therefore examined the reduction of a number of carbonyl derivatives (chosen to offer a variety of structural variations) with NaH–*t*-AmONa–Ni(OAc)$_2$.

As previously mentioned[9] this reagent may be prepared by adding the activating alcohol, *t*-AmOH, to a stirred suspension of NaH and Ni(OAc)$_2$ in the desired solvent at 60–65 °C (see Experimental Section). A deep black color rapidly develops. After stirring for 2.5 h at 60–65 °C the reagent is ready for use. It appears as a heterogeneous black suspension designated as NiCRA. Upon centrifugation, NiCRA separates as a black, nonpyrophoric solid, leaving a clear solution which was shown to contain no soluble nickel species (see Experimental Section).

Preliminary experiments showed that NiCRA was able to reduce cyclohexanone in good yield. A short systematic study demonstrated that 40 °C was the best reaction temperature and that ratios NaH/*t*-AmONa/Ni(OAc)$_2$/cyclohexanone = 40/10/10/10 mM were adequate to perform almost quantitative reduction to cyclohexanol. Among the studied solvents (THF, DME, benzene, Et$_2$O), THF permitted the most efficient reductions; DME led to faster reactions (but lower yields (70–80%)) while benzene and diethyl ether led to poor reduction yields. The experimental conditions thus defined were applied to the reduction of ketones **1–14** (Table I).

As control experiments, several of the above ketones were subjected to various mixtures of components comprising NiCRA including: (a) NaH alone; (b) NaH–*t*-AmONa; (c) *t*-AmONa–Ni(OAc)$_2$; and (d) NaH–Ni(OAc)$_2$. Although some of these systems showed reducing ability, all were greatly inferior to NiCRA. Two noteworthy exceptions were ketones **2** and **3** which were reduced with NaH–Ni(OAc)$_2$ to the alcohols in 100% (6 h) and 95% (9 h) yield, respectively. The reason for this anomaly is not obvious.

In addition, treatment of the ketone enolates with NiCRA resulted in very low conversions to alcohol (i.e., **6**, 20% reduced in 20 h) indicating the carbonyl form to be the species attacked.

The results reported in Table I deserve some comments. First, while overall yields are usually very good, with ketones **2, 8,** and **10–12,** the reduction stops, without apparent reason, after partial reduction. Second, when two isomeric alcohols may be formed, their relative ratios often vary during the reduction, even after the maximum reduction yield has been reached. This observation, emphasized for **14** (see Table I), may be explained by a classical Meerwein–Pondorf–Verley equilibration.[15] However, this oxidoreduction is not the only pathway for the observed epimerization. As a matter of fact, we observed that with most ketones, conversion to alcohol passed through a maximum for the reaction times given in Table I, and then slowly decreased, indicating a reoxidation occurred. This unexpected observation led us to investigate the reaction of some secondary alcohols with NaH–*t*-AmONa–Ni(OAc)$_2$.

Oxidation of Secondary Alcohols by NaH–*t*-AmONa–Ni(OAc)$_2$. The preliminary observations above suggested the hypothesis that the reduction of a ketone by NiCRA is accompanied by the formation of sodium and nickel alkoxides (Scheme I). In the presence of free ketone, both alkoxides may lead to oxidoreduction equilibrations.

Although sodium alkoxides are generally stable, nickel alkoxides may loose nickel hydride species by a β-elimination process often encountered in transition-metal chemistry[16,17] to give the ketone. Note that such an oxidation has precedent in the work of Eliel on Raney Nickel catalysts of alcohol equilibration.[18]

Strong evidence for the intermediacy of Ni alkoxides and β elimination to ketones was provided by treatment of 4-*tert*-butylcyclohexanol (c/t ratio = 33/67) with NiCRA to afford a mixture of 65% alcohol (c/t ratio = 2/98) and 35% ketone as shown (Scheme II).

Treatment of these same starting materials (10 mM) with NaH–*t*-AmONa (40–10 mM), NaH–Ni(OAc)$_2$ (40–10 mM),

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Table I. Reduction of Ketones with NiCRA[a] in THF[b]

ketone	registry no.	reaction time, h	alcohol yield[c]	ketone	registry no.	reaction time, h	alcohol yield[c]
dibutyl ketone (1)	502-56-7	5	80	cyclododecanone (8)	830-13-7	1	50[d]
diisopropyl ketone (2)	565-80-0	20	45[d]	2-methylcyclohexanone (9)	583-60-8	5	96[f] (91)
di-*tert*-butyl ketone (3)	815-24-7	20[e]	96	3,3,5-trimethylcyclohexanone (10)	873-94-9	0.5	55[d,g]
phenyl methyl ketone (4)	98-86-2	13	95	3,3,5,5-tetramethylcyclohexanone (11)	14376-79-5	3	32[d]
cyclohexanone (5)	108-94-1	3–5	90–95	4-*tert*-butylcyclohexanone (12)	98-53-3	8	55[d,h] (48)
cycloheptanone (6)	502-42-1	2	95	norcamphor (13)	497-38-1	1	98[i]
cyclooctanone (7)	502-49-8	20	70–75	camphor (14)	464-49-3	7	85[j,k]

[a] Unless otherwise noted, reactions were performed at 40 °C with the NaH/*t*-AmONa/Ni(OAc)$_2$/ketone ratio equal to 40/10/10/10 in mM. [b] 40–45 mL. [c] Absolute yields were determined by GLC with internal standards. Isolated yields are given in parentheses. [d] The reduction stopped at this yield. [e] Experiment performed at 63 °C. [f] c/t = 30/70. [g] ax/eq = 73/27. [h] ax/eq = 55/45. [i] exo/endo = 45/55. [j] exo/endo = 85/15. [k] The yield reached 95% after 20 h while the exo/endo ratio evolved to 70/30.

or Ni(OAc)$_2$ (10 mM) resulted in no change in isomer distribution or ketone production. Likewise, cyclohexanol, cyclooctanol, and cyclododecanol afforded ketones **5**, **7**, and **8** in 30% (66 h), 85% (40 h), and 60% (40 h), respectively.

Returning to the ketone reductions by NiCRA, it is clear that simultaneous reduction and oxidation occurred in the medium. Relative rates depend upon the experimental conditions and the structure of the ketone. The reoxidation process may account, at least partially, for the observed equilibration of isomeric alcohols (vide supra) and for the more or less good reduction yields obtained in some cases. Moreover, the reproducibility of these reactions may be altered by the reoxidation.

Reaction of Ketones with NiCRA–M^{1}X$_n$ (M^1 = alkaline or Alkaline Earth Metal, *n* = 1, 2). In order to improve the reducing capabilities of the above systems by decreasing the nickel alkoxides concentration via replacing the nickel moiety with a more strongly bonding cation (having no propensity to give β-hydride elimination), we performed ketone reductions by NiCRA in the presence of alkaline or alkaline earth metal salts.

Exploratory experiments conducted with 4-*tert*-butylcyclohexanone and a variety of salts are presented in Table II and indicated that added salts generally enhanced the reduction, with Li and Mg giving the best results.

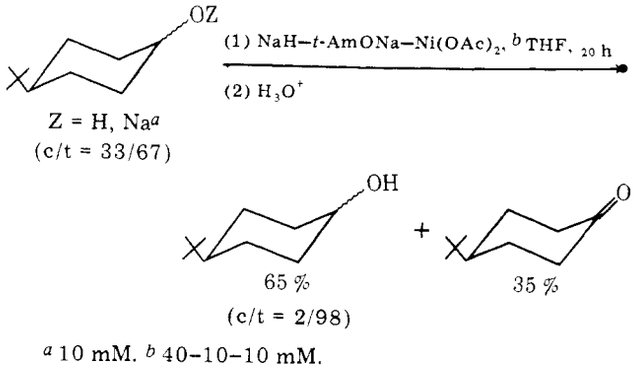
The nonintervention of MgH_2[19] as the reducing species when $MgBr_2$ was used was indicated by the observation that NaH–$MgBr_2$ (40–10 mM) exhibited no reducing properties toward **12** after 20 h at 40 °C. Furthermore, in simulated reaction conditions, the different combinations of the components of the two most active systems (namely NaH–*t*-AmONa–Ni(OAc)$_2$–M^{1}X$_n$; M^{1}X$_n$ = LiCl, $MgBr_2$) exhibited no reducing properties toward 4-*tert*-butylcyclohexanone.[20] Finally, reaction of Scheme II performed in the presence of LiCl (20 mM) or $MgBr_2$ (10 mM) showed, as expected, a strong decrease of the oxidation process (5% yield after 20 h).

Scheme I

$$R^1R^2C{=}O + \text{NiCRA} \longrightarrow HR^1R^2CONa + HR^1R^2CO''Ni''$$

$$HR^1R^2CO''Ni'' \longrightarrow R^1R^2C{=}O + ''NiH'' \rightarrow \text{reduction or destruction}$$

Scheme II



[a] 10 mM. [b] 40–10–10 mM.

Table II. Reduction of 4-*tert*-Butylcyclohexanone with NaH–*t*-AmONa–Ni(OAc)$_2$[a]–M^{1}X$_n$ in THF[b] at 40 °C

M^{1}X$_n$ (mM)	registry no.	reaction time, h	alcohol yield[c]	cis/trans ratio
LiF (20)	7789-24-4	20	55–60	50/50[d]
LiCl (20)	7447-41-8	5	92[e]	10/90[e]
LiBr (20)	7550-35-8	4	93	8/92[f]
LiI, 2H$_2$O (15)	10377-51-2	1	98	50/50[f]
LiOAc (20)	546-89-4	15	92	50/50[d]
NaCl (20)	7647-14-5	20	65	60/40[d]
NaBr (20)	7647-15-6	7	65	60/40[f]
KCl (20)	7447-40-7	20	70	40/60[d]
KBr (20)	7758-02-3	20	70–75	45/55[d]
$MgCl_2$ (10)	7786-30-3	4	99	30/70[d]
$MgBr_2$, 2THF (10)[g]	7789-48-2	1	95	25/75[f]

[a] NaH/*t*-AmONa/Ni(OAc)$_2$/ketone = 40/10/10/10 in mM. [b] 40–45 mL. [c] Absolute yields determined by GLC analysis with internal standards. [d] No large variations of isomer ratio during the reaction. [e] After 20 h, the yield reached 95–100% with a ax/eq ratio = 5/95. [f] No variation of the ax/eq ratio after 20 h. [g] Prepared by reacting 1,2-dibromoethane with Mg in THF (see Experimental Section).

Taking into account the above salt effect, reduction of representative ketones was performed with NiCRA in the presence of lithium or magnesium salts. Results reported in Table III indicate that these new reagents achieved quantitative reductions of unhindered ketones within 1 h. Of course, reduction of hindered ketones such as **2**, **3**, **10**, **11**, and **14** needed longer reaction times. In most cases, magnesium bromide led to more efficient reagents than lithium salts. The relative ratios of isomeric alcohols were depending upon M^1 and X and generally evolved during the course of the reaction (sometimes even after the maximum alcohol yield had been reached). Note that NaH–Ni(OAc)$_2$ reduced **2** and **3** (vide supra) more slowly than NiCRA–$MgBr_2$. Surprisingly, NaH–Ni(OAc)$_2$–$MgBr_2$ did not reduce these ketones!

Catalytic Reductions of Saturated Ketones. The ability of NiCRA–M^{1}X$_n$ to effect catalytic reductions of carbonyl compounds was examined on ketones **5**, **12**, and **14** using NiCRA–$MgBr_2$ systems where *t*-AmONa, Ni(OAc)$_2$, and $MgBr_2$ were present in catalytic amounts (Table IV). Control experiments showed that NaH–Ni(OAc)$_2$ or NaH–$MgBr_2$ mixtures (200–10 mM) exhibited poor reducing properties toward these ketones.

Table III. Reduction of Ketones by NiCRA[a] + M^1X_n in THF[b]

ketone[d]	M^1X_n (mM)	t, h	alcohol yield[c]	ketone[d]	M^1X_n (mM)	t, h	alcohol yield[c]	isomer ratio[f]
1	LiCl (20)	5	90	8	LiCl (20)	18	60	
	LiI, $2H_2O$ (15)	2.5	90		LiI, $2H_2O$ (15)	1	85	
	$MgBr_2$ (10)[e]	0.75	93		$MgBr^2$ (10)[e]	0.5	88 (85)	
2	LiCl (20)	28	95	9	LiCl (20)	5	85	c/t = 14/86
	LiI, $2H_2O$ (15)	3	100		LiI, $2H_2O$ (15)	1.5	100	c/t = 37/63
	$MgBr_2$ (10)[e]	2.5	98 (76)		$MgBr_2$ (10)[e]	1	98	c/t = 25/75
3	LiCl (20)	20	95	10	LiCl (20)	3	15–20	ax/eq = 55/45
	LiI, $2H_2O$ (15)	20	70		LiI, $2H_2O$ (15)	0.5	15–20	ax/eq = 75/25
	$MgBr_2$ (10)[e]	6.5	100		$MgBr_2$ (10)[e]	23	83 (82)	ax/eq = 60/40
4	LiCl (20)	13	95	11	$MgBr_2$ (10)[e]	3	85(81)	
	$MgBr_2$ (10)[e]	0.5	90					
5	LiCl (20)	3	95	12	see Table II			
	LiI, $2H_2O$ (15)	1.5	95					
	$MgBr_2$ (10)[e]	0.5	90					
6	LiCl (20)	1.5	100	13	LiCl (20)	1.5	98	exo/endo = 40/60
	LiI, $2H_2O$ (15)	0.5	100		LiI, $2H_2O$ (15)	2	96	exo/endo = 55/45
	$MgBr_2$ (10)[e]	0.25	100		$MgBr_2$ (10)[e]	0.5	100	exo/endo = 32/68
7	LiCl (20)	18	85	14	LiCl (20)	5	86	exo/endo = 85/15
	LiI, $2H_2O$ (15)	1	92		LiI, $2H_2O$ (15)	7	86	exo/endo = 45/55
	$MgBr_2$ (10)[e]	1	93 (92)		$MgBr_2$ (10)[e]	5	98 (90)	exo/endo = 50/50

[a] Unless otherwise noted, reactions were performed at 40 °C with the NaH/*t*-AmONa/Ni $(OAc)_2$/ketone ratio equal to 40/10/10/10 mM. [b] 40–45 mL. [c] Absolute yields determined by GLC analysis with internal standards. Isolated yields in parentheses. [d] See Table I for the numbering of ketones. [e] See footnote *g* of Table II. [f] At the end of the reaction.

Table IV. Catalytic Reduction of Ketones with NaH–*t*-AmONa–$Ni(OAc)_2$–$MgBr_2$ in THF[a]

ketone[b] (mM)	[NaH], mM	[*t*-AmONa] mM	[$Ni(OAc)_2$], mM	[$MgBr_2$, 2THF], mM	reaction time, h	alcohol yield owing to ketone[c]	isomer ratio
5 (30)	60	10	10	10	3	98	
5 (100)	200	10	10	10	2–3	86	
12 (30)	60	10	10	10	8–9	95	ax/eq = 25/75
12 (100)	200	10	10	10	6–7	95	ax/eq = 36/64
14 (30)	60	10	10	10	15	100	exo/endo = 68/32
14 (100)	200	10	10	10	5[d]	59	exo/endo = 85/15

[a] Reactions performed at 40 °C in 40–45 mL of solvent. [b] See Table I. [c] Absolute yields determined by GLC analysis with internal standards. [d] No further evolution after 15 h.

These results indicate that the reducing species are easily regenerated in the presence of NaH excess and exclude the alternative explanation of ketone reductions in terms of hydrogenation over Ni(0) by molecular hydrogen produced during the addition of *t*-AmOH (10 mM) on NaH–$Ni(OAc)_2$ mixtures (210–10 mM).

Reduction of Ketones by Various CRA. We have recently reported[14] that numerous MCRA, with modulated properties, might be obtained by varying the nature of the metal. Some of them and the corresponding MCRA–$MgBr_2$ systems were tested in the reduction of 4-*tert*-butylcyclohexanone (Table V).

These results confirm the dramatic effect of $MgBr_2$ on ketone reductions by CRA. It is interesting to note that besides $Ni(OAc)_2$, $ZnCl_2$ and $CdCl_2$ lead to very efficient systems.

Taking into account our previous results[11,14] on the reduction of organic halides, it now appears that CRA may exhibit, for a given metal, a great specificity depending on the function to be reduced. This property has already been evidenced for the selective reduction of alkenes by FeCRA in the presence of ketones.[10] Previous[14] and present results (Table V) suggest some further possible applications which are currently under investigation in our laboratory.

Reduction of Aldehydes by NiCRA. Reduction of representative aldehydes **15–18** by NiCRA was briefly investigated (Table VI).

NiCRA easily reduced benzaldehyde **15** and α-alkyl-substituted aldehydes **16** and **17**. Addition of lithium or magnesium salts resulted in increased reaction rates and allowed clean quantitative reductions without side reactions.

Reduction of α-unsubstituted aldehyde **18** was unsuccessful, even in the presence of magnesium bromide. However, satisfactory result (60% yield after 3 h) was obtained with ZnCRA (NaH–*t*-AmONa–$ZnCl_2$: 40–10–10 mM). In this case, addition of $MgBr_2$ resulted in a decrease of reaction time to 0.5 h but alcohol yield was not improved. This is a good illustration of the potential interest of varying the metallic salt in CRA.[11,14]

Conclusion

These first studies confirm that CRA may be of interest for the reduction of organic substrates and point out their remarkable versatility. The possibility to further modify their reducing ability by adding alkaline or alkaline earth metal salts strongly enhances their potential usefulness.

Moreover, they appear as promising selective reducing agents. For example, we have shown that numerous CRA were efficient reagents for the reduction of organic halides.[11,14] In

Table V. Reduction of 4-*tert*-Butylcyclohexanone by NaH-*t*-AmONa-MX_n[a] or NaH-*t*-AmONa-MX_n[a]-$MgBr_2$ at 40 °C in THF[b]

MX_n (10 mM)	registry no.	[$MgBr_2$, 2THF] mM	reaction time, h	alcohol[c] yield, %	ax/eq isomer ratio[c]	recovered ketone[c]
$Ni(OAc)_2$	373-02-4		see Table II			
$Co(OAc)_2$	71-48-7		1[e]	10	83/17	85
$Co(OAc)_2$		10	20	55[f]	70/30	40–45
$ZnCl_2$	7646-85-7		20	60	40/60	35–40
$ZnCl_2$		10	1	96	40/60	
$CdCl_2$	10108-64-2		20	12	58/42	85
$CdCl_2$		10	2	80–85	35/65	10–15
$FeCl_3$	7705-08-0		20	0		75
$FeCl_3$		10	5[g]	10	75/25	10–15

[a] NaH/*t*-AmONa/MX_n/12 = 40/10/10/10 mM. [b] 40–45 mL. [c] Determined by GLC analysis with internal standards. [d] 80% recovered starting ketone. [e] No further evolution in 40 h. [f] The yield may have reached 65% after 65 h with an unchanged cis/trans ratio. [g] No further evolution after 20 h.

Table VI. Reduction of Representative Aldehydes with NaH-*t*-AmONa-$Ni(OAc)_2$[a]-M^1X_n at 40 °C in THF[b]

aldehyde (10 mM)	registry no.	M^1X_n (mM)	reaction time, h	alcohol yield[c]
benzaldehyde (**15**)	100-52-7		3	96[d]
		LiCl (10)	1	98
2-methylpentanal (**16**)	123-15-9		2	72[e] (50)[e]
		$MgBr_2$, 2THF (10)	2.5	98 (80)
cyclo-$C_6H_{11}CHO$ (**17**)	2043-61-0		8	91[f]
		$MgBr_2$, 2THF (10)	1	98
		LiI, $2H_2O$ (15)	0.5	98
$CH_3(CH_2)_5CHO$ (**18**)[g]	111-71-7		5	15[d]
		$MgBr_2$, 2THF (10)	0.5	35[d]
		LiI, $2H_2O$ (15)	0.5	30[d] (25)

[a] NaH/*t*-AmONa/$Ni(OAc)_2$/aldehyde = 40/10/10/10 mM. [b] 40–45 mL. [c] Absolute yields determined by GLC analysis with internal standards; isolated yields in parentheses. [d] No remaining starting aldehyde. [e] 10% recovered starting aldehyde. [f] 8% recovered starting aldehyde. [g] Reduction yields of **18** by ZnCRA are given in the text.

the present work, it was found that some of these systems, without additional alkaline or alkaline earth metal salt, are quite inactive toward carbonyl compounds. Thus, it should be possible to achieve halide reduction in the presence of carbonyl groups. Current investigations to this effect seem to confirm this hypothesis.

Another very interesting property of CRA is the possibility to carry out reduction of base-sensitive substrates using the metallic salt (and the activating alkoxide) in catalytic proportions.

Finally, it must be emphasized that CRA constitute a new opening for the very cheap and easily handled sodium hydride. They allow it to be a concurrent candidate to the generally encountered complex metal hydrides.

Experimental Section

Materials. Fluka sodium hydride (55–60% in oil) was used and washed several times with THF. Badische Anilin reagent grade THF was distilled from benzophenone–sodium couple and stored on sodium wires. Ketones, aldehydes, or alcohols (Fluka or Aldrich) were purified by distillation; *t*-amyl alcohol was distilled from sodium before use. Metallic salts (Prolabo) were dried under vacuum for 12–15 h at 80–120 °C, as were alkaline and alkaline earth metal salts. Magnesium bromide was prepared by reaction of 1,2-dibromoethane with magnesium in refluxing THF for 20 h. At completion, the clean solution was filtered and evaporated in a rotavapor and the resulting solid dried for 10–12 h at 100–120 °C under vacuum to yield $MgBr_2$, $(C_4H_8O)_n$ (n = 2, atomic absorption). All metallic salts were stored under argon. All reactions were performed under nitrogen (R).

General. GLC analyses were performed on Girdel 3000 Apparatus using Carbowax 20 M capillary columns. Soluble nickel species concentration was determined with a Varian Techtron Atomic Absorption Photometer (Model 1200) used at 352.4 nm. Infrared spectra were recorded with a Perkin-Elmer 457 spectrometer and NMR spectra with a Perkin-Elmer R 12 instrument.

General Reduction Procedure. The general procedure is exemplified for NiCRA. The activating alcohol *t*-AmOH (10 mM) in 10 mL of THF was added dropwise to a stirred suspension of NaH (50 mM) and $Ni(OAc)_2$ (10 mM) in gently refluxing THF (20 mL). A deep black color rapidly developed. After 2.5 h the temperature was decreased (if necessary) to 40 °C and ketone or aldehyde (10 mM) in THF (10 mL) was added together with the internal standard (C_{11}—C_{16} hydrocarbons). Alkaline or alkaline earth metal salts were introduced just before the carbonyl substrate.

Small aliquots were removed periodically, acidified with dilute HCl, extracted with diethyl ether, and analyzed by GLC. Upon completion the reaction medium was cooled, quenched with water (10 mL), acidified with dilute HCl, extracted with diethyl ether, and the organic phase dried over $MgSO_4$. Isolated alcohol yields were determined after purification by liquid chromatography on Woelm silica columns. Reaction products were identified by comparison of their physical and spectroscopic properties with authentic samples.

Control Experiments. (i) NaH-*t*-AmONa (40–10 mM) was prepared as previously described.[7]

(ii) *t*-AmONa-$Ni(OAc)_2$ (10–10 mM): *t*-AmOH (10 mM) in THF (15 ml) was added to a stirred suspension of NaH (10 mM) in refluxing THF (15 mL) and after 2 h at 63 °C $Ni(OAc)_2$ (10 mM) was added. The black mixture was ready for use after 2.5 additional h.

(iii) NaH-$Ni(OAc)_2$ (40–10 mM) mixtures were stirred for 2.5 h in refluxing THF (40 mL) prior to use. No black coloration was observed.

(iv) Ketone enolates were prepared by reacting ketone (10 mM) with NaH-*t*-AmONa (40–10 mM) for 3 h in refluxing THF (40 mL) and then syringed into the NiCRA-containing flask.

(v) Control experiments on NaH-$MgBr_2$ were performed as follows: Magnesium bromide (10 mM) was added to a suspension of NaH (40 or 200 mM) in THF (40 mL) and the mixture stirred for 2.5 h at 63 °C. Then the reaction temperature was adjusted to 40 °C and ketone **12** (10 or 100 mM) in 10 mL of THF was added.

(vi) Control experiments on NaH-*t*-AmONa-M^1X_n and *t*-AmONa-$Ni(OAc)_2$-M^1X_n were performed in three ways: First, M^1X_n was added, just before the ketone, to NaH-*t*-AmONa or *t*-AmONa-$Ni(OAc)_2$ mixtures prepared as described above. Second, the ketone was added to NaH-*t*-AmONa-M^1X_n systems prepared in the same way as NiCRA (vide supra) where $Ni(OAc)_2$ was replaced by M^1X_n.

Third, the mixture t-AmONa–$Ni(OAc)_2$–M^1X_n was stirred for 2.5 h at 63 °C before adding the ketone.

Oxidation Procedure (Scheme II). Sodium alkoxides were prepared separately by reacting alcohols with NaH excess in refluxing THF for 3 h. These alkoxides, or the free alcohols, were then admitted to react with various combinations of NaH, t-AmONa, and $Ni(OAc)_2$ prepared as described above.

Catalytic Ketone Reductions (Table IV). Catalytic reductions carried out on 100 mM ketone were achieved in 50–60 mL of THF by the general procedure (vide supra) but using 210 mM initial NaH, instead of 50 mM, for the preparation of the reducing system.

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Registry No.—NaH, 7646-69-7; t-AmONa, 14593-46-5; 5-nonanol, 623-93-8; 2,4-dimethyl-3-pentanol, 600-36-2; 2,2,4,4-tetramethyl-3-pentanol, 14609-79-1; α-methylbenzenemethanol, 98-85-1; cyclohexanol, 108-93-0; cycloheptanol, 502-41-0; cyclooctanol, 696-71-9; cyclododecanol, 1724-39-6; *cis*-2-methylcyclohexanol, 7443-70-1; *trans*-2-methylcyclohexanol, 7443-52-9; *cis*-3,3,5-trimethylcyclohexanol, 933-48-2; *trans*-3,3,5-trimethylcyclohexanol, 767-54-4; 3,3,5,5-tetramethylcyclohexanol, 2650-40-0; *cis*-4-(1,1-dimethylethyl)cyclohexanol, 937-05-3; *trans*-4-(1,1-dimethylethyl)cyclohexanol, 21862-63-5; *endo*-bicyclo[2.2.1]heptan-2-ol, 497-36-9; *exo*-bicyclo[2.2.1]heptan-2-ol, 497-37-0; (1*R*-*endo*)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ol, 464-43-7; (1*R*-*exo*)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ol, 10334-13-1.

References and Notes

(1) For Part VIII, see ref 14.
(2) This work, together with ref 8 and 9, represents part of the research work of L.M. for her Ph.D. Thesis.
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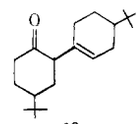
(20) When allowed to react with NaH–t-AmONa–$MgBr_2$ systems, ketone **12** afforded in near quantitative yield **19**, identified by comparison with an



19

authentic sample prepared according to J. Reese, *Ber.*, **75**, 384 (1942).

9-(2-Sulfo)fluorenylmethyloxycarbonyl Chloride, a New Reagent for the Purification of Synthetic Peptides[1,2]

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A selective method was developed for the purification of synthetic peptides. It is based on the addition of the 9-(2-sulfo)fluorenylmethyloxycarbonyl (Sulfmoc) group to the free amine of the growing peptide chains at the end of a solid-phase synthesis. After cleavage from the support, the strongly acidic Sulfmoc-peptides are separated chromatographically from the nongrowing, terminated peptides. Finally, the Sulfmoc group is removed by mild base and the purified peptide is isolated. The reagent of choice for the derivatization was 9-(2-sulfo)fluorenylmethyloxycarbonyl chloride (Sulfmoc-Cl). It was synthesized from 9-fluorenylmethyloxycarbonyl chloride (Fmoc-Cl) by sulfonation with chlorosulfonic acid. The 4-nitrophenyl ester, Fmoc-ONp, was also prepared from Fmoc-Cl and then converted with $ClSO_3H$ to Sulfmoc-ONp. Both sulfonated reagents reacted readily with the free amino groups of peptide-resins in CH_2Cl_2 in the presence of pyridine or DIEA. The Sulfmoc group is stable to HF or HBr and to pyridine, but is readily removed by anhydrous bases such as morpholine or piperidine or by dilute aqueous Et_3N, Na_2CO_3, or NaOH. The efficacy of the technique was demonstrated by the purification of neutral, acidic and basic model peptides.

A selective purification procedure has been developed for the separation of synthetic peptide chains of the desired structure from unwanted terminated chains generated during a solid-phase synthesis.[3] It depends on the reaction of the free amino groups of those chains on the solid support that are still growing with a reversible protecting group bearing a strongly acidic function. After cleavage from the support, the two classes of peptide chains are separated chromatographically and the nonterminated peptides are regenerated to the free peptides. The 9-(2-sulfo)fluorenylmethyloxycarbonyl (Sulf-

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