number of possible motivations for reordering the steps in a synthesis. The rewards of a successful reordering analysis are potentially great, however, in that elimination of pairs of protection/deprotection steps can greatly enhance the overall efficiency and elegance of a synthetic plan.

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Zinc-Modified Cyanoborohydride as a Selective Reducing Agent

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Zinc-modified cyanoborohydride generated from sodium cyanoborohydride and zinc chloride in a 2:1 molar ratio is found to be a selective and versatile reducing agent. The reagent in diethyl ether reduces aldehydes, ketones, and acid chlorides to the corresponding alcohols but does not reduce acid anhydrides, acids, esters, and tertiary amides. The reagent in methanol is very useful for reduction of enamines, reductive amination of aldehydes and ketones, reductive methylation of amines, and deoxygenation of aldehydes and ketones.

The combination of sodium borohydride with various metal halides has attracted a great deal of attention as selective and versatile reducing agents in the past decade.[1-10] In general, they modify the usual reducing ability of sodium borohydride and often reduce several functional groups which are inert to sodium borohydride alone. For instance, the reductions of acid chlorides to aldehydes,[2] alkenes to saturated hydrocarbons,[3] and alkenes to alcohols[4] can be achieved by use of the combination of sodium borohydride with Cu(I), Co(II), and Sn(IV), respectively, while such conversions can not be achieved with sodium borohydride alone.

Although the reducing properties of the combination of sodium borohydride with metal halides have been intensively investigated, there are relatively few reports in the literature on the use of the combination of sodium cyanoborohydride with metal halides. It has been reported by Hutchins that the combination of sodium cyanoborohydride with Cu(II) and triphenylphosphine,[11] Pd(0),[12] and boron trifluoride etherate[13] are capable of reducing acid chlorides to aldehydes, allylic acetates to alkenes, and epoxides to alcohols in a regio- and stereoselective manner, respectively.

As our continuous efforts toward the development of new hydride reducing agents,[14] we have reported that zinc-modified cyanoborohydride in diethyl ether reduces tertiary, allyl, and benzyl halides but it is inert toward primary alkyl, secondary alkyl, vinyl, and aryl halides.[15] This paper describes general reducing properties of zinc-modified cyanoborohydride in the reduction of selected carbonyl compounds, reduction of enamines, reductive amination of aldehydes and ketones, reductive methylation of amines, and deoxygenation of aldehydes and ketones via the intermediacy of tosylhydrazones.

Results and Discussion

Nature and Stability of Zinc-Modified Cyanoborohydride. Zinc-modified cyanoborohydride utilized in this study was prepared by mixing sodium cyanoborohydride and anhydrous zinc chloride in a 2:1 molar ratio at room temperature in several solvents such as diethyl ether, tetrahydrofuran, and methanol. When a 2:1 molar mixture of sodium cyanoborohydride and zinc chloride in diethyl ether was stirred at room temperature for 1 h, a white slurry appeared at the bottom of the flask. The white slurry contained almost all the active hydroborate species and metal chlorides, while the ether solution did not contain an appreciable amount of the hydroborate species and chloride ion. Iodometric titration revealed that the white slurry contained approximately 90% of the reducing power, while the ether solution contained only 2% of the reducing power, indicating that the present reagent is very slightly soluble in diethyl ether. However, it was found

(1) $NaBH_4$/Zn(II): (a) Corey, E. J.; Anderson, N. H.; Carlson, R. M.; Paust, J.; Vedjs, E.; Vlattas, I.; Winter, R. E. K. *J. Am. Chem. Soc.* **1968**, *90*, 3245. (b) Yoon, N. M.; Lee, H. J.; Kim, H. K.; Kang, J. *J. Korean Chem. Soc.* **1976**, *20*, 59. (c) Nagata, T.; Oishi, T. *Tetrahedron Lett.* **1980**, *21*, 1641. (d) Nagata, T.; Tanaka, T.; Oishi, T. *Ibid.* **1981**, *22*, 4723. (e) Ito, Y.; Yamaguchi, M. *Ibid.* 1983, *24*, 5385. (f) Kim, S.; Hong, C. Y.; Yang, S. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 562.

(2) $NaBH_4$/Cu(I): (a) Fleet, G. W. J.; Fuller, C. J.; Harding, P. J. C. *Tetrahedron Lett.* **1978**, 1437. (b) Sorrell, T. N.; Spillane, R. J. *Ibid.* **1978**, 2473. (c) Fleet, G. W. J.; Harding, P. J. C. *Ibid.* **1979**, 975.

(3) $NaBH_4$/Co(II): (a) Satoh, T.; Suzuki, S.; Suzuki, Y.; Miyaji, Y.; Imai, Z. *Tetrahedron Lett.* **1969**, 4555. (b) Chung, S-K. *J. Org. Chem.* **1979**, *44*, 1014. (c) Heinzman, S. W.; Ganem, B. *J. Am. Chem. Soc.* **1982**, *104*, 6801. (d) Satyanarayana, N.; Periasamy *Tetrahedron Lett.* **1984**, *25*, 2501.

(4) $NaBH_4$/Sn(IV): (a) Tsuda, Y.; Sano, T.; Watanabe, H. *Synthesis* **1977**, 652. (b) Kano, S.; Yuasa, Y.; Shibuya, S. *J. Chem. Soc., Chem. Commun.* **1979**, 796.

(5) $NaBH_4$/Sn(II): Satoh, T.; Mitsuo, N.; Nishiki, M.; Inoue, Y.; Ooi, Y. *Chem. Pharm. Bull.* **1981**, *29*, 1443.

(6) $NaBH_4$/Cd(II)/DMF: (a) Jonestone, R. A. W.; Telford, R. P. *J. Chem. Soc., Chem. Commun.* **1978**, 354. (b) Entwistle, I. D.; Boehm, P.; Jonestone, R. A. W.; Telford, R. P. *J. Chem. Soc. Perkin Trans. 1* **1980**, 27.

(7) $NaBH_4$/Ce(III): (a) Luche, J-L. *J. Am. Chem. Soc.* **1978**, *100*, 2226. (b) Luche, J-L.; Gemal, A. L. *Ibid.* **1979**, *101*, 5848. (c) Gemal, A. L.; Luche, J-L. *Ibid.* **1981**, *103*, 5454. (d) Gemal, A. L.; Luche, J-L. *J. Org. Chem.* **1979**, *44*, 4187.

(8) $NaBH_4$/Rh(III): Nishiki, M.; Miyataka, H.; Niino, Y.; Mitsuo, N.; Satoh, T. *Tetrahedron Lett.* **1982**, *23*, 193.

(9) $NaBH_4$/Ni(II): (a) Lin, S-T.; Lith, J. A. *J. Org. Chem.* **1979**, *44*, 309. (b) Nose, A.; Kudo, T. *Chem. Pharm. Bull.* **1981**, *29*, 1159.

(10) $NaBH_4$/Pd(II): (a) Egli, R. A. *Helv. Chim. Acta* **1968**, *51*, 2090. (b) Bosin, T. R.; Raymond, M. G.; Buckpitt, A. R. *Tetrahedron Lett.* **1973**, 4699.

(11) Hutchins, R. O.; Markowitz, M. *Tetrahedron Lett.* **1980**, *21*, 813.

(12) Hutchins, R. O.; Learn, K.; Fulton, R. P. *Tetrahedron Lett.* **1980**, *21*, 27.

(13) Hutchins, R. O.; Taffer, I. M.; Burgoyne, W. *J. Org. Chem.* **1981**, *46*, 5214.

(14) For our recent reports, see: (a) Kim, S.; Ahn, K. H. *J. Org. Chem.* **1984**, *49*, 1717. (b) Kim, S.; Kang, H. J.; Yang, S. *Tetrahedron Lett.* **1984**, 2985. (c) Kim, S.; Yi, K. Y. *Bull. Chem. Soc. Jpn.* **1984**, in press.

(15) Kim, S.; Kim, Y. J.; Ahn, K. H. *Tetrahedron Lett.* **1983**, *24*, 3369.

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Table I. Reduction of 4-*tert*-Butylcyclohexanone with Zinc-Modified Cyanoborohydride at Room Temperature for 4 h[a]

solvent	mol $ZnCl_2$, equiv	reduction, %[b]	proportion of less stable isomer, %[b]
Et_2O	0.5	100	15
Et_2O	0.1	40	
THF	0.5	73	15
MeOH	0.5	12	
MeOH	5.0	99	9
DME	0.5	22	9
DMF	0.5	5	18
diglyme	0.5	9	18

[a] 1 Molar equiv of $NaBH_3CN$ was used. [b] Determined by GLC.

that the reagent was soluble in tetrahydrofuran. When the reagent was prepared in tetrahydrofuran in a same manner, a white precipitate also appeared. The white precipitate did not contain an appreciable amount of the hydroborate species, while the tetrahydrofuran solution contained approximately 85% of the reducing power. Furthermore, it is believed that the white precipitate would be sodium chloride but the amount of the white precipitate was approximately 60% of the calculated value based on sodium chloride formed by metathetical reaction. When the reagent was prepared in methanol in the same manner, the solution was clear without any precipitation.

On the basis of the lack of the precipitated sodium chloride and previously reported results in similar systems,[6,16] it is believed that the reagent could be a mixture of complex salts such as $Na[ZnCl(BH_3CN)_2]$, $Na_2[ZnCl_2(BH_3CN)_2]$, $Na[Zn(BH_3CN)_3]$, and $Zn(BH_3CN)_2$ rather than pure $Zn(BH_3CN)_2$ as the reducing species. Since the exact nature of the present reagent is unclear at the present time, we designate the reagent as zinc-modified cyanoborohydride rather than zinc cyanoborohydride.

The stability of zinc-modified cyanoborohydride was briefly examined in aqueous media. The decomposition of the reagent in water as measured by hydrogen evolution using iodometric titration was approximately 2 mol% at room temperature after 24 h. Furthermore, its decomposition in 0.01 N aqueous acetic acid and pure acetic acid was 9 mol% and 64 mol%, respectively, under the same conditions. Since zinc borohydride, prepared from sodium borohydride and zinc chloride in a 2:1 molar ratio in diethyl ether, tetrahydrofuran, and dimethoxyethane, decomposes rapidly with evolution of hydrogen gas in alcoholic solvents or aqueous media,[7c] it is believed that the stability of zinc-modified cyanoborohydride in aqueous media will enhance its utility as a versatile reducing agent.

Reduction of Selected Carbonyl Compounds. We have examined several reactions to find out the optimum condition using 4-*tert*-butylcyclohexanone as a model compound. Table I shows the relative rates of the reduction of 4-*tert*-butylcyclohexanone by use of 1 mol equiv of sodium cyanoborohydride and variable amounts of anhydrous zinc chloride in various solvents at room temperature for 4 h. Among several solvents employed, diethyl ether was found to be the most effective and the reduction was complete within 4 h with 0.5 mol equiv of zinc chloride, though the reagent was slightly soluble in diethyl ether. In general, the reduction occurred to some extent in tetrahydrofuran, dimethoxyethane, methanol, diglyme, and dimethylformamide, though the use of an excess amount of zinc chloride in methanol resulted in almost completion of the reduction. It is noteworthy that the reagent consistently produced the thermodynamically more stable isomer as a major product from axial attack on 4-*tert*-butylcyclohexanone.

Table II. Reduction of Selected Carbonyl Compounds with Zinc-Modified Cyanoborohydride in Et_2O at Room Temperature[a]

compound	time, h	product or starting material	yield, %[b]
benzaldehyde	4	benzyl alcohol	(99)
4-methoxybenzaldehyde	4	4-methoxybenzyl alcohol	95
nonanealdehyde	6	nonyl alcohol	93
3-pentanone	4	3-pentanol	(98)
acetophenone	4	1-phenylethanol	(99)
cycloheptanone	4	cycloheptanol	(100)
caprylyl chloride[c]	8	1-octanol	95
benzoyl chloride[c]	12	benzyl alcohol	97
phenylacetyl chloride[c]	8	2-phenylethanol	94
benzoic anhydride	24	benzoic anhydride	80
caprylic anhydride	24	caprylic anhydride	90
methyl caprylate	24	methyl caprylate	92
methyl 2-chlorobenzoate	24	methyl 2-chlorobenzoate	96
N,N-diethylcaprylamide	24	*N,N*-diethylcaprylamide	95
N,N-diethylbenzamide	24	*N,N*-diethylbenzamide	93
benzoic acid	24	benzoic acid	93

[a] The reaction was carried out with 0.5 mol equiv of zinc-modified cyanoborohydride. [b] The yields were determined by isolation. The numbers in parentheses indicate GLC yield. [c] One mol equiv of the reagent was used.

On the basis of the reduction results with 4-*tert*-butylcyclohexanone, the remaining reductions were carried out with 0.5 mol equiv of zinc-modified cyanoborohydride, generated from 1 mol equiv of sodium cyanoborohydride and 0.5 mol equiv of zinc chloride, in anhydrous diethyl ether at room temperature. As shown in Table II, aldehydes and ketones were completely reduced to the corresponding alcohols under the present conditions.

Acid chlorides were slowly reduced to the corresponding alcohols in high yields. Partial reduction of an acid chloride to the aldehyde stage was not observed according to TLC analysis at the beginning of the reaction. However, reduction of acid anhydrides such as benzoic anhydride and caprylic anhydride did not occur to an observable extent in 24 h. Furthermore, zinc-modified cyanoborohydride in diethyl ether failed to reduce both carboxylic acids and esters for 24 h. The original starting materials were quantitatively recovered after the usual workup. Also, tertiary amides such as *N,N*-diethylbenzamide and *N,N*-diethylcaprylamide were inert to this reagent for 24 h and were recovered unchanged.

Since selective 1,2-reduction of enones is of special interest in organic synthesis, several enones were tested with the reagent in diethyl ether. Reduction of 2-cyclohexen-1-one gave a mixture of 2-cyclohexen-1-ol and cyclohexanol in roughly an equal ratio. As shown in Table III, several other enones tested in this study gave consistently a mixture of 1,2- and 1,4-reduction products in poor regioselectivities. These results are in sharp contrast with earlier findings that the reduction of enones with zinc borohydride in diethyl ether or tetrahydrofuran gives 1,2-reduction products in excellent 1,2-selectivity.[1a,b]

In its reducing properties toward selected carbonyl compounds, the present reagent is shown to be a relatively mild reducing agent and comparable to sodium borohydride in most cases. In view of the fact that sodium cyanoborohydride can readily reduce aldehydes and ketones in methanol under acidic conditions,[17] it is believed

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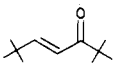
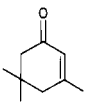
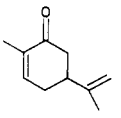
(17) Borch, R. F.; Bernstein, M. D.; Durst, H. D. *J. Am. Chem. Soc.* 1971, *93*, 2897.

Table III. Reduction of Enones with Zinc-Modified Cyanoborohydride in Et_2O at Room Temperature for 6 h[a]

enone	product ratio[b] 1,2:1,4	yield, %[b,c]
	82:18	96
	94:6	(95)
	49:51	91
	10:90	(94)
	65:35	(92)
	1:99	56
	0:100	98

[a] The reaction was carried out with 0.5 mol equiv of the reagent. [b] The product ratios and the yields were determined by GLC. The numbers in parentheses indicate the isolated yield. [c] Increase of molecular weight (+2), resulting from further reduction of saturated ketones to saturated alcohols, was neglected in the isolated yields.

that zinc-modified cyanoborohydride in diethyl ether is very useful for the mild reduction of aldehydes, ketones, and acid chlorides in the presence of other easily reducible functional groups.

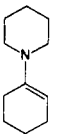
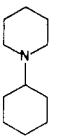
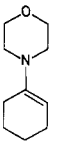
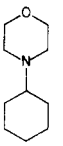
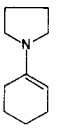
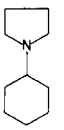
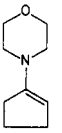
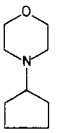
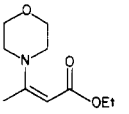
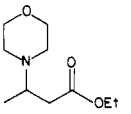
Reduction of Enamines and Oximes. The reduction of enamines with zinc-modified cyanoborohydride in methanol proceeded smoothly. The reaction was normally complete within 1 h at room temperature and the corresponding amines were obtained in high yields. Under the present conditions, hydrolysis of enamines was not observed. The present procedure does not require pH control, though the reduction of enamines with sodium cyanoborohydride occurs at an initial pH of 5.[17] Some experimental results are summarized in Table IV.

Surprisingly, the reagent in methanol failed to reduce keto oximes to the corresponding *N*-alkylhydroxylamines. When cyclohexanone oxime was reacted with the reagent in methanol or diethyl ether at room temperature for 12 h, the reduction did not occur to an observable extent and the starting material was recovered unchanged.

Reductive Amination of Aldehydes and Ketones. Since the reduction of enamines with the reagent in methanol occurred much more rapidly than that of aldehydes and ketones under the same conditions, it is expected that reductive amination of an aldehyde or a ketone can be effected by simply reacting the carbonyl compound with an amine by using the present reagent in methanol. Indeed, we found that the reduction of aldehydes or ketones to alcohols did not occur to an observable extent, but reductive amination of aldehydes and ketones proceeded smoothly.

In order to prevent the initial reduction product from undergoing further reaction with an aldehyde or a ketone,

Table IV. Reduction of Enamines with Zinc-Modified Cyanoborohydride in MeOH at Room Temperature[a]

compd	time, h	product	yield, %[b]	bp, °C (mmHg)[c]
	1		85	55-60 (1.8)
	0.5		73	66-70 (2.6)
	1		87	53-57 (3.5)
	0.5		90	69-73 (4.4)
	1		85	68-73 (1.5)

[a] The reaction was carried out with 1 mol equiv of zinc-modified cyanoborohydride. [b] The yields refer to isolated products. [c] All values are in accord with reported values.

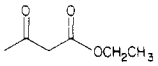
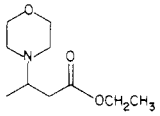
excess amounts of amines were used. In general, reductive aminations were carried out with 4 equiv of the primary amine or 2 equiv of the secondary amine by use of 1 equiv of sodium cyanoborohydride and 0.5 equiv of zinc chloride in methanol at room temperature and the reactions were complete within 6 h. In the cases of β-keto esters, the reduction became more difficult and required 48 h for completion of the reaction. The results are summarized in Table V and illustrate the efficiency and the applicability of this procedure.

Reductive Methylation of Amines. Among several synthetic methods currently available for reductive methylation of amines to tertiary methylated amines,[18] the use of sodium cyanoborohydride–formaldehyde is the most convenient and efficient.[19] As we expected from our previous results in reductive amination of aldehydes and ketones, zinc-modified cyanoborohydride in methanol was very effective in reductive methylation of amines under mild conditions.

Reaction of amines with aqueous formaldehyde and zinc-modified cyanoborohydride in methanol gave tertiary methylated amines in high yields, whereas it has been reported[19] that the reaction with sodium cyanoborohydride in methanol affords a mixture of starting material and partially methylated products. The reaction was normally complete within 4 h at room temperature and this procedure was general for a variety of aliphatic and aromatic amines. This procedure appears to be the method of choice of reductive methylation of amines with respect to the high

(18) (a) Sondengam, B. L.; Hemo, J. H.; Charles, G. *Tetrahedron Lett.* **1973**, 261. (b) Boldrini, P.; Panunzio, M.; Umani-Ronchi, A. *Synthesis* **1974**, 261. (c) Giumanini, A. G.; Chiavari, G.; Musiani, M. M.; Rossi, P. *Ibid.* **1980**, 743. (d) Krishnamurthy, S. *Tetrahedron Lett.* **1982**, *23*, 3315. (e) Loibner, H.; Prucker, A.; Stütz, A. *Tetrahedron Lett.* **1984**, *25*, 2535.
(19) Borch, R. F.; Hassid, A. I. *J. Org. Chem.* **1972**, *37*, 1673.

Table V. Reductive Aminations with Zinc-Modified Cyanoborohydride in MeOH at Room Temperature[a]

compound	amine	time, h	product	yield, %[b]	bp, °C (mmHg)[c]
benzaldehyde	aniline	2	*N*-benzylaniline	93	125–125 (3.0)
benzaldehyde	piperidine	1	*N*-benzylpiperidine	88	64–67 (0.8)
benzaldehyde	morpholine	1	*N*-benzylmorpholine	83	65–70 (1.2)
butyraldehyde	aniline	2	*N*-(*n*-butyl)aniline	78	72–77 (3.0)
nonanealdehyde	piperidine	0.5	*N*-nonylpiperidine	80	64–68 (1.0)
cyclohexanone	methylamine	3	*N*-methylcyclohexylamine	(98)	
cyclohexanone	allylamine	3	*N*-cyclohexylallylamine	72	36–41 (3.3)
cyclohexanone	aniline	2	*N*-cyclohexylaniline	85	92–96 (2.0)
cyclohexanone	diethylamine	6	*N*,*N*-diethylcyclohexylamine	52	42–47 (2.1)
cyclohexanone	piperidine	5	*N*-cyclohexylpiperidine	91	55–60 (1.8)
acetophenone	*n*-propylamine	20	*N*-(*n*-propyl)phenethylamine	73	73–78 (4.0)
	morpholine	48		65	68–73 (1.5)

[a] The reaction was carried out with 4 mol equiv of the primary amine or 2 mol equiv of the secondary amine with 1 mol equiv of zinc-modified cyanoborohydride. [b] The yields refer to isolated products and the number in parentheses indicates GLC yield. [c] All values are in accord with reported values.

Table VI. Reductive Methylations of Amines with Zinc-Modified Cyanoborohydride in MeOH at Room Temperature[a]

amine	time, h	product	yield, %[b]	bp °C (mmHg), [mp °C][c]
benzylamine	2	*N*,*N*-dimethylbenzylamine	79	30–35 (1.6)
dodecylamine	4	*N*,*N*-dimethyldodecylamine	83	87–92 (1.0)
dicyclohexylamine	6	*N*-methyldicyclohexylamine	95	[193–194][d]
aniline	2	*N*,*N*-dimethylaniline	86	38–43 (1.5)
4-methoxyaniline	2	*N*,*N*-dimethyl-4-methoxyaniline	98	70–75 (5.0)
2-nitroaniline	2	*N*,*N*-dimethyl-2-nitroaniline	90	[57–58]
p-toluidine	2	*N*,*N*-dimethyl-*p*-toluidine	83	45–51 (2.0)

[a] The reaction was carried out with 3 mol equiv of aqueous formaldehyde and 1 mol equiv of zinc-modified cyanoborohydride. [b] The yields refer to isolated products. [c] All values are in accord with reported values. [d] Determined as hydrochloride salt.

yields, the mild conditions, and simple experimental manipulation.

Deoxygenation of Aldehydes and Ketones. The reductive deoxygenation of aldehydes and ketones is of considerable interest in organic synthesis and various synthetic methods have appeared in the literature.[20] Deoxygenation of aldehydes and ketones via the intermediacy of the corresponding tosylhydrazones is accomplished by using sodium cyanoborohydride in a 1:1 mixture of *N*,*N*-dimethylformamide and sulfolane containing *p*-toluenesulfonic acid at 100–105 °C.[21]

We have found that such reductions can be also achieved with zinc-modified cyanoborohydride in methanol at reflux. First, we examined reduction of 4-*tert*-butylcyclohexanone tosylhydrazone with the reagent in methanol at room temperature and 25% of *tert*-butylcyclohexane was obtained in 2 h. However, the reaction did not proceed to completion after overnight stirring. Thus, the reaction was carried out in methanol at reflux. Several tosylhydrazones were cleanly converted into the corresponding hydrocarbons in refluxing methanol within 3 h as shown in Table VII. Furthermore, since reduction of aldehydes and ketones is much slower than the formation of tosylhydrazones under the present conditions, the prior preparation of tosylhydrazones is unnecessary. Thus, reaction of equimolar amounts of aldehydes or ketones and tosylhydrazine with the reagent in methanol at reflux afforded the corresponding hydrocarbons in good yields.

Table VII. Deoxygenation of Aldehydes and Ketones with Zinc-Modified Cyanoborohydride in MeOH at Reflux

compound	time, h	product	yield, %[a]
2-undecanone tosylhydrazone	3	undecane	89, (78), 36[b]
4-*tert*-butylcyclohexanone tosylhydrazone	2	*tert*-butylcyclohexane	85, 25[b]
cholestan-3-one tosylhydrazone	1	cholestane	(94)
nonanealdehyde	1.5	nonane	71
dodecanealdehyde	2	dodecane	66
4-dodecanone	2	dodecane	81, (70)
4-methoxybenzaldehyde	3	4-methoxytoluene	25

[a] The yields were determined by GLC. The numbers in parentheses indicate the isolated yields. [b] The reaction was carried out at room temperature for 2 h.

Aromatic aldehydes like 4-methoxybenzaldehyde proved to be quite resistant to reduction, though the formation of the corresponding tosylhydrazones occurred readily. For example, reaction of equimolar amounts of 4-methoxybenzaldehyde and tosylhydrazine with zinc-modified cyanoborohydride in refluxing methanol for 3 h gave 4-methoxytoluene in 25% yield. Such behavior has been noted with sodium cyanoborohydride.[21]

Experimental Section

Proton nuclear magnetic resonance spectra were obtained on a Varian T-60A spectrometer and infrared spectra were measured on a Perkin-Elmer 267 spectrometer. Gas chromatographic analyses were performed on a Varian 2800 gas chromatograph and all analyses were carried out on 7 ft × 0.125 in. 10% Carbowax 20M on 60/80 mesh Chromosorb W, 5 ft × 0.125 in. 5% KOH-5% Carbowax 20M on 60/80 mesh Chromosorb W, and 7 ft × 0.125 in. 5% SE-30 on 60/80 mesh Chromosorb W columns. Reported

(20) (a) For a review, see: House, H. O. "Modern Synthetic Reactions", 2nd ed.; W. A. Benzamin: Menlo Park, CA, 1972. (b) Caglioti, L. *Tetrahedron* **1966**, *22*, 487. (c) Kabalka, G. W.; Baker, J. D. *J. Org. Chem.* **1975**, *40*, 1834. (d) Hutchins, R. O.; Natale, N. R. *Ibid.* **1978**, *43*, 2299. (e) Maryanoff, B. E.; McComsey, D. F.; Nortey, S. O. *Ibid.* **1981**, *46*, 355. (f) Kabalka, G. W.; Summers, S. T. *Ibid.* **1981**, *46*, 1217.

(21) (a) Hutchins, R. O.; Maryanoff, B. E.; Milewski, C. A. *J. Am. Chem. Soc.* **1971**, *93*, 1793. (b) Hutchins, R. O.; Milewski, C. A.; Maryanoff, B. E. *Ibid.* **1973**, *95*, 3662.

boiling points are those observed during distillation with Kugelrohr apparatus and are uncorrected. Melting points were determined on an Electrothermal melting point apparatus and are uncorrected.

Sodium cyanoborohydride was obtained from Aldrich Chemical Co., Ltd., and was used without purification, and zinc chloride was freshly dried just before used. Diethyl ether was distilled over lithium aluminum hydride under nitrogen and methanol was used without purification. Most of the compounds used in this study were commercial products and some compounds were prepared by known procedures. The products obtained were readily available materials in many cases. If not, identification was effected through alternate preparation by known procedures.

Since the reactions performed are all similar in many respects, typical reactions will be described as specific examples.

Reduction of Aldehydes and Ketones. To a suspended solution of sodium cyanoborohydride (74 mg, 1.2 mmol) and zinc chloride (82 mg, 0.6 mmol) in diethyl ether (8 mL) at room temperature was added 4-*tert*-butylcyclohexanone (185 mg). The reaction mixture was stirred at room temperature for 4 h, diluted with diethyl ether (30 mL), and quenched with 0.1 M KIO_3 (10 mL). The aqueous layer was extracted with diethyl ether and the combined ether extracts were washed with water and brine, dried over anhydrous $MgSO_4$, and evaporated to dryness to give 4-*tert*-butylcyclohexanol (177 mg, 95%). GLC analysis indicated the presence of the trans and the cis isomers in a ratio of 85:15.

Reduction of Acid Chlorides. To a suspended solution of sodium cyanoborohydride (202 mg, 3.2 mmol) and zinc chloride (217 mg, 1.6 mmol) in diethyl ether (5 mL) at room temperature was added a solution of benzoyl chloride (210 mg, 1.5 mmol) in diethyl ether (5 mL). After being stirred at room temperature for 12 h, the reaction mixture was treated with methanol (4 mL) and then 0.1 M KIO_3 (20 mL). The aqueous solution was extracted with diethyl ether and the combined ether extracts were washed with water and brine, dried over anhydrous $MgSO_4$, and evaporated under reduced pressure to give benzyl alcohol (156 mg, 97%). GLC analysis indicated only one peak of benzyl alcohol.

Reduction of Enones. To a suspension of sodium cyanoborohydride (105 mg, 1.7 mmol) and zinc chloride (113 mg, 0.9 mmol) in diethyl ether (3 mL) was added a solution of 2-cyclohexen-1-one (102 mg, 1.1 mmol) and nonyl alcohol (144 mg, 1.0 mmol) as an internal standard in diethyl ether (3 mL). The reaction mixture was stirred at room temperature for 4 h and quenched with 0.1 M KIO_3 (15 mL). The ether layer was subjected to GLC and GLC analysis indicated the presence of cyclohexanone (2%), cyclohexanol (44%), and 2-cyclohexen-1-ol (45%).

Reduction of Enamines. To a solution of morpholino-1-cyclohexene (250 mg, 1.5 mmol) in methanol (3 mL) was added a solution of sodium cyanoborohydride (190 mg, 3.0 mmol) and zinc chloride (202 mg, 1.5 mmol) in methanol (5 mL). The reaction mixture was stirred at room temperature for 1 h and was taken up in 0.1 N NaOH (20 mL). After most of methanol was evaporated under reduced pressure, the aqueous solution was extracted with diethyl ether (20 mL × 3). The combined ether extracts were washed with water and brine, dried over anhydrous $MgSO_4$, and evaporated to dryness. The residue was distilled with Kugelrohr apparatus in vacuo to give *N*-cyclohexylmorpholine (185 mg, 73%), identical with an authentic sample in boiling point, GLC, and NMR data: bp 66–70 °C (2.6 mmHg) [lit.[22] bp 240–241 °C].

Reductive Amination of Aldehydes and Ketones. To a stirred solution of cyclohexanone (295 mg, 3.0 mmol) and aniline (1.12 g, 12 mmol) in methanol (8 mL) at room temperature was added a solution of sodium cyanoborohydride (190 mg, 3.0 mmol) and zinc chloride (210 mg, 1.5 mmol) in methanol (5 mL). The resulting solution was stirred at room temperature for 2 h and was taken up in 0.1 N NaOH (20 mL). After most of methanol was evaporated under reduced pressure, the aqueous solution was extracted with ethyl acetate (30 mL × 3). The combined extracts were washed with water and brine, dried over anhydrous $MgSO_4$, and evaporated to dryness. The residue was distilled in vacuo to give *N*-cyclohexylaniline (445 mg, 85%), identical with an authentic sample in boiling point, GLC, and NMR data: bp 92–96 °C (2.0 mmHg) [lit.[23] bp 279 °C].

(22) Loeff, G. D. *Chem. Abstr.* **1971**, *75*, 20415r.
(23) "Handbook of Chemistry and Physics", 53th ed.; CRC Press: Cleveland, OH.

Reductive Methylations of Amines. To a stirred solution of aniline (148 mg, 1.6 mmol) in methanol (5 mL) containing 37% aqueous formaldehyde (0.4 mL, 5 mmol) at room temperature was added a solution of sodium cyanoborohydride (105 mg, 1.6 mmol) and zinc chloride (110 mg, 0.8 mmol) in methanol (5 mL). Ater the reaction mixture was stirred at room temperature for 2 h, the solution was taken up in 0.1 N NaOH (10 mL) and most of methanol was evaporated under reduced pressure. After the aqueous solution was extracted with ethyl acetate (20 mL × 3), the combined extracts were washed with water and brine, dried over anhydrous $MgSO_4$, and evaported to dryness. The residue was distilled in vacuo to give *N,N*-dimethylaniline (165 mg, 86%), identical with an authentic sample in boiling point, GLC, and NMR data: bp 39–43 °C (1.5 mmHg) [lit.[23] bp 77 °C (13 mmHg)].

Deoxygenation of Aldehydes and Ketones. Method A. To a stirred solution of 2-undecanone tosylhydrazone (252 mg, 0.7 mmol) and decane (70 mg, 0.5 mmol) as an internal standard in methanol (3 mL) at room temperature was added a solution of sodium cyanoborohydride (62 mg, 1 mmol) and zinc chloride (70 mg, 0.5 mmol) in methanol (2 mL). The reaction mixture was stirred at 65 °C for 3 h, taken up in 0.1 N NaOH (10 mL), and extracted with petroleum ether (20 mL × 3). The combined extracts were washed with water and brine, dried, and evaporated to dryness. GLC analysis of the crude product indicated the presence of undecane in 89% yield.

Method B. To a solution of nonanealdehyde (227 mg, 1.6 mmol), (*p*-tolylsulfonyl)hydrazine (308 mg, 1.7 mmol), and decane (142 mg, 1.0 mmol) as an internal standard in methanol (4 mL) at room temperature was slowly added a solution of sodium cyanoborohydride (107 mg, 1.7 mmol) and zinc chloride (108 mg, 0.8 mmol) in methanol (3 mL). After being stirred at room temperature for 10 min, the solution was stirred at 65 °C for 1.5 h. The reaction mixture was treated with 0.1 N NaOH (10 mL) and extracted with petroleum ether (20 mL × 3). The combined extracts were washed with ether and brine, dried, and evaporated to dryness. GLC analysis of the crude product indicated the presence of nonane in 71% yield.

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Registry No. $Na(CN)BH_4$, 25895-60-7; $ZnCl_2$, 7646-85-7; PhCHO, 100-52-7; *p*-$MeOC_6H_4CHO$, 123-11-5; $CH_3(CH_2)_7CHO$, 124-19-6; $CH_3CH_2COCH_2CH_3$, 96-22-0; $PhCOCH_3$, 98-86-2; $CH_3(CH_2)_6COCl$, 111-64-8; PhCOCl, 98-88-4; $PhCH_2COCl$, 103-80-0; PhCOOCOPh, 93-97-0; $CH_3(CH_2)_6CO(O)CO(CH_2)_6CH_3$, 623-66-5; $CH_3(CH_2)_6COOMe$, 111-11-5; *o*-ClC_6H_4COOMe, 610-96-8; $CH_3(CH_2)_6CONEt_2$, 996-97-4; $PhCONEt_2$, 1696-17-9; $PhCO_2H$, 65-85-0; $PhCH_2OH$, 100-51-6; *p*-$MeOC_6H_4CH_2OH$, 105-13-5; $CH_3(CH_2)_8OH$, 143-08-8; $CH_3CH_2CH_2(OH)CH_2CH_3$, 584-02-1; $PhCH(OH)CH_3$, 98-85-1; $CH_3(CH_2)_7OH$, 111-87-5; $CH_2(OH)CH_2Ph$, 60-12-8; $CH_3CH{=}C(CH_3)COCH_3$, 565-62-8; $(CH_3)_3CCH{=}CHCOC(CH_3)_3$, 1653-94-7; $CH_3CH{=}C(CH_3)CH(OH)CH_3$, 2747-53-7; $CH_3CH(CH_2CH_3)CH(OH)CH_3$, 565-60-6; $(CH_3)_3CCH{=}CHCH(OH)C(CH_3)_3$, 69897-40-1; $(CH_3)_3CCH_2CH(OH)C(CH_3)_3$, 69897-43-4; $CH_3(CH_2)_2CHO$, 123-72-8; $CH_3COCH_2CO(OEt)$, 141-97-9; $PhNH_2$, 62-53-3; $MeNH_2$, 74-89-5; $CH_2{=}CHCH_2NH_2$, 107-11-9; Et_2NH, 109-89-7; $PrNH_2$, 107-10-8; $PhNHCH_2Ph$, 103-32-2; PhNHBu, 1126-78-9; $PhCH_2CH_2NHPr$, 27906-91-8; $PhCH_2NH_2$, 100-46-9; $CH_3(CH_2)_{11}NH_2$, 124-22-1; *p*-$MeOC_6H_4NH_2$, 104-94-9; *o*-$O_2NC_6H_4NH_2$, 88-74-4; *p*-$MeC_6H_4NH_2$, 106-49-0; $PhCH_2NMe_2$, 103-83-3; $CH_3(CH_2)_{11}NMe_2$, 112-18-5; $PhNMe_2$, 121-69-7; *p*-$MeOC_6H_4NMe$, 701-56-4; *o*-$C_2NC_6H_4NMe_2$, 610-17-3; *p*-$MeC_6H_4NMe_2$, 99-97-8; $CH_3(CH_2)_{10}CHO$, 112-54-9; $CH_3(CH_2)_2CO(CH_2)_7CH_3$, 6137-26-4; $CH_3(CH_2)_9CH_3$, 1120-21-4; $CH_3(CH_2)_7CH_3$, 111-84-2; $CH_3(CH_2)_{10}CH_3$, 112-40-3; *p*-$MeOC_6H_4Me$, 104-93-8; HCHO, 50-00-0; 4-*tert*-butylcyclohexanone, 98-53-3; *trans*-4-*tert*-butylcyclohexanol, 21862-63-5; *cis*-4-*tert*-butylcyclohexanol, 937-05-3; cycloheptanone, 502-42-1; cycloheptanol, 502-41-0; 2-cyclohexen-1-one, 930-68-7; 3-methyl-5,5-dimethyl-2-cyclohexen-1-one, 78-59-1; 2-methyl-5-isopropenyl-2-cyclohexen-1-one, 99-49-0; 2-cyclopenten-1-one, 930-30-3; 3-methyl-2-cyclopenten-1-one, 2758-18-1; 2-cyclohexen-1-ol, 822-67-3; cyclohexanol, 108-93-0; 3,5,5-trimethyl-2-cyclohexen-1-ol, 470-99-5; 3,5,5-trimethylcyclohexanol, 116-02-9;

2-methyl-5-isopropenyl-2-cyclohexen-1-ol, 99-48-9; 2-methyl-5-isopropenylcyclohexanol, 619-01-2; cyclopentanol, 96-41-3; 3-methylcyclopentanol, 18729-48-1; *N*-(1-cyclohexenyl)piperidine, 2981-10-4; *N*-(1-cyclohexenyl)morpholine, 670-80-4; *N*-(1-cyclohexenyl)pyrrolidine, 1125-99-1; *N*-(1-cyclopentenyl)morpholine, 936-52-7; ethyl 3-morpholino-2-butenoate, 36277-32-4; *N*-(cyclohexyl)piperidine, 3319-01-5; *N*-(cyclohexyl)morpholine, 6425-41-8; *N*-(cyclohexyl)pyrrolidine, 7731-02-4; *N*-(cyclopentyl)morpholine, 39198-78-2; ethyl 3-morpholinobutanoate, 42980-69-8; piperidine, 110-89-4; morpholine, 110-91-8; *N*-benzylpiperidine, 2905-56-8; *N*-benzylmorpholine, 10316-00-4; *N*-nonylpiperidine, 30538-80-8; *N*-methylcyclohexylamine, 100-60-7; *N*-cyclohexylallylamine, 6628-00-8; *N*-cyclohexylaniline, 1821-36-9; *N,N*-diethylcyclohexylamine, 91-65-6; dicyclohexylamine, 101-83-7; *N*-methyldicyclohexylamine·hydrochloride, 59325-20-1; 2-undecanone tosylhydrazone, 37826-47-4; 4-*tert*-butylcyclohexanone tosylhydrazone, 41780-53-4; cholestan-3-one tosylhydrazone, 37826-48-5; *tert*-butylcyclohexane, 3178-22-1; cholestane, 14982-53-7.

Diels–Alder Approach to Bicyclic α-Hydroxy Ketones. Facile Ketol Rearrangements of Strained α-Hydroxy Ketones

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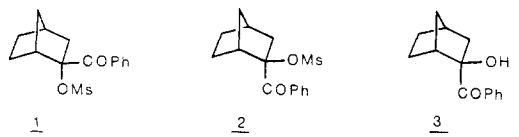
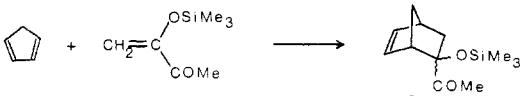
The trimethylsiloxy-substituted dienophiles 1-benzoyl-1-(trimethylsiloxy)ethylene, **6**, 1-carbomethoxy-1-(trimethylsiloxy)ethylene, **12**, and 1-acetyl-1-(trimethylsiloxy)ethylene, **4**, all reacted with cyclopentadiene to give adducts in which the carbonyl containing substituent of the major product occupied the exo position, in violation of the Alder rule. Desilylation of the Diels–Alder adducts of cyclopentadiene with **4** and **6** led to ring-expanded ketol rearrangement products on silica gel chromatography. This facile rearrangement was attributed to relief of strain in the starting α-hydroxy ketone. Equilibration studies showed that in the rearranged 2-hydroxy-2-substituted bicyclo[3.2.1]octan-3-one systems **24** and **30**, the more stable isomer is the one in which the phenyl or methyl substituent is in the axial position. The presence of a strong intramolecular hydrogen bond of the equatorial hydroxyl group with the carbonyl group accounts for the greater stability of **24** and **30**. Acetolysis of *endo*-2-benzoyl-*exo*-2-norbornyl mesylate, **2**, occurred readily, giving mainly the rearranged product of internal return, 1-benzoyl-*exo*-2-norbornyl mesylate, **38**. The high reactivity of **2** relative to the endo analogue and the α-H analogue was attributed to some transition-state carbonyl conjugation with the incipient α-keto cation center as well as possible neighboring σ-participation and/or steric rate enhancement.

During the course of studies[1] designed to generate and evaluate the properties of α-keto cations, we have prepared the *endo* mesylate **1**.[1c] We wanted to prepare the *exo* mesylate **2** in order to compare the behavior of these two



1 **2** **3**

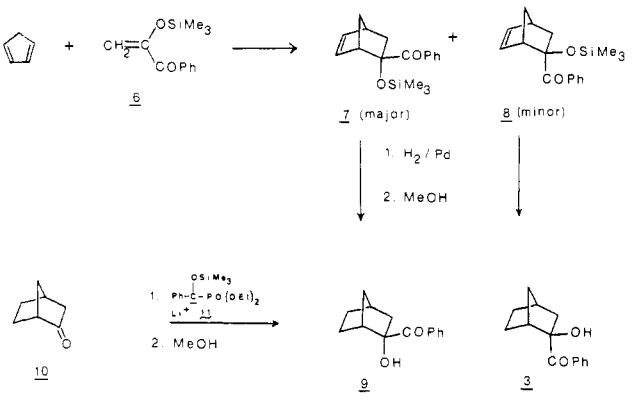
systems. Hence we desired a synthetic route to the precursor exo alcohol **3**. It has been reported[2] that cyclopentadiene reacts with **4** to give an adduct which, when desilylated, gives an α-hydroxy ketone presumed (but not proven) to have the hydroxy group in the exo position. Reported here are our attempts to prepare **3** using a similar Diels–Alder approach.



4 **5**

Results and Discussion

Diels–Alder Reactions of Trimethylsiloxy-Substituted Dienophiles. Our approach to the synthesis of **3** involved in Diels–Alder reaction of cyclopentadiene with the enone **6**. This reaction gave a 58% yield of a mixture



of **7** (3.5 parts) and **8** (1 part) in which, unexpectedly, the isomer **7**, with the endo trimethylsiloxy group, predominated. The stereochemical assignment was confirmed by catalytic hydrogenation of the mixture followed by desilylation. The major ketol **9** was identical with a sample produced independently by addition of the benzoyl anion equivalent **11** to norcamphor.[1c]

In view of the surprising stereochemistry of this Diels–Alder reaction, the reaction of other dienophiles, which are structurally similar to **6**, was examined. Reaction of **12** with cyclopentadiene gave two adducts in which, as before, the endo trimethylsiloxy adduct **13** predominates. The stereochemistry was likewise established by hydrogenation and desilylation of **13**, which gave a product indentical with **15** produced by addition of (α-methoxyvinyl)lithium to norcamphor followed by ozonolysis.[1c]

In view of these results, the previously reported[2] reaction of **4** with cyclopentadiene was repeated. The Diels–Alder adducts **16** and **17** were isolated in 48% overall yield prior

(1) (a) Creary, X. *J. Org. Chem.* **1979**, *44*, 3938–45. (b) Creary, X. *J. Am. Chem. Soc.* **1981**, *103*, 2463–5. (c) Creary, X.; Geiger, C. C. *Ibid.* **1982**, *104*, 4151–62. (d) Creary, X.; Geiger, C. C. *Ibid.* **1983**, *105*, 7123–9. (e) Creary, X. *Ibid.* **1984**, *106*, 5568–77.

(2) Ardecky, R. J.; Kerdesky, F. A. J.; Cava, M. P. *J. Org. Chem.* **1981**, *46*, 1483–5.

0022-3263/85/1950-1932$01.50/0