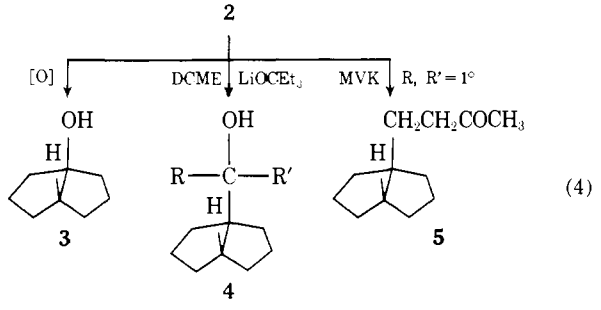
netic stirring bar, and a reflux condenser connected to a mercury bubbler maintained under a positive pressure of nitrogen, there was added 5.25 g (35.0 mmol) of *B*-Et-9-BBN and 15 ml of dry, olefin-free pentane. Stirring was begun and the flask was cooled in a dry ice–acetone bath where 19.4 ml of 1.81 M (35.1 mmol) methyllithium (from methyl chloride) in diethyl ether was added slowly via the double-ended needle technique. After stirring about 10 min at −78°, the reaction mixture was allowed to come to room temperature and stir for 1.5 h. The flask was immersed in a cold water bath while 2.75 g (35.0 mmol) of acetyl chloride (freshly distilled from calcium hydride) was added dropwise from a syringe. A vigorous, exothermic reaction occurred, and a white precipitate formed. After stirring about 2 h, the supernatant liquid was decanted via the double-ended needle technique into an evacuated short-path distillation assembly where the volatiles were flash-distilled. The precipitate was washed with dry, olefin-free pentane (3 × 10 ml), and the washings were decanted in like manner into the distillation apparatus. The residual oil was vacuum distilled giving 5.6 g (97%) of a clear, colorless oil, bp 28–32 °C at 0.005 mm. GLC showed the material to be about 97% pure. ^{13}C NMR showed only one set of peaks, indicating that probably only one isomer was present. Alkaline hydrogen peroxide oxidation of a portion of the product in THF solution provided a 95% yield (GLC) of *cis*-bicyclo[3.3.0]octan-1-ol (**3**).

As examples of the synthetic utility of these new organoboranes, we carried out three typical organoborane reactions: alkaline hydrogen peroxide oxidation, the DCME reaction, and 1,4-addition to methyl vinyl ketone. These reactions were carried out under standard conditions[8] and readily provided the products **3**, **4**, and **5** (eq 4).



(4)

The unexpected ability of the lithium dialkyl-9-BBN "ate" complexes to reduce a variety of organic substrates not only provides a novel reducing agent,[4,9] but also a new convenient route to the *cis*-bicyclo[3.3.0]oct-1-yldialkylboranes. These bicyclic organoboranes, coupled with the ever expanding battery of organoborane reactions, provide a very simple route to many compounds containing the *cis*-bicyclo[3.3.0]oct-1-yl moiety which have previously been difficult to prepare.

References and Notes

(1) G. W. Kramer and H. C. Brown, *J. Organomet. Chem.*, **90**, CI (1975).
(2) H. C. Brown, "Boranes in Organic Chemistry", Cornell University Press, Ithaca, N.Y., 1972.
(3) H. C. Brown, G. W. Kramer, A. B. Levy, and M. M. Midland, "Organic Syntheses via Boranes", Wiley-Interscience, New York, N.Y., 1975.
(4) Y. Yamamoto, H. Toi, S.-I. Murahashi, and I. Moritani, *J. Am. Chem. Soc.*, **97**, 2558 (1975).
(5) It has been recently reported that simple lithium tetraalkylboron "ate" complexes smoothly alkylate acid chlorides to give mixed ketones. E. Negishi, K.-W. Chiu, and T. Yoshida, *J. Org. Chem.*, **40**, 1676 (1975). In the present study, no evidence of such a competing alkylation was observed.
(6) Lithium dialkyl-9-BBN "ate" complexes containing secondary or tertiary alkyl groups must be prepared from the *B*-alkyl-9-BBN containing the secondary or tertiary group, since the reaction of secondary or tertiary alkyllithiums with trialkylboranes does not produce the desired "ate" complex in high yield. See ref 5 and E. J. Corey, K. R. Becker, and R. K. Varma, *J. Am. Chem. Soc.*, **94**, 8618 (1972).
(7) For a detailed account of the procedures used in this work, see ref 3, Chapter 9.
(8) Described in ref 3 for similar preparations.
(9) Y. Yamamoto, H. Toi, A. Sonoda, and S.-I. Murahashi, *J. Am. Chem. Soc.*, following paper in this issue.
(10) Graduate Research Assistant on Grant GP 41169X from the National Science Foundation.

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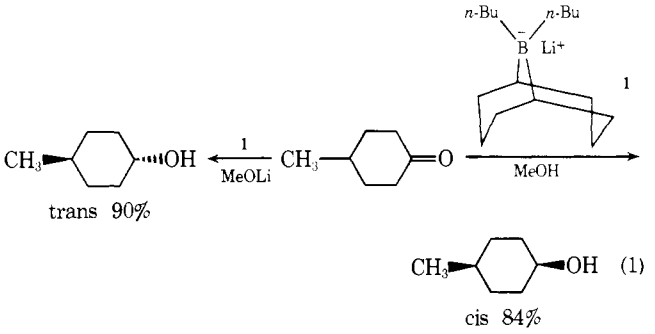
Stereo-, Chemo-, and Regioselective Reductions of Carbonyl Groups via the Lithium Di-*n*-butyl-9-borabicyclo[3.3.1]nonane "Ate" Complex

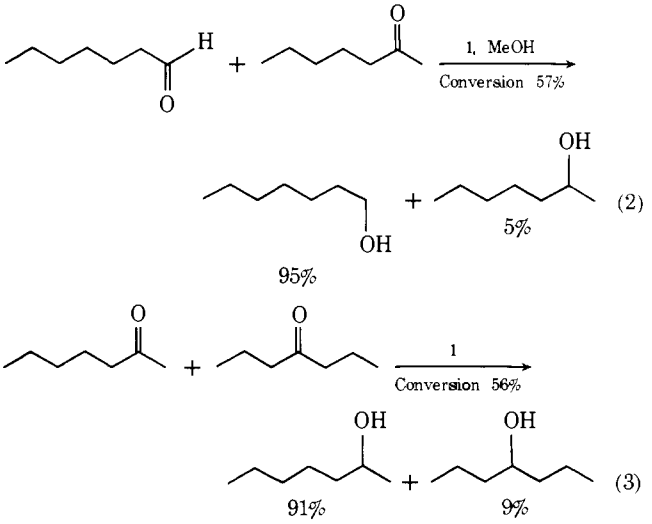
Sir:

The lithium di-*n*-butyl "ate" complex of 9-borabicyclo-[3.3.1]nonane (**1**) (9-BBN "ate" complex), a new type of reducing agent, exhibits high stereo-, chemo-, and regioselectivities[1] in the reduction of carbonyl groups. Thus both *cis*- and *trans*-4-methylcyclohexanols with reasonably high isomeric purity are independently obtainable from 4-methylcyclohexanone with a mere change in additive (eq 1). Such controllable stereoselective reduction via a unitary



(1)

reagent cannot be realized with reagents previously available.[2,5] Furthermore, aldehydes can be chemoselectively reduced in the presence of ketones (eq 2), and the reagent even discriminates between the regioisomers of ketones (eq 3).



(2)

(3)

We recently reported that the bridgehead hydrogen of the 9-BBN ring in **1** acts as a reducing moiety for halides, indicating an obvious difference between **1** and the presently known hydride reagents,[2,5] where the reducing agents contain hydride directly attached to the metal.[6] Therefore,

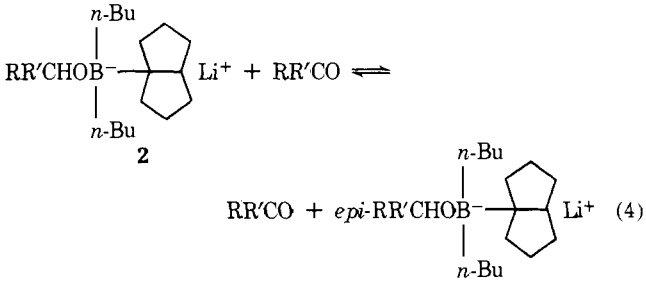
Table I. Stereoselective Reduction of Representative Cyclic Ketones[a]

Ketone	Entry	Additive	Ketone:1: additive[b]	Time, h	Conversion, %[c]	Major Isomer, %
2-Methylcyclohexanone	1	None	1:1	0.5	—	—
	2	None	1:1	18	35	Cis, 92
	3	MeOLi[d]	1:1:1	3	59	Trans, 89
3-Methylcyclohexanone	4	None	1:1	0.5	62	Trans, 91
	5	MeOH	1:2:1	3	100	Trans, 86
4-Methylcyclohexanone	6	None	1:1	0.5	63	Cis, 77
	7	None	1:1	18	77	Cis, 48
	8	None	2:1	0.5	54[e]	Cis, 47
	9	MeOH	1:2:1	3	91	Cis, 84
	10	MeOLi[d]	1:1:1	5	94	Trans, 90
	11	MeOLi[f]	1:1:1	0.5	96	Trans, 78
	12	LiBr	1:1:1	0.5	83	Trans, 79
4-*tert*-Butylcyclohexanone	13	MeOH	1:2:1	1.5	100	Cis, 88
	14	MeOLi[d]	1:1:1	3	89	Trans, 92

[a] All reactions were performed on 2-mmol scales; the ketones and additives were added *all at once* to the hexane solution of **1** at 0°, and the reaction was allowed to come to room temperature. The reaction mixture was quenched with water, and the products were analyzed by GLC. [b] Molar ratio. [c] Based on the ketone except where otherwise indicated. [d] MeOLi was prepared in situ; *B*-MeO-9-BBN was treated with 2 equiv of *n*-BuLi in hexane.[9] [e] Based on **1**. [f] Externally prepared MeOLi was added to the solution of **1** in hexane.

the reducing character of **1** toward carbonyl groups appeared to offer promising possibilities.

In order to understand the steric control in the reduction of ketones, representative cyclic ketones were treated with **1**. As is apparent from Table I, the reduction of 2-methylcyclohexanone was sluggish and required long times to achieve satisfactory conversion (entries 1, 2, 4, 6, and 7). Apparently, this resulted in equilibration of epimeric alcohols, leading to the increased formation of the more stable alcohol (entries 6 and 7). We sought means of circumventing this difficulty. Fortunately, methanol suppressed the equilibration,[7] whereas addition of MeOLi or LiBr accelerated the isomerization (entries 3, 5, and 9–14). The isomerization is presumably due to the intermolecular hydride transfer such as occurs in the Meerwein–Pondorf–Verley reduction of ketones with aluminum alkoxides (eq 4).[8] Actually, the presence of excess ketone promoted the isomerization (entry 8). Methanol may assist in the decomposition of **2** which prevents the hydride transfer,[9] while the lithium salts may facilitate the transfer by their activation of the carbonyl group. The stereoselectivity achieved in the presence of methanol appears comparable to that of Li(*sec*-Bu)$_3$BH,[5b] but slightly lower than that of Hooz's reagent.[5g] Irrespective of the precise role of the additives, the controllable stereoselectivity is highly promising.



(4)

The slow reduction of 2-methylcyclohexanone (entries 1, 4, and 6), compared to the 3- and 4-methyl derivatives, suggested that the structural environment of the carbonyl group should have considerable influence upon the rate of reduction.[10] First, differentiation between aldehydes and ketones was attempted. A benzene solution of heptanal (2 mmol), 2-heptanone (2 mmol), and methanol (2 mmol) was treated with **1** (2 mmol) in hexane. As shown in eq 2, the aldehyde and ketone were differentiated (1-heptanol 95%, 2-heptanol 5%, conversion 57%, 3 h at room temperature). Similarly, high chemoselectivity was realized in the reduction of benzaldehyde and acetophenone (benzyl alcohol 97%, 1-phenylethanol 3%, conversion 74%, 3 h at room temperature). Cyclohexenone was reduced to cyclohexanone, whereas utilization of excess reagent led to the formation of cyclohexanol. Under the reaction conditions, methyl benzoate and benzyl cyanide were not reduced. These results indicate that **1** should permit the chemoselective reduction of aldehydes in the presence of ketones, esters, and nitriles.[11]

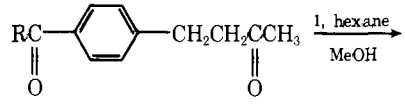
Table II. Relative Reactivity of Ketones toward **1**[a]

Ketone	R^b	Ketone	R^b
Cyclohexanone	1.00	Phenyl ethyl ketone	0.22
Cycloheptanone	0.50	Phenyl *n*-propyl ketone	0.06
Cyclooctanone	0.40	Phenyl isopropyl ketone	0.03
p-Chloroacetophenone	1.00	2-Heptanone	0.78
Acetophenone	0.51	3-Heptanone	0.43
p-Methoxyacetophenone	0.18	4-Heptanone	0.03

[a] The equimolar mixture (2 mmol scale) of **1** and substrate in hexane was stirred for 5 h, then the reaction mixture was quenched and analyzed as described in Table I. [b] R = yield of the alcohol based on ketone. R = 1.00 indicates formation of alcohol in 100% yield.

Second, the rate of reduction of various ketones was examined. The results are summarized in Table II. Evidently, the reactivity varies with the electronic and positional environment of carbonyl groups. A noteworthy feature is the discrimination between phenyl ethyl ketone and phenyl *n*-propyl ketone, and between 3-heptanone and 4-heptanone. Actually, as shown in eq 3, high regioselectivity was achieved in the reaction of **1** (4 mmol) in hexane with the mixture of 2-heptanone (2 mmol) and 4-heptanone (2 mmol) (2-heptanol 91%, 4-heptanol 9%, conversion 56%, 45 min at room temperature). In this case, the presence of methanol enhanced the regioselectivity although it decreased the conversion. Translation of these intermolecular

results to an intramolecular situation is demonstrated in eq 5.



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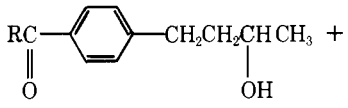

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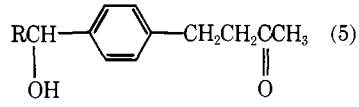

5 (5)

Isolated Yield of Ketol 4:5

3a, R = Ph	77%	~100:0
b, R = *i*-Pr	69%	>99:<1
c, R = *n*-Pr	59%	97:3
d, R = Et	57%	90:10
e, R = Me	60%	83:17

A representative example is the regioselective reduction of 4-(*p*-benzoylphenyl)-2-butanone (**3a**). A mixture of the diketone (10 mmol, 2.53 g), MeOH (11 mmol, 0.36 g), and **1** (20 mmol) in 20 ml of hexane was stirred at room temperature for 2.5 h. Water was added, and the reaction mixture was oxidized with air and extracted with ether. The extract was dried over anhydrous K_2CO_3 and concentrated. Kügelrohr distillation gave 4-(*p*-benzoylphenyl)-2-butanol, 1.96 g, 77%; 2,4-dinitrophenylhydrazone, mp 148–151 °C (lit. 155–157 °C).[12]

It is often required to reduce specific functional groups in a stereo-, chemo-, or regioselective manner. Successful approaches to such reductions have hitherto involved modification of the borohydride or aluminohydride anion by the replacement of hydrogen with sterically bulky substituents or electron-withdrawing groups.[2,5] The present development, therefore, provides an entirely new approach to this problem.

References and Notes

(1) In this manuscript the commonly used term, "selective reduction",[2] is for convenience divided into three categories: stereo-, chemo-, and regioselective reductions. The terms chemo-[3] and regioselectivities[4] seem to be used for describing the differentiation of targets in a given structural unit, namely, intramolecular discrimination. However, here, these terms are also used for such intermolecular discrimination as in eq 2 and 3.

(2) For reviews of selective reduction, see (a) R. L. Augustine, "Reduction", Marcel Dekker, New York, N.Y., 1968; (b) H. O. House, "Modern Synthetic Reactions", 2nd ed, W.A. Benjamin, New York, N.Y., 1972; (c) H. C. Brown, "Boranes in Organic Chemistry", Cornell University Press, Ithaca, N.Y., 1972.

(3) B. M. Trost and T. N. Satzmann, *J. Am. Chem. Soc.*, **95**, 6840 (1973).

(4) A. Hassner, *J. Org. Chem.*, **33**, 2684 (1968).

(5) For the well-known selective reducing agents, see ref 2. Recently developed agents for selective reduction of carbonyl groups are as follows: Brown's reagents, (a) H. C. Brown and W. C. Dickason, *J. Am. Chem. Soc.*, **92**, 709 (1970); (b) H. C. Brown and S. Krishnamurthy, *ibid.*, **94**, 7159 (1972); (c) S. Krishnamurthy and H. C. Brown, *J. Org. Chem.*, **40**, 1864 (1975); Corey's reagent, (d) E. J. Corey and R. K. Varma, *J. Am. Chem. Soc.*, **93**, 7319 (1971); Lalancette's reagent, (e) J. M. Lalancette, A. Freche, J. R. Brindle, and M. Laliberte, *Synthesis*, 562 (1972); Hutchins' reagent, (f) R. O. Hutchins and D. Kandasamy, *J. Am. Chem. Soc.*, **95**, 6131 (1973); Hooz's reagent, (g) J. Hooz, S. Akiyama, F. J. Ceder, M. J. Bennett, and R. M. Tuggle, *ibid.*, **96**, 274 (1974); copper "ate" complexes, (h) R. K. Boeckman, Jr., and R. Michalak, *ibid.*, **96**, 1623 (1974); (i) S. Masamune, G. S. Bates, and P. E. Georghiou, *ibid.*, **96**, 3686 (1974); $NaBH_3CN$, (j) C. F. Lane, *Synthesis*, 135 (1975).

(6) Y. Yamamoto, H. Toi, S.-I. Murahashi, and I. Moritani, *J. Am. Chem. Soc.*, **97**, 2558 (1975).

(7) If equimolar amounts of reagent were employed (ketone:**1**:MeOH = 1:1:1), both the conversion and selectivity achieved were somewhat low.

(8) E. L. Eliel and D. Nasipuri, *J. Org. Chem.*, **30**, 3809 (1965).

(9) It is anticipated that the decomposition of **2** into lithium alkoxide and trialkylborane is relatively sluggish in the absence of MeOH, permitting the hydride transfer. However, there is also the possibility that methanol is protonating reactive intermediates. For such alkoxyalkyl "ate" complexes, see G. W. Kramer and H. C. Brown, *J. Organomet. Chem.*, **73**, 1 (1974). When the reduction was complete, oxidation of the reaction mixture produced RR'CHOH, *n*-BuOH, and bicyclo[3.3.0]octan-1-ol along with small amounts of cyclooctanone.

(10) Even highly hindered borohydrides, such as lithium perhydro-9b-borophenalylhydride[5a] and Li(*sec*-Bu)$_3$BH,[5b] reduce 2-methylcyclohexanone quantitatively in 1 h at 0°.

(11) Cyclohexanone was preferentially reduced in the presence of benzylchloride.[6] With some ketones or aldehydes, the corresponding aldol condensation products were also formed. Here also, the selectivity is low in the absence of methanol. The reaction with 1,3-dicarbonyl compounds resulted in the formation of complex mixtures.

(12) P. T. Lansbury and J. O. Peterson, *J. Am. Chem. Soc.*, **85**, 2236 (1963).

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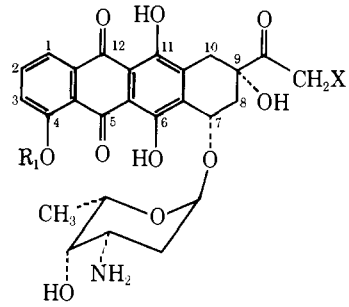
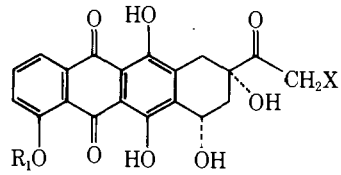
Total Synthesis of (±)-Daunomycinone and (±)-Carminomycinone

Sir:

The anthracycline antibiotics daunorubicin[1] (**1**), adriamycin[2] (**2**), and carminomycin[3] (cf. carminomycin-I, **3**)[4] are effective antineoplastic agents against a variety of experimental tumors and in certain types of human cancer. Chemotherapy employing anthracyclines **1** and **2** is known to be hampered by dose-related cardiotoxic effects,[5] so that there is great current interest in natural or synthetic sources of related compounds having improved therapeutic indices.



1, $R_1 = CH_3$; X = H
2, $R_1 = CH_3$; X = OH
3, R_1 = H; X = H



4, $R_1 = CH_3$; X = H
5, $R_1 = CH_3$; X = OH
6, R_1 = H; X = H

Wong has reported a synthesis of (±)-daunomycinone (**4**) by a 22-step procedure starting from 2,5-dimethoxybenzaldehyde.[6] Two syntheses of natural L-daunosamine have been described,[7] and the coupling of a protected L-daunosamine with daunomycinone to give natural daunorubicin has been achieved in good yield.[8] To date, however, no practical route for the large scale preparation of the agly-